Specification

Composition comprising tetracyclic compound

[Technical field]

[0001]

The present invention relates to a composition of a tetracyclic compound having an ALK inhibitory activity, and in particular to a composition for oral administration.

[Background art]

[0002]

Anaplastic Lymphoma Kinase (ALK) is one of the receptor type tyrosine kinases belonging to an insulin receptor family (Non-Patent Document Nos. 1 and 2). It is reported that gene alteration of ALK causes production of abnormal kinase fused with other gene.

Examples of the disorders accompanied with ALK abnormality include cancer and cancer metastasis (Non-Patent Document 1 and Patent Document 1), depression and cognitive function disorder (Non-Patent Document 2). Thus, an inhibitor for ALK will provide pharmaceuticals that are effective for treatment and prevention of the disorders.

Such pharmaceuticals are required to be developed in the form of orally administrable formulation. However, propriety of development of an orally administrable formulation depends on the level of bioavailability of a pharmaceutical compound. As a factor which affects bioavailability, water solubility of a pharmaceutical compound can be considered. In general, when a compound which is poorly water-soluble or insoluble in water is orally administered, it shows poor bioavailability. Improving an oral absorbability by increasing the bioavailability of an active ingredient is also important in terms of obtaining stable exhibition of pharmaceutical effect of the active ingredient. Patent Document 2 discloses a composition which comprises a poorly water-soluble ingredient such as steroids, sodium lauryl sulfate and an organic polymer for improving solubility and oral absorbability of a poorly water-soluble ingredient, that is obtained by wet granulation in the presence of water.

Until now, for example, tricyclic compounds (Patent Document 2) or the like have been reported as an ALK inhibiting substance.

However, the tetracyclic compounds that are represented by the following Formula (I) or salts thereof are not described in any document.

Meanwhile, ellipticine derivatives are known as tetracyclic compound (Non-Patent Document 3).

Although the tetracyclic compounds used in the present invention have an excellent ALK inhibitory activity, due to their poorly water-soluble or insoluble property in water, further studies have been needed to develop them in the form of orally administrable formulation.

[Document List]

[Patent Document]

[0003]

[Patent Document 1] JP2009100783 (A)

[Patent Document 2] Japanese Patent Application Laid-Open (JP-A) No. 2008-280352

[Non-Patent Document]

[0004]

[Non-Patent Document 1] Nature, Vol. 448, pages 561-566, 2007

[Non-Patent Document 2] Neuropsychopharmacology, Vol. 33, pages 685-700, 2008

[Non-Patent Document 3] Current Medicinal Chemistry: Anti-Cancer Agents, Vol. 4, Issue No. 2, pages 149-172, 2004

[Summary of the present invention]

[Problems to be Solved by the present invention]

[0005]

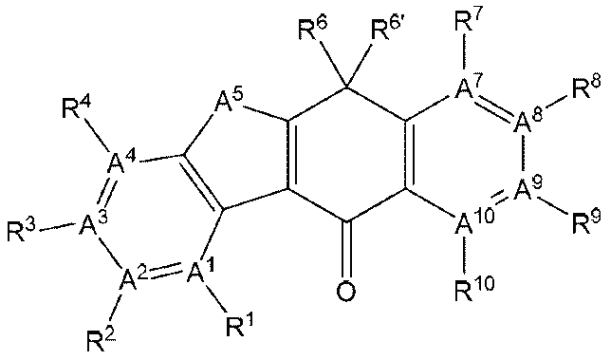
The inventors of the present invention extensively studied to solve the problems described above, and as a result, unexpectedly found that, by allowing a dissolution aid to co-exist with a poorly water-soluble or insoluble substance represented by the Formula (I), solubility of the substance can be significantly improved. The inventors carried out further studies based on these findings, and completed the present invention accordingly.

[Means for Solving the Problems]

[0006]

Specifically, the present invention relates to the followings.

[1] A composition comprising a substance represented by the Formula (I), a pharmaceutically acceptable carrier, and a dissolution aid,



(I)

[wherein,

A^1, A^2, A^3, A^4, A^7, A^8, A^9 and A^{10} all represent C, or any one of A^2, A^3, A^4, A^7, A^8 and A^9 represents N (with the proviso that, when it represents N, no substituent group exists therefor) and the remainings represent C;

A^5 is selected from NR^5, O and S;

R^1 and R^{10} each independently represent [1] a hydrogen atom, [2] a cyano group, [3] a halogen atom or [4] a 4- to 10-membered heterocycloalkyl group which may be substituted by 4- to 10-membered heterocycloalkyl group(s);

R^2 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a $C_{1\text{-}8}$ alkyl group,

(3) a $C_{2\text{-}8}$ alkenyl group,

(4) a $C_{2\text{-}8}$ alkynyl group,

(5) a cyano group,

(6) a halogen atom,

(7) a $(C_{1\text{-}8}$ alkyl$)_{m2}$-amino group which may be substituted by $C_{1\text{-}8}$ alkylsulfonyl group(s),

m2: 0~2, and

(8) a nitro group;

R^3 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a C_{1-8} alkyl group which may be substituted by [1] halogen atom(s), [2] hydroxy group(s) or [3] C_{1-8} alkoxy group(s),

(3) a C_{6-10} aryl group,

(4) a cyano group,

(5) a C_{1-8} alkanoyl group which may be substituted by C_{6-10} aryl group(s),

(6) a $(C1\text{-}8\ alkyl)_{m3a}$-aminocarbonyl group which may be substituted by one or more R^{3A},

R^{3A}: [1] a C_{6-10} aryl group, [2] a C_{1-8} alkoxy group, [3] a 5- to 14-membered heteroaryl group, or [4] a C_{6-10} arylsulfonyl group,

m3a: 0~2,

(7) a hydroxycarbonyl group,

(8) a C_{1-8} alkoxycarbonyl group which may be substituted by [1] hydroxy group(s) or [2] C_{1-8} alkoxy group(s),

(9) a halogen atom,

(10) a $(C_{1-8}\ alkyl)_{m3b}$-amino group which may be substituted by C_{6-10} aryl group(s),

m3b: 0~2,

(11) a C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by [1] C_{6-10} aryl group(s) or [2] C_{6-10} aryloxy group(s),

(12) a C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by halogen atom(s),

(13) a $(C_{1-8}\ alkyl)_{m3c}$-aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{6-10} aryl group(s),

m3c: 0~2,

(14) a nitro group,

(15) a hydroxy group,

(16) a C_{1-8} alkoxy group which may be substituted by one or more R^{3B},

R^{3B}: [1] a hydroxy group, [2] a C_{1-8} alkoxy group, [3] a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl group, [4] a $(C_{1-8}\ alkyl)_{m3d}$-amino group, or [5] a halogen atom,

m3d: 0~2,

(17) a 4- to 10-membered heterocycloalkyloxy group,

(18) a 5- to 14-membered heteroaryloxy group,

(19) a $(C_{1-8}$ alkyl$)_{m3e}$-aminocarbonyloxy group which may be substituted by C_{6-10} aryl group(s)

m3e: 0~2,

(20) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group,

(21) a C_{1-8} alkylsulfonyloxy group which may be substituted by halogen atom(s),

(22) a C_{1-8} alkylthio group,

(23) a C_{1-8} alkylsulfonyl group which may be substituted by C_{6-10} aryl group(s),

(24) a 5- to 14-membered heteroaryl group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by C_{1-8} alkoxy group(s),

(25) a C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkoxy group(s),

(26) a C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by halogen atom(s),

(27) a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted by one or more R^{3C},

R^{3C}: [1] a C_{1-8} alkyl group which may be substituted by halogen atom(s), or [2] a C_{1-8} alkoxy group,

(28) a C_{3-8} cycloalkyl (C_{0-8} alkyl) aminocarbonyloxy group, and

(29) a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group which may be substituted by substituent group(s) selected from the group consisting of [1] a C_{1-8} alkyl group and [2] a C_{1-8} alkoxy group;

R^4 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a C_{1-8} alkyl group which may be substituted by halogen atom(s),

(3) a C_{2-8} alkenyl group,

(4) a C_{2-8} alkynyl group,

(5) a C_{3-8} cycloalkyl group,

(6) a cyano group,

(7) an aminocarbonyl group,

(8) a $(C_{1\text{-}8}$ alkyl$)_{m4a}$-aminocarbonyl group,

m4a: 1~2,

(9) a hydroxycarbonyl group,

(10) a $C_{1\text{-}8}$ alkoxycarbonyl group,

(11) a halogen atom,

(12) a $(C_{1\text{-}8}$ alkyl$)_{m4b}$- amino group,

m4b: 0~2,

(13) a hydroxy group, and

(14) a $C_{1\text{-}8}$ alkoxy group which may be substituted by hydroxy group(s);

R^5 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a $C_{1\text{-}8}$ alkyl group which may be substituted by one or more R^{5A},

R^{5A}: [1] a hydroxycarbonyl group, [2] a $C_{1\text{-}8}$ alkoxycarbonyl group, [3] a hydroxy group, [4] a $C_{1\text{-}8}$ alkoxy group, [5] a $(C_{1\text{-}8}$ alkyl$)_{m5}$-amino group, [6] a $C_{6\text{-}10}$ aryl group, or [7] a $C_{1\text{-}8}$ alkylthio group,

m5: 0~2,

(3) a $C_{2\text{-}8}$ alkenyl group,

(4) a $C_{2\text{-}8}$ alkynyl group,

(5) a $C_{3\text{-}8}$ cycloalkyl group, and

(6) a $C_{1\text{-}8}$ alkylsulfonyl group;

R^6 and $R^{6'}$ are each independently selected from the group consisting of:

(1) a $C_{1\text{-}8}$ alkyl group which may be substituted by halogen atom(s),

(2) a $C_{2\text{-}8}$ alkenyl group, and

(3) a $C_{2\text{-}8}$ alkynyl group; or

R^6 and $R^{6'}$ are taken together with the carbon atoms to which they are bound to form:

(4) a $C_{3\text{-}8}$ cycloalkyl group, or

(5) a 4- to 10-membered heterocycloalkyl group which may be substituted by $C_{1\text{-}8}$ alkyl $C_{6\text{-}10}$ aryl sulfonyl group(s) which may be substituted by $C_{1\text{-}8}$ alkyl group(s);

R^7 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a halogen atom,

(3) a $C_{1\text{-}8}$ alkoxy group which may be substituted by one or more R^{7A},

R^{7A}: [1] a $(C_{1\text{-}8}$ alkyl$)_{m7a}$-amino group, [2] a hydroxy, [3] a 4- to 10-memberd heterocycloalkyl group which may be substituted by $C_{1\text{-}8}$ alkyl group(s),

m7a: 0~2,

(4) a $C_{1\text{-}8}$ alkylsulfonyl group,

(5) a nitro group, and

(6) a hydroxyl group;

R^8 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a $C_{1\text{-}8}$ alkyl group which may be substituted by one or more R^{8A},

R^{8A}: [1] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8A1}, [2] a $(C_{1\text{-}8}$ alkyl$)_{m8a}$- amino group which may be substituted by a halogen atom, or [3] a hydroxy group,

m8a:0~2,

R^{8A1}: [1] a $C_{1\text{-}8}$ alkyl group, [2] a $C_{1\text{-}8}$ alkylsulfonyl group, [3] a $(C_{1\text{-}8}$ alkyl$)_{m8b}$-aminosulfonyl group, [4] an oxo group, [5] a $C_{1\text{-}8}$ alkoxycarbonyl, or [6] a $C_{1\text{-}8}$ alkoxycarbonyl ($C_{0\text{-}8}$ alkyl) aminosulfonyl,

m8b: 0~2,

(3) a $C_{2\text{-}8}$ alkenyl group,

(4) a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8B},

R^{8B}:

<1> a $C_{1\text{-}8}$ alkyl group which may be substituted by one or more R^{8B1},

<2> a $C_{2\text{-}8}$ alkeynyl group,

<3> a $C_{2\text{-}8}$ alkynyl group,

<4> a $C_{3\text{-}8}$ cycloalkyl group which may be substituted by [1] cyano group(s) or [2] $C_{1\text{-}8}$ alkyl

group(s),

<5> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8B2},

<6> a C_{1-8} alkoxy group which may be substituted by substituent group(s) selected from the group consisting of [1] a C_{1-8} alkoxy group and [2] a C_{3-8} cycloalkyl group,

<7> a C_{1-8} alkoxycarbonyl group,

<8> a C_{1-8} alkylsulfonyl group,

<9> a 5- to 14-membered heteroarylsulfonyl group,

<10> an oxo group,

<11> a cyano group,

<12> a C_{1-8} alkanoyl group which may be substituted by one or more R^{8B3},

<13> a C_{3-8} cycloalkylcarbonyl group,

<14> a $(C_{1-8}$ alkyl$)_{m8c}$-aminosulfonyl group,

<15> a C_{1-8} alkylsulfonyl (C_{0-8} alkyl) amino group,

<16> a $(C_{1-8}$ alkyl$)_{m8d}$-amino group which may be substituted by one or more R^{8B4},

<17> a hydroxy group,

<18> a $(C_{1-8}$ alkyl$)_{m8e}$-aminocarbonyl group, or

<19> a C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group

m8c: 0~2

m8d: 0~2

m8e: 0~2

R^{8B1}: [1] a C_{3-8} cycloalkyl group, [2] a hydroxy group, or [3] a C_{1-8} alkoxy group(s) ,

R^{8B2}: [1] a halogen atom, [2] a C_{1-8} alkyl group, [3] an oxo group, [4] a hydroxy group, or [5] a deuterium atom,

R^{8B3}: a $(C_{1-8}$ alkyl$)_{m8f}$-amino group,

m8f: 0~2,

R^{8B4}: [1] a C_{3-8} cycloalkyl group, or [2] a hydroxy group,

(5) a 5- to 14-membered heteroaryl group which may be substituted by a C_{1-8} alkyl group,

(6) a $(C_{1-8}$ alkyl$)_{m8g}$-aminocarbonyl group which may be substituted by one or more R^{8C},

m8g: 0~2,

R^{8C}:[1] a hydroxy group, [2] a $(C_{1-8}$ alkyl$)_{m8h}$-amino group which may be substituted by

substituent group(s) selected from the group consisting of <1> a $(C_{1-8}$ alkyl$)_{m8i}$-aminosulfonyl group, <2> a C_{1-8} alkylsulfonyl group, <3> a C_{1-8} alkoxycarbonyl group and <4> a C_{1-8} alkoxycarbonyl(C_{0-8} alkyl) aminosulfonyl group, [3] a C_{1-8} alkylsulfonyl group, or [4] a C_{1-8} alkoxy group which may be substituted by a hydroxy group,

m8h: 0~2,

m8i: 0~2,

(7) a 4- to 10-membered heterocycloalkyl (C_{0-8} alkyl) aminocarbonyl group which may be substituted by oxo group(s),

(8) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by one or more R^{8D},

R^{8D}: [1] a C_{1-8} alkyl group which may be substituted by one or more R^{8D1}, [2] a hydroxy group, [3] a C_{1-8} alkylsulfonyl group, or [4] a C_{1-8} alkoxycarbonyl group,

R^{8D1}: [1] a hydroxy group, or [2] a C_{1-8} alkoxy group,

(9) a hydroxycarbonyl group,

(10) a C_{0-8} alkoxy (C_{0-8} alkyl) aminocarbonyl group which may be substituted by hydroxy group(s),

(11) a halogen atom,

(12) a $(C_{1-8}$ alkyl$)_{m8j}$-amino group which may be substituted by one or more R^{8H},

m8j: 0~2,

R^{8H}: [1] a hydroxy group, or [2] a 4- to 10-membered heterocycloalkyl group,

(13) a hydroxyl group,

(14) a C_{1-8} alkoxy group which may be substituted by one or more R^{8E},

R^{8E}:

<1> a hydroxy group,

<2> halogen atom,

<3> a hydroxycarbonyl group,

<4> a C_{1-8} alkoxycarbonyl group,

<5> a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by one or more R^{8E1},

<6> a $(C_{1-8}$ alkyl$)_{m8k1}$-amino group which may be substituted by one or more R^{8E2},

m8k1: 0~2,

<7> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8E3},

<8> a 5- to 14-membered heteroaryl group,

<9> a $(C_{1\text{-}8}$ alkyl$)_{m8k2}$-aminocarbonyl group which may be substituted by one or more R^{8E6},

m8k2: 0~2,

<10> a $C_{1\text{-}8}$ alkoxy group which may be substituted by one or more R^{8E7},

<11> a $C_{1\text{-}8}$ alkylthio group,

<12> a $C_{1\text{-}8}$ alkylsulfinyl group,

<13> a $C_{1\text{-}8}$ alkylsulfonyl group,

R^{8E1}:

<1> a $C_{1\text{-}8}$ alkoxycarbonyl group,

<2> a $C_{1\text{-}8}$ alkanoyl group,

<3> a $C_{1\text{-}8}$ alkylsulfonyl group,

<4> a $(C_{1\text{-}8}$ alkyl$)_{m8k3}$-aminosulfonyl group,

m8k3: 0~2, or

<5> a 4- to 10-membered heterocycloalkyl group,

R^{8E2}:

<1> a hydroxy group,

<2> a $C_{1\text{-}8}$ alkoxycarbonyl group which may be substituted by halogen atom(s),

<3> a $C_{3\text{-}8}$ cycloalkyl group which may be substituted by $C_{1\text{-}8}$ alkyl group(s) which may be substituted by hydroxy group(s),

<4> a $C_{1\text{-}8}$ alkanoyl group which may be substituted by substituent group(s) selected from the group consisting of [1] a $(C_{1\text{-}8}$ alkyl$)_{m8k4}$-amino group and [2] a halogen atom(s),

m8k4: 0~2,

<5> a $(C_{1\text{-}8}$ alkyl$)_{m8k5}$-aminocarbonyl group,

m8k5: 0~2,

<6> a $C_{1\text{-}8}$ alkylsulfonyl group,

<7> a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl group which may be substituted by $C_{1\text{-}8}$ alkyl group(s),

<8> a $(C_{1\text{-}8}$ alkyl$)_{m8k6}$-aminosulfonyl group which may be substituted by $C_{1\text{-}8}$ alkoxycarbonyl group(s),

m8k6: 0~2, or

R^{8E3}:

<1> a C_{1-8} alkyl group which may be substituted by substituent group(s) selected from the group consisting of [1] a hydroxy group and [2] a C_{1-8} alkylcarbonyloxy group,

<2> a C_{1-8} alkylcarbonyloxy group,

<3> a hydroxy group,

<4> a C_{3-8} cycloalkyl group,

<5> a C_{1-8} alkoxy group,

<6> a C_{1-8} alkoxycarbonyl group,

<7> a C_{1-8} alkylsulfonyl group,

<8> a $(C_{1-8}$ alkyl$)_{m8k8}$-aminocarbonyl group

m8k8: 0~2,

<9> a C_{1-8} alkanoyl group which may be substituted by hydroxy group(s),

<10> an oxo group, or

<11> a 4- to 10-membered heterocycloalkyl group which may be substituted by substituent group(s) selected from the group consisting of [1] a C_{1-8} alkanoyl group, [2] a C_{1-8} alkoxycarbonyl group and [3] a C_{1-8} alkylsulfonyl group,

R^{8E6}:

<1> a C_{2-8} alkenylcarbonyloxy group,

<2> a hydroxy group,

<3> a cyano group,

<4> a $(C_{1-8}$ alkyl$)_{m8k9}$-amino group which may be substituted by hydroxy group(s)

m8k9: 0~2,

<5> a C_{1-8} alkoxy group which may be substituted by hydroxy group(s),

<6> a C_{1-8} alkylcarbonyloxy group,

<7> a 4- to 10-membered heterocycloalkyl group which may be substituted by C_{1-8} alkyl group(s), or

<8> a 5- to 14-membered heteroaryl group,

R^{8E7}:

<1> a hydroxy group, or

<2> a C_{1-8} alkoxy group which may be substituted by hydroxy group(s),

(15) a 4- to 10-membered heterocycloalkyloxy group which may be substituted by one

or more R^{8F},

R^{8F}:

<1> a C_{1-8} alkyl group which may be substituted by one or more R^{8F1},

<2> a C_{3-8} cycloalkyl group,

<3> a C_{1-8} alkanoyl group which may be substituted by halogen atom(s),

<4> a C_{1-8} alkylcarbonyloxy group,

<5> a C_{1-8} alkoxycarbonyl group,

<6> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8F2},

<7> a C_{1-8} alkyl sulfonyl group,

<8> a hydroxy group, or

,<9> a C_{6-10} aryl group,

R^{8F1}: [1]a hydroxy group, [2] a C_{1-8} alkoxy group, or [3] a halogen atom,

R^{8F2}: [1] a 4- to 10-membered heterocycloalkyl group, [2] a C_{1-8} alkoxycarbonyl group, or [3] a C_{1-8} alkylsulfonyl group,

(16) a 5- to 14-membered heteroaryloxy group,

(17) a 4- to 10-membered heterocycloalkylcarbonyloxy group,

(18) a $(C_{1-8}$ alkyl$)_{m8l1}$-aminosulfonyloxy group,

m8l1: 0~2,

(19) a C_{1-8} alkyl thio group which may be substituted by [1] $(C_{1-8}$ alkyl$)_{m8l2}$-amino group(s), [2] hydroxy group(s) or [3] hydroxycarbonyl group(s),

m8l2: 0~2,

(20) a C_{1-8} alkylsulfonyl group which may be substituted by one or more R^{8G},

R^{8G}: [1] a hydroxycarbonyl group, [2] a hydroxy group, or [3] a $(C_{1-8}$ alkyl$)_{m8l3}$-amino group,

m8l3: 0~2,

(21) a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyloxy group which may be substituted by C_{1-8} alkyl group(s),

(22) a C_{2-8} alkenyloxy group, and

(23) a C_{1-8} alkylsulfonyloxy group which may be substituted by halogen atom(s);

R^9 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a C_{1-8} alkyl group which may be substituted by one or more R^{9A},

R^{9A}: [1] a C_{3-8} cycloalkyl group, [2] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9A1}, [3] a hydroxy group, [4] a C_{1-8} alkoxy group, or [5] a hydroxycarbonyl group,

R^{9A1}: [1] a C_{1-8} alkyl group, [2] a C_{3-8} cycloalkyl group, or [3] a 4- to 10-membered heterocycloalkyl group,

(3) a C_{2-8} alkenyl group which may be substituted by one or more R^{9B},

R^{9B}: [1] a $(C_{1-8}$ alkyl$)_{m9a}$-amino group, [2] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9B1},

R^{9B1}: [1] a C_{3-8} cycloalkyl group, or [2] a 4- to 10-membered heterocycloalkyl group,

m9a: 0~2,

(4) a C_{2-8} alkynyl group which may be substituted by one or more R^{9C},

R^{9C}: [1] a C_{1-8} alkoxy group, [2] a $(C_{1-8}$ alkyl$)_{m9b}$-amino group which may be substituted by C_{6-10} aryl group(s), [3] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9C1}, [4] a C_{3-8} cycloalkyl group, [5] a hydroxy group, [6] a hydroxycarbonyl group, or [7] a C_{1-8} alkyloxycarbonyl group,

m9b: 0~2,

R^{9C1}: [1] a C_{3-8} cycloalkyl group, [2] a 4- to 10-membered heterocycloalkyl group, or [3] an oxo group,

(5) a C_{3-8} cycloalkyl group,

(6) a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9D},

R^{9D}: [1] a C_{1-8} alkyl group which may be substituted by 4- to 10-membered heterocycloalkyl group(s), [2] a C_{3-8} cycloalkyl group, [3] a 4- to 10-membered heterocycloalkyl group, or [4] a C_{1-6} alkylsulfonyl group, or [5] a C_{1-8} alkoxycarbonyl group,

(7) a C_{6-10} aryl group which may be substituted by one or more R^{9E},

R^{9E}: [1] a halogen atom, [2] a hydroxy group, [3] a hydroxycarbonyl group, or [4] a C_{1-8} alkyl group which may be substituted by hydroxy group(s), or [5] a C_{1-8} alkoxy group,

(8) a 5- to 14-membered heteroaryl group which may be substituted by C_{1-8} alkyl group(s),

(9) a cyano group,

(10) a C_{1-8} alkanoyl group,

(11) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by C_{1-8} alkyl group(s),

(12) a halogen atom,

(13) a $(C_{1-8}$ alkyl$)_{m9c}$- amino group which may be substituted by one or more R^{9F},

m9c: 0~2,

(14) a C_{1-8} alkylcarbonyl(C_{0-8} alkyl)amino group which may be substituted by $(C_{1-8}$ alkyl$)_{m9d}$- amino group(s),

m9d: 0~2,

(15) a C_{1-8} alkylsulfonyl(C_{0-8} alkyl)amino group,

(16) a $(C_{1-8}$ alkyl$)_{m9e}$- aminosulfonyl(C_{0-8} alkyl)amino group,

m9e: 0~2,

(17) a nitro group,

(18) a hydroxy group,

(19) a C_{1-8} alkoxy group which may be substituted by one or more R^{9G},

R^{9G}: [1] a hydroxy group, [2] a hydroxycarbonyl group, [3] a C_{6-10} aryl group which may be substituted by C_{1-8} alkoxy group(s), [4] a $(C_{1-8}$ alkyl$)_{m9g1}$-amino group, [5] a C_{1-8} alkoxy group which may be substituted by one or more R^{9G1}, [6] a 5- to 14-membered heteroaryl group, or [7] a 4- to 10-membered heterocycloalkyloxy group which may be substituted by C_{1-8} alkyl group(s),

m9g1: 0~2,

R^{9G1}: [1] a C_{1-8} alkoxy group, or [2] a hydroxycarbonyl group,

(20) a 4- to 10-membered heterocycloalkyloxy group which may be substituted by [1] 4- to 10-membered heterocycloalkyl group(s), or [2] C_{1-8} alkoxycarbonyl group(s),

(21) a C_{1-8} alkylsulfonyloxy group which may be substituted by halogen atom(s),

(22) a C_{1-8} alkylthio group which may be substituted by $(C_{1-8}$ alkyl$)_{m9f}$- amino group(s),

m9f: 0~2,

(23) a C_{1-8} alkylsulfonyl group which may be substituted by $(C_{1-8}$ alkyl$)_{m9g}$-amino group(s),

m9g: 0~2,

(24) a ($C_{1\text{-}8}$ alkyl)$_{m9h}$-aminosulfonyl group,

m9h: 0~2,

(25) a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl group which may be substituted by $C_{1\text{-}8}$ alkyl group(s), and

(26) a hydroxycarbonyl group].

[0007]

[2] The composition according to [1] above, wherein the dissolution aid is a surfactant,

[3] The composition according to [2] above, wherein the surfactant is a non-ionic or an anionic surfactant,

[4] The composition according to [2] or [3] above, wherein the surfactant is selected from a group consisting of monoalkyl sulfate, polyoxyl 40 stearate, sorbitan trioleate, polyoxyethylene (105) polyoxypropylene (5) glycol, polyoxyethylene hydrogenated castor oil 60, polyoxyl 35 castor oil, lauromacrogol, dioctyl sodium sulfosuccinate, sodium lauroylsarcosine, sodium dodecylbenzene sulfonate, and a mixture thereof,

[4-1] The composition according to [2] or [3] above, wherein the surfactant is selected from a group consisting of monoalkyl sulfate, sorbitan trioleate, polyoxyethylene (105) polyoxypropylene (5) glycol, polyoxyethylene hydrogenated castor oil 60, polyoxyl 35 castor oil, dioctyl sodium sulfosuccinate, sodium lauroylsarcosine, sodium dodecylbenzene sulfonate and a mixture thereof,

[4-2] The composition according to [2] to [4] above, wherein the surfactant is selected from a group consisting of sodium lauryl sulfate, sodium tetradecyl sulfate, sodium hexadecyl sulfate, sodium octadecyl sulfate, and a mixture thereof,

[4-3] The composition according to [2] to [4] above, wherein the surfactant is a mixture of sodium lauryl sulfate and polyoxyethylene (105) polyoxypropylene (5) glycol,

[4-4] The composition according to [2] to [4] above, wherein the surfactant is sodium lauryl sulfate,

[4-5] The composition according to [2] to [4-4] above, wherein content of the surfactant is 0.5 to 25 parts by weight,

[4-6] The composition according to [2] to [4-4] above, wherein content of the surfactant is 1.5 to 15 parts by weight,

[5] The composition according to [2] to [4-6] above, wherein the composition further

comprises an organic polymer,

[6] The composition according to [5] above, wherein the organic polymer is selected from a group consisting of a synthetic resin, a water soluble polymer, a gastric-soluble polymer, an enteric-soluble polymer, and a mixture thereof,

[7] The composition according to [5] above, wherein the organic polymer is a synthetic resin,

[7-1] The composition according to [6] above, wherein the water soluble polymer is hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, propylene glycol alginate ester, sodium caseinate, a carboxyvinyl polymer, powdered agar, guar gum, copolyvidone, hydroxyethylmethyl cellulose, or polyvinyl alcohol, the gastric-soluble polymer is amino alkylmethacrylate copolymer E, or polyvinylacetal diethylaminoacetate, and the enteric-soluble polymer is methacrylic acid copolymer LD, purified shellac, carboxymethylethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate succinate, methacrylic acid copolymer S, casein, or zein,

[7-2] The composition according to [6] above, wherein the water soluble polymer is , propylene glycol alginate ester, sodium caseinate, a carboxyvinyl polymer, powdered agar, guar gum, copolyvidone, hydroxyethylmethyl cellulose, or polyvinyl alcohol, the gastric -soluble polymer is amino alkylmethacrylate copolymer E or polyvinylacetal diethylaminoacetate, and the enteric -soluble polymer is methacrylic acid copolymer LD, carboxymethylethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate succinate, methacrylic acid copolymer S, casein, or zein,

[7-3] The composition according to [6] above, wherein the organic polymer is selected from a group consisting of casein, sodium caseinate, sodium polystyrene sulfonate, polyvinylacetal diethylaminoacetate, carboxymethylethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate succinate, methacrylic acid copolymer S, and a mixture thereof,

[7-4] The composition according to [5] to [7-3] above, wherein the surfactant is selected from sodium lauryl sulfate and the organic polymer is selected from sodium polystyrene sulfonate,

[7-5] The composition according to [5] to [7-3] above, wherein the surfactant is a

mixture of sodium lauryl sulfate and polyoxyethylene (105) polyoxypropylene (5) glycol and the organic polymer is selected from sodium polystyrene sulfonate,

[7-6] The composition according to [7] above, wherein the synthetic resin is sodium polystyrene sulfonate or a vinyl acetate resin,

[0008]

[7-7] The composition according to [5] to [7-6] above, wherein the content of the organic polymer is 1 to 20 parts by weight,

[7-8] The composition according to [5] to [7-6] above, wherein the content of the organic polymer is 2 to 10 parts by weight,

[8] The composition according to [2] to [7-5] above, wherein the composition comprises further one or more additives which are selected from the following additive group A:

additive A: citric acid, fumaric acid, DL-malic acid, adipic acid, succinic acid, tartaric acid, lactic acid, maleic acid, sulfuric acid, phosphoric acid, sodium dehydroacetate, sodium stearyl fumarate, stearic L-ascorbate ester, L-aspartic acid, skimmed milk powder, aluminum lactate, ascorbic acid palmitate, aluminum sulfate, monobasic calcium phosphate, or acetyl tryptophan.

[8-2] The composition according to [8] above, wherein the additive group A is citric acid, fumaric acid, DL-malic acid, adipic acid, succinic acid, tartaric acid, lactic acid, maleic acid, phosphoric acid, sodium dehydroacetate, sodium stearyl fumarate, stearic L-ascorbate ester, L-aspartic acid, skimmed milk powder, or monobasic calcium phosphate,

[8-3] The composition according to [8] above, wherein the additive selected from the additive group A is sodium dehydroacetate, or skimmed milk powder,

[8-4] The composition according to [8] to [8-3] above, wherein the total content of one or more additives that are selected from the additive group A is 1 to 20 parts by weight,

[9] The composition according to [1] to [8-4] above, wherein the water solubility of the substance is less than 100 μg/mL at 25°C,

[9-1] The composition according to [1], characterized in that the dissolution aid is selected from the following group

Group:

citric acid, sodium stearyl fumarate, methacrylic acid copolymer LD, sodium lauryl

sulfate, sodium dehydroacetate, fumaric acid, DL-malic acid, stearic L-ascorbate ester, L-aspartic acid, adipic acid, amino alkylmethacrylate copolymer E, propylene glycol alginate ester, casein, sodium caseinate, a carboxyvinyl polymer, carboxymethylethyl cellulose, powdered agar, guar gum, succinic acid, copolyvidone, cellulose acetate phthalate, tartaric acid, dioctyl sodium sulfosuccinate, zein, skimmed milk powder, sorbitan trioleate, lactic acid, aluminum lactate, ascorbic acid palmitate, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose acetate succinate, polyoxyethylene (105) polyoxypropylene (5) glycol, polyoxyethylene hydrogenated castor oil 60, polyoxyl 35 castor oil, sodium polystyrene sulfonate, polyvinylacetal diethylaminoacetate, polyvinyl alcohol, maleic acid, methacrylic acid copolymer S, sulfuric acid, aluminum sulfate, phosphoric acid, monobasic calcium phosphate, sodium dodecylbenzene sulfonate, a vinyl pyrrolidone · vinyl acetate copolymer, sodium lauroylsarcosine, acetyl tryptophan, sodium methyl sulfate, sodium ethyl sulfate, sodium butyl sulfate, sodium octyl sulfate, sodium decyl sulfate, sodium tetradecyl sulfate, sodium hexadecyl sulfate, and sodium octadecyl sulfate.

[9-2] The composition according to [1], characterized in that the dissolution aid is selected from the following group

Group:

citric acid, methacrylic acid copolymer LD, sodium lauryl sulfate, sodium dehydroacetate, fumaric acid, DL-malic acid, stearic L-ascorbate ester, L-aspartic acid, adipic acid, propylene glycol alginate ester, casein, sodium caseinate, carboxymethylethyl cellulose, succinic acid, copolyvidone, dioctyl sodium sulfosuccinate, lactic acid, aluminum lactate, ascorbic acid palmitate, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose acetate succinate, polyoxyethylene hydrogenated castor oil 60, polyoxyl 35 castor oil, sodium polystyrene sulfonate, polyvinylacetal diethylaminoacetate, polyvinyl alcohol, methacrylic acid copolymer S, sulfuric acid, aluminum sulfate, sodium dodecylbenzene sulfonate, a vinyl pyrrolidone · vinyl acetate copolymer, acetyl tryptophan, sodium decyl sulfate, sodium tetradecyl sulfate, and sodium octadecyl sulfate.

[9-3] The composition according to [1], characterized in that the dissolution aid is selected from the following group

Group:

citric acid, methacrylic acid copolymer LD, sodium lauryl sulfate, sodium dehydroacetate, fumaric acid, DL-malic acid, L-aspartic acid, adipic acid, propylene glycol alginate ester, sodium caseinate, carboxymethylethyl cellulose, succinic acid, copolyvidone, dioctyl sodium sulfosuccinate, lactic acid, aluminum lactate, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose acetate succinate, sodium polystyrene sulfonate, polyvinylacetal diethylaminoacetate, methacrylic acid copolymer S, sulfuric acid, aluminum sulfate, a vinyl pyrrolidone · vinyl acetate copolymer, and sodium decyl sulfate.

[9-4] The composition according to [1], wherein the dissolution aid which is selected from the following group is used for improving a solubility of a substance of the formula (I).

Group:

citric acid, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium stearyl fumarate, methacrylic acid copolymer LD, methyl cellulose, sodium lauryl sulfate, purified shellac, sodium dehydroacetate, fumaric acid, DL-malic acid, stearic L-ascorbate ester, L-aspartic acid, adipic acid, amino alkylmethacrylate copolymer E, propylene glycol alginate ester, casein, sodium caseinate, a carboxyvinyl polymer, carboxymethylethyl cellulose, powdered agar, guar gum, succinic acid, copolyvidone, cellulose acetate phthalate, tartaric acid, dioctyl sodium sulfosuccinate, zein, skimmed milk powder, sorbitan trioleate, lactic acid, aluminum lactate, ascorbic acid palmitate, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose acetate succinate, polyoxyethylene (105) polyoxypropylene (5) glycol, polyoxyethylene hydrogenated castor oil 60, polyoxyl 35 castor oil, sodium polystyrene sulfonate, polyvinylacetal diethylaminoacetate, polyvinyl alcohol, maleic acid, methacrylic acid copolymer S, sulfuric acid, aluminum sulfate, phosphoric acid, monobasic calcium phosphate, sodium dodecylbenzene sulfonate, a vinyl pyrrolidone · vinyl acetate copolymer, sodium lauroylsarcosine, acetyl tryptophan, sodium methyl sulfate, sodium ethyl sulfate, sodium butyl sulfate, sodium octyl sulfate, sodium decyl sulfate, sodium tetradecyl sulfate, sodium hexadecyl sulfate, and sodium octadecyl sulfate,

[9-5] The composition according to [1], wherein the dissolution aid which is selected

from the following group is used for improving a solubility of a substance of the formula (I).

Group:

citric acid, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methacrylic acid copolymer LD, methyl cellulose, sodium lauryl sulfate, purified shellac, sodium dehydroacetate, fumaric acid, DL-malic acid, stearic L-ascorbate ester, L-aspartic acid, adipic acid, propylene glycol alginate ester, casein, sodium caseinate, carboxymethylethyl cellulose, succinic acid, copolyvidone, dioctyl sodium sulfosuccinate, lactic acid, aluminum lactate, ascorbic acid palmitate, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose acetate succinate, polyoxyethylene hydrogenated castor oil 60, polyoxyl 35 castor oil, sodium polystyrene sulfonate, polyvinylacetal diethylaminoacetate, polyvinyl alcohol, methacrylic acid copolymer S, sulfuric acid, aluminum sulfate, sodium dodecylbenzene sulfonate, a vinyl pyrrolidone · vinyl acetate copolymer, acetyl tryptophan, sodium decyl sulfate, sodium tetradecyl sulfate, and sodium octadecyl sulfate,

[9-6] The composition according to [1], wherein the dissolution aid which is selected from the following group is used for improving a solubility of a substance of the formula (I).

Group:

citric acid, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methacrylic acid copolymer LD, methyl cellulose, sodium lauryl sulfate, purified shellac, sodium dehydroacetate, fumaric acid, DL-malic acid, L-aspartic acid, adipic acid, propylene glycol alginate ester, sodium caseinate, carboxymethylethyl cellulose, succinic acid, copolyvidone, dioctyl sodium sulfosuccinate, lactic acid, aluminum lactate, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose acetate succinate, sodium polystyrene sulfonate, polyvinylacetal diethylaminoacetate, methacrylic acid copolymer S, sulfuric acid, aluminum sulfate, a vinyl pyrrolidone · vinyl acetate copolymer, and sodium decyl sulfate,

[0009]

[10] The composition according to [1] to [9-3] above, wherein A^1 to A^4, A^6, and A^7 are a carbon atom, A^5 is NH, R^3 is cyano, R^6 and $R^{6'}$ are both methyl for the substance,

[10-1] The composition according to [1] to [10] above, wherein A^1 to A^4, A^6, and A^7 are a carbon atom, A^5 is NH, R^3 is cyano, R^8 is a 4- to 10-membered heterocycloalkyl group or a 4- to 10-membered heterocycloalkyl group which may be substituted by a C_{3-8} cycloalkyl group for the substance,

[0010]

[11] The composition according to any one of [1] to [9-6], wherein the substance is selected from a group consisting of

9-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-cyclopropylethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-bromo-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-bromo-8-(4-cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-chloro-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6,9-trimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
9-ethynyl-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
8-(4-cyclobutyl-piperazin-1-yl)-9-ethynyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
8-(1-isopropyl-piperidin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
8-(4-cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
8-(2-tert-butylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
9-ethynyl-8-(4-methanesulfonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
9-bromo-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile; and
9-ethynyl-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

[0011]

[11-1] The composition according to any one of [1] to [8], wherein the substance is selected from a group consisting of (i) 6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, (ii) 8-(4-cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-

benzo[b]carbazole-3-carbonitrile, (iii) 8-(4-cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, and (iv) 9-ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

[0012]

[11-2] The composition according to [1] to [11-1] above, characterized in that the content of the substance is 1 to 50 parts by weight.

[11-3] The composition according to [1] to [11-1] above, characterized in that the content of the substance is 3 to 30 parts by weight.

[11-4] The composition according to [2] to [8] above, wherein the weight ratio between the substance and the surfactant is 1 : 0.01 to 1 : 25,

[11-5] The composition according to [2] to [8] above, wherein the weight ratio between the substance and the surfactant is 1 : 0.05 to 1 : 1,

[11-6] The composition according to [9] to [11-5] above, wherein the weight ratio between the substance and the organic polymer is 1 : 0.02 to 1 : 20,

[11-7] The composition according to [9] to [11-6] above, wherein the weight ratio between the substance and the organic polymer is 1 : 0.25 to 1 : 1,

[11-8] The composition according to [8] to [11-7] above, wherein the weight ratio between the substance and the total amount of one or more additives selected from the additive group A is 1 : 0.02 to 1 : 20.

The present invention further includes the aspects as follows.

[12] A pharmaceutical formulation comprising the composition according to [1] to [11-8],

[13] The pharmaceutical formulation according to [12] above, which is an orally administrable formulation,

[14] The pharmaceutical formulation according to [12] above, wherein the orally administrable formulation is a solid formulation, and

[15] The pharmaceutical formulation according to [13] above, wherein the orally administrable formulation is a tablet, a capsule, a granule, powder, a pill, a water soluble or insoluble liquid or a suspension for oral administration.

