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(54) **Title**: PROPHYLACTIC/THERAPEUTIC AGENT FOR CANCER

(57) **Abstract**: The present invention provides an agent for the prophylaxis or treatment cancer, which is superior in the safety and the like. An agent for the prophylaxis or treatment cancer, which contains a kinase inhibitory substance showing pseudo-irreversibility, particularly, an agent for the prophylaxis or treatment cancer, which contains a kinase inhibitory substance showing t1/2 relative to kinase (receptor kinase etc.) of not less than 10 minutes.

DESCRIPTION

PROPHYLACTIC/THERAPEUTIC AGENT FOR CANCER

Technical Field

[0001]

The present invention relates to a superior prophylactic/therapeutic agent for cancer, containing a kinase inhibitory substance showing pseudo-irreversibility.

[0002]

(Background of the Invention)

With the advancement in cancer research, it has been clarified that kinase is involved in cell canceration, and found that an inhibitor of kinase relating to signal transduction pathway is effective for cancer treatment. As a concrete example thereof, a VEGFR2 inhibitor is described in the following. For a solid tumor to grow to a certain size or more, the tumor cell requires neogenesis of blood vessels that supply sufficient nutrition and oxygen (e.g., non-patent document 1). One of known important factors causing angiogenesis in tumor is a vascular endothelial growth factor (VEGF). VEGF binds to a vascular endothelial growth factor receptor (VEGFR) expressed on vascular endothelial cell and transmits signal for cell proliferation (e.g., non-patent document 2). Thus, inhibition of VEGF-VEGFR signal transduction system is considered to suppress angiogenesis, and inhibit tumor growth (e.g., non-patent document 3). Moreover, since tumor blood vessels are also involved in hematogenous metastasis of cancer, inhibition of angiogenesis is considered to be effective for suppressing cancer metastasis.

[0003]

As compounds inhibiting receptor tyrosine kinase such as VEGFR, a phthalazine derivative (e.g., patent document 1), a pyrrole-substituted 2-indolinone derivative (e.g., patent document 2), a quinazoline derivative (e.g., patent document 3), a ω-carboxyaryl-substituted diphenylurea derivative (e.g.,

patent document 4), a quinoline derivative and a quinazoline derivative (e.g., patent document 5), a nitrogen-containing aromatic ring derivative (e.g., patent document 6), a fused pyrimidine compound (e.g., patent document 7), an imidazopyridazine derivative (e.g., patent document 8) and the like are known.

As enzyme inhibitory compounds showing slow dissociation from a target protein (pseudo-irreversible), Celecoxib (Celebrex; Pfizer, COX2 inhibitor), Valdecoxib (Bextra; Pfizer, COX2 inhibitor) and Rivastigmine (Exelon; Novartis, acetylcholinesterase inhibitors) are known. For example, pseudo-irreversibility to COX2 is suggested to contribute to COX2 selectivity (e.g., non-patent document 4 and non-patent document 5).

Citation List

[0004]

Patent Literature

patent document 1: WO98/35958
patent document 2: WO01/60814
patent document 3: WO01/32651
patent document 4: WO00/42012
patent document 5: WO00/43366
patent document 6: WO02/32872
patent document 7: WO05/118588
patent document 8: WO08/16192

Non Patent Literature

non-patent document 1: New England Journal of Medicine, 1971, vol. 285, No. 21, pages 1182-1186
non-patent document 2: Endocrine Reviews, 1997, vol. 18, No. 1, pages 4-25
non-patent document 3: Drug Discovery Today, 2001, vol. 6, No. 19, pages 1005-1024
non-patent document 4: Nature Reviews, Drug Discovery, vol. 3, September (2004), pages 801-808
non-patent document 5: Nature Reviews, Drug Discovery, vol. 5,

September (2006), pages 730-739

Summary of the Invention

Problems to be Solved by the Invention

[0005]

A kinase inhibitor superior in the affinity for kinase, as well as efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability is expected to provide a therapeutically superior effect. The development of a pharmaceutical product more superior in the safety and the like has been expected. Therefore, an object of the present invention is to provide an agent for the prophylaxis or treatment of cancer, which is more superior in the safety and the like.

[0006]

The present inventors have conducted intensive studies in an attempt to solve the aforementioned problem and found for the first time that a kinase inhibitor superior in the affinity for kinase and slow in dissociation from kinase (pseudo-irreversible) can exhibit a more superior treatment effect, and further found that a compound having a dissociation half-life of not less than 10 min can unexpectedly maintain efficacy even at a concentration below the effective blood concentration at which an in vivo effect is expected, and even after disappearance of the compound from the blood, which resulted in the completion of the present invention.

Accordingly, the present invention provides,

[1] an agent for the prophylaxis or treatment of cancer showing a prolonged effect for cancer treatment, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min;

[2] an agent for the prophylaxis or treatment of cancer showing a potentiated effect for cancer treatment, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min;

[3] an agent for the prophylaxis or treatment of cancer showing reduced side effects in cancer treatment, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min;

[4] an agent for the prophylaxis or treatment of cancer permitting a low dose for patients, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min;

[5] an agent for the prophylaxis or treatment of cancer permitting a long interval in administration to patients, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min;

[6] an agent for the prophylaxis or treatment of cancer showing a prolonged period of drug withdrawal, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min;

[7] the agent of any of the above-mentioned [1]-[6], wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 300 min;

[8] the agent of any of the above-mentioned [1]-[7], wherein the kinase is a receptor kinase;

[9] the agent of the above-mentioned [8], wherein the receptor kinase is a vascular endothelial growth factor receptor 2 (VEGFR2);

[10] the agent of the above-mentioned [9], wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 80 min;

[11] the agent of the above-mentioned [8], wherein the receptor kinase is a platelet-derived growth factor receptor (PDGFR);

[12] the agent of the above-mentioned [11], wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 60 min;

[13] a method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective

amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method shows a prolonged effect for cancer treatment;

[14] a method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method shows a potentiated effect for cancer treatment;

[15] a method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method shows reduced side effects in cancer treatment;

[16] a method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method permits a low dose for patients;

[17] a method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method permits a long interval in administration to patients;

[18] a method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method shows a prolonged period of drug withdrawal;

[19] the method of any of the above-mentioned [13]-[18], wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 300 min;

[20] the method of any of the above-mentioned [13]-[19], wherein the kinase is a receptor kinase;

[21] the method of the above-mentioned [20], wherein the receptor kinase is a vascular endothelial growth factor

receptor 2 (VEGFR2);

[22] the method of the above-mentioned [21], wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 80 min;

[23] the method of the above-mentioned [20], wherein the receptor kinase is a platelet-derived growth factor receptor (PDGFR);

[24] the method of the above-mentioned [23], wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 60 min;

[25] use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer showing a prolonged effect for cancer treatment;

[26] use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer showing a potentiated effect for cancer treatment;

[27] use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer showing reduced side effects in the cancer treatment;

[28] use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer permitting a low dose to patients;

[29] use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer permitting a long interval in administration to patients;

[30] use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer showing a prolonged period of drug withdrawal;

[31] the use of any of the above-mentioned [25]-[30], wherein

the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 300 min;

[32] the use of any of the above-mentioned [25]-[31], wherein the kinase is a receptor kinase;

[33] the use of the above-mentioned [32], wherein the receptor kinase is a vascular endothelial growth factor receptor 2 (VEGFR2);

[34] the use of the above-mentioned [33], wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 80 min;

[35] the method of the above-mentioned [32], wherein the receptor kinase is a platelet-derived growth factor receptor (PDGFR);

[36] the method of the above-mentioned [35], wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 60 min;

[37] a pharmaceutical composition comprising sorafenib at a daily oral dose of 400 - 600 mg;

[38] a method for the prophylaxis or treatment of cancer in a mammal, comprising orally administering sorafenib at a daily oral dose of 400 - 600 mg to the mammal;

[39] use of sorafenib for the production of an agent for the prophylaxis or treatment of cancer, comprising sorafenib at a daily oral dose of 400 - 600 mg;

[40] a pharmaceutical composition comprising lapatinib at a daily oral dose of 250 - 500 mg;

[41] a method for the prophylaxis or treatment of cancer in a mammal, comprising orally administering lapatinib at a daily oral dose of 250 - 500 mg to the mammal; and

[42] use of lapatinib for the production of an agent for the prophylaxis or treatment of cancer, comprising lapatinib at a daily oral dose of 250 - 500 mg.

Furthermore, the present invention provides,

[43] a method of screening for an agent for the prophylaxis or treatment of cancer, comprising

(1) measuring and calculating a t1/2 relative to kinase of a test substance, and

(2) selecting a substance showing a t1/2 relative to kinase of not less than 10 min;

[44] the method of the above-mentioned [43], wherein the agent for the prophylaxis or treatment of cancer shows a potentiated effect in cancer treatment;

[45] the method of the above-mentioned [43], wherein the agent for the prophylaxis or treatment of cancer shows reduced side effects in cancer treatment;

[46] the method of the above-mentioned [43], wherein the agent for the prophylaxis or treatment of cancer permits a low dose to patients;

[47] the method of the above-mentioned [43], wherein the agent for the prophylaxis or treatment of cancer permits a long interval in administration to patients;

[48] the method of the above-mentioned [43], wherein the agent for the prophylaxis or treatment of cancer shows a prolonged period of drug withdrawal; and

[49] a method of screening for a kinase inhibitor, comprising

(1) measuring and calculating a t1/2 relative to kinase of a test substance, and

(2) selecting a substance showing a t1/2 relative to kinase of not less than 10 min.

[0007]

Effect of the Invention

The present invention provides a superior agent for the prophylaxis or treatment of cancer, which comprises a kinase inhibitory substance showing pseudo-irreversibility.

[0008]

(Detailed Description of the Invention)

The present invention is explained in detail in the following.

In the present invention, kinase includes not only a substance having a phosphorylation action as a whole but also

a substance having a part showing a phosphorylation action. The phosphorylation action possessed by kinase includes both the phosphorylation action on itself and that on other substances.

Examples of the kinase include lipid kinase and protein kinase.

Examples of the lipid kinase include PI-3K and the like.

Examples of the protein kinase include non-receptor kinase and receptor kinase.

Examples of the non-receptor kinase include Src, Aurora-A, Aurora-B, ASK1, cyclin dependent kinases (CDK), B-RAF, polo-like kinases (PLK), MEK, mTOR, cdc7, Akt, FAK, p38α, MAPK, Pim-2, CAMK2 and the like.

Examples of the receptor kinase include vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), epidermal cell growth factor receptor (ErbB) and the like.

Examples of the vascular endothelial growth factor receptor (VEGFR) include vascular endothelial growth factor receptor 1 (VEGFR1, Flt-1), vascular endothelial growth factor receptor 2 (VEGFR2, KDR, Flk-1), vascular endothelial growth factor receptor 3 (VEGFR3, Flt-4) and the like. Of these, vascular endothelial growth factor receptor 2 (VEGFR2) is preferable. Examples of the platelet-derived growth factor receptor (PDGFR) include platelet-derived growth factor receptor α (PDGFRα), platelet-derived growth factor receptor β (PDGFRβ) and the like. Examples of the epidermal cell growth factor receptor (ErbB) include epidermal cell growth factor receptor (EGFR), epidermal cell growth factor receptor 2 (HER2), epidermal cell growth factor receptor 4 (HER4) and the like. Particularly, as the kinase, vascular endothelial growth factor receptor 2 (VEGFR2) and platelet-derived growth factor receptor β (PDGFRβ) are preferable.

In addition to the above, examples of the receptor kinase also include Tyrosine Kinase with Ig and EGF homology domains

2 (TIE2), fibroblast growth factor receptor 1 (FGFR1), fibroblast growth factor receptor 2 (FGFR2), fibroblast growth factor receptor 3 (FGFR3), fibroblast growth factor receptor 4 (FGFR4), stem cell factor receptor (c-Kit), FLT-3, MET, IGF-1R, ALK, EphA, EphB and the like.

In the present invention, the kinase inhibitory substance is a substance having an activity to inhibit the phosphorylation action possessed by the above-mentioned kinases.

[0009]

In the present invention, t1/2 means a dissociation half-life of a complex of a target protein and an inhibitory substance (non-patent document 5: Nature Reviews, Drug Discovery, vol. 5, September (2006), pages 730-739), and t1/2 relative to kinase is the time necessary for the complex of the target protein, specifically kinase, and the inhibitory substance to be dissociated by 50% thereof.

In the present invention, t1/2, a dissociation half-life, was calculated according to a measurement method using, as an index, recovery of enzyme activity by the dissociation of a compound (non-patent document 6 and non-patent document 7). non-patent document 6: Methods of Biochemical Analysis, Evaluation of Enzyme Inhibitors in Drug Discovery., vol. 46, 2005, pages 1-265, WILEY-INTERSCIENCE, non-patent document 7: Cancer Research, 2004, vol. 64, pages 6652-6659

[0010]

To be precise, an enzyme at a concentration 100 times that for reaction and a compound at a concentration 10 times IC_{50} (theoretical inhibition rate 91%) are left standing for a time permitting sufficient saturation, 60 min in the present invention, and diluted 100-fold with a large excess of a substrate solution to start the reaction. The concentration of the compound during the reaction is one-tenth of IC_{50} (theoretical inhibition rate 9%). When the compound is pseudo-irreversible, it inhibits the enzyme even after dilution since

the dissociation rate constant is small. The time-course changes in the amount of product resulting from the enzyme reaction after dilution was applied to a given function to calculate t1/2.

Specifically, for calculation of t1/2, signal at each reaction time was fitted to the following function (A) to give k_{obs}. The initial setpoint of v_i, which is the initial rate, was 0, and the steady state rate v_s was calculated from the rate in 20 min of the control reaction, during which the linearity is observed, and used as the setpoint. t1/2 was calculated from function (B) using the obtained k_{obs}.

$P=v_s t+[(v_i-v_s)/k_{obs}][1-\exp(-k_{obs}t)]$ (A)

$t1/2=0.693/k_{obs}$ (B)

[0011]

In the present invention, a t1/2 relative to kinase of not less than 10 min means that the time necessary for a complex of kinase and an inhibitory substance to be dissociated by 50%, as measured and calculated by the above-mentioned methods, is not less than 10 min. When t1/2 of a compound is not less than 10 min, the compound can maintain efficacy even at a concentration below the effective blood concentration at which an in vivo effect is expected, and even after disappearance of the compound from the blood.

The t1/2 relative to kinase is preferably not less than 60 min, more preferably not less than 80 min, more preferably not less than 100 min, still more preferably not less than 300 min, further more preferably not less than 500 min, and particularly preferably not less than 900 min.

While the upper limit of the t1/2 is not particularly limited, it is preferably not more than 30000 min, more preferably not more than 20000 min, still more preferably not more than 15000 min, further more preferably not more than 10000 min, yet more preferably not more than 5000 min, and particularly preferably not more than 4000 min.

[0012]

Examples of the receptor kinase inhibitory substance showing t1/2 relative to receptor kinase, particularly VEGFR2 and/or PDGFR, of not less than 10 min in the present invention (hereinafter sometimes to be referred to as the substance of the present invention) include sorafenib (Nexavar (registered trade mark)). In the below-mentioned Experimental Example, t1/2 of sorafenib (Nexavar (registered trade mark)) to VEGFR2 kinase was measured and found to be 206 min. In addition, t1/2 of sorafenib (Nexavar (registered trade mark)) to PDGFRβ kinase was measured and found to be 135 min.

In addition, examples of the kinase inhibitory substance showing t1/2 relative to receptor kinases, EGFR and HER2, of not less than 10 min include lapatinib (Tykerb (registered trade mark)). The t1/2 of lapatinib to EGFR is reported to be 224 min (non-patent document 8: Cancer Research 2008, vol. 68, No. 2, pages 571-579).

[0013]

As other substance of the present invention, the following compounds described in WO08/16192 and salts thereof are preferably used.

(1) 3-chloro-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 29),

(2) N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 97),

(3) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 111),

(4) N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 114),

(5) N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide (Example 117),

(6) N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-

b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 120),

(7) N-[3-({2-[(methoxyacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 127),

(8) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 148),

(9) N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 149),

(10) N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}sulfanyl)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 150),

(11) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide 0.5 fumarate (Example 160),

(12) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 161),

(13) N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 165),

(14) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide (Example 173),

(15) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-5-carboxamide (Example 174),

(16) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 180),

(17) N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methylpyridine-2-carboxamide (Example 187),

(18) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-

b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 208),

(19) N-{6-[3-(but-2-ynoylamino)-4-methylphenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (Example 241),

(20) N-{2-fluoro-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 243),

(21) N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 247),

(22) N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 254),

(23) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 267),

(24) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-5-carboxamide (Example 287),

(25) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-oxazole-5-carboxamide (Example 289),

(26) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-4-methyl-1,3-thiazole-5-carboxamide (Example 298),

(27) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 302),

(28) N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide (Example 314),

(29) N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-

b]pyridazin-6-yl}amino)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 317), or

(30) N-[6-(3-{[(ethylamino)carbonyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (Example 103).

[0014]

The above-mentioned compounds can be classified as follows.

(1) Receptor kinase inhibitory substances showing t1/2 relative to receptor kinase (e.g., VEGFR2 kinase) of not less than 10 min and less than 60 min:

N-[3-({2-[(methoxyacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 127),

N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 149),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}amino)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 317).

(2) Receptor kinase inhibitory substances showing t1/2 relative to receptor kinase (e.g., VEGFR2 kinase) of not less than 60 min and less than 500 min:

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 114),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 161),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 165),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-5-carboxamide (Example 174),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methoxy-1-methyl-1H-pyrazole-5-

carboxamide (Example 180),
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methylpyridine-2-carboxamide (Example 187),
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 254),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 267),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-5-carboxamide (Example 287),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-oxazole-5-carboxamide (Example 289),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-4-methyl-1,3-thiazole-5-carboxamide (Example 298),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 302),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide (Example 314).

[0015]

(3) Receptor kinase inhibitory substances showing t1/2 relative to receptor kinase (e.g., VEGFR2 kinase) of not less than 500 min:
3-chloro-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 29),
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 97),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-

carboxamide (Example 111),
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide (Example 117),
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 120),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 148),
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}sulfanyl)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 150),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide 0.5 fumarate (Example 160),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide (Example 173),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 208),
N-{6-[3-(but-2-ynoylamino)-4-methylphenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (Example 241),
N-{2-fluoro-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 243),
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 247).

[0016]

The above-mentioned compounds also can be classified as follows.

(4) Receptor kinase inhibitory substances showing t1/2

relative to receptor kinase (e.g., VEGFR2 kinase) of not less than 300 min:

3-chloro-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 29),

N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 97),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 111),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide (Example 117),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 120),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 148),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}sulfanyl)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 150),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide 0.5 fumarate (Example 160),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 161),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide (Example 173),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-5-carboxamide (Example 174),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-

6-yl}oxy)-2-fluorophenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 208),
N-{6-[3-(but-2-ynoylamino)-4-methylphenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (Example 241),
N-{2-fluoro-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 243),
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 247),
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 254),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-oxazole-5-carboxamide (Example 289),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 302), or
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide (Example 314).

[0017]

(5) Receptor kinase inhibitory substances showing t1/2 relative to receptor kinase (e.g., VEGFR2 kinase) of not less than 80 min:
3-chloro-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 29),
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 97),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 111),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 114),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide (Example 117),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 120),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 148),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}sulfanyl)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 150),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide 0.5 fumarate (Example 160),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 161),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 165),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide (Example 173),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-5-carboxamide (Example 174),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 180),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methylpyridine-2-carboxamide (Example 187),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-

6-yl}oxy)-2-fluorophenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 208),
N-{6-[3-(but-2-ynoylamino)-4-methylphenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (Example 241),
N-{2-fluoro-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 243),
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 247),
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 254),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 267),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-5-carboxamide (Example 287),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-oxazole-5-carboxamide (Example 289),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-4-methyl-1,3-thiazole-5-carboxamide (Example 298),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 302), or
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide (Example 314).

[0018]

The above-mentioned compounds can be classified as follows.

(1) Receptor kinase inhibitory substances showing t1/2 relative to receptor kinase (e.g., PDGFR kinase) of not less than 10 min and less than 60 min:

N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 97),

N-[6-(3-{[(ethylamino)carbonyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (Example 103)

N-[3-({2-[(methoxyacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 127),

N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 149),

N-{6-[3-(but-2-ynoylamino)-4-methylphenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (Example 241),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-5-carboxamide (Example 287), or

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-4-methyl-1,3-thiazole-5-carboxamide (Example 298).

[0019]

(2) Receptor kinase inhibitory substances showing t1/2 relative to receptor kinase (e.g.,PDGFR kinase) of not less than 60 min and less than 500 min:

3-chloro-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 29),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 111),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 114),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-

6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide (Example 117),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 120),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 148),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}sulfanyl)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 150),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 161),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 165),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide (Example 173),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-5-carboxamide (Example 174),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 180),

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methylpyridine-2-carboxamide (Example 187),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 208),

N-{2-fluoro-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 243),

N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-

b]pyridazin-6-yl}oxy)phenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 247),
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 254),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 267),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-oxazole-5-carboxamide (Example 289),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 302), or
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide (Example 314).

[0020]

(3) Receptor kinase inhibitory substances showing t1/2 relative to receptor kinase (e.g., PDGFR kinase) of not less than 300 min:
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 111),
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide (Example 117), or
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 247).

[0021]

(4) Receptor kinase inhibitory substances showing t1/2 relative to receptor kinase (e.g., PDGFR kinase) of not less than 60 min:
3-chloro-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-

b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 29),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 111),
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 114),
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide (Example 117),
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 120),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 148),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 161),
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 165),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide (Example 173),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-5-carboxamide (Example 174),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 180),
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methylpyridine-2-carboxamide (Example 187),
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 208),

N-{2-fluoro-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 243),

N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 247),

N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 254),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 267),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-oxazole-5-carboxamide (Example 289),

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 302), or

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide (Example 314).

[0022]

In the case of the receptor kinase is VEGFR2 kinase, the kinase inhibitory substance used in the present invention is preferably a kinase inhibitory substance showing a t1/2 relative to the receptor kinase of not less than 80 min.

In the case of the receptor kinase is PDGFR kinase, the kinase inhibitory substance used in the present invention is preferably a kinase inhibitory substance showing a t1/2 relative to the receptor kinase of not less than 60 min.

[0023]

The substance of the present invention may be used as a prodrug. A prodrug of the substance of the present invention means a compound which is converted to the substance of the

present invention with a reaction due to an enzyme, an gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to the substance of the present invention with oxidation, reduction, hydrolysis, etc. according to an enzyme; a compound which is converted to the substance of the present invention by hydrolysis etc. due to gastric acid, etc.

[0024]

A prodrug of the substance of the present invention may be a compound obtained by subjecting amino in the substance of the present invention to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting amino in the substance of the present invention to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation and tert-butylation, etc.); a compound obtained by subjecting hydroxy in the substance of the present invention to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting hydroxy in the substance of the present invention to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation, dimethylaminomethylcarbonylation, etc.); a compound obtained by subjecting carboxyl in the substance of the present invention to an esterification or amidation (e.g., a compound obtained by subjecting carboxyl in the substance of the present invention to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification and methylamidation, etc.) and the like. Any of these compounds can be produced from the substance of the present invention by a method known

per se.

[0025]

A prodrug for the substance of the present invention may also be one which is converted into the substance of the present invention under a physiological condition, such as those described in IYAKUHIN no KAIHATSU (Pharmaceutical Research and Development), Vol.7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

[0026]

When the substance of the present invention has isomers such as optical isomer, stereoisomer, positional isomer, rotational isomer and the like, any isomers and mixtures are encompassed in the substance of the present invention. For example, when the substance of the present invention has an optical isomer, an optical isomer separated from a racemate is also encompassed in the substance of the present invention. These isomers can be obtained as independent products by a synthesis means or a separation means (concentration, solvent extraction, column chromatography, recrystallization and the like) known *per se*.

[0027]

The substance of the present invention may be a crystal, and both a single crystal form and mixture of crystal forms are encompassed in the substance of the present invention. Crystals can be produced by crystallization according to crystallization methods known *per se*.

The substance of the present invention may be a cocrystal.

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

A compound labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I and the like) and the like is also encompassed in the substance of the present invention.