[16-1] A dissolution aid consisting of a substance selected from the following gr

oup for use in the improvement of a solubility of a substance of the formula (I). Group:

citric acid, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium stearyl fumarate, methacrylic acid copolymer LD, methyl cellulose, sodium lauryl sulfate, purified shellac, sodium dehydroacetate, fumaric acid, DL-malic acid, stearic L-ascorbate ester, L-aspartic acid, adipic acid, amino alkylmethacrylate copolymer E, propylene glycol alginate ester, casein, sodium caseinate, a carboxyvinyl polymer, carboxymethylethyl cellulose, powdered agar, guar gum, succinic acid, copolyvidone, cellulose acetate phthalate, tartaric acid, dioctyl sodium sulfosuccinate, zein, skimmed milk powder, sorbitan trioleate, lactic acid, aluminum lactate, ascorbic acid palmitate, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose acetate succinate, polyoxyethylene (105) polyoxypropylene (5) glycol, polyoxyethylene hydrogenated castor oil 60, polyoxyl 35 castor oil, sodium polystyrene sulfonate, polyvinylacetal diethylaminoacetate, polyvinyl alcohol, maleic acid, methacrylic acid copolymer S, sulfuric acid, aluminum sulfate, phosphoric acid, monobasic calcium phosphate, sodium dodecylbenzene sulfonate, a vinyl pyrrolidone · vinyl acetate copolymer, sodium lauroylsarcosine, acetyl tryptophan, sodium methyl sulfate, sodium ethyl sulfate, sodium butyl sulfate, sodium octyl sulfate, sodium decyl sulfate, sodium tetradecyl sulfate, sodium hexadecyl sulfate, and sodium octadecyl sulfate,

[16-2] A dissolution aid consisting of a substance selected from the following gr oup for use in the improvement of a solubility of a substande of the formula (I). Group:

citric acid, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methacrylic acid copolymer LD, methyl cellulose, sodium lauryl sulfate, purified shellac, sodium dehydroacetate, fumaric acid, DL-malic acid, stearic L-ascorbate ester, L-aspartic acid, adipic acid, propylene glycol alginate ester, casein, sodium caseinate, carboxymethylethyl cellulose, succinic acid, copolyvidone, dioctyl sodium sulfosuccinate, lactic acid, aluminum lactate, ascorbic acid palmitate, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose acetate succinate, polyoxyethylene hydrogenated castor oil 60, polyoxyl 35 castor oil, sodium polystyrene sulfonate, polyvinylacetal diethylaminoacetate, polyvinyl alcohol, methacrylic acid

copolymer S, sulfuric acid, aluminum sulfate, sodium dodecylbenzene sulfonate, a vinyl pyrrolidone · vinyl acetate copolymer, acetyl tryptophan, sodium decyl sulfate, sodium tetradecyl sulfate, and sodium octadecyl sulfate,

[16-3] A dissolution aid consisting of a substance selected from the following group for use in the improvement of a solubility of a substance of the formula (I). Group:

citric acid, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methacrylic acid copolymer LD, methyl cellulose, sodium lauryl sulfate, purified shellac, sodium dehydroacetate, fumaric acid, DL-malic acid, L-aspartic acid, adipic acid, propylene glycol alginate ester, sodium caseinate, carboxymethylethyl cellulose, succinic acid, copolyvidone, dioctyl sodium sulfosuccinate, lactic acid, aluminum lactate, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose acetate succinate, sodium polystyrene sulfonate, polyvinylacetal diethylaminoacetate, methacrylic acid copolymer S, sulfuric acid, aluminum sulfate, a vinyl pyrrolidone · vinyl acetate copolymer, and sodium decyl sulfate.

[Effect of the Invention]

[0013]

The composition of the present invention improves solubility, oral absorbability and/or absorbability in blood of the poorly water-soluble or water insoluble tetracyclic compounds having an ALK inhibitory activity which are useful as a prophylactic and/or therapeutic agent for cancer, depression, and cognitive function disorder.

[Brief Description of the Drawings]

[0014]

[FIG. 1] It is a graph to compare the effect of the additive amount of sodium lauryl sulfate on the solubility of the Compound F6-20.

[FIG. 2] It is a graph to illustrate the effect of various cellulose polymers on the solubility of the Compound F6-20 hydrochloride salt.

[FIG. 3] It is a graph to illustrate the effect of the additive amount of hydroxypropyl cellulose on the solubility of the Compound F6-20 hydrochloride salt.

[FIG. 4] It is a graph to illustrate the solubility of the Compound F6-20 hydrochloride

salt when sodium lauryl sulfate and hydroxypropyl cellulose are blended in.

[FIG. 5] It is a graph to compare the effect of the manufacturing method on the solubility of the Compound F6-20 hydrochloride salt.

[FIG. 6] It is a graph to illustrate the effect of the additive amount of sodium lauryl sulfate on the solubility of the Compound F6-20 mesylate salt.

[FIG. 7] It is a graph to illustrate the solubility of the Compound F6-20 mesylate salt when sodium lauryl sulfate and hydroxypropyl cellulose are blended in.

[FIG. 8] It is a graph to illustrate the effect of SLS and polyvinyl pyrrolidone on the solubility of the Compound B4-8 hydrochloride salt crystal.

[FIG. 9] It is a graph to illustrate the effect of SLS and polyvinyl pyrrolidone on the solubility of the Compound B4-8 mesylate salt crystal.

[FIG. 10] It is a graph to illustrate the effect of SLS and HPC on the solubility of the Compound B4-8 sulfate salt crystal.

[FIG. 11] It is a graph to illustrate the effect of SLS and HPC on the solubility of the Compound B4-8 L-tartrate salt crystal.

[FIG. 12] It is a graph to illustrate the effect of SLS and HPC on the solubility of the Compound B4-8 phosphate salt crystal.

[FIG. 13] It is a graph to illustrate the effect of polyoxyethylene (105) polyoxypropylene (5) glycol on the solubility of the Compound F6-4 hydrochloride salt crystal.

[FIG. 14] It is a graph to illustrate the effect of polyoxyethylene (105) polyoxypropylene (5) glycol on the solubility of the Compound F6-4 mesylate salt crystal.

[FIG. 15] It is a graph to illustrate the effect of SLS on the solubility of the Compound F6-17 hydrochloride salt crystal.

[FIG. 16] It is a graph to illustrate the effect of SLS on the solubility of the Compound F6-17 mesylate salt crystal.

[FIG. 17] It is a graph to illustrate the effect of SLS and polyvinyl pyrrolidone on the solubility of the Compound F6-17 mesylate salt crystal.

[FIG. 18] It is a graph to illustrate the effect of SLS on the solubility of the Compound F6-17 maleate salt crystal.

[FIG. 19] It is a graph to illustrate the effect of SLS and polyvinyl pyrrolidone on the solubility of the Compound F6-17 L-tartrate salt crystal.

[FIG. 20] It is a graph to illustrate the effect of SLS on the solubility of the Compound F6-17 citrate salt crystal.

[FIG. 21] It is a graph to illustrate the effect of SLS on the solubility of the Compound F6-17 malate salt crystal.

[FIG. 22] It is a graph to illustrate the effect of SLS on the solubility of the Compound F5-46 hydrochloride salt crystal.

[FIG. 23] It is a graph to illustrate the effect of SLS on the solubility of the Compound F5-46 mesylate salt crystal.

[FIG. 24] It is a graph to illustrate the effect of SLS on the solubility of the Compound F5-51 hydrochloride salt crystal.

[FIG. 25] It is a graph to illustrate the effect of SLS on the solubility of the Compound F5-51 mesylate salt crystal.

[FIG. 26] It is a graph to illustrate the effect of SLS, polyoxyethylene (105) polyoxypropylene (5) glycol, and poly(sodium 4-styrene sulfonate) on the solubility of the Compound F6-20 hydrochloride salt crystal.

[FIG. 27] It is a graph to illustrate the effect of a combination of SLS and polyoxyethylene (105) polyoxypropylene (5) glycol on the solubility of the Compound F6-20 hydrochloride salt crystal.

[FIG. 28] It is a graph to illustrate the effect of a combination of SLS and poly(sodium 4-styrene sulfonate) on the solubility of the Compound F6-20 hydrochloride salt crystal.

[FIG. 29] It is a graph to illustrate the effect of a combination of SLS, polyoxyethylene (105) polyoxypropylene (5) glycol, and poly(sodium 4-styrene sulfonate) on the solubility of the Compound F6-20 hydrochloride salt crystal.

[FIG. 30] It is a graph to illustrate the effect of amount of SLS on the solubility of the formulation of the Compound F6-20 hydrochloride salt crystal containing polyoxyethylene (105) polyoxypropylene (5) glycol and poly(sodium 4-styrene sulfonate).

[Mode for Carrying out the Invention]

[0015]

The term “pharmaceutically acceptable carrier”, as used in the present specification, means one or more acceptable solid or liquid filler/diluents or

encapsulating substances which are suitable for administration to a mammal. The term "acceptable", as used herein, means that the ingredients of the composition are capable of being miscible with the subject compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically acceptable carriers should, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, more preferably mammal being treated.

[0016]

The "dissolution aid" used in the present invention includes a surfactant, an organic polymer, and a pH adjusting agent, etc., and specific examples thereof are the substances given in Table 2 below. Preferred examples thereof include casein, sodium caseinate, skimmed milk powder, sodium lauryl sulfate (herein below, also referred to as SLS), dioctyl sodium sulfosuccinate, polyoxyl 40 stearate, sorbitan trioleate, polyoxyethylene (105) polyoxypropylene (5) glycol, polyoxyethylene hydrogenated castor oil 60, polyoxyl 35 castor oil, lauromacrogol, sodium lauroylsarcosine, sodium tetradecyl sulfate, sodium hexadecyl sulfate, sodium octadecyl sulfate, sodium methyl sulfate, sodium ethyl sulfate, sodium butyl sulfate, sodium octyl sulfate, sodium decyl sulfate, and sodium dodecylbenzene sulfonate.

[0017]

According to the present invention, the dissolution aid may be used in combination of two or more types that are mixed at an appropriate ratio.

Particularly preferred is a surfactant.

In the present invention, when two or more dissolution aids are used as a combination, preferred examples of the combination of dissolution aids include a combination of sodium lauryl sulfate and polyoxyethylene (105) polyoxypropylene (5) glycol and a combination of sodium lauryl sulfate and sodium polystyrene sulfonate. More preferred examples include a combination of sodium lauryl sulfate, sodium polystyrene sulfonate, and polyoxyethylene (105) polyoxypropylene (5) glycol.

Examples of sodium polystyrene sulfonate include CAS (Chemical Abstract) registration number of 9080-79-9 (a cationic exchange resin wherein a sulfonic acid

group attached to a copolymer of styrene and divinyl benzene is present in the form of a sodium, as defined in Pharmacopoeia of Japan, 15th revised edition) and poly(sodium 4-styrene sulfonate) [CAS registration number of 25704-18-1, a homopolymer obtained by polymerization of 4-ethenylbenzene sodium sulfonate], and poly(sodium 4-styrene sulfonate) is preferable.

[0018]

The term "surfactant" indicates a substance which has both a hydrophilic group and a hydrophobic group in a molecule. The surfactant includes an ionic surfactant and a non-ionic surfactant.

The ionic surfactant means an ionic surfactant which dissociates to give an ion (i.e., an atom or an atomic group having a charge) when it is dissolved in water. Depending on the charge of generated ion, the ionic surfactant is further classified into an anionic surfactant, a cationic surfactant, and an amphoteric surfactant. According to the present invention, a non-ionic surfactant and an anionic surfactant are preferable.

Examples of the non-ionic surfactant include sugar ester type surfactant such as sorbitan fatty acid ester (C_{12-18}), POE sorbitan fatty acid ester (C_{12-18}), and sucrose fatty acid ester; fatty acid ester type such as POE fatty acid ester (C_{12-18}), POE resin acid ester, and POE fatty acid diester (C_{12-18}); alcohol type such as POE alkyl ether (C_{12-18}); alkyl phenol type surfactant such as POE alkyl (C_{8-12}) phenyl ether, POE dialkyl (C_{8-12}) phenyl ether, and POE alkyl (C_{8-12}) phenyl ether formalin condensate; polyoxyethylene ・ polyoxypropylene block polymer type surfactant such as polyoxyethylene ・ polyoxypropylene block polymer and alkyl (C_{12-18}) polyoxyethylene ・ polyoxypropylene block polymer ether; alkylamine type such as POE alkylamine (C_{12-18}) and POE fatty acid amide (C_{12-18}); bisphenol type surfactant such as POE fatty acid bisphenyl ether; polyaromatic type surfactant such as POA benzylphenyl (or phenylphenyl) ether and POA styrylphenyl (or phenylphenyl) ether; POE ether and ester type silicon and fluorine-based surfactant, and; plant oil type surfactant such as POE castor oil and POE hydrogenated castor oil. Preferred examples include polyoxyl 40 stearate, sorbitan trioleate, polyoxyethylene (105) polyoxypropylene (5) glycol, polyoxyethylene hydrogenated castor oil 60, polyoxyl 35 castor oil, and lauromacrogol.

[0019]

Examples of the anionic surfactant include sulfate type surfactant such as alkyl sulfate (C_{12-18}, Na, NH_4, alkanolamine), POE alkyl ether sulfate (C_{12-18}, Na, NH_4, alkanolamine), POE alkylphenyl ether sulfate (C_{12-18}, NH_4, alkanolamine, Ca), POE benzyl (or styryl) phenyl (or phenylphenyl) ether sulfate (Na, NH_4, alkanolamine), polyoxyethylene, and polyoxypropylene block polymer sulfate (Na, NH_4, alkanolamine); sulfonate type surfactant such as paraffin (alkane) sulfonate (C_{12-22}, Na, Ca, alkanolamine), AOS (C_{14-16}, Na, alkanolamine), dialkylsulfosuccinate (C_{8-12}, Na, Ca, Mg), alkylbenzene sulfonate (C_{12}, Na, Ca, Mg, NH_4, alkylamine, alkanol, amine, cyclohexylamine), mono or dialkyl (C_{3-6}) naphthalene sulfonate (Na, NH_4, alkanolamine, Ca, Mg), naphthalene sulfonate ・ formalin condensate (Na, NH_4), alkyl (C_{8-12}) diphenyl ether disulfonate (Na, NH_4), lignin sulfonate (Na, Ca), POE alkyl (C_{8-12}) phenyl ether sulfonate (Na), and POE alkyl (C_{12-18}) ether sulfosuccinic acid half ester (Na); carboxylic acid type surfactant such as fatty acid salt (C_{12-18}, Na, K, NH_4, alkanolamine), N-methyl-fatty acid sarcocinate (C_{12-18}, Na), and resin acid salt (Na, K); and phosphate type surfactant like POE alkyl (C_{12-18}) ether phosphate (Na, alkanolamine), POE mono or dialkyl (C_{8-12}) phenyl ether phosphate (Na, alkanolamine), POE benzyl (or styryl)ated phenyl (or phenylphenyl) ether phosphate (Na, alkanolamine), polyoxyethylene ・ polyoxypropylene block polymer (Na, alkanolamine), phosphatidylcholine ・ phosphatidyl ethanolimine (lecithine), and alkyl (C_{8-12}) phosphate. Preferred examples include monoalkyl sulfate such as sodium lauryl sulfate, sodium tetradecyl sulfate, sodium hexadecyl sulfate, and sodium octadecyl sulfate, dioctyl sodium sulfosuccinate, sodium lauroylsarcosine, and sodium dodecylbenzene sulfonate.

[0020]

The organic polymer indicates a substance having molecular weight of at least 10,000 and the skeleton mainly composed of a carbon. The organic polymer includes a protein derived from an animal or a plant, polysaccharides, synthetic resin, and the like.

Specific examples of the organic polymer include polysaccharides such as hydroxypropyl cellulose (herein below, also referred to as HPC), hydroxypropylmethyl

cellulose, methyl cellulose, propylene glycol alginate ester, powdered agar, guar gum, zein, and hydroxyethylmethyl cellulose, a synthetic resin such as a carboxyvinyl polymer, polyvinyl alcohol, or a vinyl acetate resin, and sodium polystyrene sulfonate, and phosphorus protein such as casein and sodium caseinate.

Among the organic polymers, those having water solubility of 1 g/100 g or higher are called water soluble polymer. Specific examples thereof include hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, propylene glycol alginate ester, sodium caseinate, a carboxyvinyl polymer, powdered agar, guar gum, copolyvidone, hydroxyethylmethyl cellulose, and polyvinyl alcohol.

Among the organic polymers, those soluble under acidic condition of pH 1.2 to 3.5, which is the pH of gastric juice, are called gastric-soluble polymer, while those quickly soluble at enteric pH of 6 to 8 are called enteric-soluble polymer. Examples of the gastric soluble polymer include amino alkylmethacrylate copolymer E and polyvinylacetal diethylaminoacetate, and examples of the enteric-soluble polymer include methacrylic acid copolymer LD (emulsion), methacrylic acid copolymer S, purified shellac, carboxymethylethyl cellulose, cellulose acetate phthalate (cellaphate), hydroxypropylmethyl cellulose acetate succinate, casein, and zein.

[0021]

The pH adjusting agent indicates a substance which controls the pH of a solution with addition of an acid agent or an alkali agent so as to improve the solubility of a poorly water-soluble substance. The pH adjusting agent is appropriately selected according to the property of a substance to be dissolved. For example, in case of a basic poorly water-soluble substance, an acid agent is added to adjust the pH to be acidic and to improve the solubility.

Examples of the pH adjusting agent include adipic acid, citric acid, trisodium citrate, gluconic acid, sodium gluconate, glucono deltalactone, potassium gluconate, succinic acid, monosodium succinate, disodium succinate, sodium acetate, L-tartaric acid, potassium hydrogen L-tartrate, sodium L-tartrate, DL-tartaric acid, potassium hydrogen DL-tartrate, sodium DL-tartrate, sodium hydrogencarbonate, potassium carbonate (anhydrous), sodium carbonate, carbon dioxide, lactic acid, sodium lactate, glacial acetic acid, disodium dihydrogen pyrophosphate, fumaric acid, monosodium

fumarate, DL-malic acid, sodium DL-malate, phosphoric acid, monobasic potassium phosphate, sodium dihydrogen phosphate, dipotassium hydrogen phosphate, and disodium hydrogen phosphate.

Preferred examples include an acid agent such as adipic acid, citric acid, gluconic acid, glucono deltalactone, succinic acid, L-tartaric acid, DL-tartaric acid, carbon dioxide, lactic acid, glacial acetic acid, fumaric acid, DL-malic acid, and phosphoric acid.

[0022]

It is particularly preferable that the formulation of the present invention comprises a dissolution aid that is selected from casein, sodium caseinate, skimmed milk powder, sodium lauryl sulfate, sodium tetradecyl sulfate, sodium hexadecyl sulfate, and sodium octadecyl sulfate.

[0023]

The term "orally administrable formulation" indicates a formulation which can be administered orally. The oral administration means that the formulation is swallowed to enter a gastrointestinal tract, and the active ingredient is absorbed mainly in an intestinal tract.

Specific examples of the orally administrable formulation include a solid formulation such as a tablet, a capsule, a liquid, powder, a troche, a chewing formulation, granules, a gel formulation, a film formulation, and a spray formulation as well as a liquid formulation. Examples of the liquid formulation include a suspension, a liquid, a syrup, and an elixir. These formulations can be used as a filler for a soft or hard capsule, and as a carrier, water, ethanol, polyethylene glycol, propylene glycol, methyl cellulose, or suitable oil, and one or more emulsifying agent and/or a suspending agent are generally used. Furthermore, the liquid formulation can be prepared, for example, by dissolving solid state pharmaceutical formulation, for example, an individually packaged pharmaceutical formulation, in water, etc.

[0024]

In the present specification, the term "poorly water-soluble or insoluble in water" indicates that the solubility in water is less than 100 μg/mL, preferably less than 10 μg/mL at 25°C, for example. The solubility can be determined according to a

method well known in the art.

In the present specification, the expression “water solubility is improved” indicates that the solubility in FaSSIF, which is fasted state simulated intestinal fluid of human, is improved. Specifically, it indicates that the solubility is increased in significant sense ($p<0.05$) when a T-test is carried out for a comparative example. Similarly, the expression “water solubility is improved in significant sense” indicates that the solubility is increased in significant sense ($p<0.01$) when a significant difference test is carried out. Similarly, the expression “water solubility is improved in particularly significant sense” indicates that the solubility is increased in significant sense ($p<0.001$) when a significant difference test is carried out.

[0025]

In the present specification, the term “ALK” indicates “a receptor type tyrosine kinase which means anaplastic lymphoma kinase and belongs to an insulin receptor family.”

In the present specification, the “substance” represented by the Formula (I) or specific chemical name means a compound represented by a certain structure, the salts, or solvates or prodrugs thereof.

In the present specification, the term “halogen atom” means a fluorine atom, a chlorine atom, a bromine atom, an iodine atom and the like. According to the present invention, when the halogen atom is a substituent group for an aromatic carbon ring, an aromatic heterocycle and the like, the preferred halogen atom includes a fluorine atom, a chlorine atom and a bromine atom. According to the present invention, when the halogen atom is a substituent group for an alkyl group or a group which comprises the alkyl as at least a part of the group (e.g., alkoxy, alkenyl, unsaturated carbocycle, unsaturated heterocycle and the like), the preferred halogen atom includes a fluorine atom. Specific examples thereof include a trifluoromethyl group, a pentafluoroethyl group, a heptafluoropropyl group, a nonafluorobutyl group, a trifluoromethoxy group, a pentafluoroethoxy group, a heptafluoropropoxy group, a nonafluorobutoxy group, a trifluoroacetyl group, a pentafluoropropionyl group, a heptafluorobutyryl group and a nonafluoropentanoyl group.

[0026]

The "C_{1-8} alkyl group" means a monovalent group which is derived by removing any one of hydrogen atoms from a linear or branched aliphatic hydrocarbon having 1 to 8 carbon atoms. Specific examples thereof include a methyl group, an ethyl group, an isopropyl group, a butyl group, an n-butyl group, an isobutyl group, a sec-butyl group, a t-butyl group, a pentyl group, an isopentyl group, a 2,3-dimethyl propyl group, a hexyl group, a 2,3-dimethyl hexyl group, a 1,1-dimethyl pentyl group, a heptyl group and an octyl group. Preferably, it is a C_{1-6} alkyl group, more preferably a C_{1-5} alkyl group, still more preferably a C_{1-4} alkyl group, and even still more preferably a C_{1-3} alkyl group.

[0027]

The "C_{1-8} alkyl group which may be substituted" means an unsubstituted C_{1-8} alkyl group or a C_{1-8} alkyl group of which at least one hydrogen atom on the alkyl group is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. In addition, the alkyl group may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkyl group which may be substituted by certain 1 to 3 substituent group(s).

[0028]

The "C_{2-8} alkenyl group" means a monovalent group wherein at least one double bond (two adjacent SP2 carbon atoms) is comprised in a linear or branched aliphatic hydrocarbon group having 2 to 8 carbon atoms. Specific examples of the C_{2-8} alkenyl group include a vinyl group, an allyl group, a 1-propenyl group, a 2-propenyl group, a 1-butenyl group, a 2-butenyl group (including both cis and trans), a 3-butenyl group, a pentenyl group and a hexenyl group. Preferably, it is a C_{2-6} alkenyl group, more preferably a C_{2-5} alkenyl group, still more preferably a C_{2-4} alkenyl group, and even still more preferably a C_{2-3} alkenyl group.

The "C_{2-8} alkenyl group which may be substituted" means the unsubstituted C_{2-8} alkenyl group as defined above or a C_{2-8} alkenyl group of which at least one hydrogen atom on the alkenyl group is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. In addition, the single-bonded carbon atom may be substituted by a

cyclic substituent group through a spiro bond. Preferably, it is a C_{2-8} alkenyl group which may be substituted by 1 to 3 certain substituent group(s). More preferably, there are 1 to 3 substituent groups for a C_{2-6} alkenyl group and a C_{2-5} alkenyl group and 1 to 2 substituent groups for a C_{2-3} alkenyl group.

[0029]

The "C_{2-8} alkynyl group" means a monovalent group wherein at least one triple bond (two adjacent SP carbon atoms) is comprised in a linear or branched aliphatic hydrocarbon group having 2 to 8 carbon atoms. Specific examples of the C_{2-8} alkynyl group include an ethynyl group, a 1-propynyl group, a propargyl group and a 3-butynyl group. Preferably, it is a C_{2-6} alkynyl group, more preferably a C_{2-5} alkynyl group, still more preferably a C_{2-4} alkynyl group, and even still more preferably a C_{2-3} alkynyl group.

The "C_{2-8} alkynyl group which may be substituted" means the unsubstituted C_{2-8} alkynyl group as defined above or a C_{2-8} alkynyl group of which at least one hydrogen atom on the alkynyl group is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. In addition, the single-bonded carbon atom may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{2-8} alkynyl group which may be substituted by certain 1 to 3 substituent group(s). More preferably, there are 1 to 3 substituent groups for a C_{2-6} alkynyl group and a C_{2-5} alkynyl group and 1 to 2 substituent groups for a C_{2-3} alkynyl group.

[0030]

The "C_{3-8} cycloalkyl group" means an aliphatic hydrocarbon group in cyclic form. Preferably, it includes a C_{3-6} cycloalkyl group. Specific examples thereof include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group and a cyclooctyl group. Preferably, it is a C_{3-6} cycloalkyl group.

The "C_{3-8} cycloalkyl group which may be substituted" means the unsubstituted C_{3-8} cycloalkyl group as defined above or the C_{3-8} cycloalkyl group in which one or more hydrogen atoms are substituted by a certain substituent group. When there are two or more substituent groups, each substituent group may be the same or different

from each other. Preferably, it is a C_{3-8} cycloalkyl group which may be substituted by certain 1 to 3 substituent group(s).

[0031]

The "4- to 10-membered heterocycloalkyl group" means a saturated or partially unsaturated heterocyclic group which consists of 4 to 10 ring-constituting atoms and comprises 1 to 3 hetero atoms that are selected from O, S and N. The heterocycloalkyl group can be a monocyclic, a bicyclic or a spirocyclic type heterocycloalkyl group. Specific examples thereof include an oxetanyl group, a tetrahydrofuryl group, a tetrahydrothienyl group, a tetrahydropyranyl group, a pyrrolidino group, a pyrrolidinyl group, a piperidino group, a piperidinyl group, a piperazino group, a piperazinyl group, a morpholino group, a morpholinyl group, a tetrahydrothiopyranyl group, a thiomorpholino group, an imidazolidinyl group, a 1,3-dioxadinyl group, a tetrahydropyranyl group, a 1,3-dioxadinyl group, a 1,2,3,6-tetrahydropyridinyl group, a 1-oxa-8-aza-spiro[4.5]decanyl group, and a 1,4-dioxa-8-aza-spiro[4.5]decanyl group. Preferably, it is a 4- to 8-membered heterocycloalkyl group, more preferably, 4- to 6-membered heterocycloalkyl group.

[0032]

The "4- to 10-membered heterocycloalkyl group which may be substituted" means the unsubstituted 4- to 10-membered heterocycloalkyl group as defined above or a 4- to 10-membered heterocycloalkyl group of which at least one hydrogen atom on the heterocycloalkyl group is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. In addition, the alkyl moiety which may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a 4- to 10-membered heterocycloalkyl group which may be substituted by 1 to 4 certain substituent group(s). More preferably, there are 1 to 4 substituent groups for a 4- to 8-membered heterocycloalkyl group and 1 to 3 substituent group(s) for a 4- to 6-membered heterocycloalkyl group. When the substituent group is an oxo group, two oxo groups may bind to the same sulfur atom. When a quaternary ammonium salt is formed, two alkyl groups may bind to the nitrogen atom.

The "C_{6-10} aryl group" means a monovalent aromatic hydrocarbon ring.

Specific examples of the C_{6-10} aryl group include a phenyl group, a 1-naphthyl group and a 2-naphthyl group.

[0033]

The "C_{6-10} aryl group which may be substituted" means the unsubstituted C_{6-10} aryl group as defined above or a C_{6-10} aryl group of which at least one hydrogen atom is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Preferably, it is a C_{6-10} aryl group which may be substituted by certain 1 to 3 substituent group(s).

[0034]

The "5- to 14-membered heteroaryl group" means an aromatic cyclic group comprising one or more hetero atoms among 5 to 14 ring-constituting atoms. The cycle can be a monocyclic or bicyclic heteroaryl group fused to a benzene ring or a monocyclic heteroaryl ring. Specific examples thereof include a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a pyrazolyl group, a thiazolyl group, an isothiazolyl group, an oxazolyl group, an isooxazolyl group, an oxadiazolyl group, a thiadiazolyl group, a triazolyl group, a tetrazolyl group, a pyridyl group, a pyrimidyl group, a pyridazinyl group, a pyrazinyl group, a triazinyl group, a benzofuranyl group, a benzothienyl group, a benzothiadiazolyl group, a benzothiazolyl group, a benzoxazolyl group, a benzoxadiazolyl group, a benzoimidazolyl group, an indolyl group, an isoindolyl group, an indazolyl group, a quinolyl group, an isoquinolyl group, a cinnolinyl group, a quinazolinyl group, a quinoxalinyl group, a benzodioxolyl group, an indolizinyl group, an imidazopyridyl group and the like. Preferably, it is a 5- to 6-memebred heteroaryl group.

[0035]

The "5- to 14-membered heteroaryl group which may be substituted" means the unsubstituted 5- to 14-membered heteroaryl group as defined above or a 5- to 14-membered heteroaryl group of which at least one hydrogen atom on the heteroaryl group is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Preferably, it is a 5- to 14-membered heteroaryl group which may be substituted by

certain 1 to 3 substituent group(s). More preferably, there are 1 to 3 substituent group(s) or 1 to 2 substituent group(s) for a 5- to 6-membered heteroaryl group.

[0036]

The "C_{1-8} alkanoyl group" means a C_{1-8} alkyl-C(O)- group, wherein the C_{1-8} alkyl group is as defined above. Specific examples thereof include acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl and a hexanoyl group. Preferably, it is a C_{1-6} alkanoyl group, and more preferably a C_{1-3} alkanoyl group.

The "C_{1-8} alkanoyl group which may be substituted" means the unsubstituted C_{1-8} alkanoyl group as defined above or a C_{1-8} alkanoyl group of which at least one hydrogen atom on the alkanoyl group is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Preferably, it is a C_{1-8} alkanoyl group which may be substituted by certain 1 to 3 substituent group(s). More preferably, there are 1 to 2 substituent group(s) for a C_{1-6} alkanoyl group and a C_{1-3} alkanoyl group.

[0037]

The "C_{3-8} cycloalkylcarbonyl group" means a C_{3-8} cycloalkyl-C(O)- group, wherein the C_{3-8} cycloalkyl group is as defined above. Specific examples thereof include a cyclopropylcarbonyl group, a cyclobutylcarbonyl group, a cyclopentylcarbonyl group, a cyclohexylcarbonyl group, a cycloheptylcarbonyl group and a cyclooctylcarbonyl group.

The "4- to 10-membered heterocycloalkylcarbonyl group" means a 4- to 10-membered heterocycloalkyl-CO- group, and it contains the 4- to 10-membered heterocycloalkyl as defined above.

[0038]

The "C_{3-8} cycloalkyl (C_{0-8} alkyl) aminocarbonyloxy group" means a C_{3-8} cycloalkyl-NHC(O)O- group or a C_{3-8} cycloalkyl-N(C_{1-8} alkyl) C(O)O- group, wherein the C_{3-8} cycloalkyl group is as defined above. Specific examples thereof include a cyclopropylaminocarbonyloxy group, a cyclobutylaminocarbonyloxy group, a cyclopentylaminocarbonyloxy group, a cyclohexylaminocarbonyloxy group, a cyclopropyl (N-methyl) aminocarbonyloxy group, and a cyclobutyl (N-methyl) aminocarbonyloxy group.

The "(C_{1-8} alkyl)$_x$-aminocarbonyl group" (wherein, x represents the symbol as defined in the claims) means a NH_2-C(O)- group, a (C_{1-8} alkyl)-N-C(O)- group or a (C_{1-8} alkyl)$_2$-N-C(O)- group. Specific examples thereof include an N-methylaminocarbonyl group, an N-ethylaminocarbonyl group, an N-n-butyl-aminocarbonyl group, and a N,N-dimethylaminocarbonyl group.

[0039]

The "(C_{1-8} alkyl)$_x$-aminocarbonyl group which may be substituted" means the unsubstituted (C_{1-8} alkyl)$_x$ aminocarbonyl group or the group in which at least one hydrogen atom of the nitrogen atom or the alkyl moiety is substituted by a certain substituent group. When there are two or more substituent groups, each substituent group may be the same or different from each other.

[0040]

The "C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl group" means a C_{6-10} aryl NHC(O)- group or a C_{6-10} aryl N(C_{1-8} alkyl)C(O)- group. Specific examples thereof include a phenyl-NHC(O)- group and a phenyl-(N-methyl)-aminocarbonyl group. The C_{6-10} aryl and C_{1-8} alkyl are as defined above. Specific examples thereof include a phenylaminocarbonyl group and a phenyl(N-methyl)aminocarbonyl group.

[0041]

The "nitrogen-containing 4- to 10-membered heterocycloalkylcarbonyl group" means a carbonyl group to which a nitrogen-containing 4- to 10-membered heterocycloalkyl group is bonded. Herein, the a nitrogen-containing 4- to 10-membered heterocycloalkyl group (a nitrogen-containing 4- to 10-membered heterocycloalkyl group) means a heterocycloalkyl group which consists of 4 to 10 ring-constituting atoms and comprises at least one nitrogen atom as a hetero atom. Preferably, it is bonded to the carbonyl group via nitrogen atom that is comprised in the heterocycloalkyl ring. Specific examples of the heterocycloalkyl group include a pyrrolidinyl group, an imidazolidinyl group, a morpholino group, a piperazino group and a piperidino group. As for the nitrogen-containing 4- to 10-membered heterocycloalkylcarbonyl group, examples thereof include a pyrrolidinocarbonyl group, a piperidinocarbonyl group, a piperazinocarbonyl group and a morpholinocarbonyl group.

[0042]

The "nitrogen-containing 4- to 10-membered heterocycloalkylcarbonyl group which may be substituted" means the unsubstituted nitrogen-containing 4- to 10-membered heterocycloalkylcarbonyl group or the group in which at least one hydrogen atom of the heterocycloalkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Further, the heterocycloalkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a nitrogen-containing 4- to 10-membered heterocycloalkylcarbonyl group which may be substituted by certain 1 to 3 substituent group(s).

[0043]

The "4- to 10-membered heterocycloalkyl (C_{0-8} alkyl) aminocarbonyl group" means a 4- to 10-membered heterocycloalkyl NHC(O)- group or a 4- to 10-membered heterocycloalkyl N(C_{1-8} alkyl) C(O)- group. Specific examples thereof include oxetan-3-yl-amide group and a (1,1-dioxo-tetrahydrothiophen-3-yl) amide group.

The "4- to 10-membered heterocycloalkylaminocarbonyl group which may be substituted by one or more oxo group" means the unsubstituted 4- to 10-membered heterocycloalkylaminocarbonyl group or the group in which the heterocycloalkyl moiety is substituted by at least one oxo group.

[0044]

The "C_{6-10} arylsulfonyl group" means a C_{6-10} aryl-$S(O)_2$- group, wherein the C_{6-10} aryl group is as defined above. Specific examples thereof include a phenylsulfonyl group.

The "5- to 14-membered heteroarylsulfonyl group" means a 5- to 14-memebred heteroaryl-$S(O)_2$- group, wherein the 5- to 14-membered heteroaryl group is as defined above. Specific examples thereof include an imidazole sulfonyl group.

The "C_{1-8} alkylC_{6-10} arylsulfonyl group" means a C_{1-8} alkyl-C_{6-10} aryl-$S(O)_2$- group, wherein the C_{1-8} alkyl and C_{6-10} aryl group are as defined above. Specific examples thereof include a 4-methyl-phenylsulfonyl group.

[0045]

The "(C_{1-8} alkyl)$_x$-amino group" (wherein, x represents the symbol as defined in

the claims) means an amino group, a NH (C_{1-8} alkyl) group, or a NH (C_{1-8} alkyl)$_2$ group. Specific examples thereof include amino, methylamino, ethylamino, butylamino, isopropylamino, dimethylamino, and diethylamino. Preferably, it is a C_{1-3} alkylamino group.

[0046]

The "(C_{1-8} alkyl)$_x$-amino group which may be substituted" means the unsubstituted (C_{1-8} alkyl)$_x$ amino group or the group in which at least one hydrogen atom of the nitrogen atom or the alkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other.

[0047]

The "C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group" means a C_{1-8} alkyl-C(O)-NH- group, or a C_{1-8} alkyl-C(O)-N(C_{1-8} alkyl)- group, wherein the C_{1-8} alkyl is as defined above. Specific examples thereof include a methylcarbonylamino group, an ethylcarbonylamino group, a propylcarbonylamino group, and a butylcarbonylamino group.

[0048]

The "C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group which may be substituted" means the unsubstituted C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group or the group in which at least one hydrogen atom on the terminal alkyl moiety of the C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Further, the alkyl group may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by certain 1 to 3 substituent group(s).

The "C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group" means a C_{6-10} aryl-C(O)-NH- group, or a C_{6-10} aryl-C(O)-N(C_{1-8} alkyl)- group, wherein the C_{6-10} aryl group and C_{1-8} alkyl group are as defined above. Specific examples thereof include a phenylcarbonylamino group.

[0049]

The "C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group which may be substituted"

means the unsubstituted C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group or the group in which at least one hydrogen atom of the aryl moiety of the C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Preferably, it is a C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by certain 1 to 3 substituent group(s).

The "(C_{1-8} alkyl)$_x$-aminocarbonyl (C_{0-8} alkyl) amino group" (wherein, x represents the symbol as defined in the claims) means a $NH_2C(O)NH$- group, a (C_{1-8} alkyl)$NHC(O)NH$- group, a $NH_2C(O)N(C_{1-8}$ alkyl)- group, or a (C_{1-8} alkyl)$NHC(O)N(C_{1-8}$ alkyl)- group, wherein the C_{1-8} alkyl group is as defined above. Specific examples thereof include aminocarbonyl-(N-methyl) amino and (N-methyl) aminocarbonyl-(N'-methyl) amino.

The "(C_{1-8} alkyl)$_x$-aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted" means the unsubstituted (C_{1-8} alkyl)$_x$-aminocarbonyl (C_{0-8} alkyl) amino group or the (C_{1-8} alkyl)$_x$-aminocarbonyl (C_{0-8} alkyl) amino group in which at least one hydrogen atom of the nitrogen atom or the alkyl moiety of the (C_{1-8} alkyl)$_x$-aminocarbonyl (C_{0-8} alkyl) amino group is substituted by a certain substituent group. Preferably, it is a (C_{1-8} alkyl)$_x$-aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted by a phenyl group.

[0050]

The "(C_{1-8} alkyl)$_x$ aminosulfonyl (C_{0-8} alkyl) amino group" (wherein, x represents the symbol as defined in the claims) means a $NH_2S(O)_2NH$ group, a $NH(C_{1-8}$ alkyl)-$S(O)_2NH$ group, a $N(C_{1-8}$ alkyl)$_2$-$S(O)_2NH$ group, a $NH_2S(O)_2N(C_{1-8}$ alkyl)- group, a NH (C_{1-8} alkyl)-$S(O)_2(C_{1-8}$ alkyl)N- group, or a $N(C_{1-8}$ alkyl)$_2$-$S(O)_2(C_{1-8}$ alkyl)N- group wherein the C_{1-8} alkyl is as defined above. Specific examples thereof include a methylaminosulfonylamino group and a dimethylaminomethylsulfonylamino group.

[0051]

The "C_{1-8} alkoxy group" means a C_{1-8} alkyl-O- group. Specific examples thereof include a methoxy group, an ethoxy group, a 1-propoxy group, a 2-propoxy group, an n-butoxy group, an i-butoxy group, a sec-butoxy group, a t-butoxy group, a 1-

pentyloxy group, a 2-pentyloxy group, a 3-pentyloxy group, a 2-methyl-1-butyloxy group, a 3-methyl-1-butyloxy group, a 2-methyl-2-butyloxy group, a 3-methyl-2-butyloxy group, a 2,2-dimethyl-1-propyloxy group, a 1-hexyloxy group, a 2-hexyloxy group, a 3-hexyloxy group, a 2-methyl-1-pentyloxy group, a 3-methyl-1-pentyloxy group, a 4-methyl-1-pentyloxy group, a 2-methyl-2-pentyloxy group, a 3-methyl-2-pentyloxy group, a 4-methyl-2-pentyloxy group, a 2-methyl-3-pentyloxy group, a 3-methyl-3-pentyloxy group, a 2,3-dimethyl-1-butyloxy group, a 3,3-dimethyl-1-butyloxy group, a 2,2-dimethyl-1-butyloxy group, a 2-ethyl-1-butyloxy group, a 3,3-dimethyl-2-butyloxy group, a 2,3-dimethyl-2-butyloxy group and a 1-methyl-cyclopropylmethoxy group. Preferably, it is a C_{1-6} alkoxy group. More preferably, it is a C_{1-5} alkoxy group. Still more preferably, it is a C_{1-4} alkoxy group, and even still more preferably it is a C_{1-3} alkoxy group.

[0052]

The "C_{1-8} alkoxy group which may be substituted" means the unsubstituted C_{1-8} alkoxy group or the group in which at least one hydrogen atom of the alkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. In addition, the alkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkoxy group which may be substituted by certain 1 to 3 substituent group(s). More preferably, there are 1 to 3 substituent group(s) for the C_{1-6} alkoxy group and a C_{1-4} alkoxy group or 1 to 2 substituent group(s) for a C_{1-3} alkoxy group.

[0053]

The "C_{1-8} alkoxycarbonyl group" means a C_{1-8} alkyl-O-C(O)- group, wherein the C_{1-8} alkyl group is as defined above. Specific examples thereof include a methoxycarbonyl group, an ethoxycarbonyl group, an n-propoxycarbonyl group and an i-propoxycarbonyl group. Preferably, it is a C_{1-6} alkoxycarbonyl group, and more preferably a C_{1-3} alkoxycarbonyl group.

[0054]

The "C_{1-8} alkoxycarbonyl group which may be substituted" means the unsubstituted C_{1-8} alkoxycarbonyl group or the group in which at least one hydrogen

atom of the C_{1-8} alkoxycarbonyl group is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. In addition, the alkyl moiety of the alkoxycarbonyl group may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkoxycarbonyl group which may be substituted by certain 1 to 3 substituent group(s).

[0055]

The "C_{0-8} alkoxy (C_{0-8} alkyl) aminocarbonyl group" means a HO-NH-C(O)- group, a C_{1-8} alkyl-NH-C(O)- group, a HO-N(C_{1-8} alkyl)-C(O)- group, or a C_{1-8} alkyl-N(C_{1-8} alkyl)-C(O)- group, wherein the C_{1-8} alkoxy group and C_{1-8} alkyl group are as defined above. Specific examples thereof include a methoxyaminocarbonyl group, an ethoxyaminocarbonyl group, an n-propoxyaminocarbonyl group, and an i-propoxyaminocarbonyl group. Preferably, it is a C_{1-6} alkoxyaminocarbonyl group. More preferably, it is a C_{1-3} alkoxyaminocarbonyl group.

[0056]

The "C_{0-8} alkoxy (C_{0-8} alkyl) aminocarbonyl group which may be substituted" means the unsubstituted hydroxyaminocarbonyl group, C_{1-8} alkoxyaminocarbonyl group, or a hydroxy (C_{1-8} alkyl) aminocarbonyl group or the group in which or at least one hydrogen atom of the alkyl moiety of the C_{1-8} alkoxy (C_{1-8} alkyl) aminocarbonyl group is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. In addition, the alkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkoxyaminocarbonyl group which may be substituted by certain 1 to 3 substituent group(s).

[0057]

The "4- to 10-membered heterocycloalkyloxy group" means a 4- to 10-membered heterocycloalkyl-O- group having the 4- to 10-membered heterocycloalkyl defined above.

[0058]

The "4- to 10-membered heterocycloalkyloxy group which may be substituted" means the unsubstituted 4- to 10-membered heterocycloalkyloxy group as defined

above or a 4- to 10-membered heterocycloalkyloxy group in which at least one hydrogen atom of the heterocycloalkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. In addition, the heterocycloalkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a 4- to 10-membered heterocycloalkyloxy group which may be substituted by 1 to 3 certain substituent group.

[0059]

The "C_{6-10} aryloxy group" means a C_{6-10} aryl-O- group, wherein the C_{6-10} aryl group is as defined above.

[0060]

The "5- to 14-membered heteroaryloxy group" means a 5- to 14-membered heteroaryl-O- group having the 5- to 14-membered heteroaryl described above. Specific examples thereof include a pyrimidinyloxy group.

[0061]

The "C_{1-8} alkylcarbonyloxy group" means a C_{1-8} alkyl-C(O)-O- group having the C_{1-8} alkyl described above. Specific examples thereof include a methylcarbonyloxy group, an ethylcarbonyloxy group and a propylcarbonyloxy group.