[0028]

The vascular endothelial growth factor receptor 2

inhibitory activity, vascular endothelial cell proliferation inhibitory activity, antitumor activity, platelet-derived growth factor receptor α inhibitory activity, platelet-derived growth factor receptor β inhibitory activity and B-Raf inhibitory activity of the substance of the present invention can be measured according to the Experimental Examples of WO08/16192.

[0029]

Since the substance of the present invention shows t1/2 relative to kinase of not less than 10 min, it has, for example, the following characteristics.

(1) The treatment effect can be prolonged.

(2) The treatment effect can be potentiated.

(3) The side effects can be reduced.

(4) The dose for patients can be set low.

(5) The interval of administration to patients can be set long.

(6) The period of drug withdrawal can be lengthened.

Accordingly, the substance of the present invention is stable and lower toxic, and can be used safely. The dose of the substance of the present invention varies depending on the conditions and body weight of patients, the kind of compound, administration route and the like.

For example, when sorafenib is orally administered to patients for the purpose of treating cancer, the daily dose for an adult (body weight about 60 kg) is about 100 - 700 mg, preferably about 200 - 700 mg, more preferably about 400 - 600 mg, as the active ingredient (the substance of the present invention), which can be administered in one to three portions. More specifically, 1 to 3 tablets containing sorafenib (200 mg) per tablet can be administered a day.

For example, when lapatinib is orally administered to patients for the purpose of treating cancer, the daily dose for an adult (body weight about 60 kg) is about 50 - 1000 mg, preferably about 100 - 750 mg, more preferably about 250 - 500 mg, as the active ingredient (the substance of the present

invention), which can be administered in one to three portions. More specifically, 1 to 4 tablets containing lapatinib (250 mg) per tablet can be administered a day.

For example, when the compound described in the above-mentioned WO08/16192 or a salt thereof is orally administered to patients for the purpose of treating cancer, the daily dose for an adult (body weight about 60 kg) is about 0.25 - 500 mg, preferably about 0.5 - 150 mg, more preferably about 0.5 - 100 mg, particularly preferably about 0.5 - 30 mg, or about 0.25 - 10 mg, as the active ingredient (the substance of the present invention), which can be administered in one to three portions.

[0030]

When the substance of the present invention is administered parenterally, it is generally administered in the form of a liquid (e.g., injection). The single dose also varies depending on the subject of administration, target organ, symptom, administration method and the like.

For example, the compound described in the above-mentioned WO08/16192 or a salt thereof is preferably formulated into an injection and administered at about 0.1 - 800 mg, preferably about 0.25 - 200 mg, more preferably about 0.5 - 100 mg, per day to one week by intravenous injection.

[0031]

The substance of the present invention is used as a pharmaceutical agent for mammals (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human etc.), for example, an agent for the prophylaxis or treatment of cancer (e.g., large intestine cancer (e.g., familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor and the like), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma and the like), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer and the like), gastric cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous carcinoma and the like), breast

cancer (e.g., invasive ductal carcinoma, noninvasive ductal carcinoma, inflammatory breast cancer and the like), ovary cancer (e.g., ovarian epithelial carcinoma, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor and the like), prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer and the like), liver cancer (e.g., primary liver cancer, Extrahepatic Bile Duct Cancer and the like), thyroid cancer (e.g., medullary thyroid carcinoma and the like), kidney cancer (e.g., renal cell carcinoma, transitional cell cancer of renal pelvis and ureter and the like), uterus cancer, brain tumor (e.g., pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma and the like), melanoma, sarcoma, bladder cancer, blood cancer containing multiple myeloma etc.), diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, Kaposi's sarcoma, COPD, pain, asthma, endometriosis, nephritis, inflammation such as osteoarthritis and the like, and hypertension, an agent for inhibiting cancer growth, an agent for suppressing cancer metastasis, an apoptosis promoter and the like. Among these, for example, the substance of the present invention is effective for colorectal cancer, lung cancer, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, thyroid cancer, kidney cancer, brain tumor, melanoma, urinary bladder cancer and blood cancer, and particularly effective for patients with lung cancer, large intestine cancer, ovary cancer, prostate cancer or kidney cancer.

[0032]

The substance of the present invention can be administered orally or parenterally as it is or after mixing with a pharmacologically acceptable carrier.

The dosage form of the substance of the present invention for oral administration, for example, tablet (including sugar-coated tablet, film-coated tablet), pill, granule, powder,

capsule (including soft capsule, microcapsule), syrup, emulsion, suspension and the like, and the dosage form for parenteral administration is, for example, injection, injecting agent, instillation, suppository and the like. In addition, it is effective to combine the substance with a suitable base (e.g., polymer of butyric acid, polymer of glycolic acid, copolymer of butyric acid-glycolic acid, a mixture of polymer of butyric acid and polymer of glycolic acid, polyglycerol fatty acid ester etc.) and formulate a sustained release preparation. In addition, it is effective to combine the substance with a suitable base (e.g., polyethylene glycol, polyaspartic acid etc.) and formulate a micelle. In addition, it is effective to combine the substance with a suitable base (e.g., phosphatidylcholine etc.) and formulate a liposome inclusion.

[0033]

As a method to produce the substance of the present invention in the above-mentioned dosage form, a known production method generally used in the pertinent field can be applied. When the above-mentioned dosage form is produced, suitable amounts of additives such as an excipients, a binder, a disintegrant, a lubricant, a sweetening agent, a surfactant, a suspending agent, an emulsifier and the like generally used in the pertinent field are appropriately added as necessary, and produced.

[0034]

When the substance of the present invention is prepared into a tablet, for example, it can be produced by adding an excipient, a binder, a disintegrant, a lubricant and the like, and when a pill and a granule are to be prepared, they can be produced by adding an excipient, a binder, a disintegrant and the like. When a powder and a capsule are to be prepared, they can be produced by adding an excipient and the like, and when a syrup is to be prepared, it can be produced by adding a sweetener and the like, and when an emulsion or a suspension

is to be prepared, it can be produced by adding a suspending agent, a surfactant, an emulsifier and the like.

[0035]

Examples of the excipient include lactose, white soft sugar, glucose, starch, sucrose, microcrystalline cellulose, powdered glycyrrhiza, mannitol, sodium hydrogen carbonate, calcium phosphate, calcium sulfate and the like.

Examples of the binder include 5 - 10 wt% liquid starch paste, 10 - 20 wt% gum arabic solution or gelatin solution, 1 - 5 wt% tragacanth solution, carboxymethyl cellulose solution, sodium alginate solution, glycerin and the like.

Examples of the disintegrant include starch, calcium carbonate and the like.

Examples of the lubricant include magnesium stearate, stearic acid, calcium stearate, purified talc and the like.

Examples of the sweetener include glucose, fructose, invert sugar, sorbitol, xylitol, glycerin, simple syrup and the like.

Examples of the surfactant include sodium lauryl sulfate, polysorbate 80, sorbitan monofatty acid ester, polyoxyl 40 stearate and the like.

Examples of the suspending agent include gum arabic, sodium alginate, sodium carboxymethyl cellulose, methyl cellulose, bentonite and the like.

Examples of the emulsifier include gum arabic, tragacanth, gelatin, polysorbate 80 and the like.

[0036]

Furthermore, when the substance of the present invention is produced in the above-mentioned dosage form, a suitable amount of a colorant, a preservative, an aromatic, a corrigent, a stabilizer, viscous agents and the like typically used in the field of preparation can be added on demand.

[0037]

As the injection, intravenous injection as well as subcutaneous injection, intracutaneous injection,

intramuscular injection, instillation and the like are mentioned, and as a sustained release preparation, iontophoresis transdermal agent and the like are mentioned.

[0038]

Such injections are prepared by methods known *per se*, or by dissolving, suspending or emulsifying the substance of the present invention in a sterilized aqueous solution or oily liquid. As an aqueous solution for injection, physiological saline, isotonic solutions containing glucose or other auxiliary agents (e.g., D-sorbitol, D-mannitol, sodium chloride and the like) and the like can be mentioned, and they can be used in combination with suitable solubilizing agents, such as alcohols (e.g., ethanol), polyalcohols (e.g., propylene glycol, polyethylene glycol), nonionic surfactants (e.g., polysorbate 80, HCO-50) and the like. As an oily liquid, sesame oil, soybean oil and the like can be mentioned, which may be used in combination with solubilizing agents such as benzyl benzoate, benzyl alcohol and the like. In addition, buffers (e.g., phosphate buffer, sodium acetate buffer), soothing agents (e.g., benzalkonium chloride, procaine hydrochloride and the like), stabilizers (e.g., human serum albumin, polyethylene glycol and the like), preservatives (e.g., benzyl alcohol, phenol and the like) and the like. A prepared injection is generally filled in an ampoule.

[0039]

While the content of the substance of the present invention in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 0.01 to 100 wt%, preferably about 2 to 85 wt%, more preferably about 5 to 70 wt%, relative to the entire preparation.

[0040]

While the content of the additive in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 1 to

99.9 wt%, preferably about 10 to 90 wt%, relative to the entire preparation.

[0041]

The substance of the present invention can be used concurrently with other drugs. To be specific, the substance of the present invention can be used together with medicaments such as hormonal therapeutic agents, chemotherapeutic agents, immunotherapeutic agents, pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors and the like. In the following, the drugs that can be used in combination with the substance of the present invention are abbreviated as concomitant drugs.

[0042]

As examples of the "hormonal therapeutic agents", there can be used fosfestrol, diethylstylbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, allylestrenol, gestrinone, mepartricin, raloxifene, ormeloxifene, levormeloxifene, anti-estrogens (e.g., tamoxifen citrate, toremifene citrate, and the like), pill preparations, mepitiostane, testrolactone, aminoglutethimide, LH-RH agonists (e.g., goserelin acetate, buserelin, leuprorelin, and the like), droloxifene, epitiostanol, ethinylestradiol sulfonate, aromatase inhibitors (e.g., fadrozole hydrochloride, anastrozole, retrozole, exemestane, vorozole, formestane, and the like), anti-androgens (e.g., flutamide, bicartamide, nilutamide, and the like), 5α-reductase inhibitors (e.g., finasteride, epristeride, and the like), adrenocorticohormone drugs (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone, and the like), androgen synthesis inhibitors (e.g., abiraterone, and the like), retinoid and drugs that retard retinoid metabolism (e.g., liarozole, and the like), etc.

[0043]

As examples of the "chemotherapeutic agents", there can

be used alkylating agents, antimetabolites, anticancer antibiotics, plant-derived anticancer agents, and the like.

[0044]

As examples of the "alkylating agents", there can be used nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustine, estramustine phosphate sodium, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide, treosulphan, trophosphamide, zinostatin stimalamer, adozelesin, cystemustine, bizelesin and a DDS preparation thereof and the like.

[0045]

As examples of the "antimetabolites", there can be used mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, pemetrexed, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emmitefur, Capecitabine and the like), aminopterine, nelzarabine, leucovorin calcium, tabloid, butocine, folinate calcium, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, bendamustine and a DDS preparation thereof and the like.

[0046]

As examples of the "anticancer antibiotics", there can be used actinomycin-D, actinomycin-C, mitomycin-C, chromomycin-A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, daunorubicin hydrochloride, doxorubicin hydrochloride,

aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin, sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, and a DDS preparation thereof and the like.

[0047]

As examples of the "plant-derived anticancer agents", there can be used etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, vinorelbine, and a DDS preparation thereof and the like.

[0048]

As examples of the "immunotherapeutic agents (BRM)", there can be used picibanil, krestin, sizofiran, lentinan, ubenimex, interferons, interleukins, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, *Corynebacterium parvum*, levamisole, polysaccharide K, procodazole, anti-CTLA4 antibody and the like.

[0049]

As the "cell growth factor" of the "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors", there can be used any substances that promote cell proliferation, which are normally peptides having a molecular weight of not more than 20,000 that are capable of exhibiting their action at low concentrations by binding to a receptor, including (1) EGF (epidermal growth factor) or substances possessing substantially the same activity as it [e.g., TGFα, and the like], (2) insulin or substances possessing substantially the same activity as it [e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2, and the like], (3) FGF (fibroblast growth factor) or substances possessing substantially the same activity as it [e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10, and the like], (4) other cell growth 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), VEGF (vascular endothelial growth factor), heregulin, angiopoietin and the like].