[0062]

The "C_{2-8} alkenylcarbonyloxy group" means a C_{2-8} alkenyl-C(O)-O- group having the C_{2-8} alkenyl described above. Specific examples thereof include a 2-methyl-2-butenoyloxy group.

The "4- to 10-membered heterocycloalkylcarbonyloxy group" means a 4- to 10-membered heterocycloalkyl-C(O)-O- group having the 4- to 10-membered heterocycloalkyl described above.

[0063]

The "$(C_{1-8}$ alkyl$)_x$ -aminocarbonyloxy group" (wherein, x represents the symbol as defined in the claims) means a NHC(O)-O- group, a N(C_{1-8} alkyl)C(O)-O- group, or a N(C_{1-8} alkyl)$_2$C(O)-O- group. Specific examples thereof include a methyl-aminocarbonyloxy group, an ethyl-aminocarbonyloxy group, and a propyl-aminocarbonyloxy group.

The "(C_{1-8} alkyl)$_x$ -aminocarbonyloxy group which may be substituted" means the unsubstituted (C_{1-8} alkyl)$_x$ aminocarbonyloxy group or the group in which at least one hydrogen atom on the nitrogen atom or the alkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other.

The "nitrogen-containing 4- to 10-membered heterocycloalkylsulfonyl group" means the nitrogen-containing 4- to 10-membered heterocycloalkyl-$S(O)_2$- group. Specific examples thereof include a morpholino-sulfonyl group.

The "nitrogen-containing 4- to 10-membered heterocycloalkylsulfonyl group which may be substituted" means the unsubstituted nitrogen-containing 4- to 10-membered heterocycloalkylsulfonyl group or the group in which at least one hydrogen atom of the nitrogen-containing 4- to 10-membered heterocycloalkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Preferably, it is a nitrogen-containing 4- to 10-membered heterocycloalkylsulfonyl group which may be substituted by certain 1 to 3 substituent group(s).

The "nitrogen-containing 4- to 10-membered heterocycloalkylsulfonyloxy group" means a nitrogen-containing 4- to 10-membered heterocycloalkyl-$S(O)_2$-O- group. Specific examples thereof include a morpholino-sulfonyloxy group and a piperazino-sulfonyloxy group.

The "nitrogen-containing 4- to 10-membered heterocycloalkylsulfonyloxy group which may be substituted" means the unsubstituted nitrogen-containing 4- to 10-membered heterocycloalkylsulfonyloxy group or the group in which at least one hydrogen atom of the nitrogen-containing 4- to 10-membered heterocycloalkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Preferably, it is a nitrogen-containing 4- to 10-membered heterocycloalkylsulfonyloxy group which may be substituted by certain 1 to 3 substituent group(s).

The "C_{1-8} alkylsulfonyloxy group" means a C_{1-8} alkyl-$S(O)_2$-O- group, wherein the C_{1-8} alkyl is as defined above.

[0064]

The "C_{1-8} alkylsulfonyloxy group which may be substituted" means the unsubstituted C_{1-8} alkylsulfonyloxy group or the group in which at least one hydrogen atom of the alkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. In addition, the alkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkylsulfonyloxy group which may be substituted by certain 1 to 3 substituent group(s). Specific examples thereof include a trifluoromethylsulfonyloxy group.

[0065]

The "$(C_{1-8}$ alkyl$)_x$ -aminosulfonyloxy group" (wherein, x represents the symbol as defined in the claims) means a $NH_2S(O)_2O$- group, a $N(C_{1-8}$ alkyl$)S(O)_2O$- group, or a $N(C_{1-8}$ alkyl$)_2S(O)_2O$- group. Specific examples thereof include an N-methylaminosulfonyloxy group.

[0066]

The "C_{1-8} alkylthio group" means a C_{1-8} alkyl-S- group, wherein the C_{1-8} alkyl group is as defined above. Examples thereof include methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, s-butylthio, i-butylthio, t-butylthio, n-pentylthio, 3-methylbutylthio, 2-methylbutylthio, 1-methylbutylthio, 1-ethylpropylthio, n-hexylthio, 4-methylpentylthio, 3-methylpentylthio, 2-methylpentylthio, 1-methylpentylthio, 3-ethylbutylthio, and 2-ethylbutylthio and the like. Preferably, it is a C_{1-6} alkylthio group, and more preferably a C_{1-3} alkylthio group.

[0067]

The "C_{1-8} alkylthio group which may be substituted" means the unsubstituted C_{1-8} alkylthio group or the group in which at least one hydrogen atom of the alkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. In addition, the alkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkylthio group which may be substituted by certain 1 to 3 substituent group(s).

[0068]

The "C_{1-8} alkylsulfonyl group" means a C_{1-8} alkyl-$S(O)_2$- group, wherein the C_{1-}

$_8$ alkyl group is as defined above. Specific examples thereof include a methylsulfonyl group, an ethylsulfonyl group and an n-propylsulfonyl group. Preferably, it is a C_{1-6} alkylsulfonyl group, and more preferably a C_{1-3} alkylsulfonyl group.

The "C_{1-8} alkylsulfinyl group" means a C_{1-8} alkyl-S(O)- group, wherein the C_{1-8} alkyl group is as defined above. Specific examples thereof include a methylsulfinyl group, an ethylsulfinyl group and an n-propylsulfinyl group. Preferably, it is a C_{1-6} alkylsulfinyl group, and more preferably a C_{1-3} alkylsulfinyl group.

[0069]

The "C_{1-8} alkylsulfonyl group which may be substituted" means the unsubstituted C_{1-8} alkylsulfonyl group or the group in which at least one hydrogen atom of the alkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Preferably, it is a C_{1-8} alkylsulfonyl group which may be substituted by certain 1 to 3 substituent group(s).

The "C_{1-8} alkylsulfinyl group which may be substituted" means the unsubstituted C_{1-8} alkylsulfinyl group or the group in which at least one hydrogen atom of the alkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Preferably, it is a C_{1-8} alkylsulfinyl group which may be substituted by certain 1 to 3 substituent group(s).

[0070]

The "4- to 10-membered heterocycloalkylsulfonyl group" means a 4- to 10-membered heterocycloalkyl-$S(O)_2$- group having the 4- to 10-membered heterocycloalkyl defined above.

[0071]

The "4- to 10-membered heterocycloalkylsulfonyl group which may be substituted" means the unsubstituted 4- to 10-membered heterocycloalkylsulfonyl group or the group in which at least one hydrogen atom of the heterocycloalkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. In addition, the heterocycloalkyl moiety may be substituted by a cyclic substituent group

through a spiro bond. Preferably, it is a 4- to 10-membered heterocycloalkylsulfonyl group which may be substituted by certain 1 to 3 substituent group(s).

[0072]

The "(C_{1-8} alkyl)$_x$ -aminosulfonyl group" (wherein, x represents the symbol as defined in the claims) means a NH_2-$S(O)_2$- group, a C_{1-8} alkylamino-$S(O)_2$- group or a (C_{1-8} alkyl)$_2$amino-$S(O)_2$- group, wherein the C_{1-8} alkyl is as defined above. Specific examples thereof include an aminosulfonyl group, a methylaminosulfonyl group, and a dimethylaminosulfonyl group.

[0073]

The "(C_{1-8} alkyl)$_x$-aminosulfonyl group which may be substituted" means the unsubstituted aminosulfonyl group or the group in which at least one hydrogen atom on the nitrogen atom or the alkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other.

The "C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group" means a C_{1-8} alkoxy-C(O)-NH group, or a C_{1-8} alkoxy-C(O)-N(C_{1-8} alkyl) group, wherein the C_{1-8} alkoxy and C_{1-8} alkyl are as defined above. Specific examples thereof include a methoxycarbamoyl group and an N-ethylcarbonyl-N-methylamino group.

The "C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group which may be substituted" means the unsubstituted C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group or the C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group in which at least one hydrogen atom on the nitrogen atom or the alkyl moiety may be substituted by a certain substituent group. Preferably, it is a C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group which is substituted by certain 1 to 3 substituent group(s).

The "C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) aminosulfonyl group" means a C_{1-8} alkoxy-C(O)-NHS$(O)_2$- group, or C_{1-8} alkoxy-C(O)-N(C_{1-8} alkyl)S$(O)_2$- group, wherein the C_{1-8} alkoxy and C_{1-8} alkyl are as defined above. The specific examples thereof include a methoxycarbonylaminosulfonyl group and an ethoxycarbonyl-N-methylaminosulfonyl group.

The "C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group" means a C_{6-10} aryl-O-C(O)-NH group, or C_{6-10} aryl-O-C(O)-N(C_{1-8} alkyl) group, wherein the C_{6-10} aryl and

C_{1-8} alkyl group are as defined above. The specific examples thereof include a phenyloxycarbonylamino group and an N-methyl-N-phenyloxycarbonylamino group.

The "C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group which may be substituted" means the unsubstituted C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group or the C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group in which at least one hydrogen atom on the nitrogen atom or the alkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Preferably, it is a C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group which may be substituted by certain 1 to 3 substituent group(s).

The "C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group" means a C_{6-10} aryl-NH-C(O)-NH group, a C_{6-10} aryl-N(C_{1-8} alkyl)-C(O)-NH group, or C_{6-10} aryl-N(C_{1-8} alkyl)-C(O)-N(C_{1-8} alkyl) group, wherein the C_{6-10} aryl and C_{1-8} alkyl group are as defined above. Specific examples thereof include a phenylaminocarbonylamino group and a phenylaminocarbonyl (N-methyl) amino group.

The "C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted" means the unsubstituted C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group or the C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group in which at least one hydrogen atom on the nitrogen atom or the alkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or different from each other. Preferably, it is a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted by certain 1 to 3 substituent group(s).

The "C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group" means a C_{6-10} aryl-NH-C(O)-O- group, or a C_{6-10} aryl-N(C_{1-8} alkyl)-C(O)-O- group, wherein the C_{6-10} aryl and C_{1-8} alkyl group are as defined above. Specific examples thereof include a phenylaminocarbonyloxy group and a phenyl (N-methyl) aminocarbonyloxy group.

The "C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group which may be substituted" means the unsubstituted C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group or the C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group in which at least one hydrogen atom on the nitrogen atom or the alkyl moiety is substituted by a certain substituent group. When two or more substituent groups are present, each substituent group may be the same or

different from each other. Preferably, it is a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group which may be substituted by certain 1 to 3 substituent group(s).

The "C_{1-8} alkylsulfonyl (C_{0-8} alkyl) amino group" means a C_{1-8} alkyl-$S(O)_2$-NH- group or a C_{1-8} alkyl-$S(O)_2$-N(C_{1-8} alkyl)- group, wherein the C_{1-8} alkyl group is as defined above. Specific examples thereof include a methylsulfonylamino group, an ethylsulfonylamino group, and a methylsulfonyl (N-methyl) amino group.

The "C_{2-8} alkenyloxy group" means a C_{2-8} alkenyl-O- group, wherein the C_{2-8} alkenyl is as defined above. Specific examples of C_{2-8} alkenyloxy group include a vinyloxy group and an aryloxy group.

[0074]

Preferred examples of the substance represented by the Formula (I) include a substance in which A^1 to A^4 and A^6 to A^7 are a carbon atom, R^3 is cyano, and A^5 is NH.

More preferred examples of the substance represented by the Formula (I) include a substance in which A^1 to A^4 and A^6 to A^7 are a carbon atom, R^3 is cyano, A^5 is NH, R^8 is a 4- to 10-membered heterocycloalkyl group or a 4- to 10-membered heterocycloalkyl group which may be substituted by a C_{3-8} cycloalkyl group.

[0075]

Specific examples of the preferred substance represented by the Formula (I) include

9-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-cyclopropylethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-bromo-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-bromo-8-(4-cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-chloro-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6,9-trimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethynyl-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-9-ethynyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(1-isopropyl-piperidin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(2-tert-butylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethynyl-8-(4-methanesulfonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-

benzo[b]carbazole-3-carbonitrile;
9-bromo-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;
6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile; and
9-ethynyl-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

[0076]

Specific examples of the more preferred substance represented by the Formula (I) include (i) 6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, (ii) 8-(4-cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, (iii) 8-(4-cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, or (iv) 9-ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile or the salts thereof.

[0077]

(Method for production of the substances used in the present invention)

Representative production method

[0078]

The substances represented by the Formula (I) of the present invention can be produced by the method described below, for example. However, method of producing the compounds used in the present invention is not limited thereto. Further, depending on necessity, order of the reaction step such as introduction of a substituent group, etc. can be changed. Although the compounds used in the present invention are novel compounds which have not been described in literatures, the compounds can be produced according to a chemical method that is well known in the art. Still further, as for the reacting compounds that are used for the production, commercially available ones can be used or they can be produced according to a method that is generally known in the art depending on necessity.

[0079]

In the following reaction schemes showing the reaction step, A^1 to A^{10} and R^1 to R^{10} are as defined in the Formula (I). PR^1 to PR^{10} are the same as R^1 to R^{10} that are defined in the Formula (I) or represent a group which can be converted to R^1 to R^{10} according to modification or deprotection of a functional group.

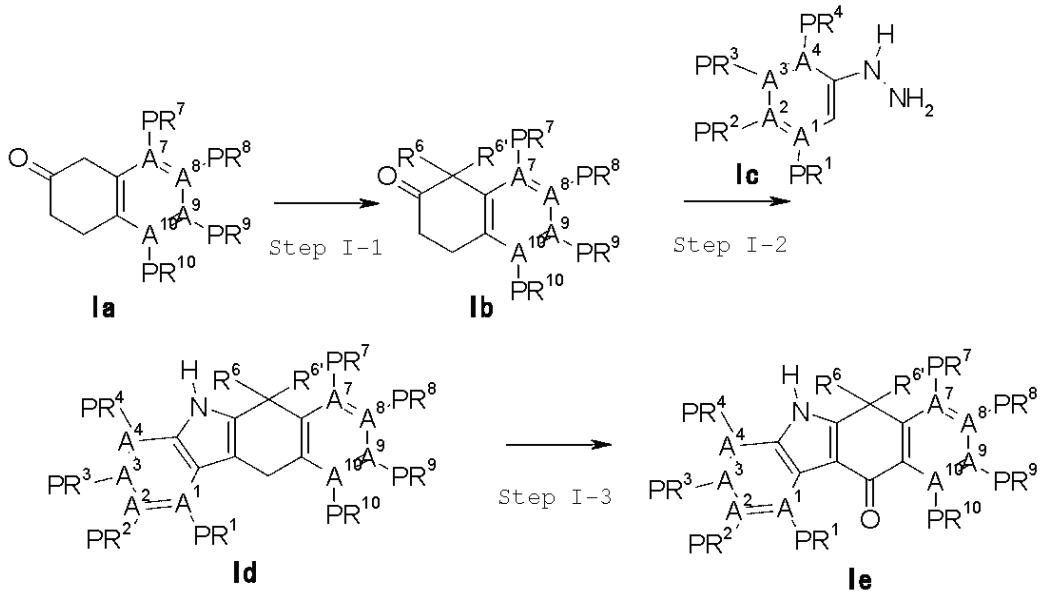
[0080]

Other abbreviated symbols described in the following reaction schemes have the general meanings that can be understood by a skilled person in the art.

[0081]

Production method I

This is one of the methods for producing the skeletons of the Formula (I) in which A^5 is N and R^5 is H.



(The symbols that are included in the formula have the meanings as defined above. P represents a protecting group, and for the production methods described below, when a defined group is subjected to undesirable chemical modification under a condition for implementing the method, desired compound can be produced by using means such as protection and deprotection of a functional group, etc. using a suitable protecting group).

[0082]

Step I-1

It is an alkylation step of a cyclic ketone derivative Ia. The step can be carried

out by reacting cyclic ketone derivative Ia with an alkylating agent corresponding to R^6 and $R^{6'}$ in the presence of a base. For example, it can be carried out in view of the method described in Journal of the American Chemical Society, 115(23), 10628-36; 1993 and Organic Letters, 9(24), 5027-5029; 2007, etc. The reaction is carried out in a solvent under the condition of a reaction temperature of -20°C to boiling point of the solvent, in the presence or the absence of a catalyst. When R^6 and $R^{6'}$ are atomic groups other than a hydrogen atom, the reaction order can be optionally selected, and separation and purification can be carried out at each step or the reaction can be carried out continuously.

[0083]

As for the alkylating agent, examples thereof include an alkyl halide such as MeI, ethyl iodide, 2-iodopropane, 1,4-dibromobutane, 1,1'-oxybis (2-bromoethane) and the like, dimethyl sulfate, and sulfonic acid ester such as dimethyl sulfuric acid methylmethane sulfonate, methyl tosylate and methyltrifluoromethane sulfonate. Preferably, it is an alkyl halide such as MeI and the like. As for the catalyst, examples thereof include a phase transfer catalyst such as tetrabutylammonium chloride and tetrabutylammonium hydrogen sulfate. Preferably, it is tetrabutylammonium hydrogen sulfate. As for the base, examples thereof include an inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, calcium hydride and the like or an organic base such as t-BuOK, t-BuONa, pyridine, TEA (trifluoroacetic acid), DIPEA (N,N-diisopropylethylamine), LDA (lithium diisopropylamide), LiHMDS (lithium hexamethyl disilazide) and n-BuLi. Preferably, it is potassium hydroxide, potassium t-butoxy, or sodium t-butoxy. As for the solvent, examples thereof include toluene, xylene, n-hexane, cyclohexane, DMF (N,N-dimethyl formamide), DMA (N,N-dimethyl acetamide), EtOAc, DMSO (dimethyl sulfoxide), dichloromethane, carbon tetrachloride, THF (tetrahydrofuran), dioxane, acetonitrile, water, methanol, ethanol and a mixture thereof. Preferably, it is a mixture solvent of water-THF or THF.

[0084]

Step I-2

It is the synthesis of carbazole skeleton Id according to Fischer method. This

step is generally carried out by using cyclic ketone Ib in the presence of hydrazine compound Ic and an acid in a solvent or by using an acid as a solvent under the condition of a reaction temperature of 0°C to boiling point of the solvent, and also can be carried out in view of the method described in Journal of Heterocyclic Chemistry, 28(2), 321-3; 1991 and Bioorganic & Medicinal Chemistry Letters (2008), 18(24), 6479-6481. Further, when the reaction proceeds slowly, a zinc chloride catalyst and the like can be also used in view of the reaction condition disclosed in Organic Letters (2006), 8(3), 367-370. The reaction includes a step of producing phenyl hydrazone and a step of sigmatropic rearrangement. Separation and purification can be carried out at each step or the reaction can be carried out continuously. Further, according to the structure of aryl hydrazine, which is a reacting material of this reaction step, mixture of a position isomer can be obtained as a reaction product. Such position isomer can be separated from each other or used as a mixture for the next reaction step.

[0085]

As for the acid used for the reaction, examples thereof include formic acid, acetic acid, methane sulfonic acid, p-toluene sulfonic acid, benzene sulfonic acid, TFA, hydrochloric acid, sulfuric acid and pyridinium p-toluene sulfonate. Preferably, it is acetic acid, sulfuric acid, or TFA. As for the solvent, examples thereof include toluene, xylene, NMP (N-methyl pyrrolidone), DMF, DMA, DMSO, sulfolane, dioxane, DME (dimethoxyethane), TFE (trifuloroethanol), diethylene glycol, triethylene glycol and a mixture thereof.

[0086]

Step I-3

It is a step of oxidation at benzyl at 11-position of carbazole skeleton Id. This step is carried out by applying an oxidizing agent to a substrate in a solvent in the presence or absence of a catalyst under the condition of a reaction temperature of -20°C to boiling point of the solvent. As for the reaction condition, the method described in Journal of Medicinal Chemistry, 51(13), 3814-3824; 2008, etc. can be considered.

[0087]

As for the oxidizing agent and the catalyst used for the reaction, DDQ, peracid such as, mCPBA and the like, cerium ammonium nitrate (IV) (CAN), permanganate

such as potassium permanganate, barium permanganate and the like, sodium chlorite, hydrogen peroxide, or N-hydroxyphthalimide and the like can be used alone or in a combination thereof. Preferably, it is DDQ (2,3-dichloro-5,6-dicyano-p-benzoquinone) or N-hydroxyphthalimide. As for the solvent used for the reaction, examples thereof include water, t-butanol, acetonitrile, THF, dichloromethane, ethyl acetate and a mixture thereof. Preferably, it is THF.

[0088]

According to the present invention, examples of the salts of the compounds that are represented by the Formula (I) include hydrochloric acid salt, hydrobromic acid salt, hydriodic acid salt, phosphoric acid salt, phosphonic acid salt, sulfuric acid salt, sulfonic acid salt such as methane sulfonic acid salt, p-toluene sulfonic acid salt and the like, carboxylic acid salt such as acetic acid salt, citric acid salt, malic acid salt, tartaric acid salt, succinic acid salt, salicylic acid salt and the like, or alkali metal salt such as sodium salt, potassium salt and the like; alkaline earth metal salt such as magnesium salt, calcium salt and the like; ammonium salt such as ammonium salt, alkyl ammonium salt, dialkyl ammonium salt, trialkyl ammonium salt, and tetraalkyl ammonium salt. Preferred examples thereof include hydrochloride salt and methane sulfonate salt. More preferred examples thereof include hydrochloride salt.

These salts are produced by bringing the compounds described above in contact with an acid or a base which can be used for the production of a pharmaceutical product.

According to the present invention, the compounds that are represented by the Formula (I) or salts thereof can be an anhydride or a solvate such as a hydrate and the like. Herein, the term “solvate” indicates a phenomenon by which solute molecules or ions contained in a solution strongly attract neighboring solvent molecules to form a huge group of molecules. When the solvent is water, it is called “hydrate.” The solvate can be any one of a hydrate and a non-hydrate. For the non-hydrate, alcohol (for example, methanol, ethanol, n-propanol), dimethylformamide and the like can be used.

[0089]

The compounds of the present invention and salts thereof may be present in several tautomer forms, for example, enol and imine form, keto and enamine form, and

a mixture thereof. In a solution, a tautomer is present as a mixture of tautomeric set. In case of solid form, one type of tautomer is generally present in dominant ratio. In this regard, even if only one type of tautomer is described, the present invention includes all types of tautomer of the compounds of the present invention.

[0090]

The present invention includes all types of stereoisomer of the compounds represented by the Formula (I) (for example, enantiomer, diastereomer (including cis and trans geometric isomer)), racemate of the isomer and a mixture thereof. For example, the compounds having the Formula (I) of the present invention may have one or more asymmetric center, and the present invention includes a racemic mixture, a diastereomer mixture and enantiomer of such compound.

[0091]

When the compounds of the present invention are obtained in free form, the compounds can be converted into a salt, a hydrate or solvate thereof which can be formed from the compounds according to a method generally known in the art.

Further, when the compounds of the present invention are obtained in the form of a salt, hydrate or solvate of the compounds, the compounds can be converted to free form according to a method generally known in the art.

[0092]

Further, the substances used in the present invention can be administered in the form of prodrug of the compounds having the Formula (I). Herein, the term “prodrug” indicates the derivatives of the compounds having the Formula (I) that can be converted to the compounds having the Formula (I) or pharmaceutically acceptable salts thereof after administration by enzymatic or non-enzymatic degradation under a physiological condition. The prodrug can be in an inactive form when it is administered to a patient. However, in living organisms, it converts to the compounds having the Formula (I) and present therein in the active form.

[0093]

For example, the prodrug converts into a desired drug form at specific pH or by an enzymatic action. Typical prodrug is a compound having a hydrolyzable ester residue which produces a free acid in living organisms. Examples of such

hydrolyzable ester residue include a residue having a carboxyl moiety of which free hydrogen (for example, a free hydrogen in a carboxyl group when Y in the Formula (I) has a carboxyl group) is substituted by a C_{1-4} alkyl group, a C_{2-7} alkanoyloxymethyl group, a 1-(alkanoyloxy)ethyl group having 4 to 9 carbon atoms, a 1-methyl-1-(alkanoyloxy)-ethyl group having 5 to 10 carbon atoms, an alkoxycarbonyloxymethyl group having 3 to 6 carbon atoms, a 1-(alkoxycarbonyloxy)ethyl group having 4 to 7 carbon atoms, a 1-methyl-1-(alkoxycarbonyloxy)ethyl group having 5 to 8 carbon atoms, an N-(alkoxycarbonyl) aminomethyl having 3 to 9 carbon atoms, a 1-(N-(alkoxycarbonyl) amino) ethyl group having 4 to 10 carbon atoms, a 3-phthalidyl group, a 4-crotonolactonyl group, a γ-butyrolacton-4-yl group, a di-N,N-(C_{1-2})alkylamino(C_{2-3})alkyl group (for example, N,N-dimethylaminoethyl group), a carbamoyl(C_{1-2})alkyl group, a N,N-di(C_{1-2})alkylcarbamoyl-(C_{1-2})alkyl group, a piperidino(C_{2-3})alkyl group, a pyrrolidino(C_{2-3})alkyl group, or a morpholino(C_{2-3})alkyl group, but not limited thereto.

[0094]

The formulation of the present invention is produced according to a method well known in the art by using additives such as a filler, a lubricating agent, a coating agent, a binding agent, a disintegrating agent, a stabilizing agent, a flavoring agent, or a diluent.

[0095]

Examples of the filler include starch such as corn starch, potato starch, wheat starch, rice starch, partially pregelatinized starch, pregelatinized starch, and porous starch; sugars or sugar alcohols such as lactose hydrate, fructose, glucose, mannitol, and sorbitol; and anhydrous dibasic calcium phosphate, microcrystalline cellulose, precipitated calcium carbonate, and calcium silicate. Preferred examples of the filler include starch such as starch, potato starch, and corn starch, lactose hydrate, microcrystalline cellulose, and anhydrous dibasic calcium phosphate.

[0096]

For the formulation of the present invention, lactose hydrate and microcrystalline cellulose are preferably used as a filler. Herein, the used amount of lactose hydrate is preferably 5 to 60 parts by weight, and more preferably 10 to 50 parts by weight with respect to 100 parts by weight of the formulation. Further, the used

amount of microcrystalline cellulose is preferably 5 to 60 parts by weight, and more preferably 10 to 50 parts by weight with respect to 100 parts by weight of the formulation.

[0097]

Examples of the disintegrating agent include the compounds mentioned above as a filler above, and chemically modified starch and celluloses such as Crosscarmellose sodium, sodium starch glycolate, and crosslinked polyvinyl pyrrolidone. Specific examples of disintegrating agent include sodium starch glycolate, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl starch, Crosscarmellose sodium, crospovidone, low-substituted hydroxypropyl cellulose, and hydroxypropyl starch. The used amount of the disintegrating agent is preferably 0.5 to 25 parts by weight, and more preferably 1 to 15 parts by weight with respect to 100 parts by weight of the formulation.

[0098]

Examples of the binding agent include polyvinyl pyrrolidone, Macrogol, and the compounds mentioned above as a filler above. Specific examples of binding agent include hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, povidone (polyvinyl pyrrolidone), and gum Arabic powder. The used amount of the binding agent is preferably 0.1 to 50 parts by weight, and more preferably 0.5 to 40 parts by weight with respect to 100 parts by weight of the formulation.

[0099]

As for the lubricating agent, suitable examples thereof include magnesium stearate, calcium stearate, talc, sucrose fatty acid ester, and sodium stearyl fumarate.

As for the surfactant or an emulsifying agent, examples thereof include polysorbate 80, polyoxyl 40 stearate and lauromacrogol.

As for the coloring agent, any of those allowed to be used in a pharmaceutical can be used. Examples thereof include a dye used for food such as Food Yellow No. 5 (Sunset yellow, US Food Yellow No. 6), Food Red No. 2, and Food Blue No. 2, Food Lake dye, and iron trioxide.

[0100]

As a stabilizing agent, examples thereof include paraoxy benzoic acid esters

such as methyl paraben, propyl paraben and the like; alcohols such as chlorobutanol, benzyl alcohol, phenylethyl alcohol and the like; benzalkonium chloride; phenols such as phenol, cresol and the like; thimerosal; dehydroacetic acid; and sorbic acid.

As a flavoring agent, examples thereof include a sweetener, an acid tasting agent, a flavor and the like that are commonly used in the art.

With respect to the fluidizing agent, it is used for the purpose of improving the fluidity of mixed powder or granules, and representative examples include talc, light anhydrous silicic acid, i.e., silicon dioxide, and hydrated silicon dioxide. Herein, the light anhydrous silicic acid is only required to contain hydrated silicon dioxide ($SiO_2 \cdot nH_2O$) (n represents an integer) as a main ingredient, and specific examples thereof include SYLYSIA 320 (trade name, manufactured by FUJI SILYSIA CHEMICAL LTD.), and AEROSIL 200 (trade name, manufactured by Nippon Aerosil Co., Ltd.).

Suitable examples of the preservatives include paraoxy benzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, and sorbic acid.

Suitable examples of the anti-oxidant include sulfite salt and ascorbic acid.

These additives may be used in combination of two or more types that are mixed at appropriate ratio.

Further, as a solvent to produce a liquid formulation, examples thereof include ethanol, phenol, chlorocresol, purified water and distilled water.

[0101]

The solid formulation of the present invention can be produced by mixing the substance used for the present invention with a dissolution aid and a pharmaceutically acceptable carrier, and performing a production method generally carried out in the art. Preferably, it is produced according to the production method decribed below.

1) The substance used for the present invention is mixed with the ingredients such as additive, filler, disintegrating agent, and lubricating agent that are selected from the additive group A, and then filled in a capsule or subjected to compression molding to produce the solid formulation of the present invention.

2) The substance used for the present invention is mixed with the ingredients such as

additive, filler, and binding agent that are selected from the additive group A, and then granulated while adding or spraying a solvent (for example, purified water, ethanol, or their mixture, and the like). To the granulate obtained, a suitable amount of a lubricating agent, and if necessary, a disintegrating agent, etc., are added and mixed, and then the mixture is filled in a capsule or subjected to compression molding to produce the solid formulation of the present invention.

3) The substance used for the present invention is mixed with the ingredients such as additive, and filler that are selected from the additive group A, and then granulated while adding or spraying a liquid that is obtained by dispersing or dissolving a binding agent, and if necessary, other additives to a solvent (for example, purified water, ethanol, or their mixture, and the like). To the granulate obtained, a suitable amount of a lubricating agent, and if necessary, a disintegrating agent, etc., are added and mixed, and then the mixture is filled in a capsule or subjected to compression molding to produce the solid formulation of the present invention.

[0102]

It is also possible to obtain a sugar-coated pellet or a film-coated pellet using a more appropriate coating agent.

Examples of a base material for sugars include sugars or sugar alcohols such as white sugar and erythritol. In addition, one kind or a combination of two or more kinds that are selected from talc, precipitated calcium carbonate, gelatin, gum Arabic, pullulan, carnauba wax, and the like may be used.

As a coating agent, examples thereof include ethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, shellac, talc, carnauba wax and paraffin.

[0103]

Examples of the base material for enteric film coating include cellulose polymers such as hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, and cellulose acetate phthalate; acrylic polymers such as methacrylic acid copolymer L [Eudragit L (trade name), Evonik Degussa Co., Ltd.], methacrylic acid copolymer LD [Eudragit L-30 D55 (trade name), Evonik Degussa Co., Ltd.], methacrylic acid copolymer S [Eudragit S (trade name), and Evonik Degussa Co., Ltd.]; and natural products such as shellac.

Examples of the base material for extended-release film coating include cellulose polymers such as ethyl cellulose; acrylate polymers such as amino alkylmethacrylate copolymer RS [Eudragit RS (trade name), Evonik Degussa Co., Ltd.], ethylacrylate methyl methacrylate copolymer suspension [Eudragit NE (trade name), Evonik Degussa Co., Ltd.]; and cellulose acetate.

[0104]

The base material for coating may be used in combination of two or more types that are mixed at appropriate ratio.

If necessary, a water soluble substance and a plasticizer, etc. may be added to the coating agent for controlling dissolution rate. Examples of the water soluble substance include at least one selected from water soluble polymers such as hydroxypropylmethyl cellulose, sugar alcohols such as mannitol, sugars such as white sugar and anhydrous maltose, and surfactants such as sucrose fatty acid ester, polyoxyethylene polyoxypropylene glycol, polysorbate, and sodium lauryl sulfate. Examples of the plasticizer that can be used include acetylated monoglyceride, trimethyl citrate, triacetin, dibutyl sebacate, dimethyl sebacate, medium chain fatty acid triglyceride, acetyltriethyl citrate, tributyl citrate, acetyltributyl citrate, dibutyl adipate, oleic acid, and oleanolic acid.

[0105]

Further, as a method for coating a tablet with a coating layer, a method commonly used in the field can be used and the examples thereof include pan coating, fluid coating, tumbling coating, and fluid tumbling coating. Further, the coating liquid used for such method is obtained by mixing the base material for coating as described above with the talc and solvent (preferably, ethanol or a mixture of ethanol and water). Further, the concentration of solid matters in the coating liquid is within the range of 5 to 15% by mass with respect to the total mass of the coating liquid.

[0106]

The method comprises a step of administering a pharmaceutically effective amount of a pharmaceutical composition containing the substance used in the disclosed present invention to a subject who is in need of treatment or in the state of having a disorder or a symptom.

The substance used in the present invention has an excellent ALK inhibitory activity and has excellent stability in a body and excellent solubility in water, and therefore, it is useful as a prophylactic or therapeutic agent (in particular, a therapeutic agent) for a proliferative disorder. The compounds of the present invention or their pharmaceutically acceptable salts are useful as a prophylactic or therapeutic agent (in particular, a therapeutic agent) for disorders including leukemia (acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphatic leukemia, and chronic lymphatic leukemia, etc.), malignant lymphoma (Hodgkin's lymphoma and Non-Hodgkin's lymphoma, etc.), and various cancers such as brain tumor, neuroblastoma, neuroglioma, thyroid cancer, myelodysplastic syndrome, head and neck cancer, esophageal cancer, stomach cancer, colon cancer, colorectal cancer, breast cancer, ovarian cancer, lung cancer, pancreas cancer, liver cancer, gallbladder cancer, skin cancer, malignant myeloma, kidney cancer, renal pelvis-ureter cancer, urinary bladder cancer, ovarian cancer, uterine cancer, testicular cancer, and prostate cancer. Further, the compounds of the present invention are useful as a prophylactic or therapeutic agent (in particular, a therapeutic agent) for infiltration and metastasis of solid tumors. Further, the substance used in the present invention is effective as a prophylactic or therapeutic agent for other disorders related to ALK, for example, depression and cognitive function disorder.

[0107]

When the pharmaceutical composition of the present invention is used as an ALK inhibitor, or a prophylactic or therapeutic agent for a proliferative disorder, or depression and cognitive function disorder, the administration method includes oral, rectal, parenteral (intravenous, intramuscular, and subcutaneous), intracisternal, intravaginal, intraperitoneal, intravesical, topical (drops, powder, ointment, gel or cream) administration and inhalation (buccal or nasal spray), etc. Examples of the administration form include a tablet, a capsule, granules, powder, a pill, an aqueous or non-aqueous oral solution and suspension, and a non-oral solution that is filled in a container appropriate for small divided dose. Further, the formulation form can be adapted to various administration methods including a regimen for release control such as subcutaneous implant, etc.

Preferably, it is an oral administration of a tablet, capsule, granules, powder, pill, or the like.

The formulation of the present invention is produced according to a method well known in the art by using additives such as a filler, a lubricating agent (i.e., coating agent), a binding agent, a disintegrating agent, a stabilizing agent, a flavoring agent, a diluent and the like.

When the pharmaceutical composition of the present invention is used as an ALK inhibitor, or a prophylactic or therapeutic agent for a proliferative disorder, or depression and cognitive function disorder, the used amount of the compounds of the present invention or their pharmaceutically acceptable salts varies depending on the symptoms, age, body weight, relative health condition, presence of other medication, and administration method, etc.

[0108]

When the pharmaceutical composition of the present invention is used as an ALK inhibitor, or a prophylactic or therapeutic agent for a proliferative disorder, or depression and cognitive function disorder, the used amount of the compounds of the present invention or their pharmaceutically acceptable salts or solvates thereof varies depending on the symptoms, age, body weight, relative health condition, presence of other medication, and administration method, etc. For a patient (i.e., warm blooded animal, in particular, human), the generally effective amount is, in terms of active ingredient (i.e., the compounds of the present invention that are represented by the Formula (I)), preferably 0.001 to 1000 mg per kg of body weight per day, and more preferably 0.01 to 300 mg per kg of body weight per day for an orally administrable formulation, for example. The daily dosage is preferably in the range of 1 to 800 mg for an adult patient with normal body weight. In case of a parenteral formulation, it is preferably 0.001 to 1000 mg per kg of body weight per day, and more preferably 0.01 to 300 mg per kg of body weight per day. It is preferably administered once or in dose divided several times per day depending on the symptoms.

[0109]

Further, the pharmaceutical composition of the present invention may be combined with other chemotherapeutic agents, hormonal therapeutic agents,

immunotherapeutic agents, molecular targeting agents, or the like.

[0110]

Examples of the "chemotherapeutic agents" include an alkylating agent, a platinum formulation, a metabolic antagonist, a topoisomerase inhibitor, an anticancer antibiotic substance, and an anticancer agent derived from plant, etc. Examples of the "alkylating agent" include nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambucil, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustin hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustin, estramustin sodium phosphate, triethylene melamine, carmustin, lomustin, streptozocin, pipobroman, etoglucid, altretamin, ambamustin, dibrospidium hydrochloride, fotemustin, prednimustin, pumitepa, ribomustin, temozolomid, treosulfan, trophosphamide, zinostatin stimalamer, carboquone, adozelesin, cystemstin, and bizelecin. Examples of the "platinum formulation" include carboplatin, cisplatin, miboplatin, nedaplatin, and oxaliplatin. Examples of the "metabolic antagonist" include mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, enocitabin, cytarabin, cytarabin ocfosfate, ancitabin hydrochloride, 5-FU based pharmaceuticals (for example, fluorouracil, tegafur, UFT, doxifluridin, carmofur, galocitabin, and emitefur, etc.), aminopterin, calcium leucovorin, tabloid, butocin, calcium folinate, calcium levofolinate, cladribin, emitefur, fludarabin, gemcitabin, hydrocycarbamide, pentostatin, piritrexim, idoxuridin, mitoguazon, tiazofurin, and ambamustin. Topoisomerase I inhibitor (for example, irinotecan and topotecan, etc.), topoisomerase II inhibitor (for example, sobuzoxan, etc.). Examples of the "anticancer antiobiotic material" include anthracycline-based anticancer agent (doxorubicin hydrochloride, daunorubicin hydrochloride, acrarubicin hydrochloride, pirarubicin hydrochloride, and epirubicin hydrochloride, etc.), actinomycin D, actinomycin C, mitomycin C, chromomycin A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, neocarzinostatin, mitramycin, sarcomycin, carzinophyllin, mitotam, zorubicin hydrochloride, mitoxantrone hydrochloride, and idarubicin hydrochloride, etc. Examples of the "anticancer agent derived from a plant" include vincalkaloid anticancer agent (vinblatin sulfate, vincristin sulfate, and vindecin sulfate), taxan anticancer agent (paclitaxel and docetaxel, etc), etoposide, etoposide phosphate, teniposide, and

vinorelbin.

[0111]

Examples of the "hormonal therapeutic agents" include adrenocortical hormone-based pharmaceuticals (for example, dexamethasone, prednisolone, betamethasone, and triamcinolone, etc.). Of these, prednisolone is preferable.

[0112]

Examples of the "immunotherapeutic agents (BRM)" include picibanil, krestin, sizofiran, lentinan, ubenimex, interferon, interleukin, macrophage colony stimulating factor, granulocyte colony stimulating factor, lymphotoxin, BCG vaccine, Corynebacterium parvum, levamisole, polysaccharide K, and procodazole.

[0113]

The "molecular targeting agents" include a "pharmaceutical which inhibits the function of a cell proliferation factor and its receptor," or the like. Examples of the "cell proliferation factor" can be any substance if only it can promote proliferation of a cell, and the included are a peptide having molecular weight of 20,000 or less which exhibits its activity at low concentration via binding to a receptor. Specific examples thereof include (1) EGF (epidermal growth factor) or a substance which has substantially the same activity [e.g., EGF, heregulin (HER2 ligand) etc.], (2) insulin or a substance which has substantially the same activity [e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2, etc.], (3) FGF (fibroblast growth factor) or a substance which has substantially the same activity [e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10 etc.], (4) VEGF (vascular endothelial growth factor), (5) other cell proliferation factors [e.g., CSF (colony stimulating factor), EPO (erythropoietin), IL-2 (interleukin-2), NGF (nerve growth factor), PDGF(platelet-derived growth factor), TGFβ (transforming growth factor β), HGF (hepatocyte growth factor), etc.], etc.

[0114]

The "receptor for cell proliferation factor" can be any receptor if only it has an ability of binding to the cell proliferation factor described above. Specific examples thereof include EGF receptor, heregulin receptor (HER2), insulin receptor, IGF receptor, FGF receptor-1 or FGF receptor-2, HGF receptor (c-met), VEGF receptor, and SCF receptor (c-kit). Examples of the "pharmaceuticals which inhibit the activity of cell

proliferation factor" include herceptin (HER2 antibody), GLEEVEC (c-kit, abl inhibitor), and Iressa (EGF receptor inhibitor).

Further, a pharmaceutical which inhibits the activity of a plurality of cell proliferation factors even as a single formulation, or a pharmaceutical which blocks cellular signal produced by cell proliferation factor are also included.

In addition to the pharmaceuticals described above, L-asparaginase, aceglaton, procarbazine hydrochloride, protoporphyrin ・ cobalt complex, mercury hematoporphyrin ・ sodium, differentiation-promoting agent (e.g., retinoid, vitamin D, etc.), angiogenesis inhibitor, and α-blocker (e.g., tamsulosin hydrochloride, etc.), etc. can be also used.

Among the above, preferred examples of a concomitant medicine include a platinum complex (e.g., carboplatin, cisplatin, and oxaliplatin, etc.), taxan-based pharmaceuticals (e.g., paclitaxel and docetaxel), topoisomerase I inhibitor (e.g., irinotecan and topotecan, etc.), vinorelbin, gemcitabin, an anticancer antibiotic material (e.g., mitomycin C), and a molecular targeting agent (e.g., VEGF inhibitor), etc. Further, they can be used in combination of the combination therapy for said pharmaceuticals. For examples, coadministration with combination therapy such as cisplatin and vinblastin and mitonycin C, cisplatin and vinorelbin, cisplatin and paclitaxel, cisplatin and gemcitabin, and carboplatin and paclitaxel, etc. can be mentioned.

[0115]

The time in which the solid formulation of the present invention and a pharmaceutical for coadministration is not limited. They can be administered to a subject either simultaneously or with time interval. Further, the solid formulation of the present invention and a pharmaceutical for coadministration can be administered to a subject in the form of single formulation comprising both of them. For example, there is multi-drug combination therapy by which a plurality of pharmaceuticals are instilled over a period of 3 to 6 months, and a method of taking an oral formulation over two years approximately.

[0116]

Further, in order to prevent recurrence caused by metastasis by inhibiting

already-propagating cancer cells, or to limit an area for operation, a pre-operative adjuvant therapy such as “chemical therapy” may be carried out before performing operation.

[0117]

Further, when topical treatment such as operation or radiation is not sufficient, in order to prevent recurrence caused by metastasis by inhibiting the growth of remaining cancer cells, a post-operative adjuvant therapy such as “chemical therapy” may be carried out.

[0118]

Meanwhile, the anticancer agent used in combination also exhibits its activity on normal cells as well as cancer cells, therefore showing a side effect. Representative examples of the side effect include nausea, vomiting, lack of appetite, stomatitis, diarrhea or constipation, and dysgeusia due to mucosal disease in digestive organ, and reduction in leucocyte · erythrocyte · blood platelet, acomia and reduced immunity due to bone marrow disorder. Thus, a pharmaceutical for reducing a side effect like them can be also used in combination. Examples thereof include an antiemetic pharmaceutical agent which can effectively inhibit nausea (e.g., granisetron hydrochloride salt) or a pharmaceutical agent for promoting recovery from a bone marrow disorder (e.g., erythropoietin, G-CSF and GM-CSF).

[0119]

Dosage of the pharmaceutical for coadministration can be appropriately selected with reference to the dosage that is clinically used. Further, the mixing ratio between the solid formulation of the present invention and the pharmaceutical for coadministration can be appropriately selected depending on the subject for administration, administration route, disease to be treated, symptoms, and combination, etc. When the subject for administration is a human, the pharmaceutical for coadministration can be used in an amount of 0.01 to 100 parts by weight with respect to 1 part by weight of the solid formulation.

[Example]

[0120]

Herein below, the present invention will be explained in greater detail in view

of the following examples and test examples. However, the present invention is not limited by these.

NMR analysis

NMR analysis was carried out by using JNM-EX270 (270 MHz, manufactured by JEOL), JNM-GSX400 (400 MHz, manufactured by JEOL), or 400 MR (400 MHz, manufactured by Varian). NMR data was expressed in ppm (parts per million; δ), while it was compared with the deuterium lock signal obtained from a sample solvent.

Mass spectrometry

The measurement was carried out by using JMS-DX303 or JMS-SX/SX102A (both manufactured by JEOL).

Mass spectrometry Data equipped with high performance liquid chromatography (LC-MS)

Measurement was carried out by using Micromass (ZMD, manufactured by Micromass) equipped with 996-600E gradient high performance liquid chromatography (manufactured by Waters) or Micromass (ZQ, manufactured by Micromass) equipped with Waters 2525 (manufactured by Waters) gradient high performance liquid chromatography.

One of the following conditions that are described in the Table 1 below was taken as a condition for high performance liquid chromatography.

Table 1

Analysis condition	Apparatus	Column used	Column temperature	Mobile phase, gradient	Rate (mL/min)	Detection wavelength
S	ZQ	Sunfire C18 (Waters) 4.5mmI.D. x50mm, 5um	Room Temp.	TFA, MeCN (A/B): 90/10 ⇒ 5/95(3.1min) ⇒ 90/10(1min) ⇒ 90/10(0.5min)	4.0	200-400nm PDA total
U	ZQ	WAKOsil 3C18 AR, (WAKO) 4.6mmI.D x 30mm	Room Temp.	A) 0.05% TFA, H2O B) 0.05% TFA, MeCN (A/B): 90/10 ⇒ 90/10(0.2min) ⇒ 5/95(3.1min) ⇒ 5/95(1.4min)	2.0	210-400nm PDA total
W	ZMD	Sunfire C18 (Waters) 4.5mmI.D. x50mm, 5um	Room Temp.	A) 0.05% TFA, H2O B) 0.05% TFA, MeCN (A/B): 90/10 ⇒ 5/95(3.1min) ⇒ 90/10(1min) ⇒ 90/10(0.5min)	4.0	200-400nm PDA total

Commercially available reagents were used without any further purification.

The room temperature indicates the temperature range of about 20 to 25°C. All the non-aqueous reaction was carried out in anhydrous solvent under nitrogen or argon atmosphere. For concentration under reduced pressure or removal of a solvent by distillation, a rotary evaporator was used.

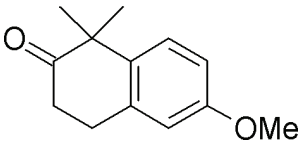
[0121]

Herein below, production examples for the substances that are used in the present invention as represented by the Formula (I) are given.

(Reference example 1)

Compound J2

6-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one



With the same condition as the method for synthesizing the Compound B1 (7-methoxy-3,4-dihydro-1H-naphthalen-2-one (Compound A1, 209 g, 1.18 mol), tetrabutylammonium hydrogen sulfate (40 g, 0.118 mol) and methyl iodide (162 g, 2.60 mol) were suspended in THF (500 ml) at room temperature. Under stirring, the mixture was added with 50% aqueous solution of potassium hydroxide (400 g) over 5 minutes. Reflux occurred as the inner temperature rapidly increases. Once the inner temperature stopped to increase, stirring was continued for 45 minutes. The reaction solution was diluted with distilled water (1 L) and extracted twice with CPME (1.5L). The combined organic layer was washed (distilled water 1 L x 3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting crude product was recrystallized with MeOH (1 L) and distilled water (500 ml) to obtain the Compound B1 (7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one) as a colorless needle-like crystal (177 g, 73%)), and the title compound was synthesized from 6-methoxy-3,4-dihydro-1H-naphthalen-2-one and iodomethane.

LCMS: m/z 205 $[M+H]^+$

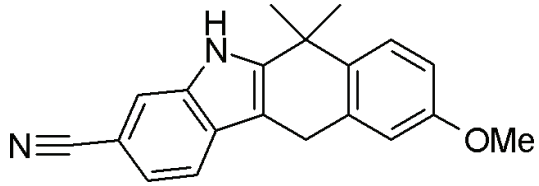
HPLC retention time: 1.54 minutes (analysis condition S)

[0122]

(Reference example 2)

Compound J3-1

9-Methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the synthesis of the Compound E2-1 (6-bromo-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (7.89 g, 27.85 mmol) and 3-hydrazino-benzonitrile (4.45 g, 1.2 eq.) were dissolved in TFA (250 mL) and stirred at 100°C for 2 hours. TFA was removed by concentration under reduced pressure. After that, the residues were added with saturated aqueous solution of $NaHCO_3$ (500 mL), and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. After filtering off the drying agent, the residues obtained after concentration under reduced pressure was added with ethyl acetate, stirred at room temperature, and the precipitated solid was filtered. By concentrating the filtrate under reduced pressure, the Compound E2-1 (9-bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile) (yellowish white powder, 2.65 g) was obtained as a mixture with the Compound E2-2 (9-bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-1-carbonitrile)), the title compound was synthesized from the Compound J2 and 3-hydrazino-benzonitrile.

LCMS: m/z 303 $[M+H]^+$

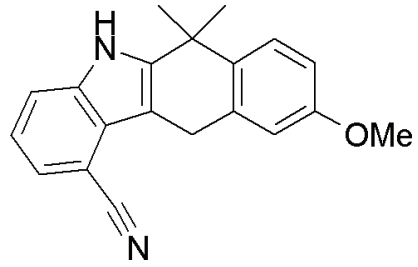
HPLC retention time: 2.73 minutes (analysis condition S)

[0123]

(Reference example 3)

Compound J3-2

9-Methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-1-carbonitrile



The Compound J3-2 was obtained as a byproduct of the Compound J3-1 synthesis.

LCMS: m/z 303 $[M+H]^+$

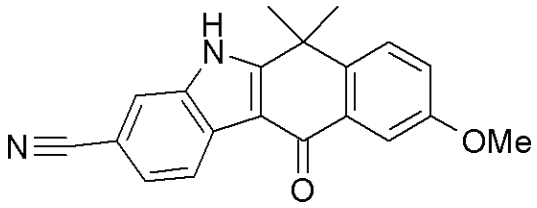
HPLC retention time: 2.67 minutes (analysis condition S)

[0124]

(Production example 1)

Compound J4

9-Methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound A4, the title compound was synthesized from the Compound J3-1 and the Compound J3-2 (mixture).

^{1}H-NMR (DMSO-D_6) δ: 12.79 (1H, s), 8.33 (1H, d, J = 8.2 Hz), 8.02 (1H, s), 7.81 (1H, d, J = 8.6 Hz), 7.69 (1H, d, J = 3.0 Hz), 7.63 (1H, dd, J = 8.3, 1.4 Hz), 7.28 (1H, dd, J = 8.7, 3.0 Hz), 3.87 (3H, s), 1.74 (6H, s).

LCMS: m/z 317 $[M+H]^+$

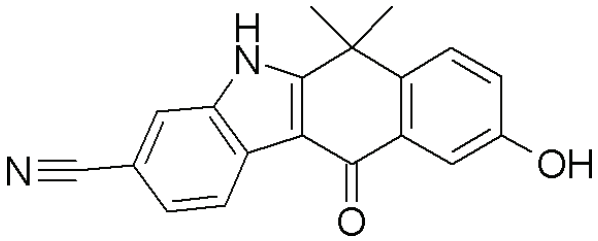
HPLC retention time: 2.25 minutes (analysis condition S)

[0125]

(Production example 2)

Compound J5

9-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound A6, the title compound was synthesized from the Compound J4.

^{1}H-NMR (DMSO-D_6) δ: 12.75 (1H, s), 9.77 (1H, s), 8.32 (1H, dd, J = 8.2, 0.7 Hz), 8.01 (1H, s), 7.68 (1H, d, J = 8.6 Hz), 7.62 (1H, dd, J = 8.2, 1.4 Hz), 7.58 (1H, d, J = 2.8 Hz), 7.10 (1H, dd, J = 8.6, 2.8 Hz), 1.72 (6H, s).

LCMS: m/z 303 $[M+H]^+$

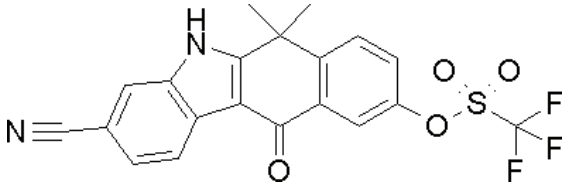
HPLC retention time: 1.75 minutes (analysis condition S)

[0126]

(Production example 3)

Compound J6

Trifluoro-methane sulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl ester



With the same condition as the method for synthesizing the Compound B1, the title compound was synthesized from the Compound J5.

^{1}H-NMR (DMSO-D_6) δ: 12.95 (1H, s), 8.31 (1H, d, J = 8.2 Hz), 8.15 (2H,m), 8.05 (1H, s), 7.87 (1H, dd, J = 9.0, 2.7 Hz), 7.65 (1H, d, J = 8.2 Hz), 1.80 (6H, s).

LCMS: m/z 435 $[M+H]^+$

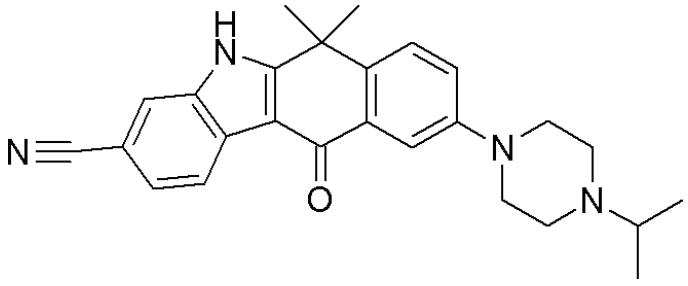
HPLC retention time: 2.75 minutes (analysis condition S)

[0127]

(Production example 4)

Compound J7-4

9-(4-Isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B2-10 (trifluoro-methane sulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound B1, 30 mg, 0.069 mmol) was dissolved in 1,4-dioxane (1 mL), added with thiomorpholine 1,1-dioxide (19 mg, 2 eq.), Pd_2dba_3 (6.3 mg, 0.1 eq.), BINAP (8.6 mg, 0.2 eq.) and K_3PO_4 (29 mg, 2 eq.), and stirred at 100°C all night and all day. The reaction solution was poured into water, and then extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the Compound B2-10 (8-(1,1-dioxothiomorpholino)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile) (white powder, 2.1 mg, 7%)), the title compound was synthesized from the Compound J6 and 1-isopropyl-piperazine.

^{1}H-NMR (270MHz,DMSO-d_6) δ: 12.80 (1H, s), 8.33 (1H, d, J = 7.6 Hz), 8.02 (1H, s), 7.66 (3H, m), 7.33 (1H, d, J = 8.2 Hz), 3.21 (4H, br), 2.66 (5H, m), 1.72 (6H, s), 1.02 (6H, d, J = 6.3 Hz).

LCMS: m/z 413 $[M+H]^+$

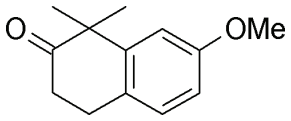
HPLC retention time: 1.38 minutes (analysis condition S)

[0128]

(Reference example 4)

Compound A2

7-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one



7-Methoxy-3,4-dihydro-1H-naphthalen-2-one (Compound A1, 209 g, 1.18 mol), tetrabutylammonium hydrogen sulfate (40 g, 0.118 mol) and methyl iodide (162 g, 2.60 mol) were suspended in THF (500 ml) at room temperature. Under stirring, the mixture was added with 50% aqueous solution of potassium hydroxide (400 g) over 5 minutes. Reflux occurred as the inner temperature rapidly increases. Once the inner temperature stopped to increase, stirring was continued for 45 minutes. The reaction

solution was diluted with distilled water (1 L) and extracted twice with CPME (1.5 L). The combined organic layer was washed (distilled water 1 L x 3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting crude product was recrystallized with MeOH (1 L) and distilled water (500 ml) to obtain the title compound as a colorless needle-like crystal (177 g, 73%).

^{1}H-NMR(400 MHz, $CDCl_3$) δ： 1. 43 (6 H, s), 2. 65 (2 H, t, 12 Hz), 3. 02 (2 H, t, 12 Hz), 3. 79 (3 H, s), 6. 74 (1 H, m), 6. 87 (1 H, m), 7. 24 (1 H, m).

LCMS: m/z 205 $[M+H]^+$

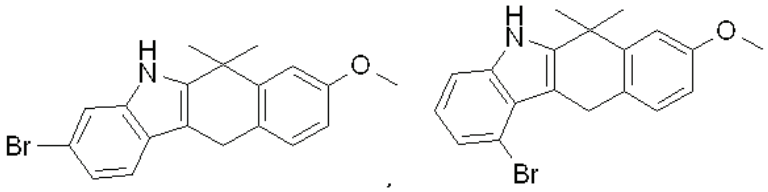
[0129]

(Reference example 5)

Compound A3-1, Compound A3-2

3-Bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole

1-Bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole



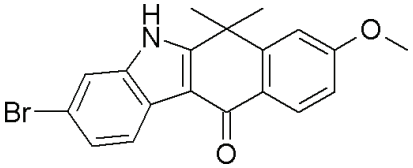
7-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 66.2 g, 324 mmol) and 3-bromophenylhydrazine hydrochloric acid salt (71.0 g, 318 mmol) were dissolved in AcOH (350 ml) and refluxed under stirring for 6 hours. The reaction solvent was removed by distillation under reduced pressure to obtain the crude product as a mixture of the title compound A3-1 and A3-2.

[0130]

(Production example 5)

Compound A4

3-Bromo-8-methoxy-6,6-dimethyl-5,6-dihydrobenzo[b]carbazol-11-one



The crude product obtained from the above (i.e., mixture of A3-1 and A3-2) was dissolved in a mixture solvent of THF (450 ml) and distilled water (50 ml), added

once with DDQ (115 g, 509 mmol), and then stirred at room temperature for 1 hour. The reaction mixture was diluted with CPME (3 L), and the organic layer was washed three times with 0.5 N aqueous solution of sodium hydroxide (1 L) and twice with distilled water (1 L) in order and dried over anhydrous sodium sulfate. The organic layer was concentrated to 500 ml under reduced pressure. The precipitated product was collected by filtration and washed with a small amount of CPME to obtain the title compound as a yellow crystal (48 g, 40%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ： 1. 73 (6 H, s), 3. 90 (3 H, s), 7. 06-7. 09 (1 H, m), 7. 32-7. 38 (2 H, m), 7. 65-7. 66 (1 H, m), 8. 09-8.17 (2 H, m), 12. 32 (1 H, br. s).

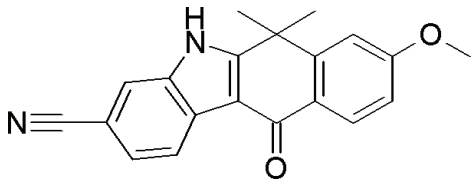
LCMS: m/z 370, 372 $[M+H]^+$

[0131]

(Production example 6)

Compound A5-2

8-Methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



3-Bromo-8-methoxy-6,6-dimethyl-5,6-dihydrobenzo[b]carbazol-11-one (Compound A4, 10.45 g, 28.2 mmol) and copper cyanide (5.0 g, 50.2 mmol) were dissolved in NMP (100 ml) and stirred at 170°C for 17 hours. The reaction mixture was suspended in ethyl acetate (500 ml) and distilled water (200 ml). The insoluble matters were filtered off using Celite, and washed with ethyl acetate (300 ml x 2). The organic layer was washed once with aqueous solution of disodium EDTA (200 ml) and twice with saturated brine (200 ml) in order, and then dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure, and the resultant was suspended and washed with a small amount of CPME to give the title compound as a colorless crystal (6.58 g, 73%).

^{1}H-NMR(400MHz, DMSO-d_6) δ: 1.71 (6 H, s), 3.89 (3H, s), 7.07-7.09 (1H, m), 7.34 (1H, s), 7.58-7.60 (1H, m), 7.99 (1H, s), 8.14-8.16 (1H, m),8.30-8.32 (1H, m), 12.32 (1H, br.s),

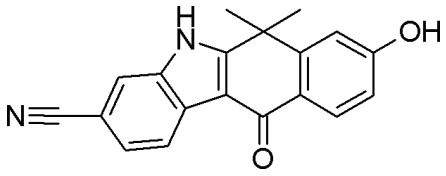
LCMS: m/z 317 $[M+H]^+$

HPLC retention time: 2.56 minutes (analysis condition U)

(Production example 7)

Compound A6

8-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



8-Methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A5-2, 6.58 g, 20.8 mmol) was dissolved in pyridine hydrochloric acid salt (25.0 g), and stirred at 170°C for 13 hours. The reaction mixture was partitioned in ethyl acetate (400 mL) and distilled water (400 mL), and the aqueous layer was extracted one more time with ethyl acetate (400 mL). The combined organic layer was washed twice with distilled water (100 mL) and once with saturated brine (100 mL) in order, and dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure to yield a product, which was suspended and washed with a small amount of CPME to obtain the title compound as a colorless crystal (5.91 g, 93%).

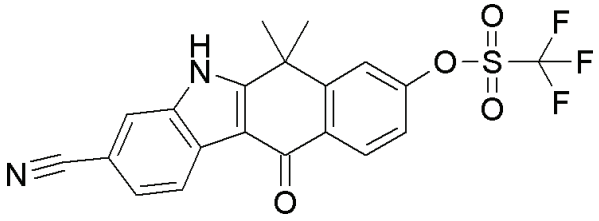
^{1}H-NMR(400MHz, DMSO-d_6) δ: 1.73 (6 H, s), 6.87-6.90 (1H, m), 7.11 (1H, s), 7.57-7.59 (1H, m), 7.97 (1H, s), 8.04-8.06 (1H, m),8.29-8.31 (1H, m), 10.27 (1H, s), 12.66 (1H, br.s),

LCMS: m/z 303 $[M+H]^+$

(Production example 8)

Compound B1

Trifluoro-methane sulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester



8-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A6, 550 mg, 0.189 mmol) was dissolved in pyridine (18 mL), added with anhydrous trifluoromethane sulfonic acid (0.758 ml, 3 eq.), and stirred at room temperature for 30 minutes. The reaction solution was poured into water and then extracted with dichloromethane. The organic layer was dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the target compound (white powder, 641 mg, 81%).

^{1}H-NMR(400MHz,DMSO-d_6) δ: 12.89 (1H, br. s), 8.36 (1H, d, J = 8.8 Hz), 8.31 (1H, dd, J = 8.1, 0.7 Hz), 8.11 (1H, d, J = 2.3 Hz), 8.04 (1H, dd, J = 1.5, 0.7 Hz), 7.65-7.60 (2H,m). 1.76 (6H,s)

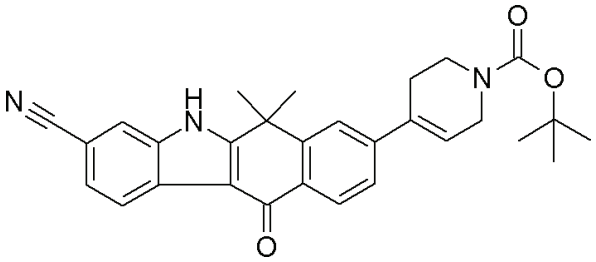
LCMS: m/z 435 $[M+H]^+$

HPLC retention time: 3. 10 minutes (analysis condition U)

(Production example 9)

Compound B2-22-1

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester



To trifluoro-methane sulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound B1, 7.80 g, 18.0 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (6.11 g, 19.8 mmol, 1.1 eq.), $Pd(PPh_3)_2Cl_2$ (630 mg, 0.898 mmol, 0.05 eq.), and sodium carbonate (5.71 g, 53.9 mmol, 3.0 eq.), DME (125 ml) and water (25 ml) were added. The mixture was subjected to reduced pressure under ultrasonication treatment, followed by filling with nitrogen. This procedure was repeated five times to remove air. After further stirring at 80°C for 2 hours under nitrogen atmosphere, the

mixture was cooled to room temperature, added with water (250 ml), and further stirred for 30 minutes. The precipitates were filtered and washed with water (50 ml). They were further washed with CH_3CN (50 ml) to obtain the target compound as a crude product (gray powder, 7.54 g, 90%).

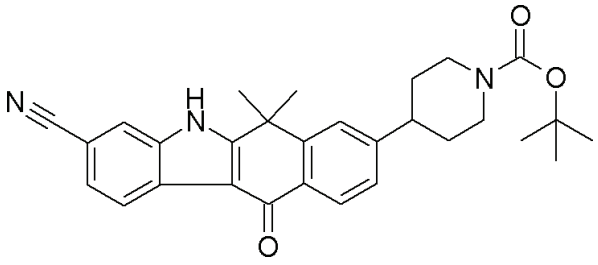
LCMS:m/z 468 $[M+H]^+$

HPLC retention time: 2.90 minutes (analysis condition S)

(Production example 10)

Compound B3-13-1

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperidin-1-carboxylic acid tert-butyl ester



4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (Compound B2-22-1, 16.2 g, 34.6 mmol) was dissolved in THF (800 ml) and methanol (230 ml), added with 10 wt% Pd/C (3.2 g), and stirred under hydrogen atmosphere for 19 hours. The solid was filtered through Celite, eluted with a mixture solvent (400 ml; THF/methanol = 4/1), and concentrated under reduced pressure. The residues were dissolved in ethyl acetate (400 ml), and then washed with 1% aqueous solution of N-acetylcysteine, saturated aqueous solution of $NaHCO_3$ and saturated brine. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues were concentrated under reduced pressure to obtain the title compound as a crude product (white powder, 14.0 g, 86%).

LCMS:m/z 470 $[M+H]^+$

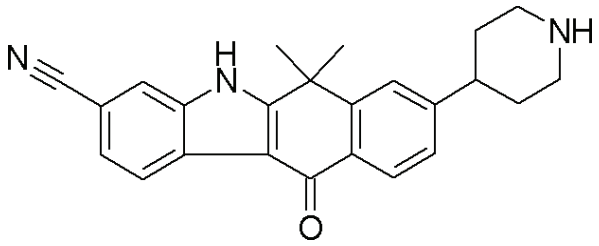
HPLC retention time: 2.88 minutes (analysis condition S)

(Production example 11)

Compound B3-13-2

6,6-Dimethyl-11-oxo-8-piperidin-4-yl-6,11-dihydro-5H-benzo[b]carbazole-3-

carbonitrile



With the same condition as the method for synthesizing the Compound A8-1 (THF (0.5 mL) and TFA (0.5 mL) were added to 4-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (Compound A7-1, 35 mg, 0.072 mmol), and the mixture was stirred at room temperature until Compound A7-1 disappears. The reaction solution was concentrated under reduced pressure and the residue was desalinated by using anionic exchange resin PL StratoSpheres (trademark) PL-HCO3 MP to obtain the Compound A8-1 (37 mg, 76%)), the title compound was synthesized from the Compound B3-13-1.

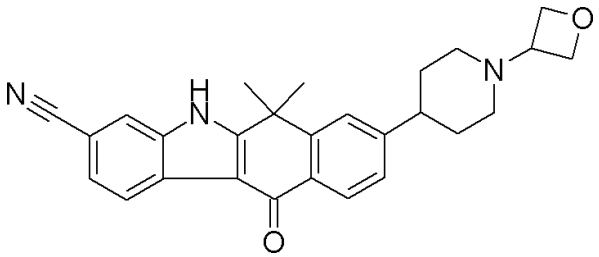
LCMS: m/z 370 $[M+H]^+$

HPLC retention time: 1.30 minutes (analysis condition S)

(Production example 12)

Compound B4-8

6,6-Dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B3-32 (morpholine (6 μl, 1.5 eq.) and sodium triacetoxy borohydride (81 mg, 2.0 eq.) were added to THF (1 ml) solution of the Compound B2-29: 8-formyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (30 mg, 0.095 mmol), and stirred at room temperature for 1 hour. The reaction solution was filtered to remove insoluble matters. The residues obtained after concentration under reduced pressure were

purified by high performance liquid chromatography to obtain the Compound B3-32 (6,6-dimethyl-8-morpholin-4-yl methyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile) (19 mg, 50%)), the title compound was synthesized from the Compound B3-13-2 and oxetan-3-one.

^{1}H-NMR(400 MHz, DMSO-d_6) δ: 12.74 (1H, s), 8.32 (1H, d, 7.9Hz), 8.13 (1H, d, 7.9Hz), 8.00 (1H, s), 7.74 (1H, s), 7.61 (1H, d, 9.8Hz), 7.40 (1H, d, 7.9Hz), 4.56 (2H, t, 6.7Hz), 4.46 (2H, t, 6.1Hz), 3.46-3.39 (1H, m), 2.85-2.82 (2H, m), 2.71-2.64 (1H, m), 1.92-1.86 (2H, m), 1.82-1.79 (4H, m), 1.77 (6H, s)

LCMS: m/z 426 $[M+H]^+$

HPLC retention time: 1.53 minutes (analysis condition S)

Compound B4-8 sulfate salt

6,6-Dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was dissolved at 80°C in a mixture of 5 v/w of DMA and 1.4 v/w of 2 N sulfuric acid. After cooling to room temperature, 15 v/w of acetone were added dropwise, and the precipitated solids were filtered and dried to obtain sulfuric acid salt of 6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

^{1}H-NMR(400 MHz, DMSO-d_6) δ: 12.81 (1H, s), 10.26 (1H,br.s),8.33 (1H, d, 8.3Hz), 8.21 (1H, d, 8.3Hz), 8.04 (1H, s), 7.75 (1H, s), 7.63 (1H, d, 8.3Hz), 7.41 (1H, d, 8.3Hz), 4.85-4.70 (4H, m), 4.50-4.40 (1H, br.s), 3.60-3.00(6H, br.m), 2.20-2.10 (2H, m), 2.05-1.90 (2H, m), 1.79 (6H, s)

LCMS: m/z 426 $[M+H]^+$

B4-8 hydrochloride salt

B4-8 was dissolved in 5 v/w of dimethyl sulfoxide and 0.41 v/w of aqueous hydrochloric acid solution (6 N), and then the dissolved solution was subjected to freeze-drying. To the freeze-dried product, a mixture of 3.7 v/w of water and 1.3 v/w of acetonitrile was added. After stirring at room temperature all night and all day, the precipitated crystals were filtered and dried to give the B4-8 monohydrochloride salt.

B4-8 mesylate salt

B4-8 was dissolved in 4 v/w of dimethyl sulfoxide and 1.2 v/w of aqueous solution of mesylic acid (2 N), and then the dissolved solution was subjected to freeze-drying. To the freeze-dried product, 0.1 v/w of water and 5 v/w of ethyl acetate were added. After stirring at room temperature all night and all day, the precipitated crystals were filtered and dried to give the B4-8 monomesylate salt.

B4-8 L-tartrate salt

B4-8 and L-tartaric acid, which is added in an amount of 0.81 times the weight of B4-8, were dissolved in 10 v/w of tetrahydrofuran and 2 v/w of water at 80°C. The dissolved solution was added with 30 v/w of ethanol. The mixture was stirred at room temperature all night and all day, and the precipitated crystals were filtered and dried to give the B4-8 hemi-L-tartrate salt. The B4-8 hemi-L-tartrate salt obtained was pulverized by using a jet mill.

B4-8 phosphate salt

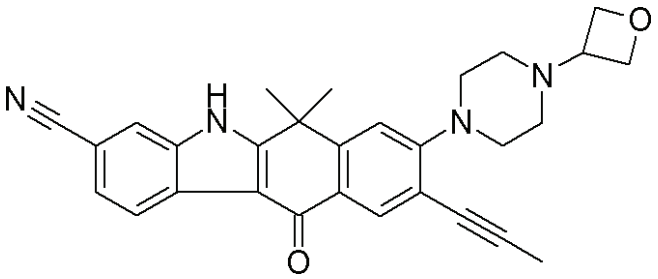
B4-8 was dissolved in 14 v/w of N,N-dimethylacetamide and 5.9 v/w of aqueous solution of phosphoric acid (2 N) under reflux with heating. The dissolved solution was added with 43 v/w of ethanol. The mixture was stirred at room temperature all night and all day, and the precipitated crystals were filtered and dried to give the B4-8 monophosphate salt. The B4-8 monophosphate salt obtained was pulverized by using a jet mill.

[0132]

(Production example 13)

Compound F5-22

6,6-Dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



The Compound E4-2-1 (9-bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E3-1-1, 50 mg, 0.13 mmol), bis (acetonitrile)dichloropalladium (II) (1.64 mg, 0.05 eq.), XPhos (9.05 mg, 0.15 eq.), cesium carbonate (185 mg, 4.5 eq.) and 3-methyl-1-butyn-1-ol (18.6 μl, 1.5 eq.) were dissolved in acetonitrile and stirred at 85°C for 2 hours. The reaction solution was poured into water, and then extracted with ethyl acetate. The organic layer was washed with aqueous solution of sodium chloride and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by HPLC, and under the same condition as the method for synthesizing the Compound E4-2-1 (9-(3-hydroxy-3-methyl-but-1-ynyl)-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile) (brown solid, 21.3 mg, 42%)), the title compound was synthesized from the Compound F4-3 and propyne.

^{1}H-NMR(400 MHz, CD_3OD) δ: 8.37 (1H, d, J = 8.2 Hz), 8.18 (1H, s), 7.84 (1H, s), 7.53 (1H, d, J = 8.2 Hz), 7.19 (1H, s), 4.70-4.77 (2H, m), 4.62-4.68 (2H, m), 3.57-3.63 (1H, m), 3.38-3.45 (4H, m), 2.54-2.61 (4H, m), 2.10 (3H, s), 1.79 (6H, s)

LCMS: m/z 465 $[M+H]^+$

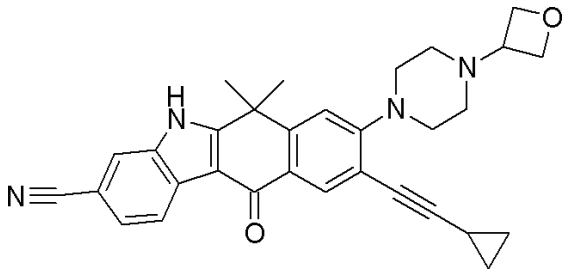
HPLC retention time: 1.90 minutes (analysis condition U)

[0133]

(Production example 14)

Compound F5-25

9-Cyclopropylethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound E4-2-1, the title compound was synthesized from the Compound F4-3 and ethynylcyclopropane.

^{1}H-NMR(270 MHz, DMSO-d_6) δ: 12.74 (1 H, br.s), 8.32-8.29 (1 H, d, 8.08 Hz), 8.05 (1 H, s), 8.00 (1 H, s), 7.62-7.58 (1 H, m), 7.21 (1 H, s), 4.62-4.57 (2 H, m), 4.51-4.47 (2 H, m), 3.53-3.48 (1 H, m), 3.34 (4 H, m), 2.46 (4 H, m), 1.76 (6 H, s), 1.64-1.58 (1 H, m), 0.97-0.89 (2 H, m), 0.76-0.70 (2 H, m)

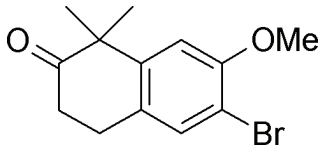
LCMS: m/z 491 $[M+H]^+$

[0134]

(Reference example 6)

Compound E1

6-Bromo-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one



7-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 2.0 g, 9.791 mmol) was dissolved in CH_3CN (40 mL), added with NBS (1.92 g, 1.1 eq.), and the mixture was stirred at room temperature for 2.5 hours. The reaction solution was poured into water (40 mL), and the precipitated solid was filtered to obtain the title compound (white powder, 2.55 g, 92%).

^{1}H-NMR (270MHz,$CDCl_3$) δ: 7.36 (1H, s), 6.84 (1H, s), 3.91 (3H, s), 3.02 (2H, t, J = 6.8 Hz), 2.66 (2H, t, J = 6.8 Hz), 1.42 (6H, s).

LCMS: m/z 283,285 $[M+H]^+$

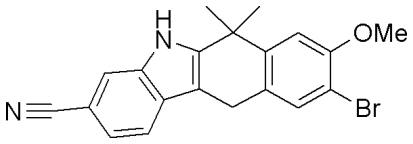
HPLC retention time: 2.67 minutes (analysis condition S)

[0135]

(Reference example 7)

Compound E2-1

9-Bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



6-Bromo-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound E1, 7.89 g, 27.85 mmol) and 3-hydrazino-benzonitrile (4.45 g, 1.2 eq.) were dissolved in TFA (250 mL), and stirred at 100°C for 2 hours. TFA was removed by concentration under reduced pressure and the residues were added with saturated aqueous solution of $NaHCO_3$ (500 mL), followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were added with ethyl acetate. After stirring at room temperature, the precipitated solid was separated by filtration (Compound E2-2). The filtrate was concentrated under reduced pressure to obtain the title compound as a mixture with E2-2 (yellowish white powder, 2.65 g).

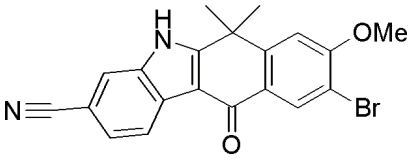
LCMS: m/z 381,383 $[M+H]^+$

HPLC retention time: 3.03 minutes (analysis condition S)

(Production example 15)

Compound E3-1-1

9-Bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound A4, the title compound was synthesized from the Compound E2-1.

^{1}H-NMR (270MHz,DMSO-D_6) δ: 12.82 (1H, s), 8.30 (2H, s+d), 8.03 (1H, s), 7.61 (1H, dd, J = 8.2, 1.4 Hz), 7.49 (1H, s), 4.04 (3H, s), 1.81 (6H, s).

LCMS: m/z 395,397 $[M+H]^+$

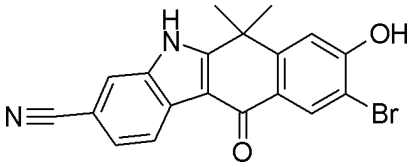
HPLC retention time: 2.77 minutes (analysis condition S)

[0136]

(Production example 16)

Compound E3-2

9-Bromo-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



9-Bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E3-1-1, 1.0 g, 2.53 mmol) was dissolved in NMP (10 mL), added with NaOMe (683 mg, 5 eq.) and 1-dodecanethiol (3.0 mL, 5 eq.), and stirred at 160°C for 1 hour. The reaction solution was poured into 0.5 N aqueous solution of hydrochloric acid, and then extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were added with MeOH, and the solid remaining after dissolution was filtered to obtain the title compound (yellow powder, 1.88 g, 65%).

^{1}H-NMR (400MHz,DMSO-d_6) δ: 12.77 (1H, s), 11.13 (1H, d, J = 2.4 Hz), 8.31 (1H, dd, J = 7.9, 2.4 Hz), 8.25 (1H, d, J = 3.0 Hz), 8.01 (1H, s), 7.61 (1H, d, J = 7.9 Hz), 7.28 (1H, d, J = 2.4 Hz), 1.74 (6H, s).

LCMS: m/z 381,383 $[M+H]^+$

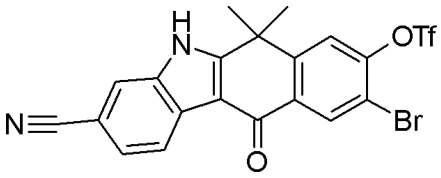
HPLC retention time: 2.40 minutes (analysis condition S)

[0137]

(Production example 17)

Compound F2

Trifluoro-methane sulfonic acid 9-bromo-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester



With the same condition as the method for synthesizing the Compound B1, the

title compound was synthesized from the Compound E3-2.

^{1}H-NMR (270MHz,DMSO-d_6) δ: 12.99 (1H, s), 8.51 (1H, s), 8.31 (1H, dd, J = 8.2, 0.7 Hz), 8.17 (1H, s), 8.07 (1H, s), 7.67 (1 H, dd, J = 8.2, 1.4 Hz), 1.81 (6H, s).

LCMS: m/z 513,515 $[M+H]^+$

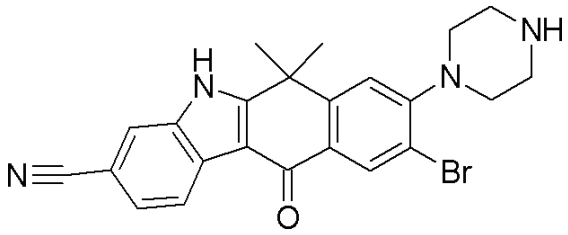
HPLC retention time: 3.13 minutes (analysis condition S)

[0138]

(Production example 18)

Compound F3-9

9-Bromo-6,6-dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B2-1 (trifluoro-methane sulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound B1, 40 mg, 0.0921 mmol) was dissolved in NMP (1 ml) and added with 1-isopropylpiperazine (236 mg, 20 eq.). The mixture was stirred at 120°C for 3 hours. After cooling to room temperature, purification was carried out by HPLC to obtain the Compound B2-1 (8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile) (white powder, 12.8 mg, 34%)), and the title compound was synthesized from the Compound F2 and piperazine.

1H-NMR (DMSO-D_6) δ: 8.30-8.24 (2H, m), 8.00 (1H, s), 7.63-7.58 (1H, m), 7.37 (1H, s), 3.10-3.01 (4H, m), 2.91-2.85 (4H,m), 1.76 (6H, s)

LCMS: m/z 449,451 $[M+H]^+$

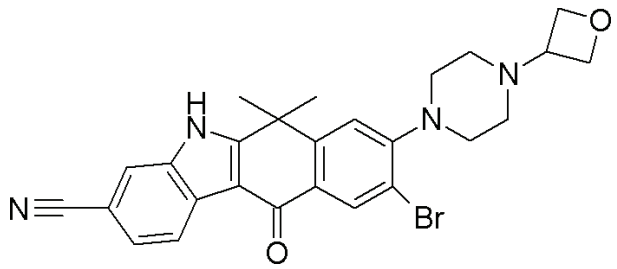
HPLC retention time: 1.45 minutes (analysis condition S)

(Production example 19)

Compound F4-3

9-Bromo-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-

benzo[b]carbazole-3-carbonitrile



With the same condition as the Compound B3-32, the title compound was synthesized from the Compound F3-9 and 1-oxetan-3-one.

^{1}H-NMR (270MHz,DMSO-d_6) δ: 12.83 (1H, br.s), 8.31-8.32 (1H, m), 8.27-8.29 (1H, m), 8.01-8.04 (1H, m), 7.59-7.64 (1H, m), 7.48 (1H, s), 4.59 (2H, dd, J = 6.3, 6.3 Hz), 4.48 (2H, dd, J = 6.3, 6.3 Hz), 3.52 (1H, t, J = 6.3 Hz), 3.12-3.25 (4H, m), 2.44-2.54 (4H, m), 1.78 (6H, s).

LCMS: m/z 505,507 $[M+H]^+$

HPLC retention time: 1.45 minutes (analysis condition S)

Compound F4-3 hydrochloride salt

9-Bromo-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was added with 1.05 eq. of 6 N hydrochloric acid and DMSO and dissolved therein. After freeze-drying, the mixture was crystallized from ethanol containing 25% water to give 9-bromo-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile monohydrochloride salt.

^{1}H-NMR (270MHz,DMSO-d_6) δ: 12.91 (1H,br.s),11.70(1H,br.s),8.32-8.29(2H, m),8.04(1H, s),7.64-7.62(1H, m),7.52(1H,s),4.89-4.62(4H,br.m),3.66-3.39(1H,m),3.31-3.05(8H, br.m),1.81 (6H,s)

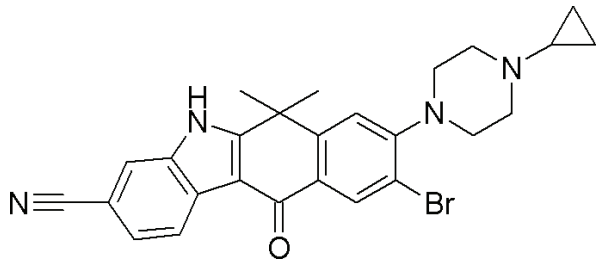
LCMS: m/z 505,507 $[M+H]^+$

[0139]

(Production example 20)

Compound F4-9

9-Bromo-8-(4-cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the Compound B3-32, the title compound was synthesized from the Compound F3-9 and (1-ethoxy-cyclopropoxy)-trimethyl-silane.

^{1}H-NMR (270MHz,DMSO-D_6) δ: 8.22-8.30 (2H, m), 8.00 (1H, s), 7.56 (1H, d, J = 7.9 Hz), 7.43 (1H, s), 3.30(1H, d, J = 5.8 Hz), 3.11 (4H, s), 2.75 (4H, s), 1.75 (6H, s), 0.47 (2H, d, J = 5.8 Hz), 0.34 (2H, d, J = 5.8 Hz)

LCMS: m/z 489,491 $[M+H]^+$

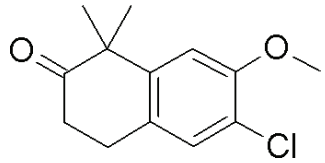
HPLC retention time: 1.68 minutes (analysis condition S)

[0140]

(Reference example 8)

Compound I1-1

6-Chloro-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one



7-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 3.37 g, 16.5 mmol) was dissolved in CH_3CN (82 mL), added with NCS (2.42 g, 1.1 eq.) and stirred at 90°C for 1.5 hours. The reaction solution was extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed and the target compound was obtained after concentration under reduced pressure (yellow oily substance, 4.45 g).

^{1}H-NMR(400 MHz, $CDCl_3$) δ: 7.16 (1H, s), 6.85 (1H, s), 3.90 (3H, s), 3.00 (2H, t, J = 6.8 Hz), 2.65 (2H, t, J = 6.8 Hz), 1.42 (6H, s).