[0050]

As the "cell growth factor receptor", any can be used as long as it is capable of binding to the aforementioned cell growth factors, and examples thereof include EGF receptor, heregulin receptor (HER2, HER4 etc.), insulin receptor, IGF receptor-1, IGF receptor-2, FGF receptor-1 or FGF receptor-2, VEGF receptor, angiopoietin receptor (Tie2 etc.), PDGF receptor, FLT3 receptor, c-Kit receptor, ALK receptor, Met receptor and the like.

[0051]

As the "pharmaceutical agent inhibiting the action of cell growth factors or cell growth factor receptors", EGF inhibitor, TGFα inhibitor, heregulin inhibitor, insulin inhibitor, IGF inhibitor, FGF inhibitor, KGF inhibitor, CSF inhibitor, EPO inhibitor, IL-2 inhibitor, NGF inhibitor, PDGF inhibitor, TGFβ inhibitor, HGF inhibitor, VEGF inhibitor, angiopoietin inhibitor, EGF receptor inhibitor, HER2 inhibitor, HER4 inhibitor, insulin receptor inhibitor, IGF-1 receptor inhibitor, IGF-2 receptor inhibitor, FGF receptor-1 inhibitor, FGF receptor-2 inhibitor, FGF receptor-3 inhibitor, FGF receptor-4 inhibitor, VEGF receptor inhibitor, Tie-2 inhibitor, PDGF receptor inhibitor, Abl inhibitor, Raf inhibitor, FLT3 receptor inhibitor, c-Kit receptor inhibitor, FAK inhibitor, Src inhibitor, PKC inhibitor, Trk inhibitor, Ret inhibitor, mTOR inhibitor, Aurora inhibitor, PLK inhibitor, MEK (MEK 1/2) inhibitor, MET receptor inhibitor, CDK inhibitor, Akt inhibitor, ERK inhibitor, PI3K inhibitor, ALK receptor inhibitor, Eph receptor inhibitor and the like. More specifically, these can be used anti VEGF antibody (Bevacizumab etc.), anti-HER2 antibody (Trastuzumab,

Pertuzumab etc.), anti-EGFR antibody (Cetuximab, Panitumumab, Matuzumab, Nimotuzumab etc.), anti-VEGFR antibody, Imatinib, Erlotinib, Gefitinib, Sorafenib, Sunitinib, Dasatinib, Lapatinib, Vatalanib, 4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-7-[3-(1-pyrrolidinyl)propoxy]quinazoline (AZD-2171), Lestaurtinib, Pazopanib, Canertinib, Tandutinib, 3-(4-bromo-2,6-difluorobenzyloxy)-5-[3-[4-(1-pyrrolidinyl)butyl]ureido]isothiazole-4-carboxamide (CP-547632), Axitinib, N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(pyridin-4-ylmethylamino)pyridine-3-carboxamide (AMG-706), Nilotinib, 6-[4-(4-ethylpiperazin-1-ylmethyl)phenyl]-N-[1(R)-phenylethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (AEE-788), Vandetanib, Temsirolimus, Everolimus, Enzastaurin, N-[4-[4-(4-methylpiperazin-1-yl)-6-(3-methyl-1H-pyrazol-5-ylamino)pyrimidin-2-ylsulfanyl]phenyl]cyclopropanecarboxamide (VX-680), phosphoric acid 2-[N-[3-[4-[5-[N-(3-fluorophenyl)carbamoylmethyl]-1H-pyrazol-3-ylamino]quinazolin-7-yloxy]propyl]-N-ethylamino]ethyl ester (AZD-1152), 4-[9-chloro-7-(2,6-difluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-ylamino]benzoic acid (MLN-8054), N-[2-methoxy-5-[(E)-2-(2,4,6-trimethoxyphenyl)vinylsulfonylmethyl]phenyl]glycine sodium salt (ON-1910Na), 4-[8-cyclopentyl-7(R)-ethyl-5-methyl-6-oxo-5,6,7,8-tetrahydropteridin-2-ylamino]-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide (BI-2536), 5-(4-bromo-2-chlorophenylamino)-4-fluoro-1-methyl-1H-benzimidazole-6-carbohydroxamic acid 2-hydroxyethyl ester (AZD-6244), N-[2(R),3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide (PD-0325901) and the like can be used.

[0052]

In addition to the aforementioned drugs, L-asparaginase, aceglatone, procarbazine hydrochloride, protoporphyrin-cobalt complex salt, mercuric hematoporphyrin-sodium, topoisomerase I inhibitors (e.g., irinotecan, topotecan etc.), topoisomerase II inhibitors (e.g., sobuzoxane etc.), differentiation

inducers (e.g., retinoid, vitamin D etc.), other angiogenesis inhibitors (e.g., fumagillin, shark extract, COX-2 inhibitor etc.), α-blockers (e.g., tamsulosin hydrochloride etc.), bisphosphonic acid (pamidronate, zoledronate etc.), thalidomide, 5-azacytidine, decitabine, bortezomib, antitumor antibody such as anti-CD20 antibody and the like, toxin-labeled antibody and the like can also be used.

[0053]

The following effects can be obtained by combining the substance of the present invention and a concomitant drug.

(1) Since the dose of the substance of the present invention can be set low, the dose of the concomitant drug can be set high.

(2) Since the dose of the substance of the present invention can be set low, the toxicity due to the combined use can be reduced.

(3) Since the substance of the present invention can prolong the treatment effect, the dose of the concomitant drug can be set low.

(4) Since the substance of the present invention can prolong the treatment effect, the administration interval of the concomitant drug can be set long.

(5) Since the substance of the present invention can prolong the treatment effect, the drug withdrawal period of the concomitant drug can lengthened.

[0054]

In the present specification, a pharmaceutical agent for use of the substance of the present invention and a concomitant drug in combination may be referred to as the "combination drug of the present invention".

When using the combination drug of the present invention, the administration time of the substance of the present invention and the concomitant drug is not restricted, and the substance of the present invention or the concomitant drug can be administered to an administration subject simultaneously,

or may be administered at different times. The dosage of the concomitant drug may be determined according to the dose clinically used, and can be appropriately selected depending on an administration subject, administration route, disease, combination and the like.

[0055]

Examples of such administration mode include the following:

(1) administration of a single preparation obtained by simultaneously processing the substance of the present invention and the concomitant drug, (2) simultaneous administration of two kinds of preparations of the substance of the present invention and the concomitant drug, which have been separately produced, by the same administration route, (3) administration of two kinds of preparations of the substance of the present invention and the concomitant drug, which have been separately produced, by the same administration route in a staggered manner, (4) simultaneous administration of two kinds of preparations of the substance of the present invention and the concomitant drug, which have been separately produced, by different administration routes, (5) administration of two kinds of preparations of the substance of the present invention and the concomitant drug, which have been separately produced, by different administration routes in a staggered manner (e.g., administration in the order of the substance of the present invention and the concomitant drug, or in the reverse order) and the like. The dose of the concomitant drug can be appropriately determined based on the dose employed in clinical situations. The mixing ratio of the substance of the present invention and a concomitant drug can be appropriately determined depending on the administration subject, administration route, target disease, symptom, combination and the like. When the subject of administration is human, for example, a concomitant drug can be used in 0.01 - 100 parts by

weight relative to 1 part by weight of the substance of the present invention.

[0056]

A combination drug of the present invention has low toxicity, and for example, the substance of the present invention and/or the above-mentioned concomitant drug can be mixed, according to a method known *per se*, with a pharmacologically acceptable carrier to give pharmaceutical compositions, such as tablets (including sugar-coated tablet, film-coated tablet), powders, granules, capsules (including soft capsule), solutions, injections, suppositories, sustained release agents and the like, which can be safely administered orally or parenterally (e.g., local, rectum, vein, and the like). An injection can be administered by intravenous, intramuscular, subcutaneous or intra-tissue administration directly to the lesion.

[0057]

As a pharmacologically acceptable carrier which may be used for preparing a preparation of a combination drug of the present invention, those similar to the aforementioned pharmacologically acceptable carriers that can be used for the production of the pharmaceutical agent of the present invention can be mentioned. Where necessary, the aforementioned additives that can be used for the production of the pharmaceutical agent of the present invention, such as preservatives, antioxidants, colorants, sweetening agents, adsorbents, wetting agents and the like can be also used in appropriate amounts.

[0058]

The compounding ratio of the substance of the present invention to the concomitant drug in the combination drug of the present invention can be appropriately selected depending on an administration subject, administration route, diseases and the like.

For example, the content of the substance of the present

invention in the combination drug of the present invention differs depending on the form of a preparation, and usually from about 0.01 to 100% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the preparation.

The content of the concomitant drug in the combination drug of the present invention differs depending on the form of a preparation, and usually from about 0.01 to 90% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the preparation.

The content of additives in the combination drug of the present invention differs depending on the form of a preparation, and usually from about 1 to 99.99% by weight, preferably from about 10 to 90% by weight, based on the preparation.

In the case when the substance of the present invention and the concomitant drug are separately prepared, the same contents may be adopted.

[0059]

These preparations can be produced by a method known *per se* usually used in a preparation process.

For example, the substance of the present invention and the concomitant drug can be made into an aqueous injection together with a dispersing agent (e.g., Tween 80 (Atlas Powder, US), HCO 60 (manufactured by Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, hydroxypropylmethylcellulose, dextrin and the like), a stabilizer (e.g., ascorbic acid, sodium pyrosulfite, and the like), a surfactant (e.g., Polysorbate 80, macrogol and the like), a solubilizer (e.g., glycerin, ethanol and the like), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent (e.g., sodium chloride, potassium chloride, mannitol, sorbitol, glucose and the like), a pH regulator (e.g., hydrochloric acid, sodium hydroxide and the like), a

preservative (e.g., ethyl parahydroxybenzoate, benzoic acid, methylparaben, propylparaben, benzyl alcohol and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a solubilizing agent (e.g., propylene glycol, white sugar and the like), a soothing agent (e.g., glucose, benzyl alcohol and the like), and the like, or can be dissolved, suspended or emulsified in a vegetable oil such as olive oil, sesame oil, cotton seed oil, corn oil and the like or a solubilizing agent such as propylene glycol and prepared into an oily injection, whereby an injection is afforded.

[0060]

In addition, an excipient (e.g., lactose, sucrose, starch and the like), a disintegrating agent (e.g., starch, calcium carbonate and the like), a binder (e.g., starch, gum Arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxpropylcellulose and the like), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000 and the like) and the like, for example, can be added to the substance of the present invention or the concomitant drug, according to a method known *per se*, and the mixture can be compression-molded, then if desirable, the molder product can be coated by a method known *per se* for the purpose of masking of taste, enteric property or durability, to obtain a preparation for oral administration. As this coating agent, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudoragit (methacrylic acid·acrylic acid copolymer, manufactured by Rohm, DE), pigment (e.g., iron oxide red, titanium dioxide, etc.) and the like can be used. The preparation for oral administration may be any of a immediate-release preparation and a sustained release preparation.

[0061]

Moreover, the substance of the present invention and the concomitant drug can be made into an oily or aqueous solid, semisolid or liquid suppository according to a method known *per se*, by mixing with an oily substrate, aqueous substrate or aqueous gel substrate. As the above-mentioned oily substrate, for example, glycerides of higher fatty acids [e.g., cacao butter, Witepsols (manufactured by Dynamit Nobel, Germany), etc.], glycerides of medium chain fatty acid [e.g., Miglyols (manufactured by Dynamit Nobel, Germany), etc.], or vegetable oils (e.g., sesame oil, soybean oil, cotton seed oil and the like), and the like are listed. Further, as the aqueous substrate, for example, polyethylene glycols, propylene glycol are listed, and as the aqueous gel substrate, for example, natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers and the like are listed.

[0062]

As the above-mentioned sustained release preparation, sustained release microcapsules and the like are listed. The sustained release microcapsule can be produced by a method known *per se*, such as the method shown in the following [2].

[0063]

The substance of the present invention is preferably molded into an oral administration preparation such as a solid preparation (e.g., powder, granule, tablet, capsule) and the like, or molded into a rectal administration preparation such as a suppository. Particularly, an oral administration preparation is preferable.

The concomitant drug can be made into the above-mentioned dosage form depending on the kind of the drug.

[0064]

[1] An injection of the substance of the present invention or the concomitant drug, and preparation thereof, [2] a sustained release preparation or immediate-release preparation of the substance of the present invention or the concomitant drug, and preparation thereof, [3] a sublingual,

buccal or intraoral rapid integrating agent of the substance of the present invention or the concomitant drug, and preparation thereof, will be described below specifically.