LCMS: m/z 239 $[M+H]^+$

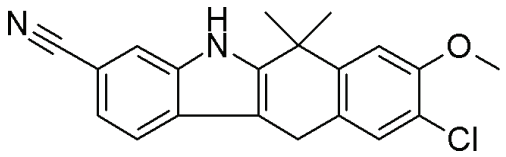
HPLC retention time: 2.80 minutes (analysis condition U)

[0141]

(Reference example 9)

Compound I1-2

9-Chloro-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



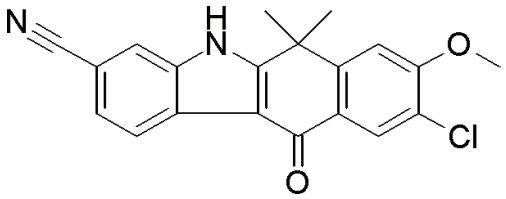
6-Chloro-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound I1-1, 4.45 g, 16.5 mmol) and 3-hydrazinobenzonitrile (2.63 g, 1.2 eq.) were dissolved in TFA (91 mL), and stirred at 90°C for 3 hours. According to the concentration under reduced pressure, TFA was removed and the residues were added with saturated aqueous solution of $NaHCO_3$, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were added with ethyl acetate. After stirring at room temperature, the precipitated solid was separated by filtration. The filtrate was concentrated under reduced pressure to obtain the target compound as a mixture with I1-3 (red powder, 6.46 g).

[0142]

(Production example 21)

Compound I3

9-Chloro-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound A4, the title compound was synthesized from the Compound I1-2.

^{1}H-NMR(400 MHz, DMSO-d_6) δ: 12.79 (1H, s), 8.27-8.31 (1H, m), 8.12 (1H, s), 8.00-8.02 (1H, m), 7.58-7.63 (1H, m), 7.51 (1H, s), 4.03 (3H, s), 1.80 (6H, s).

LCMS: m/z 351 $[M+H]^+$

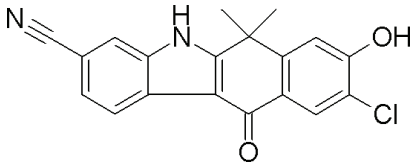
HPLC retention time: 2.87 minutes (analysis condition U)

[0143]

(Production example 22)

Compound I4

9-Chloro-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound E3-2 (9-bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E3-1-1, 1.0 g, 2.53 mmol) was dissolved in NMP (10 mL), added with NaOMe (683 mg, 5 eq.) and 1-dodecanethiol (3.0 mL, 5 eq.), and stirred at 160°C for 1 hour. The reaction solution was poured into 0.5 N aqueous solution of hydrochloric acid, and then extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were added with MeOH, the solid remaining after dissolution was filtered to obtain the Compound E3-2 (9-bromo-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile) (yellow powder, 1.88 g, 65%)), and the title compound was synthesized from the Compound I3.

LCMS: m/z 337 $[M+H]^+$

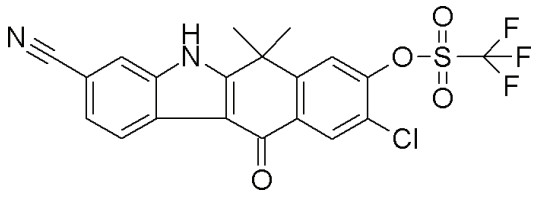
HPLC retention time: 2.47 minutes (analysis condition U)

[0144]

(Production example 23)

Compound I5

Trifluoro-methane sulfonic acid 9-chloro-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester



With the same condition as the method for synthesizing the Compound B1, the title compound was synthesized from the Compound I4.

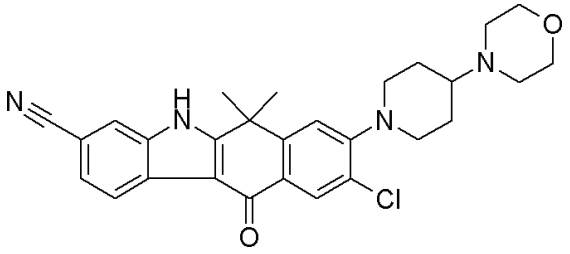
LCMS: m/z 469 $[M+H]^+$

HPLC retention time: 3.40 minutes (analysis condition U)

(Production example 24)

Compound I6-4

9-Chloro-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B2-1, the title compound was synthesized from the Compound I5 and 4-piperidin-4-yl-morpholine.

^{1}H-NMR(400 MHz, DMSO-d_6) δ: 12.75 (1H, s), 8.28 (1H, d, 8.0 Hz), 8.07 (1H, s), 8.00 (1H, s), 7.59 (1H, d, 8.0 Hz), 7.41 (1H, s), 3.55-3.62 (4H, m), 3.47-3.56 (4H, m), 2.75-2.86 (2H, m), 2.45-2.55 (4H, m), 2.28-2.39 (1H, m), 1.86-1.96 (2H, m), 1.76 (6H, s), 1.52-1.66 (2H, m)

LCMS: m/z 489 $[M+H]^+$

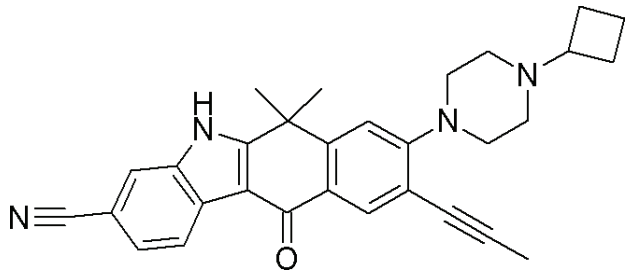
HPLC retention time: 1.97 minutes (analysis condition U)

[0145]

(Production example 25)

Compound F5-44

8-(4-Cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound E4-2-1, the title compound was synthesized from the Compound F4-10 under atmosphere of propyne gas.

^{1}H-NMR(400 MHz, DMSO-d_6) δ: 12.71 (1 H,s), 8.30 (1 H, d, 7.9 Hz), 8.06 (1 H, s),8.00 (1 H, s), 7.59 (1 H, d, 7.9 Hz), 7.20 (1 H, s), 2.75-2.83 (1 H, m), 2.40-2.48 (4 H, m), 2.11 (3 H, s), 1.97-2.06 (2 H, m), 1.76 (6 H, s), 1.62-1.71 (2 H, m)

LCMS: m/z 463 $[M+H]^+$

HPLC retention time: 2.80 minutes (analysis condition W)

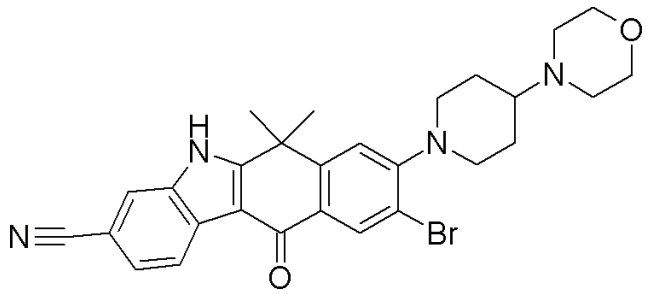
[0146]

[Example 282]

(Production example 26)

Compound F3-11

9-Bromo-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B2-1, the title compound was synthesized from the Compound F2 and 4-piperidin-4-yl morpholine.

1H-NMR(DMSO-D_6) δ: 8.30-8.24 (2H,m), 8.00 (1H, s), 7.59 (1H, d, J=8.2Hz), 7.42 (1H, s), 3.66-3.45 (6H, m), 2.80 (2H, t, J=11.1 Hz), 2.38-2.28 (1H, m), 1.96-1.87 (2H, m), 1.75 (6H, s), 1.66-1.56 (2H, m)

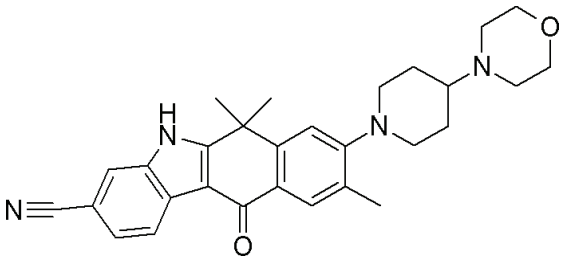
LCMS: m/z 533,535 $[M+H]^+$

HPLC retention time: 1.53 minutes (analysis condition S)

(Production example 27)

Compound F5-51

6,6,9-Trimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound F5-47 (under nitrogen atmosphere, to the N,N-dimethyl formamide (1.5 ml) solution of 9-bromo-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound F4-10, 50 mg, 0.099 mmol), trimethyl boroxine (12 mg, 0.1 eq.), tetrakis triphenylphosphine palladium (39 mg, 0.2 eq.), and potassium carbonate (41 mg, 3.0 eq.) were added, and the mixture was stirred at 100°C for 24 hours. Upon the completion of the reaction, distilled water was poured into the reaction solution, which was then extracted with ethyl acetate. The organic layer was washed with aqueous solution of sodium chloride and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/methanol) to obtain the Compound F5-47 (8-(4-cyclobutyl-piperazin-1-yl)-6,6,9-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile) (25 mg, 58%)), the title compound was synthesized from the Compound F3-11.

^{1}H-NMR(270 MHz, DMSO-d_6) δ: 12.70 (1 H, br.s), 8.33-8.30 (1 H, d, 8.08 Hz), 8.00 (1 H, s), 7.95 (1 H, s), 7.61-7.58 (1 H, m), 7.28 (1 H, s), , 3.60 (4 H, m), 3.32-3.26 (2 H, m), 2.79-2.69 (2 H, m), 2.32 (3 H, s), 1.95-1.90 (2 H, m), 1.74 (6 H, s), 1.65-1.52 (2 H, m),

LCMS: m/z 469 $[M+H]^+$

Compound F5-51 methane sulfonic acid salt

6,6,9-Trimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was added with 1.05 eq. of 2 N methane sulfonic acid and DMSO and dissolved therein. After freeze-drying, the mixture was crystallized from ethanol to give 6,6,9-trimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile methane sulfonic acid salt.

^{1}H-NMR(270 MHz, DMSO-d_6) δ: 12.72(1H,br.s),9.60(1H,br.s),8.33-8.31(1H,d,9.8Hz), 8.01(1H,s),7.99(1H,s),7.61-7.59(1H,m),7.31 (1H,s),4.07-4.04 (2H,m),3.73-3.67(2H,m), 3.55-3.40(8H,m),3.32-3.26(1H,m),2.70-2.60(2H,m),2.34(3H,s),2.30(3H,s),1.95-1.90 (2 H,m),1.75(6H,s)

LCMS: m/z 469 $[M+H]^+$

F5-51 hydrochloride salt

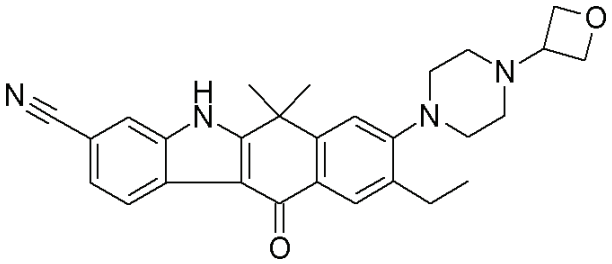
F5-51 was dissolved in 5 v/w of dimethyl sulfoxide and 0.37 v/w of aqueous solution of hydrochloric acid (6 N), and then the dissolved solution was subjected to freeze-drying. To the freeze-dried product, 5 v/w of ethanol was added. The precipitated crystals were filtered and dried to give the F5-51 hydrochloride salt.

[0147]

(Production example 28)

Compound F6-4

9-Ethyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B3-13-1, the title compound was synthesized from the Compound F5-16.

^{1}H-NMR (400MHz,DMSO-d_6) δ: 12.70 (1H, br. s), 8.29 (1H, d, 8.0 Hz), 8.03-7.94 (2H, m), 7.59-7.55 (1H, m), 7.38 (1H, s), 4.59-4.47 (4H, m), 3.53-5.47 (1H, m), 3.03-2.97 (2H, m), 2.73-2.62 (2H, m), 1.74 (6H, s), 1.29-1.98 (3H, m)

LCMS: m/z 455 $[M+H]^+$

HPLC retention time: 1.92 minutes (analysis condition U)

Compound F6-4 hydrochloride salt

9-Ethyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was added with 1.05 eq. of 6 N hydrochloric acid and DMSO and dissolved therein. After freeze-drying, the mixture was crystallized from ethanol containing 25% water to give 9-ethyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile monohydrochloride salt.

^{1}H-NMR (270MHz,DMSO-d_6) δ: 12.83 (1H,br.s),11.59(1H,br.s),8.33-8.31(1H,m), 8.09(1H,s),8.02(1H,s),7.63-7.61(1H,m),7.39(1H,s),4.91-4.60(4H,br.m),3.58-3.40(1H,m), 3.31-3.05(8H, br.m),2.73(2H,q,,J=7.3),1.81(6H,s),1.29(3H,t,J=7.3)

LCMS: m/z 455 $[M+H]^+$

F6-4 mesylate salt

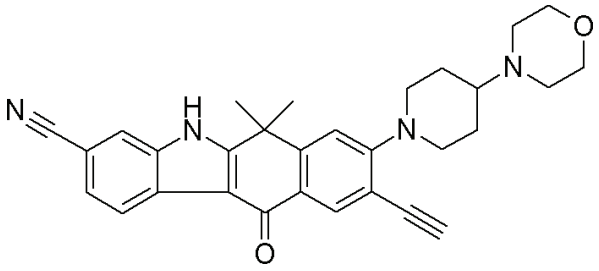
F6-4 was dissolved in 5 v/w of dimethyl sulfoxide and 1.2 v/w of aqueous solution of mesylic acid (2 N), and then the dissolved solution was subjected to freeze-drying. To the freeze-dried product, a mixture of 3.8 v/w of water and 1.3 v/w of ethanol was added. The precipitated crystals were filtered and dried to give the F6-4 mesylate salt.

[0148]

(Production example 29)

Compound F5-49

9-Ethynyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound F5-43, the title compound was synthesized from the Compound F3-11.

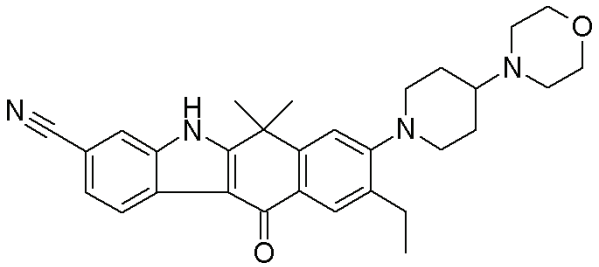
LCMS: m/z 479 $[M+H]^+$

HPLC retention time: 1.90 minutes (analysis condition U)

(Production example 30)

Compound F6-20

9-Ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B3-13-1, the title compound was synthesized from the Compound F5-49.

^{1}H-NMR (400MHz,DMSO-D_6) δ: 12.70 (1H, s), 8.32 (1H, d, J = 7.9 Hz), 8.04 (1H, s), 8.00 (1H, s), 7.61 (1H, d, J = 8.5 Hz), 7.34 (1H, s), 3.64-3.57 (4H, m), 3.27-3.18(2H, m), 2.82-2.66 (4H, m), 2.39-2.28 (1H,m), 1.96-1.87 (2H, m), 1.76 (6H, s), 1.69-1.53 (2H, m), 1.29 (3H, t, J = 7.3 Hz)

LCMS: m/z 483 $[M+H]^+$

HPLC retention time: 1.98 minutes (analysis condition U)

Compound F6-20 hydrochloride salt

9-Ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was dissolved in a mixture of 10 v/w of methyl ethyl ketone, 4 v/w of water, and 3 v/w of acetic acid at 60°C. To the dissolved solution, 1 v/w of hydrochloric acid (2 N) was added dropwise. After stirring at 60°C for 30 minutes, 25 v/w of ethanol was added dropwise. The precipitated solid was filtered and dried to give 9-ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile monohydrochloride salt. 9-Ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-

benzo[b]carbazole-3-carbonitrile monohydrochloride salt obtained was pulverized by using a jet mill.

^{1}H-NMR (400MHz,DMSO-D_6) δ: 12.78(1H,s),10.57(1H,br.s),8.30(1H,J = 8.4 Hz),8.05(1H,s),7.99(1H,s),7.59(1H,d,J = 7.9 Hz),7.36(1H,s),4.02-3.99(2H,m),3.84-3.78(2H,m),3.51-3.48(2H,m),3.15-3.13(1H,s),2.83-2.73(2H,s),2.71-2.67(2H,s),2.23-2.20(2H,m),1.94-1.83(2H,m),1.75(6H,s),1.27(3H,t,J = 7.5 Hz)

FABMS: m/z 483 $[M+H]^+$

F6-20 mesylate salt

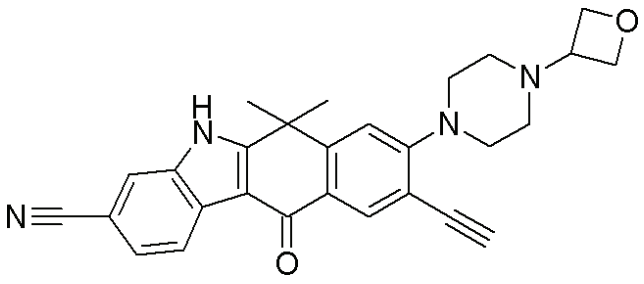
F6-20 was dissolved in 33 v/w of dimethyl acetamide at 90°C. The dissolved solution was added with 1.2 v/w of aqueous solution of mesylic acid (2 N) and 168 v/w of ethyl acetate followed by stirring for 4 hours. The precipitated crystals were filtered and dried to give the F6-20 monomesylate salt. The F6-20 monomesylate salt obtained was pulverized by using a jet mill.

[0149]

(Production example 31)

Compound F5-16

9-Ethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound F5-43, the title compound was synthesized from the Compound F4-3.

^{1}H-NMR (270MHz,DMSO-D_6) δ: 12.77 (1H, br.s), 8.31 (1H, d, J = 8.2 Hz), 8.16 (1H, s), 8.02 (1H, s), 7.61 (1H, dd, J = 8.2, 1.3 Hz), 7.27 (1H, s), 4.59 (2H, dd, J = 6.6, 6.6 Hz), 4.51 (1H, s), 4.49 (2H, dd, J = 6.6, 6.6 Hz), 3.51 (1H, t, J = 6.6 Hz), 3.35-3.43 (4H, m), 2.43-2.50 (4H, s), 1.78 (6H, s).

LCMS: m/z 451 $[M+H]^+$

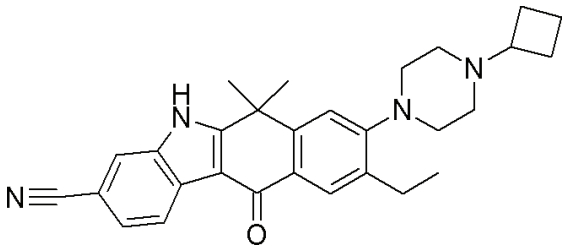
HPLC retention time: 1.40 minutes (analysis condition S)

[0150]

(Production example 32)

Compound F6-17

8-(4-Cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B3-13-1, the title compound was synthesized from the Compound F5-43.

^{1}H-NMR(400 MHz, DMSO-d_6) δ: 12.80 (1 H,s), 8.32 (1 H, d, 7.9 Hz), 8.10 (1 H, s),8.02 (1 H, s), 7.62 (1 H, d, 7.9 Hz), 7.38 (1 H, s), 3.78-3.88 (1 H, m), 3.79-3.89 (1 H, m), 3.48-3.54 (2 H, m), 3.40-3.47 (2 H, m), 3.30-3.39 (2 H, m), 3.02-3.24 (4 H, m), 2.73 (2 H, q, 7.3 Hz), 2.30-2.41 (2 H, m), 2.17-2.26 (2 H, m), 1.71-1.86 (8 H, m), 1.29 (3 H, t, 7.3 Hz)

LCMS: m/z 453 $[M+H]^+$

HPLC retention time: 2.76 minutes (analysis condition W)

Compound F6-17 methane sulfonic acid salt

8-(4-Cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was dissolved at room temperature and added with 6 v/w of DMF and added dropwise with 1.05 eq. of an aqueous solution of methane sulfonic acid (2 M). The resulting solution was added dropwise to 60 v/w of acetonitrile. The precipitated solid was filtered and dried to give 8-(4-cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile monomethane sulfonic acid salt.

^{1}H-NMR (400MHz,DMSO-D_6) δ: 12.75(1H,s),8.31(1H,J = 8.4 Hz),8.07(1H,s),

8.01(1H,s),7.59(1H,d,J = 7.9 Hz),7.38(1H,s),3.58-2.84(10H,m),2.71(2H,q,J = 7.5 Hz),2.34(3H,s),2.20-2.04(4H,m),1.76-1.68(8H,m),1.26(3H,t,J = 7.5 Hz)

FABMS: m/z 453 $[M+H]^+$

F6-17 hydrochloride salt

F6-17 was dissolved in 5 v/w of dimethyl sulfoxide and 0.39 v/w of aqueous solution of hydrochloric acid (6 N), and then the dissolved solution was subjected to freeze-drying. To the freeze-dried product, a mixture of 4.0 v/w of water and 1.3 v/w of ethanol was added. The precipitated crystals were filtered and dried to give the F6-17 hydrochloride salt.

F6-17 maleate salt

A mixture containing F6-17 and maleic acid, which is added in an amount of 0.38 times the weight of F6-17, was dissolved in 10 v/w of dimethyl acetamide at 80°C. The dissolved solution was cooled to room temperature, and added dropwise with a mixture of 5.8 v/w of acetone and 5.8 v/w of water followed by stirring at room temperature. 3.5 v/w of water was further added dropwise, and the precipitated crystals were filtered and dried to give the F6-17 maleate salt.

F6-17 L-tartrate salt

A mixture containing F6-17 and L-tartaric acid, which is added in an amount of 0.51 times the weight of F6-17, was dissolved in 6 v/w of dimethyl acetamide at 80°C. The dissolved solution was cooled to room temperature, and added dropwise with 37 v/w of acetonitrile followed by stirring at room temperature all night and all day. The precipitated crystals were filtered and dried to give the F6-17 tartrate salt. The F6-17 tartrate salt obtained was pulverized by using a jet mill.

F6-17 citrate salt

A mixture containing F6-17 and citric acid, which is added in an amount of 0.50 times the weight of F6-17, was dissolved in 6 v/w of dimethyl acetamide at 80°C. The dissolved solution was cooled to room temperature, and added dropwise with 12 v/w of

acetonitrile. The precipitated crystals were filtered and dried to give the F6-17 citrate salt. The F6-17 citrate salt obtained was pulverized by using a jet mill.

F6-17 malate salt

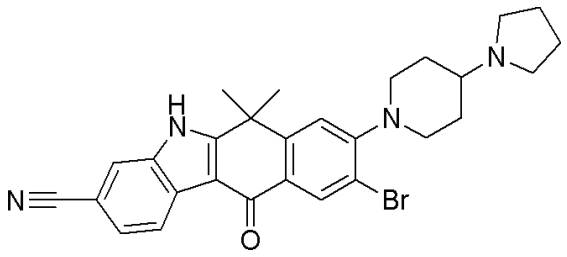
A mixture containing F6-17 and L-malic acid, which is added in an amount of 0.46 times the weight of F6-17, was dissolved in 8 v/w of dimethyl acetamide at 80°C. The dissolved solution was cooled to room temperature, and added dropwise with 62 v/w of acetonitrile. The precipitated crystals were filtered and dried to give the F6-17 malate salt.

[0151]

(Production example 33)

Compound F3-2

9-Bromo-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the Compound B2-1, the title compound was synthesized from the Compound F2 and 4-pyrrolidin-1-yl-piperidine.

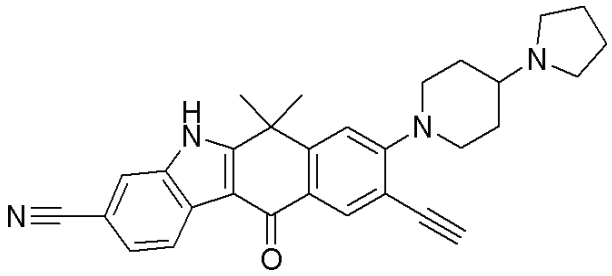
LCMS: m/z 517,519 $[M+H]^+$

HPLC retention time: 1.70 minutes (analysis condition S)

(Production example 34)

Compound F5-4

9-Ethynyl-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound E4-2-1, the Compound E4-2-2 (9-(3-hydroxy-3-methyl-but-1-ynyl)-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E4-2-1, 21.3 mg, 0.05 mmol) and sodium hydride (3.2 mg, 1.5 eq.) were dissolved in THF, and the mixture was stirred overnight at 50°C. Water was added to the reaction solution and the residues obtained after concentration under reduced pressure were purified by HPLC to obtain the Compound E4-2-2 (9-ethynyl-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile) (brown solid, 9.6 mg, 31%)), the title compound was synthesized from the Compound F3-2.

^{1}H-NMR (270MHz,DMSO-D_6) δ: 8.29 (1H, d, J = 8.2 Hz), 8.14 (1H, s), 8.00 (1H, s), 7.58 (1H, dd, J = 8.1, 1.3 Hz), 7.24 (1H, s), 4.50 (1H, s), 3.70-3.83 (2H, m), 3.34-3.48 (1H, m), 2.83-2.98 (2H, m), 2.45-2.58 (2H, m), 2.10-2.23 (2H, m), 1.90-2.03 (2H, m), 1.76 (6H, s), 1.51-1.74 (6H, m).

LCMS: m/z 463 $[M+H]^+$

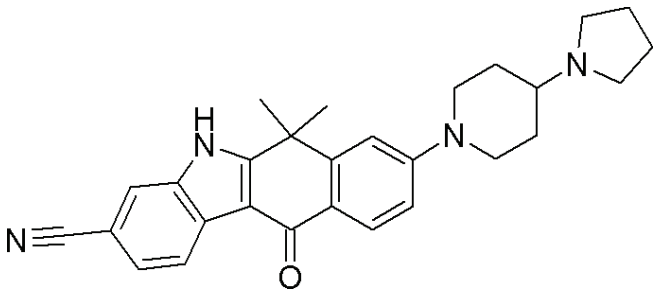
HPLC retention time: 1.60 minutes (analysis condition S)

[0152]

(Production example 35)

Compound B2-4

6,6-Dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B2-1, the title compound was synthesized from the Compound B1 and 4-pyrrolidin-1-yl-piperidine.

^{1}H-NMR(270 MHz, DMSO-d_6) δ: 8.30 (1H, d, 8.1Hz), 8.01 (1H, d, 8.7Hz), 7.97 (1H, s), 7.56 (1H, d, 8.6Hz), 7.20 (1H, s), 3.94-3.90 (2H, m), 3.30-3.28 (4H, m), 2.95 (2H, t, 11.8Hz), 2.24-2.20 (1H, m), 1.95-1.91 (2H, m), 1.75 (6H, s), 1.70-1.66 (4H, m), 1.54-1.52 (2H, m)

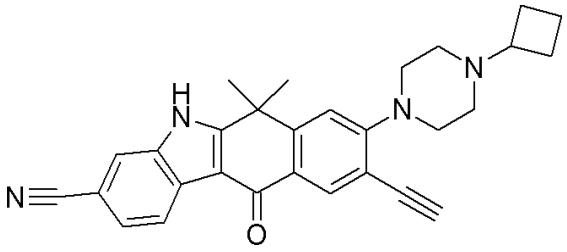
LCMS: m/z 439 $[M+H]^+$

[0153]

(Production example 36)

Compound F5-43

8-(4-Cyclobutyl-piperazin-1-yl)-9-ethynyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



Under nitrogen atmosphere, to the MeCN (8 ml) suspension of 9-bromo-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound F4-10, 200 mg, 0.397 mmol), ethynyltriisopropylsilane (268 mg, 3.0 eq.), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) (39 mg, 0.2 eq.), $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.1 eq.) and cesium carbonate (518 mg, 4.0 eq.) were added and the mixture was stirred and heated under reflux condition until the reaction is completed. Upon the completion of the reaction, distilled water was poured into the reaction solution, which was then extracted with ethyl acetate. The organic layer was washed with aqueous solution of sodium chloride and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/methanol) to obtain 8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-[(triisopropylsilanyl)-ethynyl]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (179

mg, 74%). To the THF (6 ml) solution of the obtained compound (179 mg, 0.295 mmol), 1 M THF solution (710 μl) of tetrabutylammonium fluoride was added and the mixture was stirred until the reaction was completed. Upon the completion of the reaction, ethyl acetate was poured into the reaction solution, which was then washed with distilled water and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were washed with a mixture solvent of ethanol and distilled water to obtain the title compound (67 mg, 92%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ: 12.85 (1 H,s), 8.31 (1 H, d, 7.9 Hz), 8.20 (1 H, s),8.03 (1 H, s), 7.62 (1 H, d, 7.9 Hz), 7.35 (1 H, s), 4.62 (1 H, s), 3.94-4.03 (2 H, m), 3.79-3.89 (1 H, m), 3.48-3.54 (2 H, m), 3.27-3.38 (2 H, m), 2.96-3.16 (2 H, m), 2.30-2.41 (2 H, m), 2.16-2.26 (2 H, m), 1.72-1.85 (8 H, m)

LCMS: m/z 449 $[M+H]^+$

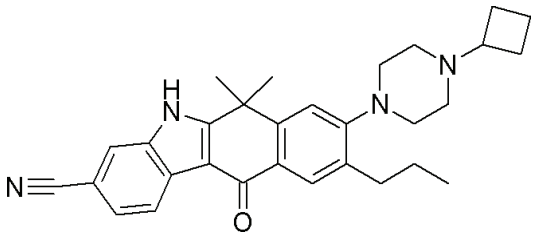
HPLC retention time: 2.69 minutes (analysis condition W)

[0154]

(Production example 37)

Compound F6-18

8-(4-Cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B3-13-1, the title compound was synthesized from the Compound F5-44.

^{1}H-NMR(400 MHz, DMSO-d_6) δ: 12.69 (1 H,s), 8.31 (1 H, d, 7.9 Hz), 8.01 (1 H, s),7.99 (1 H, s), 7.60 (1 H, d, 7.9 Hz), 7.39 (1 H, s), 2.92-3.02 (4 H, m), 2.75-2.84 (1 H, m), 2.65 (2 H, t, 7.3 Hz), 2.38-2.48 (4 H, m), 1.96-2.06 (2 H, m), 1.78-1.87 (2 H, m), 1.75 (6 H, s), 1.62-1.73 (4 H, m), 0.97 (3 H, t, 7.3 Hz)

LCMS: m/z 467 $[M+H]^+$

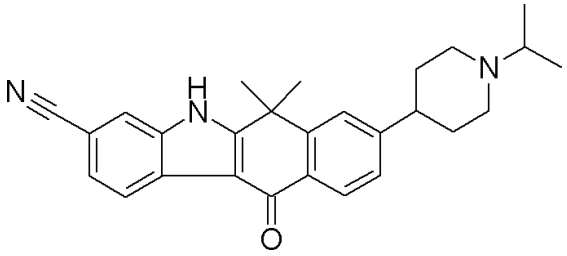
HPLC retention time: 2.96 minutes (analysis condition W)

[0155]

(Production example 38)

Compound B4-7

8-(1-Isopropyl-piperidin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B3-32, the title compound was synthesized from the Compound B3-13-2 and acetone.

^{1}H-NMR(400 MHz, DMSO-d_6) δ: 12.77 (1H, s), 8.32 (1H, d, 7.9Hz), 8.13 (1H, d, 7.9Hz), 8.01 (1H, s), 7.73 (1H, s), 7.61 (1H, d, 9.1Hz), 7.39 (1H, d, 9.8Hz), 2.93 (2H, d, 11.0Hz), 2.77-2.71 (1H, m), 2.67- 2.62 (1H, m), 2.25 (2H, t, 10.1Hz), 1.80-1.73 (10H, m), 1.02 (6H, d, 6.7 Hz)

LCMS: m/z 412 $[M+H]^+$

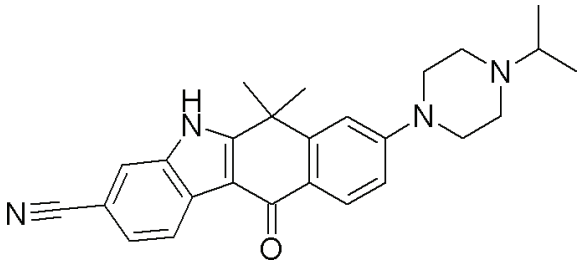
HPLC retention time: 1.60 minutes (analysis condition S)

[0156]

(Production example 39)

Compound B2-1

8-(4-Isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



Trifluoro-methane sulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound B1, 40 mg, 0.0921 mmol) was dissolved in

NMP (1 ml) and added with 1-isopropylpiperazine (236 mg, 20 eq.). The mixture was stirred at 120°C for 3 hours. After cooling to room temperature, purification was carried out by HPLC to obtain the target compound (white powder, 12.8 mg, 34%).

^{1}H-NMR(270 MHz, DMSO-d_6) δ: 8.30 (1H, d, 8.1Hz), 8.03 (1H, d, 8.6Hz), 7.98 (1H, s), 7.56 (1H, d, 8.6Hz), 7.21 (1H, s), 7.04 (1H, d, 9.1Hz), 3.40-3.37 (4H, m), 2.73-2.65 (1H, m), 2.61-2.58 (4H, m), 1.75 (6H, s), 1.02 (6H, d, 6.6Hz)

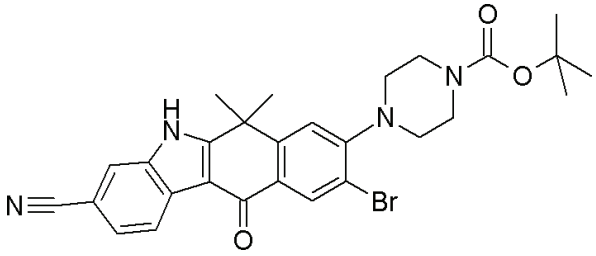
LCMS: m/z 413 $[M+H]^+$

[0157]

(Production example 40)

Compound F3-10

4-(9-Bromo-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperazine-1-carboxylic acid tert-butyl ester



With the same condition as the method for synthesizing the Compound B2-1, the title compound was synthesized from the Compound F2 and piperazine-1-carboxylic acid tert-butyl ester.

LCMS: m/z 549,551 $[M+H]^+$

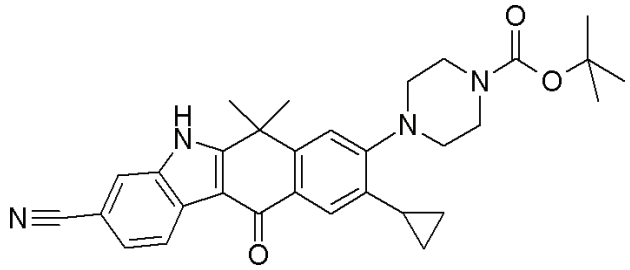
HPLC retention time: 4.61 minutes (analysis condition W)

[0158]

(Production example 41)

Compound F5-15-1

4-(3-Cyano-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperazine-1-carboxylic acid tert-butyl ester



With the same condition as the method for synthesizing the Compound E4-7-1 (to 9-bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E3-1-1, 300 mg, 0.759 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (282 mg, 0.911 mmol, 1.2 eq.), $Pd(PPh_3)_2Cl_2$ (26.6 mg, 0.0379 mmol, 0.05 eq.) and sodium carbonate (241 mg, 2.28 mmol, 3.0 eq.), DME (5 ml) and water (1 ml) were added. The mixture was subjected to reduced pressure under ultrasonication treatment, followed by filling with nitrogen. This procedure was repeated five times to remove air. The mixture was stirred at 80°C for 80 minutes under nitrogen atmosphere. $Pd(PPh_3)_2Cl_2$ (26.6 mg, 0.0379 mmol, 0.05 eq.) was added and the mixture was further stirred at 80°C for 20 minutes. Then, the mixture was cooled to room temperature, and added with water and ethyl acetate. The insoluble matters were filtered through Celite. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration, followed by concentration under reduced pressure to obtain the Compound E4-7-1 (4-(3-cyano-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester) as a crude product (gray powder)), the title compound was synthesized from the Compound F3-10 and potassium cyclopropyltrifluoroborate.

^{1}H-NMR(400 MHz, DMSO-d_6) δ: 8.55(1H,s), 8.28-8.25(1H, m), 7.98-7.95(1H, m), 7.62(1H, s), 7.32(1H, s), 3.56-3.53(4h, m),3.09-3.07(4H, m), 2.22-2.18(1H, m), 1.73(6H, br s), 1.44(9H, s), 1.08-1.05(2H, m), 0.77-0.76(2H,m)

LCMS: m/z 511 $[M+H]^+$

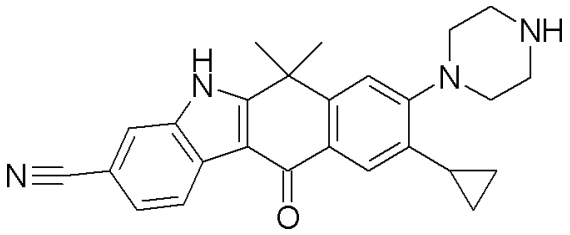
HPLC retention time: 4.50 minutes (analysis condition W)

[0159]

(Production example 42)

Compound F5-15-2

9-Cyclopropyl-6,6-dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound A8-1, the title compound was synthesized from the Compound F5-15-1.

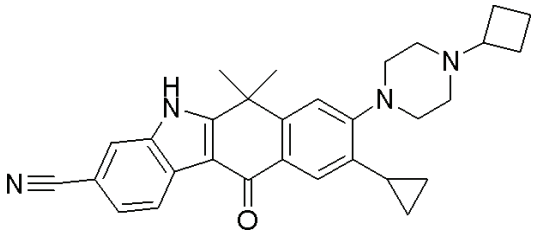
LCMS: m/z 411 $[M+H]^+$

HPLC retention time: 2.67 minutes (analysis condition W)

(Production example 43)

Compound F5-46

8-(4-Cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B3-32, the title compound was synthesized from the Compound F5-15-2 and cyclobutanone.

^{1}H-NMR(400 MHz, DMSO-d_6) δ:8.23(1H, d, 8Hz), 7.92(1H, br.s), 7.59(1H, s), 7.47(1H, br.d, 8Hz), 7.28(1H, s), 3.12(4H, br.s), 2.80(1H, dddd, 8,8,8,8Hz), 2.20-2.13(1H, m), 2.01(2H, br.s), 1.86-1.68(10H, m), 1.05(2H, d, 8Hz), 0.76(2H, d, 4Hz)

LCMS: m/z 465 $[M+H]^+$

HPLC retention time: 2.79 minutes (analysis condition W)

Compound F5-46 hydrochloride salt

8-(4-Cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was added with 1.05 eq. of 6 N

hydrochloric acid and DMSO and dissolved therein. After freeze-drying, the mixture was crystallized from ethanol containing 25% water to give 8-(4-cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile monohydrochloride salt.

^{1}H-NMR(400 MHz, DMSO-d_6)δ:12.81(1H,s),10.64(1H,br.s),8.32-8.29(1H, m),8.01(1H, s),7.67(1H,s),7.61-7.60(1H,m),7.33(1H,s),4.00-3.39(6H,m),3.28-3.02(3H,m),2.45-2.05(5H,m),1.83-1.77(8H,m),1.09-1.07(2H,m),0.81-0.80(2H,m)

LCMS: m/z 465 $[M+H]^+$

F5-46 mesylate salt

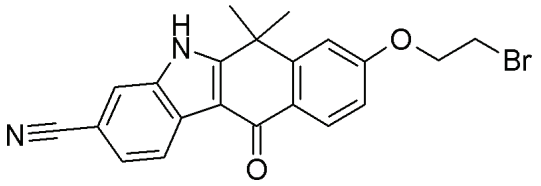
F5-46 was dissolved in 5 v/w of dimethyl sulfoxide and 1.1 v/w of aqueous solution of mesylic acid (2 N), and then the dissolved solution was subjected to freeze-drying. To the freeze-dried product, 5 v/w of benzyl alcohol was added. The precipitated crystals were filtered and dried to give the F5-46 monomesylate salt.

[0160]

(Production example 44)

Compound A7-24

8-(2-Bromo-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the Compound A7-1 (8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A6, 30 mg, 0.099 mmol) was dissolved in THF (1 mL), added with 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (40 mg, 2 eq.), triphenylphosphine (52 mg, 2 eq.), and diisopropyl azo dicarboxlyate (43 μL, 2 eq.) in order, and stirred at room temperature for 4 hours. The reaction solution was poured into water, and then extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under

reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the Compound A7-1 (4-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl oxy)-piperidin-1-carboxylic acid tert-butyl ester) (37 mg, 76%)), the title compound was synthesized from the Compound A6 and 2-bromoethanol.

^{1}H-NMR(270MHz,DMSO-d_6) δ: 12.75 (1H, br.s), 8.32 (1H, d, J = 8.2 Hz), 8.17 (1H, d, J = 8.6 Hz), 8.01 (1H, s), 7.61 (1H, dd, J = 8.2, 1.4 Hz), 7.40 (1H, d, J = 2.2 Hz), 7.12 (1H, dd, J = 8.6, 2.2 Hz), 4.50 (2H, t, J = 5.3 Hz), 3.88 (2H, t, J = 5.3 Hz), 1.77 (6H, s).

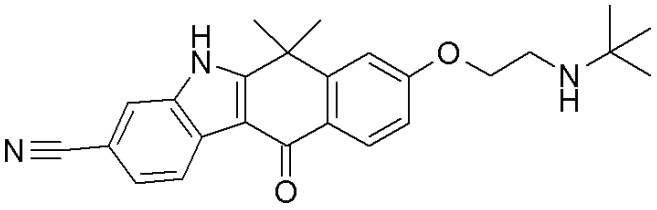
LCMS: m/z 409,411 $[M+H]^+$

HPLC retention time: 2.48 minutes (analysis condition S)

(Production example 45)

Compound A8-10

8-(2-Tert-butylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same synthesis condition as the Compound A7-17 (8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A6, 25 mg, 0.083 mmol) was dissolved in N,N-dimethylacetamide (1 mL), added with 2-chloroethyldiethylamine (16 mg, 1.1 eq.) and cesium carbonate (54 mg, 2 eq.) in order and stirred at 100°C for 4 hours. The reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by amino silica gel column chromatography (ethyl acetate/hexane) to obtain the Compound A7-17 (8-(2-diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile) (11 mg, 32%)), the title compound was synthesized from the Compound A7-24 and tert-butyl amine.

^{1}H-NMR(400MHz, DMSO-d_6) δ: 12.71 (1 H, s), 8.32 (1 H, d, 7.9 Hz), 8.15 (1 H, d, 9.1 Hz),8.07 (1 d, 1.8 Hz), 7.60 (1 H, dd, 1.8, 7.9 Hz), 7.35 (1 H, d, 2.4 Hz),7.09 (1 H, dd, 2.4, 9.1 Hz), 4.16 (2 H, t, 6.1 Hz), 2.91 (2 H, t, 6.1 Hz), 1.77 (6 H, s), 1.08 (9 H, s)

LCMS: m/z 402 $[M+H]^+$

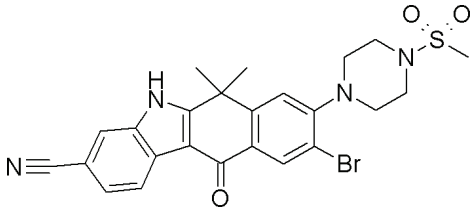
HPLC retention time: 2.55 minutes (analysis condition W)

[0161]

(Production example 46)

Compound F3-3

9-Bromo-8-(4-methanesulfonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B2-1, the title compound was synthesized from the Compound F2 and 1-methanesulfonyl piperazine.

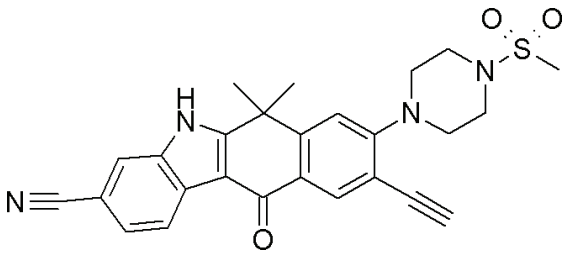
LCMS: m/z 527, 529 $[M+H]^+$

HPLC retention time: 2.48 minutes (analysis condition S)

(Production example 47)

Compound F5-1

9-Ethynyl-8-(4-methanesulfonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound F5-43, the title compound was synthesized from the Compound F3-3.

^{1}H-NMR (270MHz,DMSO-D_6) δ: 12.78 (1H, s), 8.31 (1H, dd, J = 8.1, 0.7 Hz), 8.19

(1H, s), 8.02 (1H, dd, J = 1.4, 0.7 Hz), 7.61 (1H, dd, J = 8.2, 1.4 Hz), 7.33 (1H, s), 4.55 (1H, s), 3.43 (4H, br), 2.98 (3H, s), 1.79 (6H, s).

LCMS: m/z 473 $[M+H]^+$

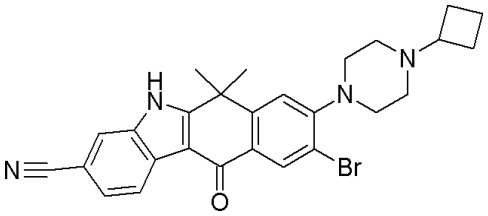
HPLC retention time: 2.27 minutes (analysis condition S)

[0162]

(Production example 48)

Compound F4-10

9-Bromo-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B3-32, the title compound was synthesized from the Compound F3-9 and cyclobutanone.

^{1}H-NMR(400 MHz, DMSO-d_6) δ: 8.23-8.29 (2 H, m), 8.00 (1 H, s),7.55 (1 H, d, 7.9 Hz), 7.45 (1 H, s), 4.04-4.15 (1 H, m), 3.10-3.20 (4 H, m), 2.39-2.48 (4 H, m), 1.97-2.06 (2 H, m), 1.78-1.88 (2 H, m), 1.77 (6 H, s), 1.61-1.72 (2 H, m)LCMS: m/z 503, 505 $[M+H]^+$

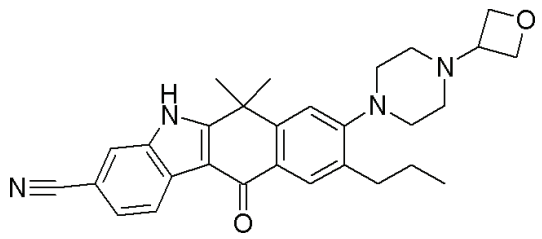
HPLC retention time: 2.78 minutes (analysis condition W)

[0163]

(Production example 49)

Compound F6-8

6,6-Dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B3-13-1,

the title compound was synthesized from the Compound F5-22.

^{1}H-NMR (270mHz DMSO-D_6) δ: 12.75 (1H, s), 8.30 (1H, d, J = 8.2 Hz), 8.01-7.97 (2H, m), 7.59 (1H, d, J = 7.1 Hz), 7.38 (1H, s), 4.51 (4H, dt, J = 27.7, 6.3 Hz), 3.55-3.49 (1H, m), 3.02-2.96 (4H, m), 2.63 (2H, t, J = 7.3 Hz), 2.47-2.41 (4H, m), 1.73 (6H, s), 1.70-1.61 (2H, m), 0.94 (3H, t, J = 7.4 Hz).

LCMS: m/z 469 $[M+H]^+$

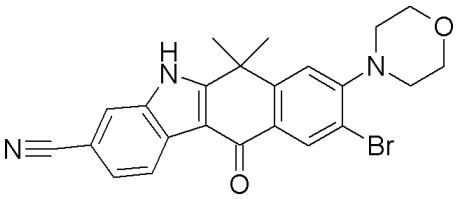
HPLC retention time: 1.57 minutes (analysis condition S)

[0164]

(Production example 50)

Compound F3-4

9-Bromo-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound B2-1, the title compound was synthesized from the Compound F2 and morpholine.

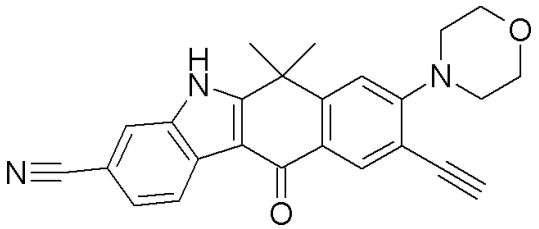
LCMS: m/z 450, 452 $[M+H]^+$

HPLC retention time: 2.65 minutes (analysis condition S)

(Production example 51)

Compound F5-5

9-Ethynyl-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile



With the same condition as the method for synthesizing the Compound E4-2-1 and the Compound E4-2-2, the title compound was synthesized from the Compound F3-

4.

^{1}H-NMR (400MHz、DMSO-d_6) δ: 12.82 (1H, s), 8.31 (1H, d, J = 7.9 Hz), 8.18 (1H, s), 8.02 (1H, s), 7.61 (1H, d, J = 7.9 Hz), 7.28 (1H, s), 4.53 (1H, s), 3.80 (4H, s), 3.36 (4H, s), 1.79 (6H, s).

LCMS: m/z 396 $[M+H]^+$

HPLC retention time: 2.32 minutes (analysis condition S)

[0165]

Examples 1 to 269: Ultramicro scale dissolution test

(Materials)

Materials for the Compound F6-20 (free form) were produced according to the method described in the Production example 30 and used. Additives shown in Table 2 were used as additives for the formulation.

(Preparation of composition)

For the Examples 1 to 269, the Compound F6-20 was dissolved in DMSO to the concentration of 0.5 mg/mL and added with hydrochloric acid in the same molar equivalent of the Compound F6-20. Then, various dissolution aids which have been dissolved or dispersed in the solvent shown in Table 2 were added to the Compound F6-20 to have 100% weight ratio. The resultant was freeze-dried to obtain a mixture of the Compound F6-20 and various dissolution aids.

[0166]

Table 2 Dissolution aids and solvents for dissolving them

Example	Dissolution aid	Manufacturer	Solvent
1	D-Sorbitol	B Food Science	DMSO
2	D-Mannitol	Towa Chemical Co. Ltd	DMSO
3	Pregelatinized starch	Nippon Starch Chemical Co., Ltd.	DMSO
4	Ethylcellulose	Colorcon	DMSO
5	Sodium carboxymethyl starch	DMV	water
6	Citric acid	Showa Kako Corporation	DMSO

Example	Dissolution aid	Manufacturer	Solvent
7	Sodium citrate	Showa Kako Corporation	water
8	Crosscarmellose sodium	Asahi Kasei Chemicals Corporation	DMSO
9	Microcrystalline cellulose	Asahi Kasei Chemicals Corporation	water
10	Titanium oxide	Freund Industrial Co., Ltd.	DMSO
11	Stearic acid	NOF Corporation	DMSO
12	Magnesium stearate	Merck & Co., Inc.	DMSO
13	Sucrose	Ensuiko Sugar Refining	DMSO
14	Tocopherol	Eisai Co., Ltd.	DMSO
15	Lactose	DMV	DMSO
16	Hydroxypropyl cellulose	Nippon Soda Co., Ltd.	DMSO
17	Hydroxypropylmethyl cellulose 2910	Shin-Etsu Chemical Co., Ltd.	DMSO
18	Sodium stearyl fumarate	Kimura Sangyo Co., Ltd.	DMSO
19	Propylene glycol	Kanto Chemical Co., Inc.	DMSO
20	Povidone	BASF	DMSO
21	Polysorbate 80	Nihon Surfactant Kogyo K.K.	DMSO
22	Methacrylic acid copolymer LD	Rohm GmbH	DMSO
23	Methyl cellulose	Shin-Etsu Chemical Co., Ltd.	DMSO
24	Sodium lauryl sulfate	Nikko Chemicals Co., Ltd.	DMSO

Example	Dissolution aid	Manufacturer	Solvent
25	Ascorbic acid	Wako Pure Chemical Industries Ltd.	DMSO
26	Sodium alginate	Wako Pure Chemical Industries Ltd.	water
27	Disodium edetate	Wako Pure Chemical Industries Ltd.	water
28	Caramel	Semba Tohka Industries	DMSO
29	Carmellose calcium	Nichirin Chemical Industries, Ltd.	water
30	Dried aluminum hydroxide gel	Kyowa Chemical Industry Co., Ltd.	water
31	Calcium citrate	Kanto Chemical Co., Inc.	DMSO
32	Triethyl citrate	Wako Pure Chemical Industries Ltd.	DMSO
33	Cholesterol	Wako Pure Chemical Industries Ltd.	DMSO
34	Magnesium oxide	Kyowa Chemical Industry Co., Ltd.	DMSO
35	Dibutylhydroxy toluene	Kanto Chemical Co., Inc.	DMSO
36	Sodium hydroxide	Wako Pure Chemical Industries Ltd.	water
37	Stearyl alcohol	NOF Corporation	DMSO
38	Polyoxyl 40 stearate	Nikko Chemicals Co., Ltd.	DMSO
39	Purified shellac	The Japan Shellac Industries, Ltd.	DMSO
40	Cetostearyl alcohol	NOF Corporation	DMSO

Example	Dissolution aid	Manufacturer	Solvent
41	Soy bean oil	Kaneda	DMSO
42	Sodium hydrogencarbonate	Wako Pure Chemical Industries Ltd.	water
43	Magnesium carbonate	Kyowa Chemical Industry Co., Ltd.	DMSO
44	Sodium dehydroacetate	Wako Pure Chemical Industries Ltd.	DMSO
45	Triacetin	Yuki Gosei Kogyo Co., Ltd.	DMSO
46	Fumaric acid	Kanto Chemical Co., Inc.	DMSO
47	Macrogol 1500	NOF Corporation	DMSO
48	Macrogol 400	Wako Pure Chemical Industries Ltd.	DMSO
49	Macrogol 6000	Sanyo Chemical Industries, Ltd.	water
50	Sorbitan monolaurate	Kao Corporation	DMSO
51	Magnesium sulfate	Wako Pure Chemical Industries Ltd.	water
52	Sodium dihydrogen phosphate	Nacalai Tesque	water
53	1,3-Butylene glycol	Daicel Chemical Industries Ltd.	DMSO
54	2-Mercaptobenzimidazole	Kawaguchi Chemical Industry Co., Ltd.	DMSO
55	β-Cyclodextrin	Funakoshi Co., Ltd.	DMSO
56	Tocopherol	Tama Biochemical Co., Ltd.	DMSO
57	DL-Malic acid	Wako Pure Chemical Industries Ltd.	DMSO

Example	Dissolution aid	Manufacturer	Solvent
58	Stearic L-ascorbate ester	Tokyo Chemical Industry Co., Ltd.	DMSO
59	L-Aspartic acid	Kanto Chemical Co., Inc.	DMSO
60	L-Glutamine	Wako Pure Chemical Industries Ltd.	water
61	Sodium L-tartrate	Wako Pure Chemical Industries Ltd.	water
62	L-Phenylalanine	Kanto Chemical Co., Inc.	DMSO
63	N-Cocoyl-L-arginineethylester DL-pyrrolidonecarboxylate	Ajinomoto Co., Inc.	DMSO
64	Ethyl actylrate • methyl methacrylate copolymer dispersion	EVONIK	DMSO
65	Starch grafted acrylate 1000	Sanyo Chemical Industries, Ltd.	water
66	Adipic acid	Kanto Chemical Co., Inc.	DMSO
67	Aminoalkyl methacrylate copolymer E	Rohm GmbH	DMSO
68	Taurine	Wako Pure Chemical Industries Ltd.	DMSO
69	Powdered acacia	San-Ei Yakuhin Boeki Co., Ltd.	water
70	Sodium bisulfite	Junsei Chemical Co., Ltd.	DMSO
71	Sodium sulfite	Kanto Chemical Co.,	water

Example	Dissolution aid	Manufacturer	Solvent
		Inc.	
72	Alginic acid	Wako Pure Chemical Industries Ltd.	DMSO/water
73	Propylene glycol alginate	Wako Pure Chemical Industries Ltd.	water
74	Alpha thioglycerol	Wako Pure Chemical Industries Ltd.	DMSO
75	Ammonia water	Wako Pure Chemical Industries Ltd.	DMSO
76	Inositol	Wako Pure Chemical Industries Ltd.	DMSO
77	Erythorbic acid	Wako Pure Chemical Industries Ltd.	DMSO
78	Hydrochloric acid	Junsei Chemical Co., Ltd.	DMSO
79	Cysteine hydrochloride	Sigma	DMSO
80	Olive oil	Nikko Chemicals Co., Ltd.	DMSO
81	Casein	Wako Pure Chemical Industries Ltd.	DMSO
82	Sodium caseinate	Wako Pure Chemical Industries Ltd.	water
83	Fructose	Wako Pure Chemical Industries Ltd.	DMSO
84	Carnauba wax	Freund Corporation	DMSO
85	Carboxy vinyl polymer	Lubrizol	DMSO
86	Carboxymethyl ethyl cellulose	Sanyo Chemical Industries, Ltd.	DMSO
87	Carmellose	Nichirin Chemical	DMSO/water

Example	Dissolution aid	Manufacturer	Solvent
		Industries Ltd.	
88	Powdered agar	Ina Food Industry Co., Ltd.	DMSO
89	Xylitol	Mitsubishi Shoji Foodtech Co., Ltd.	DMSO
90	Guar gum	San-Ei Yakuhin Boeki Co., Ltd.	DMSO
91	Monobasic sodium citrate	Kanto Chemical Co., Inc.	DMSO
92	Dibasic sodium citrate	Kanto Chemical Co., Inc.	water
93	Glycine	Wako Pure Chemical Industries Ltd.	water
94	Glycerol esters of fatty acids	Sasol Germany	DMSO
95	Calcium glycerophosphate	Kanto Chemical Co., Inc.	water
96	Glucono-δ-lactone	Wako Pure Chemical Industries Ltd.	DMSO
97	Gluconic acid	Kanto Chemical Co., Inc.	DMSO
98	Calcium gluconate	Wako Pure Chemical Industries Ltd.	water
99	Sodium gluconate	Wako Pure Chemical Industries Ltd.	water
100	Magnesium aluminosilicate	Fuji Chemical Industry Co., Ltd.	DMSO
101	Calcium silicate	Tomita Pharmaceutical Co., Ltd.	DMSO
102	Magnesium silicate	Kyowa Chemical	DMSO

Example	Dissolution aid	Manufacturer	Solvent
		Industry Co., Ltd.	
103	Synthetic aluminum silicate	Kyowa Chemical Industry Co., Ltd.	DMSO
104	Concentrated glycerin	NOF Corporation	DMSO
105	Powdered hydrogenated maltose starch syrup	Mitsubishi Shoji Foodtech Co., Ltd.	DMSO
106	Succinic acid	Wako Pure Chemical Industries Ltd.	DMSO
107	Copolyvidone	BASF	DMSO
108	Sesame oil	Kaneda	DMSO
109	Acetic acid	Kanto Chemical Co., Inc.	DMSO
110	Calcium acetate	Nacalai Tesque	water
111	Tocopherol acetate	Eisai Co., Ltd.	DMSO
112	Cellulose acetate phthalate	Sigma	DMSO
113	Tartaric acid	Wako Pure Chemical Industries Ltd.	DMSO
114	Potassium bitartrate	Wako Pure Chemical Industries Ltd.	water
115	Safflower oil	Nikko Chemicals Co., Ltd.	DMSO
116	Diisopropanolamine	Wako Pure Chemical Industries Ltd.	DMSO
117	Dioctyl sodium sulfosuccinate	Sanyo Chemical Industries, Ltd.	DMSO
118	Dihydroxy aluminum aminoacetate	Kyowa Chemical Industry Co., Ltd.	DMSO
119	Dimethyl polysiloxane	Sigma	DMSO/water
120	Potassium sodium tartrate	Wako Pure Chemical	water

Example	Dissolution aid	Manufacturer	Solvent
		Industries Ltd.	
121	Sucrose esters of fatty acids	Dai-ichi Kogyo Seiyaku Co., Ltd.	DMSO
122	Potassium hydroxide	Junsei Chemical Co., Ltd.	water
123	Calcium hydroxide	Junsei Chemical Co., Ltd.	DMSO/water
124	Magnesium hydroxide	Kyowa Chemical Industry Co., Ltd.	DMSO
125	Squalane	Mitsuba Trading Co., Ltd.	DMSO
126	Aluminum stearate	Wako Pure Chemical Industries Ltd.	DMSO
127	Purified gelatin	Nippi Inc.	DMSO
128	Zein	Wako Pure Chemical Industries Ltd.	DMSO
129	Sorbitan sesquioleate	Nihon Surfactant Kogyo K.K.	DMSO
130	Cetanol	Nikko Chemicals Co., Ltd.	DMSO
131	Cetomacrogol 1000	Nihon Surfactant Kogyo K.K.	DMSO
132	Diethyl sebacate	Nihon Surfactant Kogyo K.K.	DMSO
133	Sorbitan esters of fatty acids	Lion Corporation	DMSO
134	Tribasic calcium phosphate	Kanto Chemical Co., Inc.	DMSO
135	Soybean lecithin	Tsuji Oil Mill Co., Ltd.	water
136	Skimmed milk powder	Wako Pure Chemical	DMSO/water

Example	Dissolution aid	Manufacturer	Solvent
		Industries Ltd.	
137	Ammonium carbonate	Wako Pure Chemical Industries Ltd.	DMSO
138	Calcium carbonate	Kanto Chemical Co., Inc.	DMSO
139	Sodium carbonate	Wako Pure Chemical Industries Ltd.	water
140	Sodium thioglycolate	Wako Pure Chemical Industries Ltd.	water
141	Dextran 40	Wako Pure Chemical Industries Ltd.	water
142	Dextrin	Nippon Starch Chemical Co., Ltd.	DMSO
143	Starch	Wako Pure Chemical Industries	DMSO
144	Tragacanth	Suzu Pharmaceutical Co., Ltd.	DMSO
145	Triisopropanolamine	Wako Pure Chemical Industries Ltd.	DMSO
146	Triethanolamine	Wako Pure Chemical Industries Ltd.	DMSO
147	Sorbitan trioleate	Nihon Surfactant Kogyo K.K.	DMSO
148	Lactic acid	Acros	DMSO
149	Aluminum lactate	Wako Pure Chemical Industries Ltd.	DMSO
150	Calcium lactate	Wako Pure Chemical Industries Ltd.	DMSO
151	Sodium lactate solution	Wako Pure Chemical	DMSO

Example	Dissolution aid	Manufacturer	Solvent
		Industries Ltd.	
152	Ascorbic acid palmitate	Wako Pure Chemical Industries Ltd.	DMSO
153	Hydroxyethyl cellulose	Wako Pure Chemical Industries Ltd.	DMSO
154	Hydroxyethyl methyl cellulose	Tokyo Chemical Co., Ltd.	DMSO
155	Hydroxypropyl starch	Freund Industrial Co., Ltd.	DMSO
156	Hydroxypropylmethyl cellulose acetate succinate	Shin-Etsu Chemical Co., Ltd.	DMSO
157	Hydroxypropylmethyl cellulose phthalate	Shin-Etsu Chemical Co., Ltd.	DMSO
158	Piperonyl butoxide	Wako Pure Chemical Industries Ltd.	DMSO
159	Castor oil	Itoh Oil Chemicals Co., Ltd.	DMSO
160	Sunflower oil	Nikko Chemicals Co., Ltd.	DMSO
161	Sodium pyrosulfite	Wako Pure Chemical Industries Ltd.	DMSO
162	Phytic acid	Wako Pure Chemical Industries Ltd.	DMSO
163	Diethyl phthalate	Wako Pure Chemical Industries Ltd.	DMSO
164	Dibutyl phthalate	Wako Pure Chemical Industries Ltd.	DMSO
165	Butylhydroxy anisole	Wako Pure Chemical Industries Ltd.	DMSO

Example	Dissolution aid	Manufacturer	Solvent
166	Butyl phthalyl butyl glycolate	Wako Pure Chemical Industries Ltd.	DMSO
167	Glucose	Kanto Chemical Co., Inc.	DMSO
168	Monosodium fumarate	Wako Pure Chemical Industries Ltd.	water
169	Pullulan	Hayashibara Co., Ltd.	DMSO
170	Sodium propionate	Wako Pure Chemical Industries Ltd.	DMSO
171	Pectin	Wako Pure Chemical Industries Ltd.	water
172	Benzotriazole	Wako Pure Chemical Industries Ltd.	DMSO
173	Boric acid	Junsei Chemical Co., Ltd.	DMSO
174	Borax	Wako Pure Chemical Industries Ltd.	DMSO
175	Sodium polyacrylate	Wako Pure Chemical Industries Ltd.	water
176	Polyoxyethylene (105) polyoxypropylene (5) glycol	Freund Industrial Co., Ltd.	DMSO
177	Polyoxyethylene (160) polyoxypropylene (30) glycol	ADEKA	DMSO
178	Polyoxyethylene (20) polyoxypropylene (20) glycol	ADEKA	DMSO
179	Polyoxyethylene alkyl ether	Dai-ichi Kogyo Seiyaku Co., Ltd.	DMSO
180	Polyoxyethylene octyl phenyl ether	Wako Pure Chemical Industries Ltd.	DMSO

Example	Dissolution aid	Manufacturer	Solvent
181	Polyoxyethylene hydrogenated castor oil 20	NOF Corporation	DMSO
182	Polyoxyethylene hydrogenated castor oil 60	Nikko Chemicals Co., Ltd.	DMSO
183	Polyoxyethylene stearyl ether	Nihon Surfactant Kogyo K.K.	DMSO
184	Polyoxyethylene cetyl ether	Nihon Surfactant Kogyo K.K.	DMSO
185	Polyoxyl 35 castor oil	Sigma	DMSO
186	Poly(sodium 4-styrene sulfonate)	Sigma	water
187	Polysorbate 20	Nacalai Tesque	DMSO
188	Polysorbate 40	Nihon Surfactant Kogyo K.K.	DMSO
189	Polysorbate 60	Nihon Surfactant Kogyo K.K.	DMSO
190	Polyvinyl acetal diethyl aminoacetate	Mitsubishi-Kagaku Foods Corporation	DMSO
191	Polyvinyl alcohol	Japan Vam & Poval Co., Ltd.	DMSO
192	Polybutene	NOF Corporation	water
193	Sodium polyphosphate	Wako Pure Chemical Industries Ltd.	water
194	Macrogol 1540	NOF Corporation	DMSO
195	Macrogol 20000	Sanyo Chemical Industries, Ltd.	water
196	Macrogol 4000	NOF Corporation	DMSO
197	Macrogol 600	NOF Corporation	DMSO
198	Maltitol	Mitsubishi Shoji	DMSO

Example	Dissolution aid	Manufacturer	Solvent
		Foodtech Co., Ltd.	
199	Maltose	Hayashibara Shoji Inc.	DMSO
200	Maleic acid	Wako Pure Chemical Industries Ltd.	DMSO
201	Strach syrup	Hayashibara Shoji Inc.	DMSO
202	Isopropyl myristate	Nihon Surfactant Kogyo K.K.	DMSO
203	Anhydrous sodium sulfate	Wako Pure Chemical Industries Ltd.	water
204	Meglumine	Tokyo Chemical Industry Co., Ltd.	DMSO
205	Methacrylic acid copolymer L	Rohm GmbH	DMSO
206	Methacrylic acid copolymer S	Rohm GmbH	DMSO
207	Magnesium aluminometasilicate	Fuji Chemical Industry Co., Ltd.	DMSO/water
208	Sodium metaphosphate	Kanto Chemical Co., Inc.	DMSO
209	Methane sulfonic acid	Wako Pure Chemical Industries Ltd.	DMSO
210	Cotton seed oil	Okamura Oil Mill Ltd.	DMSO
211	Monoethanolamine	Wako Pure Chemical Industries Ltd.	DMSO
212	Sorbitan monooleate	Nihon Surfactant Kogyo K.K.	DMSO
213	Sorbitan monostearate	Nihon Surfactant Kogyo K.K.	DMSO
214	Lauryl dimethylamine oxide solution	Sigma	DMSO
215	Lauric acid diethanolamide	Kao Corporation	DMSO

Example	Dissolution aid	Manufacturer	Solvent
216	Lauromacrogol	NOF Corporation	DMSO
217	Peanut oil	Kaneda	DMSO
218	Isopropyl linolate	Nihon Surfactant Kogyo K.K.	DMSO
219	Sulfuric acid	Junsei Chemical Co., Ltd.	DMSO
220	Aluminum sulfate	Wako Pure Chemical Industries Ltd.	water
221	Aluminum potassium sulfate	Wako Pure Chemical Industries Ltd.	DMSO
222	Calcium sulfate	Wako Pure Chemical Industries Ltd.	water
223	Phosphoric acid	Kanto Chemical Co., Inc.	DMSO
224	Calcium monohydrogen phosphate	Wako Pure Chemical Industries Ltd.	DMSO/water
225	Trisodium phosphate	Sigma	DMSO
226	Dibasic calcium phosphate	Fuji Chemical Industry Co., Ltd.	DMSO/water
227	Dibasic sodium phosphate hydrate	Wako Pure Chemical Industries Ltd.	water
228	Dibasic potassium phosphate	Wako Pure Chemical Industries Ltd.	water
229	Monobasic potassium phosphate	Wako Pure Chemical Industries Ltd.	DMSO
230	Monobasic calcium phosphate	Wako Pure Chemical Industries Ltd.	water
231	Powdered hydrolyzed gelatin	Nippi Inc.	DMSO
232	Hydrated silicon dioxide	Freund Industrial Co.,	DMSO

Example	Dissolution aid	Manufacturer	Solvent
		Ltd.	
233	Light anhydrous silicic acid	Freund Industrial Co., Ltd.	DMSO/water
234	Partly pregelatinized starch	Asahi Kasei Chemicals Corporation	DMSO
235	Propyl gallate	Wako Pure Chemical Industries Ltd.	DMSO
236	Amylopectin	Nippon Starch Chemical Co., Ltd.	DMSO
237	Epoxydation soybean oil	Kao Corporation	DMSO
238	Ammonium acetate	Kanto Chemical Co., Inc.	DMSO
239	Magnesia alumina hydrate	Kyowa Chemical Industry Co., Ltd.	DMSO
240	Sodium dodecyl benzene sulfonate	Kao Corporation	DMSO
241	Vinyl pyrrolidone · vinyl acetate copolymer	Sigma	DMSO
242	Ammonium pentaborate	Kanto Chemical Co., Inc.	DMSO
243	Polyoxyethylene sorbitan monolaurate	Nihon Surfactant Kogyo K.K.	DMSO
244	Anhydrous sodium acetate	Wako Pure Chemical Industries Ltd.	DMSO
245	Sodium lauroyl sarcosinate	Nikko Chemicals Co., Ltd.	DMSO
246	Sodium polyoxyethylene laurylether phosphate	Nihon Surfactant Kogyo K.K.	DMSO
247	Amorphous silicon oxide	DSL.Japan Co., Ltd.	DMSO

Example	Dissolution aid	Manufacturer	Solvent
	hydrate		
248	DL-Alanine	Showa Chemical Industry Co., Ltd.	water
249	Sodium L-ascorbate	Wako Pure Chemical Industries Ltd.	DMSO
250	Sodium L-aspartate	Wako Pure Chemical Industries Ltd.	water
251	L-Arginine	Kanto Chemical Co., Inc.	water
252	L-Arginine hydrochloride	Wako Pure Chemical Industries Ltd.	water
253	Acetyl tryptophan	Wako Pure Chemical Industries Ltd.	DMSO
254	Acetanilide	Wako Pure Chemical Industries Ltd.	DMSO
255	Benzoic acid	Junsei Chemical Co., Ltd.	DMSO
256	Sodium benzoate	Wako Pure Chemical Industries Ltd.	DMSO
257	Hydroxypropyl cyclodextrin	Nihon Shokuhin Kako Co., Ltd.	DMSO
258	Sodium ß-cyclodextrin sulfobutyl ether	CYDEX	DMSO
259	Polyoxyethylene (54) polyoxypropylene (39) glycol	ADEKA	DMSO
260	Sodium methyl sulfate	Tokyo Chemical Industry Co., Ltd.	DMSO
261	Sodium ethyl sulfate	Tokyo Chemical Industry Co., Ltd.	DMSO

Example	Dissolution aid	Manufacturer	Solvent
262	Sodium butyl sulfate	Sigma	DMSO
263	Sodium octyl sulfate	Sigma	DMSO
264	Sodium decyl sulfate	Kanto Chemical Co., Inc.	DMSO
265	Sodium tetradecyl sulfate	Wako Pure Chemical Industries Ltd.	DMSO
266	Sodium hexadecylsulfate	Wako Pure Chemical Industries Ltd.	DMSO
267	Sodium octadecyl sulfate	Wako Pure Chemical Industries Ltd.	DMSO
268	Sodium chondroitin sulfate	Wako Pure Chemical Industries Ltd.	water
269	Dodecane	Wako Pure Chemical Industries Ltd.	DMSO

[0167]

(Comparative example 1)

For Comparative example 1, the Compound F6-20 was dissolved in DMSO to the concentration of 0.5 mg/mL, added with hydrochloric acid in the same molar equivalent of the Compound F6-20, and freeze-dried.

(Test example 1)

To Nos. 1 to 269 and Comparative example 1, FaSSIF (Fasted state simulated intestinal fluid, E. Galia et al. Pharm. Res. 15: 698Y705 (1998)), which is simulating fasted human intestinal fluids, was added and stirred with a shaker (trade name: Bio Shaker, manufactured by TAITEC) at stirring rate of 200 rpm. After stirring for 10 minutes and 240 minutes, respectively, the concentration was measured with high performance liquid chromatography (trade name; UFLC, manufactured by Shimadzu).

As a result, as shown in Table 3, it was found that solubility of the Compound F6-20 was significantly increased for citric acid (Example 6), hydroxypropyl cellulose (Example 16), hydroxypropylmethyl cellulose (Example 17), sodium stearyl fumarate

(Example 18), methacrylate copolymer LD (Example 22), methyl cellulose (Example 23), sodium lauryl sulfate (Example 24), polyoxyl 40 stearate (Example 38), purified shellac (Example 39), sodium dehydroacetate (Example 44), fumaric acid (Example 46), DL-malic acid (Example 57), stearic L-ascorbate ester (Example 58), L-aspartic acid (Example 59), adipic acid (Example 66), amino alkylmethacrylate copolymer E (Example 67), propylene glycol alginate ester (Example 73), casein (Example 81), sodium caseinate (Example 82), a carboxyvinyl polymer (Example 85), carboxymethylethyl cellulose (Example 86), powdered agar (Example 88), guar gum (Example 90), succinic acid (Example 106), copolyvidone (Example 107), cellulose acetate phthalate (Example 112), tartaric acid (Example 113), dioctyl sodium sulfosuccinate (Example 117), zein (Example 128), skimmed milk powder (Example 136), sorbitan trioleate (Example 147), lactic acid (Example 148), aluminum lactate (Example 149), ascorbic acid palmitate (Example 152), hydroxyethylmethyl cellulose (Example 154), hydroxypropylmethyl cellulose acetate succinate (Example 156), polyoxyethylene (105) polyoxypropylene (5) glycol (Example 176), polyoxyethylene hydrogenated castor oil 60 (Example 182), polyoxyl 35 castor oil (Example 185), poly(sodium 4-styrene sulfonate) (Example 186), polyvinylacetal diethylaminoacetate (Example 190), polyvinyl alcohol (Example 191), maleic acid (Example 200), methacrylate copolymer S (Example 206), lauromacrogol (Example 216), sulfuric acid (Example 219), aluminum sulfate (Example 220), phosphoric acid (Example 223), monobasic calcium phosphate (Example 230), sodium dodecylbenzene sulfonate (Example 240), vinyl pyrrolidone · vinyl acetate copolymer (Example 241), sodium lauroylsarcosine (Example 245), acetyl tryptophan (Example 253), sodium methyl sulfate (Example 260), sodium ethyl sulfate (Example 261), sodium butyl sulfate (Example 262), sodium octyl sulfate (Example 263), sodium decyl sulfate (Example 264), sodium tetradecyl sulfate (Example 265), sodium hexadecyl sulfate (Example 266), and sodium octadecyl sulfate (Example 267).

[0168]

Among them, the effect was remarkable for citric acid (Example 6), hydroxypropyl cellulose (Example 16), hydroxypropylmethyl cellulose (Example 17), methacrylate copolymer LD (Example 22), methyl cellulose (Example 23), sodium

lauryl sulfate (Example 24), purified shellac (Example 39), sodium dehydroacetate (Example 44), fumaric acid (Example 46), DL-malic acid (Example 57), stearic L-ascorbate ester (Example 58), L-aspartic acid (Example 59), adipic acid (Example 66), propylene glycol alginate ester (Example 73), casein (Example 81), sodium caseinate (Example 82), carboxymethylethyl cellulose (Example 86), succinic acid (Example 106), copolyvidone (Example 107), dioctyl sodium sulfosuccinate (Example 117), lactic acid (Example 148), aluminum lactate (Example 149), ascorbic acid palmitate (Example 152), hydroxyethylmethyl cellulose (Example 154), hydroxypropylmethyl cellulose acetate succinate (Example 156), polyoxyethylene hydrogenated castor oil 60 (Example 182), polyoxyl 35 castor oil (Example 185), poly(sodium 4-styrene sulfonate) (Example 186), polyvinylacetal diethylaminoacetate (Example 190), polyvinyl alcohol (Example 191), methacrylate copolymer S (Example 206), lauromacrogol (Example 216), sulfuric acid (Example 219), aluminum sulfate (Example 220), sodium dodecylbenzene sulfonate (Example 240), vinyl pyrrolidone ・ vinyl acetate copolymer (Example 241), acetyl tryptophan (Example 253), sodium decyl sulfate (Example 264), sodium tetradecyl sulfate (Example 265), and sodium octadecyl sulfate (Example 267).

[0169]

Among them, the effect was particularly remarkable for citric acid (Example 6), hydroxypropyl cellulose (Example 16), hydroxypropylmethyl cellulose (Example 17), methacrylate copolymer LD (Example 22), methyl cellulose (Example 23), sodium lauryl sulfate (Example 24), purified shellac (Example 39), sodium dehydroacetate (Example 44), fumaric acid (Example 46), DL-malic acid (Example 57), L-aspartic acid (Example 59), adipic acid (Example 66), propylene glycol alginate ester (Example 73), sodium caseinate (Example 82), carboxymethylethyl cellulose (Example 86), succinic acid (Example 106), copolyvidone (Example 107), dioctyl sodium sulfosuccinate (Example 117), lactic acid (Example 148), aluminum lactate (Example 149), hydroxyethylmethyl cellulose (Example 154), hydroxypropylmethyl cellulose acetate succinate (Example 156), poly(sodium 4-styrene sulfonate) (Example 186), polyvinylacetal diethylaminoacetate (Example 190), methacrylate copolymer S (Example 206), sulfuric acid (Example 219), aluminum sulfate (Example 220), vinyl pyrrolidone ・ vinyl acetate copolymer (Example 241), and sodium decyl sulfate

(Example 264).

[0170]

Table 3 Effect of various dissolution aids on the solubility of Compound F6-20 hydrochloride salt (* p<0.05, **p<0.01, ***p<0.001)

Example	Dissolution aid	Concentration after 10 min (μg/mL)	Concentration after 240 min (μg/mL)
Comparative example 1	Not added	5.0 ± 2.4	0.8 ± 0.3
1	D-Sorbitol	1.1 ± 0.3	0.6 ± 0.1
2	D-Mannitol	1.0 ± 0.1	0.5 ± 0.0
3	Pregelatinized starch	2.6 ± 0.5	0.5 ± 0.0
4	Ethylcellulose	3.1 ± 0.2	0.9 ± 0.1
5	Sodium carboxymethyl starch	2.0 ± 0.7	0.4 ± 0.1
6	Citric acid	5.1 ± 1.0	3.2 ± 0.1 ***
7	Sodium citrate	1.0 ± 0.3	0.3 ± 0.1
8	Crosscarmellose sodium	4.1 ± 2.6	1.2 ± 0.1
9	Microcrystalline cellulose	4.4 ± 0.7	0.3 ± 0.1
10	Titanium oxide	2.5 ± 0.3	1.1 ± 0.0
11	Stearic acid	1.9 ± 0.8	0.4 ± 0.0
12	Magnesium stearate	1.6 ± 0.3	0.5 ± 0.1
13	Purified sucrose	1.1 ± 0.2	0.5 ± 0.1
14	Tocopherol	1.9 ± 0.4	0.8 ± 0.1
15	Lactose	1.3 ± 0.4	0.4 ± 0.0
16	Hydroxypropyl cellulose	9.4 ± 2.5 **	2.9 ± 0.6 ***
17	Hydroxypropylmethyl cellulose 2910	7.3 ± 2.1	2.2 ± 0.3 ***
18	Sodium stearyl fumarate	3.0 ± 0.3	1.3 ± 0.2 *
19	Propylene glycol	1.3 ± 0.1	0.6 ± 0.2
20	Povidone	5.8 ± 1.3	0.6 ± 0.1

Example	Dissolution aid	Concentration after 10 min (μg/mL)	Concentration after 240 min (μg/mL)
21	Polysorbate 80	2.9 ± 0.8	0.5 ± 0.0
22	Methacrylic acid copolymer LD	4.9 ± 0.5	6.0 ± 0.5 ***
23	Methyl cellulose	7.2 ± 4.0	2.5 ± 0.0 ***
24	Sodium lauryl sulfate	19.6 ± 2.2 ***	6.3 ± 1.0 ***
25	Ascorbic acid	1.9 ± 0.6	0.6 ± 0.1
26	Sodium alginate	4.3 ± 0.4	0.3 ± 0.1
27	Disodium edetate	4.9 ± 2.1	0.3 ± 0.0
28	Caramel	3.0 ± 0.4	0.8 ± 0.1
29	Carmellose calcium	7.5 ± 1.7	0.7 ± 0.1
30	Dried aluminum hydroxide gel	3.2 ± 0.3	0.3 ± 0.1
31	Calcium citrate	0.5 ± 0.1	0.3 ± 0.2
32	Triethyl citrate	2.1 ± 0.4	0.6 ± 0.0
33	Cholesterol	2.3 ± 0.9	0.4 ± 0.1
34	Magnesium oxide	1.1 ± 0.1	0.1 ± 0.0
35	Dibutylhydroxy toluene	2.2 ± 0.3	0.5 ± 0.1
36	Sodium hydroxide	2.2 ± 0.2	0.4 ± 0.3
37	Stearyl alcohol	1.8 ± 0.1	0.6 ± 0.0
38	Polyoxyl 40 stearate	2.6 ± 0.4	1.4 ± 0.5 *
39	Purified shellac	2.7 ± 0.2	2.6 ± 0.3 ***
40	Cetostearyl alcohol	1.9 ± 0.1	0.3 ± 0.0
41	Soy bean oil	1.5 ± 0.4	0.4 ± 0.0
42	Sodium hydrogencarbonate	1.9 ± 0.7	1.1 ± 0.8
43	Magnesium carbonate	1.5 ± 0.0	0.5 ± 0.2
44	Sodium dehydroacetate	12.7 ± 1.7 ***	14.8 ± 1.3 ***
45	Triacetin	2.4 ± 0.2	0.4 ± 0.0
46	Fumaric acid	5.5 ± 0.9	1.9 ± 0.0 ***

Example	Dissolution aid	Concentration after 10 min (μg/mL)	Concentration after 240 min (μg/mL)
47	Macrogol 1500	1.7 ± 0.2	0.6 ± 0.1
48	Macrogol 400	1.7 ± 0.3	0.9 ± 0.1
49	Macrogol 6000	3.8 ± 0.9	0.3 ± 0.1
50	Sorbitan monolaurate	0.7 ± 0.1	0.4 ± 0.0
51	Magnesium sulfate	2.4 ± 0.2	0.2 ± 0.1
52	Sodium dihydrogen phosphate	2.7 ± 0.2	0.3 ± 0.1
53	1,3-Butylene glycol	1.3 ± 0.1	0.6 ± 0.0
54	2-Mercaptobenzimidazole	0.7 ± 0.1	0.6 ± 0.1
55	β-Cyclodextrin	1.1 ± 0.3	0.6 ± 0.1
56	Tocopherol	1.5 ± 0.0	0.9 ± 0.1
57	DL-Malic acid	5.2 ± 0.6	2.8 ± 0.4 ***
58	Stearic L-ascorbate ester	2.6 ± 0.3	1.7 ± 0.2 **
59	L-Aspartic acid	5.2 ± 1.0	1.8 ± 0.2 ***
60	L-Glutamine	1.6 ± 0.4	0.2 ± 0.1
61	Sodium L-tartrate	4.8 ± 0.4	0.2 ± 0.1
62	L-Phenylalanine	2.7 ± 0.2	0.6 ± 0.1
63	N-Cocoyl-L-arginineethylester DL-pyrrolidonecarboxylate	0.3 ± 0.1	0.3 ± 0.0
64	Ethyl actylrate • methyl methacrylate copolymer dispersion	1.4 ± 0.0	0.7 ± 0.2
65	Starch grafted acrylate 1000	1.8 ± 0.8	0.4 ± 0.2
66	Adipic acid	5.4 ± 0.6	1.9 ± 0.2 ***
67	Aminoalkyl methacrylate copolymer E	2.8 ± 1.0	1.3 ± 0.2 *
68	Taurine	1.1 ± 0.2	0.6 ± 0.1

Example	Dissolution aid	Concentration after 10 min (μg/mL)				Concentration after 240 min (μg/mL)			
69	Powdered acacia	7.2	±	2.3		0.6	±	0.1	
70	Sodium bisulfite	3.3	±	0.3		0.9	±	0.1	
71	Sodium sulfite	2.8	±	1.2		0.6	±	0.1	
72	Alginic acid	2.4	±	1.1		1.0	±	0.4	
73	Propylene glycol alginate	15.7	±	0.5	***	1.1	±	0.2	
74	Alpha thioglycerol	1.5	±	0.3		0.7	±	0.2	
75	Ammonia water	1.3	±	0.2		0.4	±	0.0	
76	Inositol	1.2	±	0.1		0.5	±	0.0	
77	Erythorbic acid	1.2	±	0.1		0.5	±	0.0	
78	Hydrochloric acid	1.4	±	0.2		0.6	±	0.1	
79	Cysteine hydrochloride	2.3	±	0.2		1.1	±	0.1	
80	Olive oil	1.7	±	0.5		0.8	±	0.0	
81	Casein	14.1	±	2.5	***	7.1	±	0.9	**
82	Sodium caseinate	17.1	±	3.0	***	15.8	±	4.8	***
83	Fructose	0.7	±	0.1		0.7	±	0.2	
84	Carnauba wax	2.8	±	0.5		2.0	±	2.1	
85	Carboxy vinyl polymer	7.4	±	0.4	*	1.1	±	0.2	
86	Carboxymethyl ethyl cellulose	8.7	±	3.1		9.5	±	2.2	***
87	Carmellose	1.9	±	0.3		0.9	±	0.1	
88	Powdered agar	3.2	±	0.1		1.3	±	0.1	*
89	Xylitol	1.3	±	0.1		0.5	±	0.0	
90	Guar gum	2.8	±	0.3		1.3	±	0.1	*
91	Monobasic sodium citrate	4.1	±	0.6		0.7	±	0.1	
92	Dibasic sodium citrate	2.2	±	0.5		0.9	±	0.3	
93	Glycine	2.7	±	1.2		0.4	±	0.0	
94	Glycerol esters of fatty acids	1.1	±	0.1		0.5	±	0.1	
95	Calcium glycerophosphate	0.9	±	0.1		0.3	±	0.0	