[0065]

[1] Injection and preparation thereof

An injection prepared by dissolving the substance of the present invention or the concomitant drug into water is preferable. This injection may be allowed to contain a benzoate and/or salicylate.

The injection is obtained by dissolving the substance of the present invention or the concomitant drug, and if desirable, a benzoate and/or salicylate, into water.

[0066]

As the above-mentioned salts of benzoic acid and salicylic acid, for example, salts of alkali metals such as sodium, potassium and the like, salts of alkaline earth metals such as calcium, magnesium and the like, ammonium salts, meglumine salts, salts with organic bases such as tromethamol and the like, etc. are listed.

[0067]

The concentration of the substance of the present invention or the concomitant drug in an injection is from 0.5 to 50 w/v%, preferably from about 3 to 20 w/v%. The concentration of a benzoate or/and salicylate is from 0.5 to 50 w/v%, preferably from about 3 to 20 w/v%.

[0068]

Into an injection of the present invention, additives usually used in an injection, for example, a stabilizer (e.g., ascorbic acid, sodium pyrosulfite and the like), a surfactant (e.g., Polysorbate 80, macrogol and the like), a solubilizer (e.g., glycerin, ethanol and the like), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent (e.g., sodium chloride, potassium chloride and the like), a dispersing agent (e.g., hydroxypropylmethylcellulose, dextrin),

a pH regulator (e.g., hydrochloric acid, sodium hydroxide and the like), a preservative (e.g., ethyl parahydroxybenzoate, benzoic acid and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a solubilizing agent (e.g., propylene glycol, sucrose and the like), a soothing agent (e.g., glucose, benzyl alcohol and the like), and the like, can be appropriately blended. These additives are generally blended in a proportion usually used in an injection.

[0069]

It is advantageous that pH of an injection is controlled from pH 2 to 12, preferably from pH 2.5 to 8.0 by addition of a pH regulator.

An injection is obtained by dissolving the substance of the present invention or the concomitant drug and if desirable, a benzoate and/or a salicylate, and if necessary, the above-mentioned additives into water. These may be dissolved in any order, and can be appropriately dissolved in the same manner as in a conventional method of producing an injection.

[0070]

An aqueous solution for injection may be advantageously heated, and filter sterilization, high pressure heat sterilization and the like can be conducted in the same manner as for a usual injection, to provide an injection.

It may be advantageous that an aqueous solution for injection is subjected to high pressure heat sterilization at 100 to 121°C for 5 to 30 min.

Further, a preparation endowed with an antibacterial property of a solution may also be produced so that it can be used as a preparation which is divided and administered multiple-times.

[0071]

[2] Sustained release preparation or immediate-release preparation, and preparation thereof

A sustained release preparation is preferable which is obtained, if desirable, by coating a nucleus containing the

substance of the present invention or the concomitant drug with a film agent such as a water-insoluble substance, swellable polymer and the like. For example, a sustained release preparation for oral administration of once administration per day type is preferable.

[0072]

As the water-insoluble substance used in a film agent, there are listed, for example, cellulose ethers such as ethylcellulose, butylcellulose and the like, cellulose esters such as cellulose acetate, cellulose propionate and the like, polyvinyl esters such as polyvinyl acetate, polyvinyl butyrate and the like, acrylic acid/methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylate/cinnamoethyl methacrylate/aminoalkyl methacrylate copolymers, polyacrylic acid, polymethacrylic acid, methacrylic acid alkylamide copolymers, poly(methyl methacrylate), polymethacrylate, polymethacrylamide, aminoalkyl methacrylate copolymers, poly(methacrylic anhydride), glycidyl methacrylate copolymer, particularly, acrylic acid-based polymers such as Eudoragit (Rohm Pharma) such as Eudoragit RS-100, RL-100, RS-30D, RL-30D, RL-PO, RS-PO (ethyl acrylate/methyl methacrylate/trimethylammoniumethyl methacrylate chloride copolymer), Eudoragit NE-30D (methyl methacrylate/ethyl acrylate copolymer), and the like, hydrogenated oils such as hydrogenated castor oil (e.g., Lubri wax (Freund Corporation) and the like), waxes such as carnauba wax, glycerin fatty acid ester, paraffin and the like, polyglycerin fatty esters, and the like.

[0073]

As the swellable polymer, polymers having an acidic dissociating group and showing pH dependent swell are preferable, and polymers having an acidic dissociating group, which manifest small swelling in acidic regions such as in stomach and large swelling in neutral regions such as in small intestine and large intestine, are preferable.

As such a polymer having an acidic dissociating group and showing pH dependent swell, cross-linkable polyacrylic acid copolymers such as, for example, Carbomer 934P, 940, 941, 974P, 980, 1342 and the like, polycarbophil, calcium polycarbophil (all above are manufactured by BF Goodrich), Hiviswako 103, 104, 105, 304 (all are manufactured by Wako Pure Chemical Industries, Ltd.), and the like, are listed.

[0074]

The film agent used in a sustained release preparation may further contain a hydrophilic substance.

As the hydrophilic substance, for example, polysaccharides which may contain a sulfate group such as pullulan, dextrin, alkali metal alginate and the like, polysaccharides having hydroxyalkyl or carboxyalkyl such as hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose sodium and the like, methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol and the like can be mentioned.

[0075]

The content of a water-insoluble substance in the film agent of a sustained release preparation is from about 30 to about 90% (w/w), preferably from about 35 to about 80% (w/w), further preferably from about 40 to about 75% (w/w), the content of a swellable polymer is from about 3 to about 30% (w/w), preferably from about 3 to about 15% (w/w). The film agent may further contain a hydrophilic substance, and in which case, the content of a hydrophilic substance in the film agent is about 50% (w/w) or less, preferably about 5 to 40% (w/w), further preferably from about 5 to 35% (w/w). This % (w/w) indicates % by weight based on a film agent composition which is obtained by removing a solvent (e.g., water, lower alcohols such as methanol, ethanol and the like) from a film agent solution.

[0076]

The sustained release preparation is produced by

preparing a nucleus containing a drugs as exemplified below, then, coating the resulted nucleus with a film agent solution prepared by heat-solving a water-insoluble substance, swellable polymer and the like or by dissolving or dispersing it in a solvent.

[0077]

I. Preparation of nucleus containing drug

The form of nucleus containing a drug to be coated with a film agent (hereinafter, sometimes simply referred to as nucleus) is not particularly restricted, and preferably, the nucleus is formed into particles such as a granule or fine particle.

When the nucleus is composed of granules or fine particles, the average particle size thereof is preferably from about 150 to about 2000 μm, further preferably, from about 500 to about 1400 μm.

Preparation of the nucleus can be effected by a usual production method. For example, a suitable excipient, binding agent, disintegrating agent, lubricant, stabilizer and the like are mixed with a drug, and the mixture is subjected to a wet extrusion granulating method, fluidized bed granulating method or the like, to prepare a nucleus.

The content of drugs in a nucleus is from about 0.5 to about 95% (w/w), preferably from about 5.0 to about 80% (w/w), further preferably from about 30 to about 70% (w/w).

[0078]

As the excipient contained in the nucleus, for example, saccharides such as sucrose, lactose, mannitol, glucose and the like, starch, crystalline cellulose, calcium phosphate, corn starch and the like are used. Among them, crystalline cellulose, corn starch are preferable.

[0079]

As the binding agent, for example, polyvinyl alcohol, hydroxypropylcellulose, polyethylene glycol, polyvinyl pyrrolidone, Pluronic F68, gum Arabic, gelatin, starch and the

like are used. As the disintegrating agent, for example, carboxymethylcellulose calcium (ECG505), croscarmelose sodium (Ac-Di-Sol), crosslinked polyvinylpyrrolidone (Crospovidone), low substituted hydroxypropylcellulose (L-HPC) and the like are used. Among them, hydroxypropylcellulose, polyvinylpyrrolidone, lower substituted hydroxypropylcellulose are preferable. As the lubricant and coagulation inhibitor, for example, talc, magnesium stearate and inorganic salts thereof are used, and as the lubricant, polyethylene glycol and the like are used. As the stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, are used.

[0080]

A nucleus can also be prepared by, in addition to the above-mentioned, for example, a rolling granulation method in which a drug or a mixture of a drug with an excipient, lubricant and the like is added portionwise onto an inert carrier particle which is the core of the nucleus while spraying a binder dissolved in a suitable solvent such as water, lower alcohol (e.g., methanol, ethanol and the like) and the like, a pan coating method, a fluidized bed coating method or a melt granulating method. As the inert carrier particle, for example, those made of sucrose, lactose, starch, crystalline cellulose or waxes can be used, and the average particle size thereof is preferably from about 100 μm to about 1500 μm.

[0081]

For separating a drug contained in a nucleus and a film agent, the surface of the nucleus may be coated with a protective agent. As the protective agent, for example, the above-mentioned hydrophilic substances, water-insoluble substances and the like are used. As the protective agent, preferably polyethylene glycol, and polysaccharides having hydroxyalkyl or carboxyalkyl are used, more preferably, hydroxypropylmethylcellulose and hydroxypropylcellulose are

used. The protective agent may contain, as stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, and lubricants such as talc and the like. When the protective agent is used, the coating amount is from about 1 to about 15% (w/w), preferably from about 1 to about 10% (w/w), further preferably from about 2 to about 8% (w/w), based on the nucleus.

[0082]

The protective agent can be coated by a usual coating method, and specifically, the protective agent can be coated by spray-coating the nucleus, for example, by a fluidized bed coating method, pan coating method and the like.

[0083]

II. Coating of nucleus with film agent

A nucleus obtained in the above-mentioned step I is coated with a film agent solution obtained by heat-solving the above-mentioned water-insoluble substance and pH-dependent swellable polymer, and a hydrophilic substance, or by dissolving or dispersing them in a solvent, to give a sustained release preparation.

As the method for coating a nucleus with a film agent solution, for example, a spray coating method and the like are listed.

The composition ratio of a water-insoluble substance, swellable polymer or hydrophilic substance in a film agent solution is appropriately selected so that the contents of these components in a coated film are the above-mentioned contents, respectively.

The coating amount of a film agent is from about 1 to about 90% (w/w), preferably from about 5 to about 50% (w/w), further preferably from about 5 to about 35% (w/w), based on a nucleus (not including coating amount of protective agent).

[0084]

As the solvent in a film agent solution, water or an organic solvent can be used alone or in admixture thereof. In

the case of use in admixture, the mixing ratio of water to an organic solvent (water/organic solvent: by weight) can be varied in the range from 1 to 100%, and preferably from 1 to about 30%. The organic solvent is not particularly restricted providing it dissolves a water-insoluble substance, and for example, lower alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol, n-butyl alcohol and the like, lower alkanone such as acetone and the like, acetonitrile, chloroform, methylene chloride and the like are used. Among them, lower alcohols are preferable, and ethyl alcohol and isopropyl alcohol are particularly preferable. Water, and a mixture of water with an organic solvent are preferably used as a solvent for a film agent. In this case, if necessary, an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like may also be added into a film agent solution for stabilizing the film agent solution.

[0085]

An operation of coating by spray coating can be effected by a usual coating method, and specifically, it can be effected by spray-coating a film agent solution onto a nucleus by a fluidized bed coating method, pan coating method and the like. In this case, if necessary, talc, titanium oxide, magnesium stearate, calcium stearate, light anhydrous silicic acid and the like may also be added as a lubricant, and glycerin fatty acid ester, hydrogenated castor oil, triethyl citrate, cetyl alcohol, stearyl alcohol and the like may also be added as a plasticizer.

[0086]

After coating with a film agent, if necessary, an antistatic agent such as talc and the like may be mixed.

The immediate-release preparation may be liquid (solution, suspension, emulsion and the like) or solid (particle, pill, tablet and the like). As the immediate-release preparation, Oral agents and parenteral agents such as an injection and the like are used, and oral agents are preferable.