Example	Dissolution aid	Concentration after 10 min (μg/mL)				Concentration after 240 min (μg/mL)			
96	Glucono-δ-lactone	1.6	±	0.5		0.7	±	0.0	
97	Gluconic acid	1.0	±	0.1		3.3	±	2.0	
98	Calcium gluconate	2.3	±	0.9		0.3	±	0.1	
99	Sodium gluconate	5.7	±	0.6		0.5	±	0.2	
100	Magnesium aluminosilicate	2.2	±	0.1		0.5	±	0.1	
101	Calcium silicate	3.1	±	1.2		0.5	±	0.2	
102	Magnesium silicate	2.8	±	0.9		0.7	±	0.2	
103	Synthetic aluminum silicate	2.2	±	0.5		0.5	±	0.1	
104	Concentrated glycerin	0.9	±	0.0		1.9	±	1.3	
105	Powdered hydrogenated maltose starch syrup	0.8	±	0.1		0.6	±	0.1	
106	Succinic acid	5.6	±	0.5		3.8	±	0.2	***
107	Copolyvidone	14.1	±	2.7	***	2.0	±	0.1	***
108	Sesame oil	0.8	±	0.1		1.0	±	0.1	
109	Acetic acid	1.0	±	0.1		0.8	±	0.0	
110	Calcium acetate	2.5	±	1.1		0.5	±	0.1	
111	Tocopherol acetate	1.1	±	0.1		1.1	±	0.1	
112	Cellulose acetate phthalate	5.4	±	0.6		19.0	±	5.1	*
113	Tartaric acid	3.3	±	0.5		1.4	±	0.2	*
114	Potassium bitartrate	5.1	±	0.8		0.4	±	0.2	
115	Safflower oil	0.8	±	0.1		1.0	±	0.1	
116	Diisopropanolamine	0.3	±	0.1		0.6	±	0.1	
117	Dioctyl sodium sulfosuccinate	4.9	±	1.7		2.3	±	0.1	***
118	Dihydroxy aluminum aminoacetate	1.8	±	0.2		0.4	±	0.1	
119	Dimethyl polysiloxane	1.6	±	0.3		0.8	±	0.1	
120	Potassium sodium tartrate	4.6	±	0.1		0.3	±	0.1	

Example	Dissolution aid	Concentration after 10 min (μg/mL)	Concentration after 240 min (μg/mL)
121	Sucrose esters of fatty acids	2.4 ± 0.2	0.8 ± 0.1
122	Potassium hydroxide	3.4 ± 0.5	0.2 ± 0.1
123	Calcium hydroxide	0.7 ± 0.1	0.9 ± 0.1
124	Magnesium hydroxide	1.4 ± 0.1	0.5 ± 0.1
125	Squalane	1.2 ± 0.1	0.7 ± 0.3
126	Aluminum stearate	2.3 ± 0.5	0.6 ± 0.0
127	Purified gelatin	1.7 ± 0.2	0.7 ± 0.3
128	Zein	1.2 ± 0.1	1.4 ± 0.3 *
129	Sorbitan sesquioleate	0.9 ± 0.2	0.7 ± 0.2
130	Cetanol	1.7 ± 0.1	0.3 ± 0.1
131	Cetomacrogol 1000	4.5 ± 0.5	0.7 ± 0.1
132	Diethyl sebacate	1.0 ± 0.1	0.9 ± 0.0
133	Sorbitan esters of fatty acids	0.6 ± 0.1	0.7 ± 0.0
134	Tribasic calcium phosphate	5.0 ± 1.8	0.6 ± 0.1
135	Soybean lecithin	7.0 ± 1.4	0.4 ± 0.2
136	Skimmed milk powder	7.3 ± 3.3	10.0 ± 2.0 *
137	Ammonium carbonate	1.1 ± 0.3	0.9 ± 0.1
138	Calcium carbonate	2.1 ± 0.4	0.5 ± 0.1
139	Sodium carbonate	2.5 ± 1.0	0.8 ± 0.2
140	Sodium thioglycolate	3.5 ± 0.2	0.3 ± 0.0
141	Dextran 40	3.9 ± 1.0	0.4 ± 0.0
142	Dextrin	2.2 ± 0.1	0.9 ± 0.1
143	Starch	2.6 ± 0.3	1.0 ± 0.1
144	Tragacanth	6.7 ± 6.0	0.5 ± 0.1
145	Triisopropanolamine	0.2 ± 0.0	0.5 ± 0.1
146	Triethanolamine	1.2 ± 0.1	1.1 ± 0.0
147	Sorbitan trioleate	1.0 ± 0.2	1.4 ± 0.1 *
148	Lactic acid	2.7 ± 0.2	1.8 ± 0.2 ***

Example	Dissolution aid	Concentration after 10 min (μg/mL)	Concentration after 240 min (μg/mL)	
149	Aluminum lactate	3.5 ± 0.7	2.5 ± 0.3	***
150	Calcium lactate	1.9 ± 0.2	0.5 ± 0.1	
151	Sodium lactate solution	1.4 ± 0.2	0.5 ± 0.1	
152	Ascorbic acid palmitate	3.6 ± 0.2	1.8 ± 0.2	**
153	Hydroxyethyl cellulose	1.8 ± 0.2	0.6 ± 0.1	
154	Methyl hydroxylethylcellulose	4.3 ± 1.2	4.3 ± 0.7	***
155	Hydroxypropyl starch	1.5 ± 0.2	0.6 ± 0.1	
156	Hydroxypropylmethyl cellulose acetate succinate	6.1 ± 1.3	16.0 ± 3.5	***
157	Hydroxypropylmethyl cellulose phthalate	7.6 ± 3.2	2.8 ± 1.4	
158	Piperonyl butoxide	1.7 ± 0.3	0.6 ± 0.0	
159	Castor oil	1.4 ± 0.3	0.4 ± 0.1	
160	Sunflower oil	1.8 ± 0.2	0.4 ± 0.1	
161	Sodium pyrosulfite	3.4 ± 0.2	0.8 ± 0.0	
162	Phytic acid	4.9 ± 0.2	1.2 ± 0.1	
163	Diethyl phthalate	0.9 ± 0.0	0.5 ± 0.0	
164	Dibutyl phthalate	0.9 ± 0.1	0.4 ± 0.1	
165	Butylhydroxy anisole	1.3 ± 0.1	0.5 ± 0.1	
166	Butyl phthalyl butyl glycolate	0.7 ± 0.0	0.5 ± 0.1	
167	Glucose	0.8 ± 0.1	0.5 ± 0.0	
168	Monosodium fumarate	6.8 ± 1.6	0.5 ± 0.0	
169	Pullulan	1.5 ± 0.3	0.5 ± 0.0	
170	Sodium propionate	0.7 ± 0.1	0.4 ± 0.1	
171	Pectin	2.5 ± 1.7	0.5 ± 0.2	
172	Benzotriazole	1.0 ± 0.3	0.7 ± 0.0	

Example	Dissolution aid	Concentration after 10 min (μg/mL)	Concentration after 240 min (μg/mL)
173	Boric acid	0.7 ± 0.1	0.4 ± 0.0
174	Borax	1.0 ± 0.1	0.5 ± 0.1
175	Sodium polyacrylate	2.4 ± 0.5	0.5 ± 0.2
176	Polyoxyethylene (105) polyoxypropylene (5) glycol	1.7 ± 0.1	4.9 ± 1.7 *
177	Polyoxyethylene (160) polyoxypropylene (30) glycol	0.7 ± 0.1	0.5 ± 0.1
178	Polyoxyethylene (20) polyoxypropylene (20) glycol	2.2 ± 0.1	0.7 ± 0.1
179	Polyoxyethylene alkyl ether	1.5 ± 0.1	0.6 ± 0.1
180	Polyoxyethylene octyl phenyl ether	1.0 ± 0.3	0.6 ± 0.0
181	Polyoxyethylene hydrogenated castor oil 20	1.8 ± 0.2	1.4 ± 0.9
182	Polyoxyethylene hydrogenated castor oil 60	3.3 ± 0.5	1.8 ± 0.3 **
183	Polyoxyethylene stearyl ether	1.1 ± 0.2	0.3 ± 0.0
184	Polyoxyethylene cetyl ether	1.8 ± 0.3	0.4 ± 0.0
185	Polyoxyl 35 castor oil	4.5 ± 0.5	2.2 ± 0.6 **
186	Poly(sodium 4-styrene sulfonate)	11.2 ± 2.3 ***	63.7 ± 14.6 ***
187	Polysorbate 20	2.4 ± 0.5	0.5 ± 0.1
188	Polysorbate 40	3.1 ± 0.2	0.8 ± 0.1
189	Polysorbate 60	2.5 ± 0.1	0.7 ± 0.1
190	Polyvinyl acetal diethyl	8.4 ± 1.1 *	11.2 ± 0.3 ***

Example	Dissolution aid	Concentration after 10 min (μg/mL)	Concentration after 240 min (μg/mL)
	aminoacetate		
191	Polyvinyl alcohol	1.7 ± 0.6	1.5 ± 0.2 **
192	Polybutene	4.4 ± 1.8	0.5 ± 0.0
193	Sodium polyphosphate	1.5 ± 0.5	0.7 ± 0.4
194	Macrogol 1540	2.1 ± 0.1	0.5 ± 0.1
195	Macrogol 20000	2.6 ± 0.3	0.5 ± 0.1
196	Macrogol 4000	2.0 ± 0.2	0.4 ± 0.1
197	Macrogol 600	1.7 ± 0.1	0.6 ± 0.1
198	Maltitol	0.8 ± 0.0	0.5 ± 0.0
199	Maltose	0.9 ± 0.1	0.5 ± 0.1
200	Maleic acid	1.4 ± 0.3	1.3 ± 0.1 *
201	Starch syrup	1.3 ± 0.1	0.4 ± 0.0
202	Isopropyl myristate	1.3 ± 0.0	0.4 ± 0.1
203	Anhydrous sodium sulfate	1.6 ± 0.8	0.4 ± 0.1
204	Meglumine	1.0 ± 0.1	0.4 ± 0.0
205	Methacrylic acid copolymer L	5.1 ± 0.1	0.9 ± 0.1
206	Methacrylic acid copolymer S	2.3 ± 0.6	6.6 ± 0.4 ***
207	Magnesium aluminometasilicate	2.9 ± 0.7	0.7 ± 0.1
208	Sodium metaphosphate	1.2 ± 0.1	0.5 ± 0.0
209	Methane sulfonic acid	4.9 ± 0.9	1.1 ± 0.5
210	Cotton seed oil	0.5 ± 0.1	0.5 ± 0.0
211	Monoethanolamine	1.1 ± 0.0	0.4 ± 0.0
212	Sorbitan monooleate	1.0 ± 0.3	0.5 ± 0.1
213	Sorbitan monostearate	1.5 ± 0.2	0.4 ± 0.0
214	Lauryl dimethylamine oxide	0.3 ± 0.1	0.4 ± 0.0

Example	Dissolution aid	Concentration after 10 min (μg/mL)	Concentration after 240 min (μg/mL)
	solution		
215	Lauric acid diethanolamide	0.3 ± 0.1	0.3 ± 0.1
216	Lauromacrogol	10.1 ± 2.3 **	0.8 ± 0.0
217	Peanut oil	0.8 ± 0.0	0.4 ± 0.1
218	Isopropyl linolate	0.9 ± 0.1	0.5 ± 0.1
219	Sulfuric acid	12.5 ± 2.2 ***	3.0 ± 0.0 ***
220	Aluminum sulfate	5.7 ± 0.5	3.5 ± 0.6 ***
221	Aluminum potassium sulfate	2.0 ± 0.5	0.8 ± 0.0
222	Calcium sulfate	5.3 ± 0.4	0.7 ± 0.4
223	Phosphoric acid	3.8 ± 1.1	1.3 ± 0.2 *
224	Potassium monohydrogen phosphate	1.8 ± 0.3	0.6 ± 0.1
225	Trisodium phosphate	1.5 ± 0.3	0.5 ± 0.1
226	Dibasic calcium phosphate	1.6 ± 0.3	0.6 ± 0.0
227	Dibasic sodium phosphate hydrate	1.2 ± 0.0	1.2 ± 0.8
228	Dibasic potassium phosphate	1.1 ± 0.3	0.7 ± 0.1
229	Monobasic potassium phosphate	1.4 ± 0.1	0.6 ± 0.2
230	Monobasic calcium phosphate	4.5 ± 0.0	1.5 ± 0.6 *
231	Powdered hydrolyzed gelatin	3.3 ± 0.1	0.6 ± 0.1
232	Hydrated silicon dioxide	1.1 ± 0.1	0.6 ± 0.1
233	Light anhydrous silicic acid	1.8 ± 0.3	0.7 ± 0.4
234	Partly pregelatinized starch	1.3 ± 0.0	0.5 ± 0.1
235	Propyl gallate	4.9 ± 0.7	0.7 ± 0.1
236	Amylopectin	1.2 ± 0.1	5.5 ± 2.9
237	Epoxydation soybean oil	0.5 ± 0.0	0.7 ± 0.1

Example	Dissolution aid	Concentration after 10 min (μg/mL)	Concentration after 240 min (μg/mL)
238	Ammonium acetate	0.8 ± 0.1	0.4 ± 0.1
239	Magnesia alumina hydrate	3.9 ± 1.5	0.4 ± 0.0
240	Sodium dodecyl benzene sulfonate	4.5 ± 1.1	2.1 ± 0.4 **
241	Vinyl pyrrolidone • vinyl acetate copolymer	14.7 ± 4.1 ***	2.0 ± 0.8
242	Ammonium pentaborate	0.6 ± 0.0	5.5 ± 3.1
243	Polyoxyethylene sorbitan monolaurate	1.6 ± 0.2	0.5 ± 0.1
244	Anhydrous sodium acetate	1.5 ± 0.2	0.2 ± 0.1
245	Sodium N-lauroyl sarcosinate	5.4 ± 0.5	1.3 ± 0.1 *
246	Sodium polyoxyethylene laurylether phosphate	3.6 ± 1.0	0.7 ± 0.0
247	Amorphous silicon oxide hydrate	2.5 ± 0.7	0.5 ± 0.0
248	DL-Alanine	3.6 ± 1.7	0.7 ± 0.4
249	Sodium L-ascorbate	1.1 ± 0.1	1.7 ± 1.2
250	Sodium L-aspartate	1.3 ± 0.3	0.4 ± 0.2
251	L-Arginine	1.5 ± 0.6	0.4 ± 0.1
252	L-Arginine hydrochloride	1.1 ± 0.2	1.0 ± 0.4
253	Acetyl tryptophan	3.9 ± 0.7	1.5 ± 0.1 **
254	Acetanilide	0.6 ± 0.0	1.1 ± 0.1
255	Benzoic acid	2.8 ± 0.2	1.3 ± 0.5
256	Sodium benzoate	1.1 ± 0.4	0.4 ± 0.2
257	Hydroxypropyl cyclodextrin	2.1 ± 0.2	0.4 ± 0.1
258	Sodium β-cyclodextrin sulfobutyl ether	2.4 ± 0.4	0.6 ± 0.3

Example	Dissolution aid	Concentration after 10 min (μg/mL)	Concentration after 240 min (μg/mL)
259	Polyoxyethylene (54) polyoxypropylene (39) glycol	3.7 ± 0.8	0.8 ± 0.1
260	Methyl sodium sulfate	1.0 ± 0.1	1.5 ± 0.3 *
261	Ethyl sodium sulfate	0.9 ± 0.0	1.3 ± 0.2 *
262	Butyl sodium sulfate	2.4 ± 0.5	1.3 ± 0.3 *
263	Octyl sodium sulfate	4.2 ± 0.4	1.3 ± 0.1 *
264	Decyl sodium sulfate	18.8 ± 2.0 ***	3.4 ± 0.4 ***
265	Tetradecyl sodium sulfate	46.5 ± 17.9 **	19.8 ± 9.0 **
266	Hexadecyl sodium sulfate	32.1 ± 18.3 *	13.2 ± 8.3 *
267	Octadecyl sodium sulfate	20.9 ± 7.1 **	8.1 ± 2.8 **
268	Sodium chondroitin sulfate	3.0 ± 1.0	0.5 ± 0.1
269	Dodecane	2.3 ± 0.3	0.8 ± 0.1

[0171]

(Examples 270 to 281)

(Materials)

Hydrochloride salt crystal of the Compound F6-20 was obtained according a method generally known in the art (for example, the method described in the Production example 30). For the Examples 270 to 281, hydrochloride salt crystal of the Compound F6-20 was prepared according to dry blending method using agate mortar and pestle with the formula shown in Tables 4 to 8. Sodium lauryl sulfate passed with 100 mesh was used. For the Comparative example 2, hydrochloride salt crystal of the Compound F6-20 and lactose were mixed with each other at weight ratio of 1 : 9.

[0172]

Test example 2 (small scale dissolution test)

For the small dissolution scale test (R. Takano et al, Pharm. Res.23: 1144-1156 (2006)), a small scale dissolution tester (Vankel Technologies, Inc.) was used and the

solubilities in FaSSIF were determined at 37°C with paddle stirred rate of 50 rpm. For each test sample, after 5, 10, 15, 20, 25, 30, 45, 60, 120, and 240 minutes lapse, concentration of the Compound F6-20 in FaSSIF was measured by high performance liquid chromatography.

[0173]

(Examples 270 to 272)

Using the Examples 270 to 272 shown in Table 4 and the above Comparative Example 2, the effect of the additive amount of SLS on solubility of the Compound F6-20 hydrochloride salt crystal was determined. As a result, it was found that the solubility of the Compound F6-20 is improved in accordance with the additive amount of sodium lauryl sulfate as shown in FIG. 1.

[0174]

Table 4

	Example 270	Example 271	Example 272
Compound F6-20 hydrochloride salt	20.0%	20.0%	20.0%
Lactose hydrate	60.0%	75.0%	79.0%
Sodium lauryl sulfate	20.0%	5.0%	1.0%

[0175]

(Examples 273 to 275)

Using the Examples 273 to 275 shown in Table 5 and the above Comparative Example 2, the effect of various cellulose polymers on solubility of the Compound F6-20 hydrochloride salt crystal was determined. As a result, it was found that, among the various cellulose polymers, HPC exhibits the most excellent effect of improving the solubility of the Compound F6-20 as shown in FIG. 2, even though it is slightly.

[0176]

Table 5

	Example 273	Example 274	Example 275
Compound F6-20 hydrochloride salt	21.5%	21.5%	21.5%

Lactose hydrate	67.5%	67.5%	67.5%
Sodium lauryl sulfate	1.0%	1.0%	1.0%
Low substituted hydroxypropyl cellulose	5.0%	5.0%	5.0%
Methyl cellulose	5.0%	0.0%	0.0%
Hydroxypropylmethyl cellulose	0.0%	5.0%	0.0%
Hydroxypropyl cellulose	0.0%	0.0%	5.0%

[0177]

(Examples 276 to 278)

Using the Examples 276 to 278 shown in Table 6 and the above Comparative Example 2, the effect of additive amount of HPC on solubility of the Compound F6-20 hydrochloride salt crystal was determined. As a result, it was found that the Examples 276 to 278 have higher solubility than Comparative example 2 as shown in FIG. 3. Thus, at least by adding the HPC in an amount of 25 to 100% by weight compared to the Compound F6-20, the solubility improving effect can be obtained.

[0178]

Table 6

	Example 276	Example 277	Example 278
Compound F6-20 hydrochloride salt	21.5%	21.5%	21.5%
Lactose hydrate	68.5%	63.5%	53.5%
Low substituted hydroxypropyl cellulose	5.0%	5.0%	5.0%
Hydroxypropyl cellulose	5.0%	10.0%	20.0%

[0179]

(Example 279)

Using the Example 279 shown in Table 7, the solubility of the Compound F6-20 hydrochloride salt crystal when SLS and HPC were added thereto was determined. As a result, as illustrated in FIG. 4, it was found that the solubility was higher than the Example 276 in which only HPC was added, and the higher solubility was maintained

compared to the Example 270 in which only SLS was added.

[0180]

Table 7

	Example 279
Compound F6-20 hydrochloride salt	21.5%
Lactose hydrate	48.5%
Sodium lauryl sulfate	20.0%
Low substituted hydroxypropyl cellulose	5.0%
Hydroxypropyl cellulose	5.0%

[0181]

(Examples 280 to 281)

Using the Examples 280 to 281 shown in Table 8 and the above Comparative Example 2, effect of the difference in manufacturing method on the solubility of the Compound F6-20 hydrochloride salt crystal was determined. For the dry blending method, Compound F6-20 hydrochloride salt crystal and each formula ingredient were mixed by using agate mortar and pestle. For the wet granulation method, the dissolution aids other than magnesium stearate and the Compound F6-20 were mixed using agate mortar and pestle. After adding water dropwise, the wet powder was subjected to granulating using a mesh with sieve opening of 850 μm. After drying at 60°C for 3 hours, particle size regulating was carried out by using an 850 μm mesh again. As a result, it was found that there is no significant difference in the solubility of the Compound F6-20 hydrochloride salt crystal between different production methods, as shown in FIG. 5. Thus, it was shown that the effect of improving the solubility by SLS and the polymer does not depend on production method.

[0182]

Table 8

	Example 280	Example 281
Compound F6-20 hydrochloride salt	20.0%	20.0%

Lactose hydrate	41.5%	41.5%
Microcrystalline cellulose	20.0%	20.0%
Crosscarmellose sodium	3.0%	3.0%
Hydroxypropyl cellulose	5.0%	5.0%
Sodium lauryl sulfate	10.0%	10.0%
Magnesium stearate	0.5%	0.5%
Production method	Dry blending	Wet granulation

[0183]

(Examples 282 to 284)

For the Examples 282 to 284 and Comparative example 3, mesylate salt crystal of the Compound F6-20 was used in preparing the Compound according to dry production method using agate mortar and pestle with the formula shown in Table 9. For the Comparative example 3, mesylate salt crystal of the Compound F6-20 and lactose were mixed with each other at weight ratio of 1 : 9.

The effect of the additive amount of SLS on solubility of the Compound F6-20 mesylate salt crystal was determined. As a result, it was found that the solubility of the Compound F6-20 mesylate salt is improved in accordance with the additive amount of sodium lauryl sulfate as shown in FIG. 6.

[0184]

Table 9

	Example 282	Example 283	Example 284
Compound F6-20 mesylate salt	20.0%	20.0%	20.0%
Lactose hydrate	60.0%	75.0%	79.0%
Sodium lauryl sulfate	20.0%	5.0%	1.0%

[0185]

(Example 285)

Solubility of the Compound F6-20 mesylate salt crystal in the case when SLS and HPC were added using the Example 285 shown in Table 10 and the above Comparative Example 3 was determined. As a result, it was found that high solubility

was obtained by adding SLS and HPC, as shown in FIG. 7.

[0186]

Table 10

	Example 285
Compound F6-20 mesylate salt	24.0%
Lactose hydrate	46.0%
Sodium lauryl sulfate	20.0%
Low substituted hydroxypropyl cellulose	5.0%
Hydroxypropyl cellulose	5.0%

[0187]

(Examples 286 to 298)

For the Comparative example 4 and the Examples 286 to 298, the effect of various dissolution aids on the solubility of the Compound B4-8 (Production example 12) was determined in the same manner as the Examples 1 to 269. The results are shown in Table 11.

[0188]

Table 11 Effect of various dissolution aids on the solubility of Compound B4-8 hydrochloride salt

Example	Dissolution aid	Dissolved concentration after 10 min (μg/mL)	Dissolved concentration after 240 min (μg/mL)
Comparative example 4	Not added	8.3 ± 1.5	3.8 ± 2.6
286	Methyl cellulose	5.8 ± 1.3	1.9 ± 0.6
287	Hydroxypropylmethyl cellulose	6.8 ± 0.9	1.4 ± 0.1
288	Hydroxypropyl cellulose	14.2 ± 3.2 *	3.2 ± 2.7
289	Povidone	4.8 ± 0.4	1.1 ± 0.3
290	Macrogol 6000	3.8 ± 0.2	0.9 ± 0.1

291	Glycerin monostearate	4.8	±	0.8		1.5	±	0.1
292	Sodium lauryl sulfate	31.7	±	7.3	**	7.2	±	1.0
293	Sucrose esters of fatty acids	6.8	±	2.7		3.5	±	2.0
294	Polyoxyl 40 stearate	5.6	±	1.2		2.3	±	0.2
295	Sorbitan esters of fatty acids	4.6	±	0.3		1.6	±	0.1
296	Polyoxyethylene hydrogenated castor oil 60	3.3	±	0.1		2.7	±	0.5
297	Polyoxyethylene (105) polyoxypropylene (5) glycol	4.1	±	0.4		3.5	±	0.6
298	Polyoxyethylene (160) polyoxypropylene (30) glycol	3.2	±	0.2		1.9	±	0.1

[0189]

(Examples 299 to 311)

For the Comparative example 5 and the Examples 299 to 311, the effect of various dissolution aids on the solubility of the Compound F4-3 (Production example 19) was determined in the same manner as the Examples 1 to 269. The results are shown in Table 12.

[0190]

Table 12 Effect of various dissolution aids on the solubility of Compound F4-3 hydrochloride salt

Example	Dissolution aid	Dissolved concentration after 10 min (μg/mL)	Dissolved concentration after 240 min (μg/mL)
Comparative example 5	Not added	4.4 ± 0.4	4.8 ± 0.3
299	Methyl cellulose	17.8 ± 3.7 *	13.9 ± 5.8
300	Hydroxypropylmethyl cellulose	16.9 ± 11.1	23.7 ± 6.1 *
301	Hydroxypropyl cellulose	13.7 ± 4.0	8.8 ± 7.8
302	Povidone	48.1 ± 19.7	22.5 ± 3.8 *
303	Macrogol 6000	4.6 ± 0.5	4.6 ± 0.8
304	Glycerin monostearate	3.8 ± 0.4	3.0 ± 0.6
305	Sodium lauryl sulfate	8.1 ± 0.2 ***	6.8 ± 1.3
306	Sucrose esters of fatty acids	4.9 ± 0.7	5.2 ± 0.5
307	Polyoxyl 40 stearate	11.6 ± 1.5 **	20.3 ± 1.4 ***
308	Sorbitan esters of fatty acids	2.2 ± 0.7	3.1 ± 0.3
309	Polyoxyethylene hydrogenated castor oil 60	10.4 ± 2.5 *	21.0 ± 8.4
310	Polyoxyethylene (105) polyoxypropylene (5) glycol	90.0 ± 5.1 **	43.2 ± 8.5 *
311	Polyoxyethylene (160) polyoxypropylene	54.9 ± 18.9 *	6.7 ± 1.4

	(30) glycol		

[0191]

(Examples 312 to 324)

For the Comparative example 6 and the Examples 312 to 324, the effect of various dissolution aids on the solubility of the Compound F4-9 (Production example 20) was determined in the same manner as the Examples 1 to 269. The results are shown in Table 13.

[0192]

Table 13 Effect of various dissolution aids on the solubility of Compound F4-9 hydrochloride salt

Example	Dissolution aid	Dissolved concentration after 10 min (μg/mL)	Dissolved concentration after 240 min (μg/mL)
Comparative example 6	Not added	18.2 ± 0.1	3.7 ± 0.5
312	Methyl cellulose	21.0 ± 4.6	6.4 ± 0.5 **
313	Hydroxypropylmethyl cellulose	26.1 ± 3.7	9.9 ± 1.0 ***
314	Hydroxypropyl cellulose	28.8 ± 3.4 *	7.4 ± 6.4
315	Povidone	82.6 ± 10.4 ***	40.0 ± 15.8
316	Macrogol 6000	18.8 ± 0.6	9.8 ± 0.8 ***
317	Glycerin monostearate	8.7 ± 0.4	7.2 ± 1.3 *
318	Sodium lauryl sulfate	72.7 ± 2.0 ***	37.6 ± 3.1 **
319	Sucrose esters of fatty acids	31.9 ± 7.5	9.1 ± 0.7 ***
320	Polyoxyl 40 stearate	24.9 ± 14.8	55.4 ± 21.0
321	Sorbitan esters of fatty acids	6.3 ± 2.3	4.6 ± 0.6

322	Polyoxyethylene hydrogenated castor oil 60	62.2 ± 58.9	77.6 ± 68.1
323	Polyoxyethylene (105) polyoxypropylene (5) glycol	50.4 ± 13.1	14.3 ± 4.0 *
324	Polyoxyethylene (160) polyoxypropylene (30) glycol	60.1 ± 18.1	31.1 ± 14.5

[0193]

(Examples 325 to 337)

For the Comparative example 7 and the Examples 325 to 337, the effect of various dissolution aids on the solubility of the Compound F6-4 (Production example 28) was determined in the same manner as the Examples 1 to 269. The results are shown in Table 14.

[0194]

Table 14 Effect of various dissolution aids on the solubility of Compound F6-4 hydrochloride salt

Example	Dissolution aid	Dissolved concentration after 10 min (μg/mL)	Dissolved concentration after 240 min (μg/mL)
Comparative example 7	Not added	0.4 ± 0.2	0.4 ± 0.4
325	Methyl cellulose	10.8 ± 2.9 *	8.3 ± 4.0
326	Hydroxypropylmethyl cellulose	16.8 ± 12.7	18.4 ± 7.7
327	Hydroxypropyl cellulose	3.6 ± 0.4 ***	2.6 ± 0.5 **

328	Povidone	12.9	±	3.8	*	24.5	±	5.0	
329	Macrogol 6000	0.7	±	0.5		0.4	±	0.1	
330	Glycerin monostearate	0.3	±	0.1		0.7	±	0.2	
331	Sodium lauryl sulfate	1.8	±	0.3	**	3.7	±	0.9	**
332	Sucrose esters of fatty acids	1.2	±	0.9		1.6	±	0.7	
333	Polyoxyl 40 stearate	36.0	±	6.5	*	43.9	±	6.8	**
334	Sorbitan esters of fatty acids	0.3	±	0.2		0.1	±	0.0	
335	Polyoxyethylene hydrogenated castor oil 60	16.3	±	2.2	**	27.1	±	4.5	**
336	Polyoxyethylene (105) polyoxypropylene (5) glycol	50.1	±	8.3	**	52.6	±	8.9	**
337	Polyoxyethylene (160) polyoxypropylene (30) glycol	19.3	±	2.3	**	15.4	±	4.0	*

[0195]

(Examples 338 to 350)

For the Comparative example 8 and the Examples 338 to 350, the effect of various dissolution aids on the solubility of the Compound F5-43 (Production example 36) was determined in the same manner as the Examples 1 to 269. The results are shown in Table 15.

[0196]

Table 15 Effect of various dissolution aids on the solubility of Compound F5-43 hydrochloride salt

Example	Dissolution aid	Dissolved concentration after 10 min (μg/mL)	Dissolved concentration after 240 min (μg/mL)

Comparative example 8	Not added	12.7	±	1.8		5.5	±	0.6		
338	Methyl cellulose	32.5	±	3.8	**	5.8	±	1.3		
339	Hydroxypropylmethyl cellulose	35.4	±	5.8	**	7.9	±	0.7	*	
340	Hydroxypropyl cellulose	17.6	±	4.2		6.8	±	0.5	*	
341	Povidone	40.9	±	0.6	***	5.0	±	0.7		
342	Macrogol 6000	37.4	±	1.1	***	3.4	±	0.3		
343	Glycerin monostearate	9.9	±	2.0		2.5	±	0.4		
344	Sodium lauryl sulfate	35.8	±	5.5	**	39.5	±	1.4	***	
345	Sucrose esters of fatty acids	24.1	±	1.8	**	2.6	±	0.1		
346	Polyoxyl 40 stearate	23.6	±	2.4	**	3.5	±	0.1		
347	Sorbitan esters of fatty acids	8.6	±	2.0		2.3	±	0.6		
348	Polyoxyethylene hydrogenated castor oil 60	15.1	±	2.1		3.2	±	0.1		
349	Polyoxyethylene (105) polyoxypropylene (5) glycol	38.9	±	4.4	***	3.4	±	0.6		
350	Polyoxyethylene (160) polyoxypropylene (30) glycol	37.8	±	1.5	***	4.4	±	0.9		

[0197]

(Examples 351 to 363)

For the Comparative example 9 and the Examples 351 to 363, the effect of various dissolution aids on the solubility of the Compound F6-17 (Production example 32) was determined in the same manner as the Examples 1 to 269. The results are shown in Table 16.

[0198]

Table 16 Effect of various dissolution aids on the solubility of Compound F6-17 hydrochloride salt

Example	Dissolution aid	Dissolved concentration after 10 min (μg/mL)	Dissolved concentration after 240 min (μg/mL)
Comparative example 9	Not added	9.2 ± 1.3	5.2 ± 0.5
351	Methyl cellulose	16.9 ± 3.2	8.7 ± 2.4
352	Hydroxypropylmethyl cellulose	20.6 ± 4.9	10.6 ± 1.5 **
353	Hydroxypropyl cellulose	8.8 ± 3.3	7.7 ± 0.6 **
354	Povidone	20.8 ± 1.4 *	5.2 ± 0.6
355	Macrogol 6000	23.2 ± 2.2 **	3.3 ± 0.2
356	Glycerin monostearate	8.7 ± 0.7	2.4 ± 0.5
357	Sodium lauryl sulfate	36.6 ± 5.4 **	40.5 ± 4.4 **
358	Sucrose esters of fatty acids	13.6 ± 1.4 *	5.3 ± 0.5
359	Polyoxyl 40 stearate	22.6 ± 1.4 **	8.7 ± 8.0
360	Sorbitan esters of fatty acids	5.3 ± 0.3	4.2 ± 1.1
361	Polyoxyethylene hydrogenated castor oil 60	18.1 ± 1.6 **	8.0 ± 1.2 *

362	Polyoxyethylene (105) polyoxypropylene (5) glycol	23.6	±	3.7	*	9.1	±	0.6	***
363	Polyoxyethylene (160) polyoxypropylene (30) glycol	30.0	±	3.9	**	4.6	±	0.6	

[0199]

(Examples 364 to 376)

For the Comparative example 10 and the Examples 364 to 376, the effect of various dissolution aids on the solubility of the Compound F5-46 (Production example 43) was determined in the same manner as the Examples 1 to 269. The results are shown in Table 17.

[0200]

Table 17 Effect of various dissolution aids on the solubility of Compound F5-46 hydrochloride salt

Example	Dissolution aid	Dissolved concentration after 10 min (μg/mL)				Dissolved concentration after 240 min (μg/mL)			
Comparative example 10	Not added	7.5	±	0.6		5.6	±	0.8	
364	Methyl cellulose	13.1	±	1.1	**	4.0	±	0.9	
365	Hydroxypropylmethyl cellulose	12.3	±	0.7	***	5.2	±	0.4	
366	Hydroxypropyl cellulose	10.0	±	1.3	*	5.5	±	1.2	
367	Povidone	14.5	±	1.8	**	4.3	±	1.3	
368	Macrogol 6000	25.7	±	3.4	***	5.8	±	0.8	
369	Glycerin monostearate	8.5	±	1.0		2.3	±	0.4	

370	Sodium lauryl sulfate	33.4	±	4.1	**	23.1	±	1.1	***
371	Sucrose esters of fatty acids	10.8	±	0.3	***	3.0	±	0.7	
372	Polyoxyl 40 stearate	9.8	±	1.6		4.1	±	0.3	
373	Sorbitan esters of fatty acids	1.8	±	0.8		1.5	±	0.9	
374	Polyoxyethylene hydrogenated castor oil 60	9.3	±	3.0		3.4	±	0.4	
375	Polyoxyethylene (105) polyoxypropylene (5) glycol	18.3	±	7.6		11.7	±	6.6	
376	Polyoxyethylene (160) polyoxypropylene (30) glycol	12.6	±	0.9	***	3.0	±	0.2	

[0201]

(Examples 377 to 389)

For the Comparative example 11 and the Examples 377 to 389, the effect of various dissolution aids on the solubility of the Compound F6-18 (Production example 37) was determined in the same manner as the Examples 1 to 269. The results are shown in Table 18.

[0202]

Table 18 Effect of various dissolution aids on the solubility of Compound F6-18 hydrochloride salt

Example	Dissolution aid	Dissolved concentration after 10 min (μg/mL)				Dissolved concentration after 240 min (μg/mL)			
Comparative example 11	Not added	10.0	±	2.0		1.8	±	0.2	
377	Methyl cellulose	6.3	±	0.3		2.9	±	0.2	**

378	Hydroxypropylmethyl cellulose	6.0	±	5.2		3.5	±	0.9	*
379	Hydroxypropyl cellulose	7.8	±	1.7		5.1	±	0.6	***
380	Povidone	8.2	±	0.1		1.9	±	1.7	
381	Macrogol 6000	7.1	±	1.4		1.3	±	0.1	
382	Glycerin monostearate	1.8	±	0.4		0.7	±	0.1	
383	Sodium lauryl sulfate	19.0	±	0.8	**	23.4	±	3.3	**
384	Sucrose esters of fatty acids	9.2	±	7.1		3.7	±	0.3	***
385	Polyoxyl 40 stearate	5.4	±	0.2		3.9	±	0.4	***
386	Sorbitan esters of fatty acids	1.0	±	0.1		1.4	±	0.2	
387	Polyoxyethylene hydrogenated castor oil 60	6.3	±	1.6		3.1	±	0.8	
388	Polyoxyethylene (105) polyoxypropylene (5) glycol	9.8	±	4.0		1.4	±	2.4	
389	Polyoxyethylene (160) polyoxypropylene (30) glycol	3.7	±	0.4		1.5	±	0.8	

[0203]

(Examples 390 to 402)

For the Comparative example 12 and the Examples 390 to 402, the effect of various dissolution aids on the solubility of the Compound F5-51 (Production example 27) was determined in the same manner as the Examples 1 to 269. The results are shown in Table 19.

[0204]

Table 19 Effect of various dissolution aids on the solubility of Compound F5-51

hydrochloride salt

Example	Dissolution aid	Dissolved concentration after 10 min (μg/mL)	Dissolved concentration after 240 min (μg/mL)
Comparative example 12	Not added	7.1 ± 0.9	0.0 ± 0.1
390	Methyl cellulose	8.5 ± 0.4	0.5 ± 0.8
391	Hydroxypropylmethyl cellulose	10.8 ± 1.5 *	0.5 ± 0.2 *
392	Hydroxypropyl cellulose	11.2 ± 0.3 **	0.5 ± 0.2 *
393	Povidone	10.8 ± 1.5 *	0.0 ± 0.1
394	Macrogol 6000	4.6 ± 0.7	0.0 ± 0.1
395	Glycerin monostearate	2.4 ± 0.2	0.1 ± 0.1
396	Sodium lauryl sulfate	20.2 ± 1.3 ***	15.7 ± 0.8 ***
397	Sucrose esters of fatty acids	6.8 ± 1.5	0.1 ± 0.1
398	Polyoxyl 40 stearate	1.2 ± 0.4	0.4 ± 0.3
399	Sorbitan esters of fatty acids	0.5 ± 0.3	0.8 ± 0.3 **
400	Polyoxyethylene hydrogenated castor oil 60	7.0 ± 0.5	0.8 ± 1.0
401	Polyoxyethylene (105) polyoxypropylene (5) glycol	2.7 ± 1.0	0.1 ± 0.2
402	Polyoxyethylene (160)	3.9 ± 0.4	0.0 ± 0.1

	polyoxypropylene (30) glycol		

[0205]

(Examples 403 to 415)

For the Comparative example 13 and the Examples 403 to 415, the effect of various dissolution aids on the solubility of the Compound I6-4 (Production example 24) was determined in the same manner as the Examples 1 to 269. The results are shown in Table 20.

[0206]

Table 20 Effect of various dissolution aids on the solubility of Compound I6-4 hydrochloride salt

Example	Dissolution aid	Dissolved concentration after 10 min (μg/mL)	Dissolved concentration after 240 min (μg/mL)
Comparative example 13	Not added	9.3 ± 3.4	0.0 ± 0.1
403	Methyl cellulose	1.6 ± 0.3	0.0 ± 0.1
404	Hydroxypropylmethyl cellulose	2.9 ± 1.7	0.0 ± 0.1
405	Hydroxypropyl cellulose	8.9 ± 1.3	0.7 ± 0.3 *
406	Povidone	9.9 ± 3.1	0.0 ± 0.1
407	Macrogol 6000	3.4 ± 0.2	0.0 ± 0.1
408	Glycerin monostearate	1.3 ± 0.1	0.0 ± 0.1
409	Sodium lauryl sulfate	35.0 ± 5.9 **	30.0 ± 2.7 **
410	Sucrose esters of fatty acids	0.6 ± 0.3	0.0 ± 0.1
411	Polyoxyl 40 stearate	0.3 ± 0.3	0.3 ± 0.2 *
412	Sorbitan esters of fatty acids	1.9 ± 0.3	0.1 ± 0.1

413	Polyoxyethylene hydrogenated castor oil 60	0.4 ± 0.2	0.3 ± 0.2
414	Polyoxyethylene (105) polyoxypropylene (5) glycol	2.5 ± 2.6	0.0 ± 0.1
415	Polyoxyethylene (160) polyoxypropylene (30) glycol	1.9 ± 0.9	0.2 ± 0.2

[0207]

(Examples 416 to 418)

With the Examples 416 to 418 shown in Table 21, the effect of SLS and polyvinyl pyrrolidone on solubility of the Compound B4-8 hydrochloride salt crystal was determined based on a small scale dissolution test. For the Comparative example 14, the Compound B4-8 hydrochloride salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 8.

[0208]

Table 21

	Example 416	Example 417	Example 418
Compound B4-8 hydrochloride salt	10.0%	10.0%	10.0%
Lactose hydrate	80.0%	80.0%	70.0%
Polyvinyl pyrrolidone	0.0%	10.0%	10.0%
Sodium lauryl sulfate	10.0%	0.0%	10.0%

[0209]

(Examples 419 to 421)

With the Examples 419 to 421 shown in Table 22, the effect of SLS and polyvinyl pyrrolidone on solubility of the Compound B4-8 mesylate salt crystal was determined based on a small scale dissolution test. For the Comparative example 15, the Compound B4-8 mesylate salt crystal and lactose were mixed at weight ratio of 1 : 9.

The results are shown in FIG. 9.

[0210]

Table 22

	Example 419	Example 420	Example 421
Compound B4-8 mesylate salt	10.0%	10.0%	10.0%
Lactose hydrate	80.0%	80.0%	70.0%
Polyvinyl pyrrolidone	0.0%	10.0%	10.0%
Sodium lauryl sulfate	10.0%	0.0%	10.0%

[0211]

(Examples 422 to 424)

With the Examples 422 to 424 shown in Table 23, the effect of SLS and HPC on solubility of the Compound B4-8 sulfate salt crystal was determined based on a small scale dissolution test. For the Comparative example 16, the Compound B4-8 sulfate salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 10.

[0212]

Table 23

	Example 422	Example 423	Example 424
Compound B4-8 sulfate salt	24.6%	24.6%	24.6%
Lactose hydrate	55.4%	70.4%	50.4%
Sodium lauryl sulfate	20.0%	0.0%	20.0%
Hydroxypropyl cellulose	0.0%	5.0%	5.0%

[0213]

(Examples 425 to 427)

With the Examples 425 to 427 shown in Table 24, the effect of SLS and HPC on solubility of the Compound B4-8 L-tartrate salt crystal was determined based on a small scale dissolution test. For the Comparative example 17, the Compound B4-8 L-tartrate salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are

shown in FIG. 11.

[0214]

Table 24

	Example 425	Example 426	Example 427
Compound B4-8 L-tartrate salt	24.4%	24.4%	24.4%
Lactose hydrate	55.6%	70.6%	50.6%
Sodium lauryl sulfate	20.0%	0.0%	20.0%
Hydroxypropyl cellulose	0.0%	5.0%	5.0%

[0215]

(Examples 428 to 429)

With the Examples 428 to 429 shown in Table 25, the effect of SLS and HPC on solubility of the Compound B4-8L-phosphate salt crystal was determined based on a small scale dissolution test. For the Comparative example 18, the Compound B4-8 phosphate salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 12.

[0216]

Table 25

	Example 428	Example 429
Compound B4-8 phosphate salt	26.3%	26.3%
Lactose hydrate	53.7%	48.7%
Sodium lauryl sulfate	20.0%	20.0%
Hydroxypropyl cellulose	0.0%	5.0%

[0217]

(Example 430)

With the Example 430 shown in Table 26, the effect of polyoxyethylene (105) polyoxypropylene (5) glycol on solubility of the Compound F6-4 hydrochloride salt crystal was determined based on a small scale dissolution test. For the Comparative example 19, the Compound F6-4 hydrochloride salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 13.

[0218]

Table 26

	Example 430
Compound F6-4 hydrochloride salt	8.3%
Lactose hydrate	83.3%
Polyoxyethylene (105) polyoxypropylene (5) glycol	8.3%

[0219]

(Example 431)

With the Example 431 shown in Table 27, the effect of polyoxyethylene (105) polyoxypropylene (5) glycol on solubility of the Compound F6-4 mesylate salt crystal was determined based on a small scale dissolution test. For the Comparative example 20, the Compound F6-4 mesylate salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 14.

[0220]

Table 27

	Example 431
Compound F6-4 mesylate salt	8.3%
Lactose hydrate	83.3%
Polyoxyethylene (105) polyoxypropylene (5) glycol	8.3%

[0221]

(Example 432)

With the Example 432 shown in Table 28, the effect of SLS on solubility of the Compound F6-17 hydrochloride salt crystal was determined based on a small scale dissolution test. For the Comparative example 21, the Compound F6-17 hydrochloride salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 15.

[0222]

Table 28

	Example 432
Compound F6-17 hydrochloride salt	8.3%

Lactose hydrate	83.3%
Sodium lauryl sulfate	8.3%

[0223]

(Examples 433 to 435)

With the Examples 433 to 435 shown in Table 29, the effect of SLS on solubility of the Compound F6-17 mesylate salt crystal was determined based on a small scale dissolution test. For the Comparative example 22, the Compound F6-17 mesylate salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 16.

[0224]

Table 29

	Example 433	Example 434	Example 435
Compound F6-17 mesylate salt	20.0%	20.0%	20.0%
Lactose hydrate	60.0%	75.0%	79.0%
Sodium lauryl sulfate	20.0%	5.0%	1.0%

[0225]

(Examples 436 to 437)

With the Examples 436 to 437 shown in Table 30 and the above Comparative Example 22, the effect of SLS and polyvinyl pyrrolidone on solubility of the Compound F6-17 mesylate salt crystal was determined based on a small scale dissolution test. The results are shown in FIG. 17.

[0226]

Table 30

	Example 436	Example 437
Compound F6-17 mesylate salt	24.2%	24.2%
Lactose hydrate	70.8%	50.8%
Sodium lauryl sulfate	0.0%	20.0%
Polyvinyl pyrrolidone	5.0%	5.0%

[0227]

(Example 438)

With the Example 438 shown in Table 31, the effect of SLS on solubility of the Compound F6-17 maleate salt crystal was determined based on a small scale dissolution test. For the Comparative example 23, the Compound F6-17 maleate salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 18.

[0228]

Table 31

	Example 438
Compound F6-17 maleate salt	8.3%
Lactose hydrate	83.3%
Sodium lauryl sulfate	8.3%

[0229]

(Examples 439 to 440)

With the Examples 439 to 440 shown in Table 32, the effect of SLS and polyvinyl pyrrolidone on solubility of the Compound F6-17 L-tartrate salt crystal was determined based on small scale dissolution test. For the Comparative example 24, the Compound F6-17 L-tartrate salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 19.

[0230]

Table 32

	Example 439	Example 440
Compound F6-17 L-tartrate salt	26.6%	26.6%
Lactose hydrate	53.4%	48.4%
Sodium lauryl sulfate	20.0%	20.0%
Polyvinyl pyrrolidone	0.0%	5.0%

[0231]

(Examples 441 to 443)

With the Examples 441 to 443 shown in Table 33, the effect of SLS on solubility of the Compound F6-17 citrate salt crystal was determined based on a small scale dissolution test. For the Comparative example 25, the Compound F6-17 citrate salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 20.

[0232]

Table 33

	Example 441	Example 442	Example 443
Compound F6-17 citrate salt	24.1%	24.1%	24.1%
Lactose hydrate	55.9%	70.9%	74.9%
Sodium lauryl sulfate	20.0%	5.0%	1.0%

[0233]

(Examples 444 to 446)

With the Examples 444 to 446 shown in Table 34, the effect of SLS on solubility of the Compound F6-17 malate salt crystal was determined based on a small scale dissolution test. For the Comparative example 26, the Compound F6-17 malate salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 21.

[0234]

Table 34

	Example 444	Example 445	Example 446
Compound F6-17 malate salt	25.9%	25.9%	25.9%
Lactose hydrate	54.1%	69.1%	73.1%
Sodium lauryl sulfate	20.0%	5.0%	1.0%

[0235]

(Example 447)

With the Example 447 shown in Table 35, the effect of SLS on solubility of the Compound F5-46 hydrochloride salt crystal was determined based on a small scale

dissolution test. For the Comparative example 27, the Compound F5-46 hydrochloride salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 22.

[0236]

Table 35

	Example 447
Compound F5-46 hydrochloride salt	8.3%
Lactose hydrate	83.3%
Sodium lauryl sulfate	8.3%

[0237]

(Example 448)

With the Example 448 shown in Table 36, the effect of SLS on solubility of the Compound F5-46 mesylate salt crystal was determined based on small scale dissolution test. For the Comparative example 28, the Compound F5-46 mesylate salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 23.

[0238]

Table 36

	Example 448
Compound F5-46 mesylate salt	8.3%
Lactose hydrate	83.3%
Sodium lauryl sulfate	8.3%

[0239]

(Example 449)

With the Example 449 shown in Table 37, the effect of SLS on solubility of the Compound F5-51 hydrochloride salt crystal was determined based on a small scale dissolution test. For the Comparative example 29, the Compound F5-51 hydrochloride salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 24.

[0240]

Table 37

	Example 449
Compound F5-51 hydrochloride salt	8.3%
Lactose hydrate	83.3%
Sodium lauryl sulfate	8.3%

[0241]

(Example 450)

With the Example 450 shown in Table 38, the effect of SLS on solubility of the Compound F5-51 mesylate salt crystal was determined based on a small scale dissolution test. For the Comparative example 30, the Compound F5-51 mesylate salt crystal and lactose were mixed at weight ratio of 1 : 9. The results are shown in FIG. 25.

[0242]

Table 38

	Example 450
Compound F5-51 mesylate salt	8.3%
Lactose hydrate	83.3%
Sodium lauryl sulfate	8.3%

[0243]

(Example for producing a formulation)

Each component described in Tables 39 to 41 (except the lubricating agent) was added to a high speed mixing granulator for pre-mixing. The resulting mixture was sprayed with purified water and granulated under stirring. After drying under vacuum, dried powder was obtained. The dried powder was then granulated using a granulator. The granule powder obtained and the lubricating agent were admixed with each other with a V-type mixer to obtain powder blend, which was then filled in a capsule to produce a capsule formulation which contains 20 mg of active ingredient per capsule.

[0244]

Table 39

Component name	Mixing ratio (%)							
	F1	F2	F3	F4	F5	F6	F7	F8
Compound F6-20 hydrochloride salt	20	20	20	20	20	20	20	20
Lactose hydrate	46.5	46.5	46.5	46.5	46.5	46.5	46.5	46.5
Microcrystalline cellulose	15	15	15	15	15	15	15	15
Crosscarmellose sodium	3	3	3	3				
Crospovidone					3	3	3	3
Hydroxypropyl cellulose	5				5			
Hydroxypropylmethyl cellulose		5				5		
Methyl cellulose			5				5	
Sodium caseinate				5				5
Sodium lauryl sulfate	10	10	10	10	10	10	10	10
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	100	100	100	100	100	100	100	100

[0245]

Table 40

Component name	Mixing ratio (%)							
	F9	F10	F11	F12	F13	F14	F15	F16
Compound F6-20 mesylate salt	20	20	20	20	20	20	20	20
Lactose hydrate	46.5	46.5	46.5	46.5	46.5	46.5	46.5	46.5
Microcrystalline cellulose	15	15	15	15	15	15	15	15
Sodium glycolate starch	3	3	3	3	3	3	3	3
Hydroxypropyl cellulose	5							
Hydroxypropylmethyl cellulose		5						

Methyl cellulose			5					
Sodium caseinate				5				
Aminoalkyl methacrylate copolymer E					5			
Polyvinyl acetal diethyl aminoacetate						5		
Methacrylic acid copolymer S							5	
Hydroxypropylmethyl cellulose acetate succinate								5
Sodium lauryl sulfate	10	10	10	10	10	10	10	10
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	100	100	100	100	100	100	100	100

[0246]

Table 41

Component name	Mixing ratio (%)							
	F17	F18	F19	F20	F21	F22	F23	F24
Compound B4-8 L-tartrate salt	20	20	20	20				
Compound F6-17 citrate salt					20	20	20	20
Lactose hydrate	46.5	46.5	46.5	46.5	46.5	46.5	46.5	46.5
Microcrystalline cellulose	15	15	15	15	15	15	15	15
Sodium glycolate starch	3	3	3	3	3	3	3	3
Hydroxypropyl cellulose	5				5			
Hydroxypropylmethyl cellulose		5				5		
Methyl cellulose			5				5	

Sodium caseinate				5				5
Sodium lauryl sulfate	10	10	10	10	10	10	10	10
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	100	100	100	100	100	100	100	100

[0247]

(Examples 451 to 453)

For the Examples 451 to 453, preparation was carried out by using hydrochloride salt crystal of the Compound F6-20 according to dry production method using agate mortar and pestle with the formula shown in Table 42. The Comparative example 31 was prepared by mixing hydrochloride salt crystal of the Compound F6-20 with lactose.

Effect of SLS, polyoxyethylene (105) polyoxypropylene (5) glycol, and poly(sodium 4-styrene sulfonate) on the solubility of the Compound F6-20 hydrochloride salt crystal was determined. As a result, as it is shown in FIG. 26, it was evident that the solubility of the Compound F6-20 hydrochloride salt crystal is improved by addition of SLS and poly(sodium 4-styrene sulfonate). It was also evident that the initial solubility of the Compound F6-20 hydrochloride salt crystal is improved by addition of polyoxyethylene (105) polyoxypropylene (5) glycol.

As for the poly(sodium 4-styrene sulfonate), the compound from Sigma Chemical Company was used (i.e., product number 243051).

[0248]

Table 42

	Example 451	Example 452	Example 453
Compound F6-20 hydrochloride salt crystal	10.8%	10.8%	10.8%
Lactose hydrate	79.2%	79.2%	79.2%
Sodium lauryl sulfate	10.0%	0.0%	0.0%
Polyoxyethylene (105) polyoxypropylene (5) glycol	0.0%	10.0%	0.0%
Poly(sodium 4-styrene sulfonate)	0.0%	0.0%	10.0%

Total	100.0%	100.0%	100.0%

[0249]

(Examples 454 to 457)

With the Examples 454 to 457 shown in Table 43, the effect of a combination of SLS and polyoxyethylene (105) polyoxypropylene (5) glycol on the solubility of the Compound F6-20 hydrochloride salt crystal was determined. As a result, as it is shown in FIG. 27, it was evident that the solubility of the Compound F6-20 hydrochloride salt crystal improved by SLS is further enhanced by adding at least 1% of polyoxyethylene (105) polyoxypropylene (5) glycol to the formulation, especially in the early phase.

[0250]

Table 43

	Example 454	Example 455	Example 456	Example 457
Compound F6-20 hydrochloride salt crystal	10.8%	10.8%	10.8%	10.8%
Lactose hydrate	84.2%	83.2%	81.7%	74.2%
Sodium lauryl sulfate	5.0%	5.0%	5.0%	5.0%
Polyoxyethylene (105) polyoxypropylene (5) glycol	0.0%	1.0%	2.5%	10.0%
Total	100.0%	100.0%	100.0%	100.0%

[0251]

(Examples 458 to 460)

With the Examples 458 to 460 shown in Table 44, the effect of a combination of SLS and poly(sodium 4-styrene sulfonate) on the solubility of the Compound F6-20 hydrochloride salt crystal was determined. As a result, as it is shown in FIG. 28, it was evident that the effect of improving the solubility of the Compound F6-20 hydrochloride salt crystal by SLS is further enhanced depending on the additive amount of poly(sodium 4-styrene sulfonate).

As for the poly(sodium 4-styrene sulfonate), the compound from Sigma Chemical Company was used (i.e., product number 243051).

[0252]

Table 44

	Example 458	Example 459	Example 460
Compound F6-20 hydrochloride salt crystal	10.8%	10.8%	10.8%
Lactose hydrate	83.2%	81.7%	74.2%
Sodium lauryl sulfate	5.0%	5.0%	5.0%
Poly(sodium 4-styrene sulfonate)	1.0%	2.5%	10.0%
Total	100.0%	100.0%	100.0%

[0253]

(Examples 461 to 465)

With the Examples 461 to 465 shown in Table 45, the effect of a combination of SLS, polyoxyethylene (105) polyoxypropylene (5) glycol, and poly(sodium 4-styrene sulfonate) on the solubility of the Compound F6-20 hydrochloride salt crystal was determined. As a result, as it is shown in FIG. 29, it was evident that the solubility of the Compound F6-20 hydrochloride salt crystal is improved by the combination of SLS, polyoxyethylene (105) polyoxypropylene (5) glycol, and poly(sodium 4-styrene sulfonate).

As for the poly(sodium 4-styrene sulfonate), the compound from Sigma Chemical Company was used (i.e., product number 243051).

[0254]

Table 45

	Example 461	Example 462	Example 463	Example 464	Example 465
Compound F6-20 hydrochloride salt crystal	16.5%	16.5%	16.5%	16.5%	16.5%
Lactose hydrate	52.0%	44.3%	40.5%	21.2%	2.0%
Microcrystalline cellulose	20.0%	20.0%	20.0%	20.0%	20.0%
Sodium glycolate starch	6.0%	6.0%	6.0%	6.0%	6.0%
Hydroxy propyl cellulose	5.0%	5.0%	5.0%	5.0%	5.0%
Sodium lauryl sulfate	0.0%	7.7%	0.0%	0.0%	7.7%
Polyoxyethylene (105) polyoxy	0.0%	0.0%	11.5%	0.0%	11.5%

propylene (5) glycol					
Poly(sodium 4-styrene sulfonate)	0.0%	0.0%	0.0%	30.8%	30.8%
Magnesium stearate	0.5%	0.5%	0.5%	0.5%	0.5%
Total	100.0%	100.0%	100.0%	100.0%	100.0%

[0255]

(Examples 466 and 467)

With the Examples 466 and 467 shown in Table 46, the effect of the amount of SLS on the solubility of the formulation of the Compound F6-20 hydrochloride salt crystal containing polyoxyethylene (105) polyoxypropylene (5) glycol and poly(sodium 4-styrene sulfonate) was determined. As a result, as it is shown in FIG. 30, it was evident that the solubility of the formulation of the Compound F6-20 hydrochloride salt crystal containing polyoxyethylene (105) polyoxypropylene (5) glycol and poly(sodium 4-styrene sulfonate) remained the same even when the amount of SLS was cut to half.

As for the poly(sodium 4-styrene sulfonate), the compound from Sigma Chemical Company was used (i.e., product number 243051).

[0256]

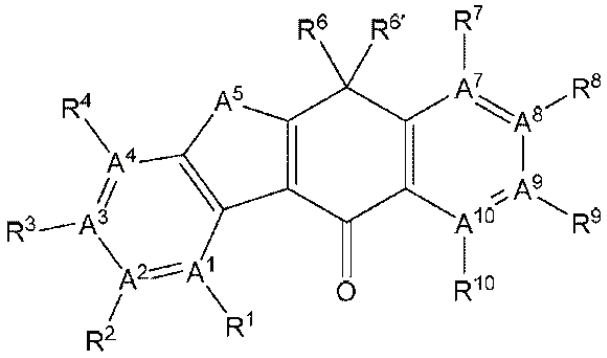
Table 46

	Example 466	Example 467
Compound F6-20 hydrochloride salt crystal	16.5%	16.5%
Lactose hydrate	27.3%	31.2%
Microcrystalline cellulose	20.0%	20.0%
Sodium glycolate starch	6.0%	6.0%
Hydroxy propyl cellulose	5.0%	5.0%
Sodium lauryl sulfate	7.7%	3.8%
Polyoxyethylene (105) polyoxypropylene (5) glycol	1.5%	1.5%
Poly(sodium 4-styrene sulfonate)	15.4%	15.4%
Magnesium stearate	0.5%	0.5%
Total	100.0%	100.0%

CLAIMS

[Claim 1]

A composition comprising a substance represented by the Formula (I), a pharmaceutically acceptable carrier, and a dissolution aid,



(I)

[wherein,

A^1, A^2, A^3, A^4, A^7, A^8, A^9 and A^{10} all represent C, or any one of A^2, A^3, A^4, A^7, A^8 and A^9 represents N (with the proviso that, when it represents N, no substituent group exists therefor) and the remainings represent C;

A^5 is selected from NR^5, O and S;

R^1 and R^{10} each independently represent [1] a hydrogen atom, [2] a cyano group, [3] a halogen atom or [4] a 4- to 10-membered heterocycloalkyl group which may be substituted by 4- to 10-membered heterocycloalkyl group(s);

R^2 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a $C_{1\text{-}8}$ alkyl group,

(3) a $C_{2\text{-}8}$ alkenyl group,

(4) a $C_{2\text{-}8}$ alkynyl group,

(5) a cyano group,

(6) a halogen atom,

(7) a $(C_{1\text{-}8}$ alkyl$)_{m2}$-amino group which may be substituted by $C_{1\text{-}8}$ alkylsulfonyl group(s),

m2: 0~2, and

(8) a nitro group;

R^3 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a C_{1-8} alkyl group which may be substituted by [1] halogen atom(s), [2] hydroxy group(s) or [3] C_{1-8} alkoxy group(s),

(3) a C_{6-10} aryl group,

(4) a cyano group,

(5) a C_{1-8} alkanoyl group which may be substituted by C_{6-10} aryl group(s),

(6) a $(C1\text{-}8\ alkyl)_{m3a}$-aminocarbonyl group which may be substituted by one or more R^{3A},

R^{3A}: [1] a C_{6-10} aryl group, [2] a C_{1-8} alkoxy group, [3] a 5- to 14-membered heteroaryl group, or [4] a C_{6-10} arylsulfonyl group,

m3a: 0~2,

(7) a hydroxycarbonyl group,

(8) a C_{1-8} alkoxycarbonyl group which may be substituted by [1] hydroxy group(s) or [2] C_{1-8} alkoxy group(s),

(9) a halogen atom,

(10) a $(C_{1-8}\ alkyl)_{m3b}$-amino group which may be substituted by C_{6-10} aryl group(s),

m3b: 0~2,

(11) a C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by [1] C_{6-10} aryl group(s) or [2] C_{6-10} aryloxy group(s),

(12) a C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by halogen atom(s),

(13) a $(C_{1-8}\ alkyl)_{m3c}$-aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{6-10} aryl group(s),

m3c: 0~2,

(14) a nitro group,

(15) a hydroxy group,

(16) a C_{1-8} alkoxy group which may be substituted by one or more R^{3B},

R^{3B}: [1] a hydroxy group, [2] a C_{1-8} alkoxy group, [3] a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl group, [4] a $(C_{1-8}\ alkyl)_{m3d}$-amino group, or [5] a halogen atom,

m3d: 0~2,

(17) a 4- to 10-membered heterocycloalkyloxy group,

(18) a 5- to 14-membered heteroaryloxy group,

(19) a $(C_{1-8}$ alkyl$)_{m3e}$-aminocarbonyloxy group which may be substituted by C_{6-10} aryl group(s)

m3e: 0~2,

(20) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group,

(21) a C_{1-8} alkylsulfonyloxy group which may be substituted by halogen atom(s),

(22) a C_{1-8} alkylthio group,

(23) a C_{1-8} alkylsulfonyl group which may be substituted by C_{6-10} aryl group(s),

(24) a 5- to 14-membered heteroaryl group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by C_{1-8} alkoxy group(s),

(25) a C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkoxy group(s),

(26) a C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by halogen atom(s),

(27) a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted by one or more R^{3C},

R^{3C}: [1] a C_{1-8} alkyl group which may be substituted by halogen atom(s), or [2] a C_{1-8} alkoxy group,

(28) a C_{3-8} cycloalkyl (C_{0-8} alkyl) aminocarbonyloxy group, and

(29) a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group which may be substituted by substituent group(s) selected from the group consisting of [1] a C_{1-8} alkyl group and [2] a C_{1-8} alkoxy group;

R^4 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a C_{1-8} alkyl group which may be substituted by halogen atom(s),

(3) a C_{2-8} alkenyl group,

(4) a C_{2-8} alkynyl group,

(5) a C_{3-8} cycloalkyl group,

(6) a cyano group,

(7) an aminocarbonyl group,

(8) a $(C_{1-8}$ alkyl$)_{m4a}$-aminocarbonyl group,

m4a: 1~2,

(9) a hydroxycarbonyl group,

(10) a C_{1-8} alkoxycarbonyl group,

(11) a halogen atom,

(12) a $(C_{1-8}$ alkyl$)_{m4b}$- amino group,

m4b: 0~2,

(13) a hydroxy group, and

(14) a C_{1-8} alkoxy group which may be substituted by hydroxy group(s);

R^5 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a C_{1-8} alkyl group which may be substituted by one or more R^{5A},

R^{5A}: [1] a hydroxycarbonyl group, [2] a C_{1-8} alkoxycarbonyl group, [3] a hydroxy group, [4] a C_{1-8} alkoxy group, [5] a $(C_{1-8}$ alkyl$)_{m5}$-amino group, [6] a C_{6-10} aryl group, or [7] a C_{1-8} alkylthio group,

m5: 0~2,

(3) a C_{2-8} alkenyl group,

(4) a C_{2-8} alkynyl group,

(5) a C_{3-8} cycloalkyl group, and

(6) a C_{1-8} alkylsulfonyl group;

R^6 and $R^{6'}$ are each independently selected from the group consisting of:

(1) a C_{1-8} alkyl group which may be substituted by halogen atom(s),

(2) a C_{2-8} alkenyl group, and

(3) a C_{2-8} alkynyl group; or

R^6 and $R^{6'}$ are taken together with the carbon atoms to which they are bound to form:

(4) a C_{3-8} cycloalkyl group, or

(5) a 4- to 10-membered heterocycloalkyl group which may be substituted by C_{1-8} alkyl C_{6-10} aryl sulfonyl group(s) which may be substituted by C_{1-8} alkyl group(s);

R^7 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a halogen atom,

(3) a $C_{1\text{-}8}$ alkoxy group which may be substituted by one or more R^{7A},

R^{7A}: [1] a $(C_{1\text{-}8}$ alkyl$)_{m7a}$-amino group, [2] a hydroxy, [3] a 4- to 10-memberd heterocycloalkyl group which may be substituted by $C_{1\text{-}8}$ alkyl group(s),

m7a: 0~2,

(4) a $C_{1\text{-}8}$ alkylsulfonyl group,

(5) a nitro group, and

(6) a hydroxyl group;

R^8 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a $C_{1\text{-}8}$ alkyl group which may be substituted by one or more R^{8A},

R^{8A}: [1] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8A1}, [2] a $(C_{1\text{-}8}$ alkyl$)_{m8a}$- amino group which may be substituted by a halogen atom, or [3] a hydroxy group,

m8a:0~2,

R^{8A1}: [1] a $C_{1\text{-}8}$ alkyl group, [2] a $C_{1\text{-}8}$ alkylsulfonyl group, [3] a $(C_{1\text{-}8}$ alkyl$)_{m8b}$-aminosulfonyl group, [4] an oxo group, [5] a $C_{1\text{-}8}$ alkoxycarbonyl, or [6] a $C_{1\text{-}8}$ alkoxycarbonyl ($C_{0\text{-}8}$ alkyl) aminosulfonyl,

m8b: 0~2,

(3) a $C_{2\text{-}8}$ alkenyl group,

(4) a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8B},

R^{8B}:

<1> a $C_{1\text{-}8}$ alkyl group which may be substituted by one or more R^{8B1},

<2> a $C_{2\text{-}8}$ alkeynyl group,

<3> a $C_{2\text{-}8}$ alkynyl group,

<4> a $C_{3\text{-}8}$ cycloalkyl group which may be substituted by [1] cyano group(s) or [2] $C_{1\text{-}8}$ alkyl

group(s),

<5> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8B2},

<6> a C_{1-8} alkoxy group which may be substituted by substituent group(s) selected from the group consisting of [1] a C_{1-8} alkoxy group and [2] a C_{3-8} cycloalkyl group,

<7> a C_{1-8} alkoxycarbonyl group,

<8> a C_{1-8} alkylsulfonyl group,

<9> a 5- to 14-membered heteroarylsulfonyl group,

<10> an oxo group,

<11> a cyano group,

<12> a C_{1-8} alkanoyl group which may be substituted by one or more R^{8B3},

<13> a C_{3-8} cycloalkylcarbonyl group,

<14> a $(C_{1-8}$ alkyl$)_{m8c}$-aminosulfonyl group,

<15> a C_{1-8} alkylsulfonyl (C_{0-8} alkyl) amino group,

<16> a $(C_{1-8}$ alkyl$)_{m8d}$-amino group which may be substituted by one or more R^{8B4},

<17> a hydroxy group,

<18> a $(C_{1-8}$ alkyl$)_{m8e}$-aminocarbonyl group, or

<19> a C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group

m8c: 0~2

m8d: 0~2

m8e: 0~2

R^{8B1}: [1] a C_{3-8} cycloalkyl group, [2] a hydroxy group, or [3] a C_{1-8} alkoxy group(s) ,

R^{8B2}: [1] a halogen atom, [2] a C_{1-8} alkyl group, [3] an oxo group, [4] a hydroxy group, or [5] a deuterium atom,

R^{8B3}: a $(C_{1-8}$ alkyl$)_{m8f}$-amino group,

m8f: 0~2,

R^{8B4}: [1] a C_{3-8} cycloalkyl group, or [2] a hydroxy group,

(5) a 5- to 14-membered heteroaryl group which may be substituted by a C_{1-8} alkyl group,

(6) a $(C_{1-8}$ alkyl$)_{m8g}$-aminocarbonyl group which may be substituted by one or more R^{8C},

m8g: 0~2,

R^{8C}:[1] a hydroxy group, [2] a $(C_{1-8}$ alkyl$)_{m8h}$-amino group which may be substituted by

substituent group(s) selected from the group consisting of <1> a $(C_{1-8}$ alkyl$)_{m8i}$-aminosulfonyl group, <2> a C_{1-8} alkylsulfonyl group, <3> a C_{1-8} alkoxycarbonyl group and <4> a C_{1-8} alkoxycarbonyl(C_{0-8} alkyl) aminosulfonyl group, [3] a C_{1-8} alkylsulfonyl group, or [4] a C_{1-8} alkoxy group which may be substituted by a hydroxy group,

m8h: 0~2,

m8i: 0~2,

(7) a 4- to 10-membered heterocycloalkyl (C_{0-8} alkyl) aminocarbonyl group which may be substituted by oxo group(s),

(8) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by one or more R^{8D},

R^{8D}: [1] a C_{1-8} alkyl group which may be substituted by one or more R^{8D1}, [2] a hydroxy group, [3] a C_{1-8} alkylsulfonyl group, or [4] a C_{1-8} alkoxycarbonyl group,

R^{8D1}: [1] a hydroxy group, or [2] a C_{1-8} alkoxy group,

(9) a hydroxycarbonyl group,

(10) a C_{0-8} alkoxy (C_{0-8} alkyl) aminocarbonyl group which may be substituted by hydroxy group(s),

(11) a halogen atom,

(12) a $(C_{1-8}$ alkyl$)_{m8j}$-amino group which may be substituted by one or more R^{8H},

m8j: 0~2,

R^{8H}: [1] a hydroxy group, or [2] a 4- to 10-membered heterocycloalkyl group,

(13) a hydroxyl group,

(14) a C_{1-8} alkoxy group which may be substituted by one or more R^{8E},

R^{8E}:

<1> a hydroxy group,

<2> halogen atom,

<3> a hydroxycarbonyl group,

<4> a C_{1-8} alkoxycarbonyl group,

<5> a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by one or more R^{8E1},

<6> a $(C_{1-8}$ alkyl$)_{m8k1}$-amino group which may be substituted by one or more R^{8E2},

m8k1: 0~2,

<7> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8E3},

<8> a 5- to 14-membered heteroaryl group,

<9> a $(C_{1\text{-}8}$ alkyl$)_{m8k2}$-aminocarbonyl group which may be substituted by one or more R^{8E6},

m8k2: 0~2,

<10> a $C_{1\text{-}8}$ alkoxy group which may be substituted by one or more R^{8E7},

<11> a $C_{1\text{-}8}$ alkylthio group,

<12> a $C_{1\text{-}8}$ alkylsulfinyl group,

<13> a $C_{1\text{-}8}$ alkylsulfonyl group,

R^{8E1}:

<1> a $C_{1\text{-}8}$ alkoxycarbonyl group,

<2> a $C_{1\text{-}8}$ alkanoyl group,

<3> a $C_{1\text{-}8}$ alkylsulfonyl group,

<4> a $(C_{1\text{-}8}$ alkyl$)_{m8k3}$-aminosulfonyl group,

m8k3: 0~2, or

<5> a 4- to 10-membered heterocycloalkyl group,

R^{8E2}:

<1> a hydroxy group,

<2> a $C_{1\text{-}8}$ alkoxycarbonyl group which may be substituted by halogen atom(s),

<3> a $C_{3\text{-}8}$ cycloalkyl group which may be substituted by $C_{1\text{-}8}$ alkyl group(s) which may be substituted by hydroxy group(s),

<4> a $C_{1\text{-}8}$ alkanoyl group which may be substituted by substituent group(s) selected from the group consisting of [1] a $(C_{1\text{-}8}$ alkyl$)_{m8k4}$-amino group and [2] a halogen atom(s),

m8k4: 0~2,

<5> a $(C_{1\text{-}8}$ alkyl$)_{m8k5}$-aminocarbonyl group,

m8k5: 0~2,

<6> a $C_{1\text{-}8}$ alkylsulfonyl group,

<7> a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl group which may be substituted by $C_{1\text{-}8}$ alkyl group(s),

<8> a $(C_{1\text{-}8}$ alkyl$)_{m8k6}$-aminosulfonyl group which may be substituted by $C_{1\text{-}8}$ alkoxycarbonyl group(s),

m8k6: 0~2, or

R^{8E3}:

<1> a C_{1-8} alkyl group which may be substituted by substituent group(s) selected from the group consisting of [1] a hydroxy group and [2] a C_{1-8} alkylcarbonyloxy group,

<2> a C_{1-8} alkylcarbonyloxy group,

<3> a hydroxy group,

<4> a C_{3-8} cycloalkyl group,

<5> a C_{1-8} alkoxy group,

<6> a C_{1-8} alkoxycarbonyl group,

<7> a C_{1-8} alkylsulfonyl group,

<8> a $(C_{1-8}$ alkyl$)_{m8k8}$-aminocarbonyl group

m8k8: 0~2,

<9> a C_{1-8} alkanoyl group which may be substituted by hydroxy group(s),

<10> an oxo group, or

<11> a 4- to 10-membered heterocycloalkyl group which may be substituted by substituent group(s) selected from the group consisting of [1] a C_{1-8} alkanoyl group, [2] a C_{1-8} alkoxycarbonyl group and [3] a C_{1-8} alkylsulfonyl group,

R^{8E6}:

<1> a C_{2-8} alkenylcarbonyloxy group,

<2> a hydroxy group,

<3> a cyano group,

<4> a $(C_{1-8}$ alkyl$)_{m8k9}$-amino group which may be substituted by hydroxy group(s)

m8k9: 0~2,

<5> a C_{1-8} alkoxy group which may be substituted by hydroxy group(s),

<6> a C_{1-8} alkylcarbonyloxy group,

<7> a 4- to 10-membered heterocycloalkyl group which may be substituted by C_{1-8} alkyl group(s), or

<8> a 5- to 14-membered heteroaryl group,

R^{8E7}:

<1> a hydroxy group, or

<2> a C_{1-8} alkoxy group which may be substituted by hydroxy group(s),

(15) a 4- to 10-membered heterocycloalkyloxy group which may be substituted by one

or more R^{8F},

R^{8F}:

<1> a C_{1-8} alkyl group which may be substituted by one or more R^{8F1},

<2> a C_{3-8} cycloalkyl group,

<3> a C_{1-8} alkanoyl group which may be substituted by halogen atom(s),

<4> a C_{1-8} alkylcarbonyloxy group,

<5> a C_{1-8} alkoxycarbonyl group,

<6> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8F2},

<7> a C_{1-8} alkyl sulfonyl group,

<8> a hydroxy group, or

<9> a C_{6-10} aryl group,

R^{8F1}: [1]a hydroxy group, [2] a C_{1-8} alkoxy group, or [3] a halogen atom,

R^{8F2}: [1] a 4- to 10-membered heterocycloalkyl group, [2] a C_{1-8} alkoxycarbonyl group, or [3] a C_{1-8} alkylsulfonyl group,

(16) a 5- to 14-membered heteroaryloxy group,

(17) a 4- to 10-membered heterocycloalkylcarbonyloxy group,

(18) a $(C_{1-8}$ alkyl$)_{m8l1}$-aminosulfonyloxy group,

m8l1: 0~2,

(19) a C_{1-8} alkyl thio group which may be substituted by [1] $(C_{1-8}$ alkyl$)_{m8l2}$-amino group(s), [2] hydroxy group(s) or [3] hydroxycarbonyl group(s),

m8l2: 0~2,

(20) a C_{1-8} alkylsulfonyl group which may be substituted by one or more R^{8G},

R^{8G}: [1] a hydroxycarbonyl group, [2] a hydroxy group, or [3] a $(C_{1-8}$ alkyl$)_{m8l3}$-amino group,

m8l3: 0~2,

(21) a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyloxy group which may be substituted by C_{1-8} alkyl group(s),

(22) a C_{2-8} alkenyloxy group, and

(23) a C_{1-8} alkylsulfonyloxy group which may be substituted by halogen atom(s);

R^9 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a C_{1-8} alkyl group which may be substituted by one or more R^{9A},

R^{9A}: [1] a C_{3-8} cycloalkyl group, [2] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9A1}, [3] a hydroxy group, [4] a C_{1-8} alkoxy group, or [5] a hydroxycarbonyl group,

R^{9A1}: [1] a C_{1-8} alkyl group, [2] a C_{3-8} cycloalkyl group, or [3] a 4- to 10-membered heterocycloalkyl group,

(3) a C_{2-8} alkenyl group which may be substituted by one or more R^{9B},

R^{9B}: [1] a $(C_{1-8}$ alkyl$)_{m9a}$-amino group, [2] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9B1},

R^{9B1}: [1] a C_{3-8} cycloalkyl group, or [2] a 4- to 10-membered heterocycloalkyl group,

m9a: 0~2,

(4) a C_{2-8} alkynyl group which may be substituted by one or more R^{9C},

R^{9C}: [1] a C_{1-8} alkoxy group, [2] a $(C_{1-8}$ alkyl$)_{m9b}$-amino group which may be substituted by C_{6-10} aryl group(s), [3] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9C1}, [4] a C_{3-8} cycloalkyl group, [5] a hydroxy group, [6] a hydroxycarbonyl group, or [7] a C_{1-8} alkyloxycarbonyl group,

m9b: 0~2,

R^{9C1}: [1] a C_{3-8} cycloalkyl group, [2] a 4- to 10-membered heterocycloalkyl group, or [3] an oxo group,

(5) a C_{3-8} cycloalkyl group,

(6) a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9D},

R^{9D}: [1] a C_{1-8} alkyl group which may be substituted by 4- to 10-membered heterocycloalkyl group(s), [2] a C_{3-8} cycloalkyl group, [3] a 4- to 10-membered heterocycloalkyl group, or [4] a C_{1-6} alkylsulfonyl group, or [5] a C_{1-8} alkoxycarbonyl group,

(7) a C_{6-10} aryl group which may be substituted by one or more R^{9E},

R^{9E}: [1] a halogen atom, [2] a hydroxy group, [3] a hydroxycarbonyl group, or [4] a C_{1-8} alkyl group which may be substituted by hydroxy group(s), or [5] a C_{1-8} alkoxy group,

(8) a 5- to 14-membered heteroaryl group which may be substituted by C_{1-8} alkyl group(s),

(9) a cyano group,

(10) a C_{1-8} alkanoyl group,

(11) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by C_{1-8} alkyl group(s),

(12) a halogen atom,

(13) a $(C_{1-8}$ alkyl$)_{m9c}$- amino group which may be substituted by one or more R^{9F},

m9c: 0~2,

(14) a C_{1-8} alkylcarbonyl(C_{0-8} alkyl)amino group which may be substituted by $(C_{1-8}$ alkyl$)_{m9d}$- amino group(s),

m9d: 0~2,

(15) a C_{1-8} alkylsulfonyl(C_{0-8} alkyl)amino group,

(16) a $(C_{1-8}$ alkyl$)_{m9e}$- aminosulfonyl(C_{0-8} alkyl)amino group,

m9e: 0~2,

(17) a nitro group,

(18) a hydroxy group,

(19) a C_{1-8} alkoxy group which may be substituted by one or more R^{9G},

R^{9G}: [1] a hydroxy group, [2] a hydroxycarbonyl group, [3] a C_{6-10} aryl group which may be substituted by C_{1-8} alkoxy group(s), [4] a $(C_{1-8}$ alkyl$)_{m9g1}$-amino group, [5] a C_{1-8} alkoxy group which may be substituted by one or more R^{9G1}, [6] a 5- to 14-membered heteroaryl group, or [7] a 4- to 10-membered heterocycloalkyloxy group which may be substituted by C_{1-8} alkyl group(s),

m9g1: 0~2,

R^{9G1}: [1] a C_{1-8} alkoxy group, or [2] a hydroxycarbonyl group,

(20) a 4- to 10-membered heterocycloalkyloxy group which may be substituted by [1] 4- to 10-membered heterocycloalkyl group(s), or [2] C_{1-8} alkoxycarbonyl group(s),

(21) a C_{1-8} alkylsulfonyloxy group which may be substituted by halogen atom(s),

(22) a C_{1-8} alkylthio group which may be substituted by $(C_{1-8}$ alkyl$)_{m9f}$- amino group(s),

m9f: 0~2,

(23) a C_{1-8} alkylsulfonyl group which may be substituted by $(C_{1-8}$ alkyl$)_{m9g}$-amino group(s),

m9g: 0~2,

(24) a ($C_{1\text{-}8}$ alkyl)$_{m9h}$-aminosulfonyl group,

m9h: 0~2,

(25) a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl group which may be substituted by $C_{1\text{-}8}$ alkyl group(s), and

(26) a hydroxycarbonyl group].

[Claim 2]

The composition according to Claim 1, wherein said dissolution aid is a surfactant.

[Claim 3]

The composition according to Claim 2, wherein said surfactant is a non-ionic or an anionic surfactant.

[Claim 4]

The composition according to Claim 2 or 3, wherein said surfactant is selected from a group consisting of monoalkyl sulfate, polyoxyl 40 stearate, sorbitan trioleate, polyoxyethylene (105) polyoxypropylene (5) glycol, polyoxyethylene hydrogenated castor oil 60, polyoxyl 35 castor oil, lauromacrogol, dioctyl sodium sulfosuccinate, sodium lauroylsarcosine, sodium dodecylbenzene sulfonate, and a mixture thereof.

[Claim 5]

The composition according to any one of Claims 2 to 4, wherein said composition further comprises an organic polymer.

[Claim 6]

The composition according to Claim 5, wherein said organic polymer is selected from a group consisting of a synthetic resin, a water soluble polymer, a gastric-soluble polymer, an enteric-soluble polymer, and a mixture thereof.

[Claim 7]

The composition according to Claim 5, wherein said organic polymer is a synthetic resin.

[Claim 8]

The composition according to any one of Claims 2 to 7, wherein said composition further comprises one or more additives which are selected from the following additive group A:

additive A: citric acid, fumaric acid, DL-malic acid, adipic acid, succinic acid, tartaric acid, lactic acid, maleic acid, sulfuric acid, phosphoric acid, sodium dehydroacetate, sodium stearyl fumarate, stearic L-ascorbate ester, L-aspartic acid, skimmed milk powder, aluminum lactate, ascorbic acid palmitate, aluminum sulfate, monobasic calcium phosphate, or acetyl tryptophan.

[Claim 9]

The composition according to any one of Claims 1 to 8, wherein said water solubility of the substance is less than 100 μg/mL at 25°C.

[Claim 10]

The composition according to any one of Claims 1 to 8, wherein A^1 to A^4, A^6, and A^7 are a carbon atom, A^5 is NH, R^3 is cyano, R^6 and $R^{6'}$ are both methyl for the substance.

[Claim 11]

The composition according to any one of Claims 1 to 8, wherein said substance is selected from

9-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-cyclopropylethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-bromo-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-bromo-8-(4-cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-chloro-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6,9-trimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethynyl-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-9-ethynyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(1-isopropyl-piperidin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(2-tert-butylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethynyl-8-(4-methanesulfonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-bromo-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-propyl-6,11-dihydro-5H-

benzo[b]carbazole-3-carbonitrile; and

9-ethynyl-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

[Claim 12]

An orally administrable formulation comprising the composition described in any one of Claims 1 to 11.