[0087]

The immediate-release preparation, usually, may contain, in addition to an active component drug, also carriers, additives and excipients conventionally used in the production field (hereinafter, sometimes abbreviated as excipient). The excipient used is not particularly restricted providing it is an excipient ordinarily used as a preparation excipient. For example, as the excipient for an oral solid preparation, lactose, starch, corn starch, crystalline cellulose (Avicel PH101, manufactured by Asahi Kasei Corporation, and the like), powder sugar, granulated sugar, mannitol, light anhydrous silicic acid, magnesium carbonate, calcium carbonate, L-cysteine and the like are listed, and preferably, corn starch and mannitol and the like are listed. These excipients can be used alone or in combination of two or more. The content of the excipient is, for example, from about 4.5 to about 99.4 w/w%, preferably from about 20 to about 98.5 w/w%, further preferably from about 30 to about 97 w/w%, based on the total amount of the immediate-release preparation.

[0088]

The content of a drug in the immediate-release preparation can be appropriately selected in the range from about 0.5 to about 95%, preferably from about 1 to about 60% based on the total amount of the immediate-release preparation.

[0089]

When the immediate-release preparation is an oral solid preparation, it usually contains, in addition to the above-mentioned components, also a disintegrating agent. As this disintegrating agent, for example, carboxymethylcellulose calcium (ECG-505, manufactured by Gotoku Yakuhin), croscarmelose sodium (e.g., Actisol, manufactured by Asahi Kasei Corporation), crospovidone (e.g., Kollidon CL, manufactured by BASF), low substituted hydroxypropylcellulose (manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethylstarch (manufactured by Matsutani Kagaku K.K.),

carboxymethylstarch sodium (Exprotab, manufactured by Kimura Sangyo), partially pregelatinized starch (PCS, manufactured by Asahi Kasei Corporation), and the like are used, and for example, those which disintegrate a granule by adsorbing water swelling, or making a channel between an effective ingredient constituting the nucleus and an excipient, in contact with water, can be used. These disintegrating agents can be used alone or in combination of two or more. The amount of the disintegrating agent used is appropriately selected depending on the kind and blending amount of a drug used, design of releasing property, and the like, and for example, from about 0.05 to about 30 w/w%, preferably from about 0.5 to about 15 w/w%, based on the total amount of the rapid releasing agent.

[0090]

When the immediate-release preparation is an oral solid preparation, it may further contain, in addition to the above-mentioned composition, if desired, additives conventional in solid preparations. As such an additive, there are used, for example, a binder (e.g., sucrose, gelatin, gum Arabic powder, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, pullulan, dextrin and the like), a lubricant (e.g., polyethylene glycol, magnesium stearate, talc, light anhydrous silicic acid (e.g., Aerosil (Nippon Aerosil)), a surfactant (e.g., anionic surfactants such as sodium alkylsulfate and the like, nonionic surfactants such as polyoxyethylene fatty acid ester and polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil derivatives and the like), a colorant (e.g., tar coloring matter, caramel, iron oxide red, titanium oxide, riboflavins), if necessary, an appetizing agent (e.g., sweetening agent, flavoring agent and the like), an adsorbent, preservative, wetting agent, antistatic agent, and the like. Further, as the stabilizer, an organic acid such as tartaric acid, citric acid, succinic acid, fumaric acid and the like may also be added.

[0091]

As the above-mentioned binder, hydroxypropylcellulose, polyethylene glycol and polyvinylpyrrolidone and the like are preferably used.

[0092]

The immediate-release preparation can be prepared by, based on a usual technology of producing preparations, mixing the above-mentioned components, and if necessary, further kneading the mixture, and molding it. The above-mentioned mixing is conducted by generally used methods, for example, mixing, kneading and the like. Specifically, when a immediate-release preparation is formed, for example, into a particle, it can be prepared, according to the same means as in the above-mentioned method for preparing a nucleus of a sustained release preparation, by mixing the components using a vertical granulator, universal kneader (manufactured by Hata Tekkosho), fluidized bed granulator FD-5S (manufactured by Powrex Corporation), and the like, and then, granulating the mixture by a wet extrusion granulation method, fluidized bed granulation method and the like.

[0093]

Thus obtained immediate-release preparation and sustained release preparation may be themselves made into products or made into products appropriately together with preparation excipients and the like, separately, by an ordinary method, then, may be administered simultaneously or may be administered in combination at any administration interval, or they may be themselves made into one oral preparation (e.g., granule, fine particle, tablet, capsule and the like) or made into one oral preparation appropriately together with preparation excipients and the like. It may also be permissible that they are made into granules or fine particles, and filled in the same capsule to be used as a preparation for oral administration.

[0094]

[3] Sublingual, buccal or intraoral rapid disintegrating agent and preparation thereof

Sublingual, buccal or intraoral rapid disintegrating agents may be a solid preparation such as tablet and the like, or may be an oral mucosa membrane patch (film).

As the sublingual, buccal or intraoral rapid disintegrating agent, a preparation containing the substance of the present invention or the concomitant drug and an excipient is preferable. It may contain also auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer and the like. Further, for easy absorption and increased *in vivo* use efficiency, β-cyclodextrin or β-cyclodextrin derivatives (e.g., hydroxypropyl-(-cyclodextrin and the like) and the like may also be contained.

[0095]

As the above-mentioned excipient, lactose, sucrose, D-mannitol, starch, crystalline cellulose, light anhydrous silicic acid and the like are listed. As the lubricant, magnesium stearate, calcium stearate, talc, colloidal silica and the like are listed, and particularly, magnesium stearate and colloidal silica are preferable. As the isotonizing agent, sodium chloride, glucose, fructose, mannitol, sorbitol, lactose, saccharose, glycerin, urea and the like are listed, and particularly, mannitol is preferable. As the hydrophilic carrier, swellable hydrophilic carriers such as crystalline cellulose, ethylcellulose, crosslinkable polyvinylpyrrolidone, light anhydrous silicic acid, silicic acid, dicalcium phosphate, calcium carbonate and the like are listed, and particularly, crystalline cellulose (e.g., microcrystalline cellulose and the like) is preferable. As the water-dispersible polymer, gums (e.g., gum tragacanth, acacia gum, guar gum), alginates (e.g., sodium alginate), cellulose derivatives (e.g., methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose,

hydroxypropylmethylcellulose), gelatin, aqueous starch, polyacrylic acids (e.g., Carbomer), polymethacylic acid, polyvinyl alcohol, polyethylene glycol, polyvinylpyrrolidone, polycarbophil, ascorbate palmitates and the like are listed, and hydroxypropylmethylcellulose, polyacrylic acid, alginate, gelatin, carboxymethylcellulose, polyvinylpyrrolidone, polyethylene glycol and the like are preferable. Particularly, hydroxypropylmethylcellulose is preferable. As the stabilizer, cysteine, thiosorbitol, tartaric acid, citric acid, sodium carbonate, ascorbic acid, glycine, sodium sulfite and the like are listed, and particularly, citric acid and ascorbic acid are preferable.

[0096]

The sublingual, buccal or intraoral rapid disintegrating agent can be produced by mixing the substance of the present invention or the concomitant drug and an excipient by a method known per se. Further, if desired, auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer, colorant, sweetening agent, preservative and the like may be mixed. The sublingual, buccal or intraoral rapid disintegrating agent is obtained by mixing the above-mentioned components simultaneously or at a time interval, then subjecting the mixture to tablet-making molding under pressure. For obtaining suitable hardness, it may also be permissible that the materials are moistened by using a solvent such as water, alcohol and the like if desired before and after the tablet making process, and after the molding, the materials are dried, to obtain a product.

[0097]

In the case of molding into a mucosa membrane patch (film), the substance of the present invention or the concomitant drug and the above-mentioned water-dispersible polymer (preferably, hydroxypropylcellulose, hydroxypropylmethylcellulose), excipient and the like are dissolved in a solvent such as water and the like, and the

resulted solution is cast to give a film. Further, additives such as a plasticizer, stabilizer, antioxidant, preservative, colorant, buffer, sweetening agent and the like may also be added. For imparting suitable elasticity to the film, glycols such as polyethylene glycol, propylene glycol and the like may be contained, or for enhancing adhesion of the film to an intraoral mucosa membrane lining, a bio-adhesive polymer (e.g., polycarbophil, carbopol) may also be contained. In the casting, a solution is poured on the non-adhesive surface, spread to uniform thickness (preferably, about 10 to 1000 micron) by an application tool such as a doctor blade and the like, then, the solution is dried to form a film. It may be advantageous that thus formed film is dried at room temperature or under heat, and cut into a desired area.

[0098]

As the preferable intraoral rapid disintegrating agent, there are listed solid rapid scattering dose agents composed of a network body comprising the substance of the present invention or the concomitant drug, and a aqueous or water-diffusible carrier which is inert to the substance of the present invention or concomitant drug, are listed. This network body is obtained by sublimating a solvent from the solid composition constituted of a solution prepared by dissolving the substance of the present invention or the concomitant drug in a suitable solvent.

[0099]

It is preferable that the composition of an intraoral rapid disintegrating agent contains a matrix forming agent and a secondary component, in addition to the substance of the present invention or the concomitant drug.

[0100]

Examples of the matrix forming agent include gelatins, dextrins, animal proteins or vegetable proteins such as soybean, wheat and psyllium seed protein and the like; rubber substances such as gum Arabic, guar gum, agar, xanthane gum

and the like; polysaccharides; alginic acids; carboxymethylcelluloses; carageenans; dextrans; pectines; synthetic polymers such as polyvinylpyrrolidone and the like; substances derived from a gelatin-gum Arabic complex, and the like. Further, saccharides such as mannitol, dextrose, lactose, galactose, trehalose and the like; cyclic saccharides such as cyclodextrin and the like; inorganic salts such as sodium phosphate, sodium chloride and aluminum silicate and the like; amino acids having 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine, L-phenylalanine and the like, are contained.

[0101]

One or more of the matrix forming agents can be introduced in a solution or suspension before solidification. Such as matrix forming agent may be present in addition to a surfactant, or may be present while a surfactant being excluded. The matrix forming agents aid to maintain the substance of the present invention or the concomitant drug in the solution or suspension in diffused condition, in addition to formation of the matrix.

[0102]

The composition may contain secondary components such as preservative, antioxidant, surfactant, thickening agent, colorant, pH controlling agent, flavoring agent, sweetening agent and food taste masking agent, and the like. As the suitable colorant, there are listed red, black and yellow iron oxides, and FD & C dyes such as FD & C Blue 2, FD & C Red 40 and the like manufactured by Ellis and Everard. Examples of the suitable flavoring agent include mint, raspberry, licorice, orange, lemon, grapefruit, caramel, vanilla, cherry, grape flavor and combinations thereof. Examples of the suitable pH controlling agent include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Examples of the suitable sweetening agent include aspartame, acesulfame

K and thaumatin and the like. Examples of the suitable food taste masking agent include sodium bicarbonate, ion exchange resin, cyclodextrin-inclusion compounds, adsorbent substances and microcapsulated apomorphine.

[0103]

The preparation contains the substance of the present invention or the concomitant drug in an amount usually from about 0.1 to about 50% by weight, preferably from about 0.1 to about 30% by weight, and preferable are preparations (such as the above-mentioned sublingual agent, buccal and the like) which can dissolve 90% or more of the substance of the present invention or the concomitant drug (into water) within the time range of about 1 to about 60 min, preferably of about 1 to about 15 min, more preferably of about 2 to about 5 min, and oral rapid disintegrating preparations which are disintegrated within the range of 1 to 60 sec, preferably of 1 to 30 sec, further preferably of 1 to 10 sec, after placed in an oral cavity.

[0104]

The content of the above-mentioned excipient in the whole preparation is from about 10 to about 99% by weight, preferably from about 30 to about 90% by weight. The content of β-cyclodextrin or β-cyclodextrin derivative in the whole preparation is from 0 to about 30% by weight. The content of the lubricant in the whole preparation is from about 0.01 to about 10% by weight, preferably from about 1 to about 5% by weight. The content of the isotonizing agent in the whole preparation is from about 0.1 to about 90% by weight, preferably, from about 10 to about 70% by weight. The content of the hydrophilic carrier in the whole preparation is from about 0.1 to about 50% by weight, preferably, from about 10 to about 30% by weight. The content of the water-dispersible polymer in the whole preparation is from about 0.1 to about 30% by weight, preferably, from about 10 to about 25% by weight. The content of the stabilizer in the whole preparation

is from about 0.1 to about 10% by weight, preferably, from about 1 to 5% by weight. The above-mentioned preparation may further contain additives such as a colorant, sweetening agent, preservative and the like, if necessary.

[0105]

The dose of a combination drug of the present invention varies depending on the kind of the substance of the present invention and concomitant drug, age, body weight, condition, dosage form, administration method, administration period and the like.

The dose of the substance of the present invention is as defined above.

The concomitant drug is administered intravenously to a cancer patient (adult, body weight: about 60 kg) at a dose of generally about 0.005 to about 1000 mg/kg, preferably about 0.01 to about 100 mg/kg, more preferably about 0.1 to about 100 mg/kg, particularly about 0.02 to about 50 mg/kg, especially about 0.1 to about 30 mg/kg, in one to several portions a day.

As described above, since the dose varies depending on various conditions, amounts smaller than the above-mentioned dose may sometimes be sufficient, further, amounts over that range sometimes have to be administered.

[0106]

The amount of the concomitant drug can be set at any value unless side effects are problematical. The daily dosage in terms of the concomitant drug differs depending on the severity of the symptom, age, sex, body weight, sensitivity difference of the subject, administration time, interval, and nature, formulation, kind of the pharmaceutical preparation, kind of effective ingredient, and the like, and not particularly restricted, and the amount of a drug is, in the case of oral administration for example, usually from about 0.001 to 2000 mg, preferably from about 0.01 to 500 mg, further preferably from about 0.1 to 100 mg, per 1 kg of a

mammal and this is usually administered once to 4-times in division a day.

[0107]

In administration of a combination drug of the present invention, the substance of the present invention may be administered after administration of the concomitant drug or the concomitant drug may be administered after administration of the substance of the present invention, though they may be administered simultaneously. When administered in a staggered manner, the lag time varies depending on the effective ingredient to be administered, dosage form and administration method, and for example, when the concomitant drug is administered first, a method in which the substance of the present invention is administered within time range of from 1 min to 3 days, preferably from 10 min to 1 day, more preferably from 15 min to 1 hr after administration of the concomitant drug is exemplified. When the substance of the present invention is administered first, a method in which the concomitant drug is administered within time range of from 1 min to 1 day, preferably from 10 min to 6 hrs, more preferably from 15 min to 1 hr after administration of the substance of the present invention is exemplified.

[0108]

Furthermore, the substance of the present invention or the combination drug of the present invention can be used concurrently with a non-drug therapy. To be precise, the substance of the present invention and the combination drug of the present invention can be combined with a non-drug therapy such as (1) surgery, (2) hypertensive chemotherapy using angiotensin II etc., (3) gene therapy, (4) thermotherapy, (5) cryotherapy, (6) laser cauterization, (7) radiotherapy, and the like.

[0109]

For example, effects such as prevention of resistance expression, prolongation of Disease-Free Survival, suppression

of cancer metastasis or recurrence, life prolonging and the like can be obtained by the use of the substance of the present invention or combination drug of the present invention before or after an operation and the like, or before or after a treatment combining two or three kinds of the therapy.

[0110]

In addition, it is possible to combine a treatment using the substance of the present invention or combination drug of the present invention and a supportive therapy [(i) administration of antibiotic (e.g., β-lactam series such as pansporin etc., macrolide series such as clarithromycin etc., and the like) for various complicating infectious diseases, (ii) administration of intravenous hyperalimentation, amino acid preparation and general vitamin preparation for improving malnutrition, (iii) administration of morphine for pain mitigation, (iv) administration of a pharmaceutical agent which improves side effects such as nausea, vomiting, anorexia, diarrhea, leucopenia, thrombocytopenia, decreasing of hemoglobin concentration, hair loss, hepatopathy, renopathy, DIC, fever and the like and (v) administration of a pharmaceutical agent to suppress multiple drug resistances of cancer and the like].

[0111]

Preferably, the substance of the present invention or the combination drug of the present invention is administered orally (including sustained-release preparations), intravenously (including boluses, infusions and clathrates), subcutaneously and intramuscularly (including boluses, infusions and sustained-release preparations), transdermally, intratumorally or proximally before or after the above-described treatment is conducted.

[0112]

As the timing of administration of the substance of the present invention or the combination drug of the present invention before the surgery, etc., for example, it can be

administrated 1-time about 30 min to 24 hrs before the surgery, etc., or in 1 to 3 cycles about 3 months to 6 months before the surgery, etc. In this way, the surgery, etc. can be conducted easily because, for example, a cancer tissue would be reduced by administering the substance of the present invention or the combination drug of the present invention before the surgery, and the like.

[0113]

As the timing of administration of the substance of the present invention or the combination drug of the present invention after the surgery, etc., for example, it can be administrated repeatedly per a few weeks to 3 months, about 30 min to 24 hrs after the surgery, and the like. In this way, it makes an effect of the surgery, etc. increasing by administering the substance of the present invention or the combination drug of the present invention after the surgery, and the like.

[0114]

The present invention further relates to a method of screening for an agent for the prophylaxis or treatment of cancer, comprising measuring t1/2 relative to kinase of a test substance (hereinafter sometimes to be abbreviated as the screening method A of the present invention). The screening method A of the present invention specifically comprises the following steps (1) and (2).

(1) Step of measuring and calculating a t1/2 relative to kinase of a test substance

In this step, t1/2 of the test compound is measured and calculated. The method used for this step is not particularly limited as long as t1/2 relative to kinase can be calculated as a value permitting evaluation. For example, "the measurement method using, as an index, recovery of enzyme activity by the dissociation of compound" mentioned above or described in detail in the Examples can be employed. Here, examples of the kinase include those similar to the

aforementioned kinases, and those desired to be measured are used. Examples of the test compound include peptide, protein, nonpeptidic compound, synthesized compound, fermentation product, cell extract, plant extract, animal tissue extract and the like. These compounds may be novel or known.

(2) Step of selecting a substance showing a t1/2 relative to kinase of not less than 10 min

In this step, a substance is selected based on the value (t1/2) obtained in the above-mentioned step (1). While the t1/2 to be the index is appropriately set for the kinase to be used, it is generally not less than 10 min. The t1/2 relative to kinase is preferably not less than 60 min, more preferably not less than 80 min, more preferably not less than 100 min, still more preferably not less than 300 min, further more preferably not less than 500 min, and particularly preferably not less than 900 min.

While the upper limit of the t1/2 is not particularly limited, it is preferably not more than 30000 min, more preferably not more than 20000 min, still more preferably not more than 15000 min, further more preferably not more than 10000 min, yet more preferably not more than 5000 min, and particularly preferably not more than 4000 min.

Since the substance selected in this step shows t1/2 relative to kinase of not less than 10 min, the agent containing it has, for example, the following characteristics.

(1) The treatment effect can be prolonged.

(2) The treatment effect can be potentiated.

(3) The side effects can be reduced.

(4) The dose for patients can be set low.

(5) The interval of administration to patients can be set long.

(6) The period of drug withdrawal can be lengthened.

[0115]

The present invention further relates to a method of screening for a kinase inhibitor, comprising measuring t1/2 relative to kinase of a test substance (hereinafter sometimes

to be abbreviated as the screening method B of the present invention). The screening method B of the present invention specifically comprises the following steps (1) and (2).

(1) Step of measuring and calculating t1/2 relative to kinase of a test substance

This step can be performed in the same manner as in the screening method A, step (1), of the present invention.

(2) Step of selecting substance showing t1/2 relative to kinase of not less than 10 min

This step can be performed in the same manner as in the screening method A, step (2), of the present invention.

Examples

[0116]

The present invention is explained in more detail in the following by referring to Formulation Examples and Experimental Examples, which are not to be construed as limitative.

Formulation Example 1

As compound A, the compound described in the above-mentioned WO08/16192 is used.

1. Capsule of compound A

(1) compound A	10 mg
(2) lactose	70 mg
(3) microcrystalline cellulose	9 mg
(4) magnesium stearate	1 mg
1 capsule	90 mg

After blending (1), (2), (3) and 1/2 of (4), the mixture is granulated. The rest of (4) is added thereto and the whole mixture is packed in a gelatin capsule.

[0117]

2. Tablet of compound A

(1) compound A	10 mg
(2) lactose	58 mg
(3) cornstarch	18 mg
(4) microcrystalline cellulose	3.5 mg

(5) magnesium stearate 0.5 mg

1 tablet 90 mg

After blending (1), (2), (3), 2/3 of (4) and 1/2 of (5), the mixture is granulated. The rest of (4) and (5) is added to the granule and the mixture is to press-molded to give a tablet.

[0118]

3. Tablet of lapatinib (Tykerb)

Lapatinib (Tykerb) 250 mg tablet contains 405 mg of lapatinib ditosylate monohydrate (corresponding to 398 mg of lapatinib ditosylate or 250 mg of lapatinib (free base)).

As the inert ingredients of Tykerb tablet, the following are contained.

tablet core component; magnesium stearate, microcrystalline cellulose, povidone, sodium carboxymethyl starch (sodium starch glycolate)

coating component (orange film coat); FD&C Yellow #6/Sunset yellow FCF aluminum lake, hydroxypropylmethylcellulose (hypromellose), macrogol/PEG 400, polysorbate 80, titanium dioxide

[0119]

4. Tablet of sorafenib (Nexavar)

A red and round film-coated tablet of Nexavar contains sorafenib tosylate (274 mg) (corresponding to sorafenib 200 mg).

As the inert ingredients, the following are contained. croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethylcellulose (hypromellose), sodium lauryl sulfate, magnesium stearate, polyethylene glycol, titanium dioxide and red iron oxide (bengara)

[0120]

Reference Example 1 Cloning of human VEGF receptor 2 (VEGFR2) gene and preparation of recombinant baculovirus

Human VEGF receptor 2 (hereinafter to be abbreviated as VEGFR2) gene was cloned by PCR using cDNA Libraries Human

Placenta (Clontech) as a template. The primer used for PCR was prepared by adding a base sequence encoding a flag peptide and a restriction enzyme recognition sequence to a base sequence (2671-4374 in Genbank Accession AF035121) encoding a VEGFR2 intracellular domain, based on the information of VEGFR2 gene base sequence (Genbank Accession AF035121), such that a flag tag is added to the N-terminal of a protein. The primer base sequences are shown below.

VEGFR2-U:

5′-AATTAAGTCGACATGGACTACAAGGATGACGATGACAAGAAGCGGGCCAATGGAGGGGAACTGAAGACA-3′ (SEQ ID NO: 1)

and

VEGFR2-L:

5′-AATTAAGCATGCTTAAACAGGAGGAGAGCTCAGTGTGGTCCC-3′ (SEQ ID NO: 2)

PCR was performed using KOD-plus kit (TOYOBO). The obtained PCR product was subjected to agarose gel (1%) electrophoresis, DNA fragment amplified by PCR was recovered from the gel, and digested with restriction enzymes Sal I and Sph I. DNA after treatment with the restriction enzymes was subjected to agarose gel (1%) electrophoresis, and the obtained DNA fragment was recovered, and ligated to plasmid pFASTBAC1 (Invitrogen) digested with restriction enzymes Sal I and Sph I to give expression plasmid pFB-VEGFR2. The base sequence of the inserted fragment was confirmed to match the base sequence (2671-4374 in Genbank Accession AF035121) of VEGFR2 intracellular domain. Using BAC-TO-BAC Baculovirus Expression System (Invitrogen), moreover, virus stock BAC-VEGFR2 of recombinant Baculovirus was prepared.

[0121]

Reference Example 2 Preparation of VEGF receptor 2 (VEGFR2) intracellular domain protein

SF-21 cells were inoculated to Sf-900IISFM medium (Invitrogen, 1 L) containing 10% fetal bovine serum (Thermo

Trace Ltd.), 50 mg/L Gentamicin (Invitrogen) and 0.1% Pluronic F-68 (Invitrogen) at 1×10^6 cells/ml, and cultured with shaking in 2L Erlenmeyer flask at 27°C, 100 rpm. After culturing for 24 hr, recombinant Baculovirus BAC-VEGFR2 (13.4 mL) was added and the cells were further cultured for 3 days. The culture medium was centrifuged at 2,000 rpm for 5 min to give virus-infected cells. The infected cells were washed with phosphate physiological saline (Invitrogen) and centrifuged under the same conditions. The obtained cells were cryopreserved at -80°C. The cryopreserved cells were thawed in ice and suspended in buffer A (50 mM tris buffer (pH 7.4) containing 20% Glycerol and 0.15 M NaCl, 30 mL) supplemented with Complete Protease Inhibitor (Boehringer) and homogenized 3 times in a polytron homogenizer (Kinematica) at 20,000 rpm, 30 sec. The cell lysate was clarified by centrifugation at 40,000 rpm, 30 min, and filtered through a 0.45 μm filter. The filtrate was passed through a column packed with 4 mL of Anti-FLAG M2 Affinity Gel (Sigma Ltd.) at a flow rate of about 0.5 mL/min. The column was washed with buffer A and eluted with buffer A containing 100 μg/mL FLAG peptide. The eluate was concentrated with Vivaspin 20 (Vivascience) with a molecular weight cut off of 30K. The concentrated solution was subjected to buffer exchange using a NAP™ 25 column (Amersham Biosciences) equilibrated with buffer A. Fractions containing VEGFR2 intracellular domain protein were collected, added with glycerol to a final concentration of 50%, and cryopreserved at -80°C.

[0122]

Experimental Example 1 t1/2 calculation test with recovery of VEGFR2 enzyme activity as index

The kinase activity of VEGFR2 was measured according to a measurement method using AlphaScreen (registered trade mark, PerkinElmer) using anti-phosphorylation tyrosine antibody. As a reaction buffer, a kinase reaction solution (50 mmol/L Tris-HCl, pH 7.5, 5 mmol/L $MnCl_2$, 0.01% Tween-20 and 2 mmol/L

dithiothreitol) was used. A compound at a concentration 10 times IC_{50} obtained in the enzyme inhibitory test and 400 ng/ml of VEGFR2 kinase protein were left standing at room temperature for 60 min, and diluted 100-fold with a kinase reaction solution containing 1 mmol/L ATP and 0.1 μg/mL biotin-labeled poly-Glu-Tyr (4:1) to start an enzyme reaction. EDTA was added to 0.166 mol/L at each reaction time, the enzyme reaction was stopped, a detection buffer (62.5 mmol/L HEPES buffer (pH 7.4), 250 mmol/L NaCl, 0.1% BSA, 10 μg/mL streptavidin donor beads, 10 μg/mL PY-100 acceptor beads) was added, an antibody reaction was performed at room temperature for 16 hr, and the count was measured using EnVision. To perform a control reaction, DMSO solution without addition of the compound and 400 ng/ml of VEGFR2 kinase protein were left standing at room temperature.

For calculation of t1/2, signal at each reaction time was fitted to the following function (A) (Methods of Biochemical Analysis, Evaluation of Enzyme Inhibitors in Drug Discovery, vol. 46, 2005, pages 1-265, Wiley-Interscience and Cancer Research, 2004, vol. 64, pages 6652-6659) to give k_{obs}. The initial setpoint of v_i, which is the initial rate, was 0, and the steady state rate v_s was calculated from the rate in 20 min of the control reaction, during which the linearity is observed, and used as the setpoint. t1/2 was calculated from function (B) (Methods of Biochemical Analysis, Evaluation of Enzyme Inhibitors in Drug Discovery, vol. 46, 2005, pages 1-265, Wiley-Interscience and Cancer Research, 2004, vol. 64, pages 6652-6659) using the obtained k_{obs}.

$$P=v_s t+[(v_i-v_s)/k_{obs}][1-\exp(-k_{obs}t)] \quad (A)$$

$$t1/2=0.693/k_{obs} \quad (B)$$

[0123]

The test results are shown below. Example Nos. of the compounds are those indicated in WO08/16192.

compound	t1/2 (min)
Example 29	not less than 900

Example 97	not less than 900
Example 111	not less than 900
Example 114	103
Example 117	not less than 900
Example 120	not less than 900
Example 127	57
Example 148	not less than 900
Example 149	38
Example 150	not less than 900
Example 160	not less than 900
Example 161	335
Example 165	119
Example 173	693
Example 174	301
Example 180	96
Example 187	89
Example 208	653
Example 241	not less than 900
Example 243	not less than 900
Example 247	577
Example 254	482
Example 267	119
Example 287	161
Example 289	473
Example 298	116
Example 302	439
Example 314	312
Example 317	12
sunitinib	4
sorafenib	206

[0124]

Experimental Example 2 t1/2 calculation test with recovery of PDGFR β enzyme activity as index

The kinase activity of PDGFR β was measured according to a measurement method using AlphaScreen (registered trade mark,

PerkinElmer) using anti-phosphorylation tyrosine antibody. As a reaction buffer, a kinase reaction solution (50 mmol/L Tris-HCl, pH 7.5, 5 mmol/L $MnCl_2$, 0.01% Tween-20 and 2 mmol/L dithiothreitol) was used. A compound at a concentration 10 times IC_{50} obtained in the enzyme inhibitory test and 1000 ng/ml of PDGFR β kinase protein (Millipore) were left standing at room temperature for 60 min, and diluted 100-fold with a kinase reaction solution containing 1 mmol/L ATP and 0.1 μg/mL biotin-labeled poly-Glu-Tyr (4:1) to start an enzyme reaction. EDTA was added to 0.166 mol/L at each reaction time, the enzyme reaction was stopped, a detection buffer (62.5 mmol/L HEPES buffer (pH 7.4), 250 mmol/L NaCl, 0.1% BSA, 10 μg/mL streptavidin donor beads, 10 μg/mL PT66 acceptor beads) was added, an antibody reaction was performed at room temperature for 16 hr, and the count was measured using EnVision. To perform a control reaction, DMSO solution without addition of the compound and 1000 ng/ml of PDGFR β kinase protein were left standing at room temperature.

For calculation of t1/2, signal at each reaction time was fitted to the following function (A) (Methods of Biochemical Analysis, Evaluation of Enzyme Inhibitors in Drug Discovery, vol. 46, 2005, pages 1-265, Wiley-Interscience and Cancer Research, 2004, vol. 64, pages 6652-6659) to give k_{obs}. The initial setpoint of v_i, which is the initial rate, was 0, and the steady state rate v_s was calculated from the rate in 20 min of the control reaction, during which the linearity is observed, and used as the setpoint. t1/2 was calculated from function (B) (Methods of Biochemical Analysis, Evaluation of Enzyme Inhibitors in Drug Discovery, vol. 46, 2005, pages 1-265, Wiley-Interscience and Cancer Research, 2004, vol. 64, pages 6652-6659) using the obtained k_{obs}.

$$P=v_s t+[(v_i-v_s)/k_{obs}][1-\exp(-k_{obs}t)] \quad (A)$$

$$t1/2=0.693/k_{obs} \quad (B)$$

[0125]

The test results are shown below. Example Nos. of the

compounds are those indicated in WO08/16192.

compound	t1/2 (min)
Example 29	202
Example 97	35
Example 103	14
Example 111	363
Example 114	68
Example 117	304
Example 120	206
Example 127	45
Example 148	217
Example 149	48
Example 150	268
Example 161	80
Example 165	101
Example 173	87
Example 174	78
Example 180	86
Example 187	180
Example 208	143
Example 241	35
Example 243	187
Example 247	300
Example 254	164
Example 267	78
Example 287	51
Example 289	79
Example 298	29
Example 302	143
Example 314	141
sunitinib	2
sorafenib	not less than 900

[0126]

Sequence Listing Free Text

[SEQ ID NO: 1]

Designed oligonucleotide primer to amplify DNA encoding human VEGFR2

[SEQ ID NO: 2]

Designed oligonucleotide primer to amplify DNA encoding human VEGFR2

Industrial Applicability

[0127]

A receptor kinase inhibitory substance showing pseudo-irreversibility is useful as an agent for the prophylaxis or treatment of cancer, which is superior in safety and the like.

This application is based on patent application No. 241729/2008 filed in Japan, and U.S. provisional application No. 61/150,180 filed in United States, the contents of which are hereby incorporated by reference.

CLAIMS

1. An agent for the prophylaxis or treatment of cancer showing a prolonged effect for cancer treatment, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min.

2. An agent for the prophylaxis or treatment of cancer showing a potentiated effect for cancer treatment, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min.

3. An agent for the prophylaxis or treatment of cancer showing reduced side effects in cancer treatment, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min.

4. An agent for the prophylaxis or treatment of cancer permitting a low dose for patients, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min.

5. An agent for the prophylaxis or treatment of cancer permitting a long interval in administration to patients, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min.

6. An agent for the prophylaxis or treatment of cancer showing a prolonged period of drug withdrawal, which comprises a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min.

7. The agent of any one of claims 1 to 6, wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 300 min.

8. The agent of any one of claims 1 to 7, wherein the kinase is a receptor kinase.

9. The agent of claims 8, wherein the receptor kinase is a vascular endothelial growth factor receptor 2 (VEGFR2).

10. The agent of claim 9, wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 80 min.

11. The agent of claim 8, wherein the receptor kinase is a platelet-derived growth factor receptor (PDGFR).

12. The agent of claim 11, wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 60 min.

13. A method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method shows a prolonged effect for cancer treatment.

14 A method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method shows a potentiated effect for cancer treatment.

15. A method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method shows reduced side effects in cancer treatment.

16 A method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method permits a low dose for patients.

17. A method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method permits a long interval in administration to patients.

18. A method for the prophylaxis or treatment of cancer in a mammal, comprising administering, to the mammal, an effective amount of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min, which method shows a prolonged period of drug withdrawal.

19. The method of any one of claims 13 to 18, wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 300 min.

20. The method of any one of claims 13 to 19, wherein the kinase is a receptor kinase.

21. The method of claim 20, wherein the receptor kinase is a vascular endothelial growth factor receptor 2 (VEGFR2).

22. The method of claim 21, wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 80 min.

23. The method of claim 20, wherein the receptor kinase is a platelet-derived growth factor receptor (PDGFR).

24. The method of claim 23, wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 60 min.

25. Use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer showing a prolonged effect for cancer treatment.

26. Use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer showing a potentiated effect for cancer treatment.

27. Use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer showing reduced side effects in the cancer treatment.

28. Use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer permitting a low dose to patients.

29. Use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer permitting a long interval in administration to patients.

30. Use of a kinase inhibitory substance showing a t1/2 relative to kinase of not less than 10 min for the production of an agent for the prophylaxis or treatment of cancer showing a prolonged the period of drug withdrawal.

31. The use of any one of claims 25 to 30, wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 300 min.

32. The use of any one of claims 25 to 31, wherein the kinase is a receptor kinase.

33. The use of claim 32, wherein the receptor kinase is a vascular endothelial growth factor receptor 2 (VEGFR2).

34. The use of claim 33, wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 80 min.

35. The method of claim 32, wherein the receptor kinase is a platelet-derived growth factor receptor (PDGFR).

36. The method of claim 35, wherein the kinase inhibitory substance shows a t1/2 relative to kinase of not less than 60 min.

37. A pharmaceutical composition comprising sorafenib at a daily oral dose of 400 - 600 mg.

38. A method for the prophylaxis or treatment of cancer in a mammal, comprising orally administering sorafenib at a daily oral dose of 400 - 600 mg to the mammal.

39. Use of sorafenib for the production of an agent for the prophylaxis or treatment of cancer, comprising sorafenib at a daily oral dose of 400 - 600 mg.

40. A pharmaceutical composition comprising lapatinib at a daily oral dose of 250 - 500 mg.

41. A method for the prophylaxis or treatment of cancer in a mammal, comprising orally administering lapatinib at a daily oral dose of 250 - 500 mg to the mammal.

42. Use of lapatinib for the production of an agent for the prophylaxis or treatment of cancer, comprising lapatinib at a daily oral dose of 250 - 500 mg.

43. A method of screening for an agent for the prophylaxis or treatment of cancer, comprising
(1) measuring and calculating a t1/2 relative to kinase of a test substance, and
(2) selecting a substance showing a t1/2 relative to kinase of not less than 10 min.

44. The method of claim 43, wherein the agent for the prophylaxis or treatment of cancer shows a potentiated effect in cancer treatment.

45. The method of claim 43, wherein the agent for the prophylaxis or treatment of cancer shows reduced side effects in cancer treatment.

46. The method of claim 43, wherein the agent for the prophylaxis or treatment of cancer permits a low dose to patients.

47. The method of claim 43, wherein the agent for the prophylaxis or treatment of cancer permits a long interval in administration to patients.

48. The method of claim 43, wherein the agent for the prophylaxis or treatment of cancer shows a prolonged period of drug withdrawal.

49. A method of screening for a kinase inhibitor, comprising

(1) measuring and calculating a t1/2 relative to kinase of a test substance, and

(2) selecting a substance showing a t1/2 relative to kinase of not less than 10 min.