

COMBINATION OF ANTICANCER AGENTS COMPRISING A BIFUNCTIONAL COMPOUND WITH G12D MUTANT KRAS INHIBITORY ACTIVITY

Field of the invention

- 5 The present invention relates to combinations of specific anti-cancer compounds, and pharmaceutical compositions and kits comprising the same, for use in treatment of cancers, such as pancreatic, colorectal and lung cancers.

Background of the invention

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KRAS (Kirsten rat sarcoma virus) is a gene that provides instructions for making a protein called K-Ras, a part of the RAS/MAPK pathway. The protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow and divide (proliferate) or to mature and take on specialized functions (differentiate).

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KRAS mutations have been implicated in various malignancies, including cancer, such as lung adenocarcinoma, mucinous adenoma, ductal carcinoma of the pancreas and colorectal cancer.

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Colorectal cancer is a cancer with a high morbidity and fatality, with about 1.4 million new cases being reported per year in the world (World Cancer Report 2014). The most effective means for treating colorectal cancer is a surgery, whereas chemotherapy, radiotherapy, and the like have recently been significantly advanced. Large scale clinical trials performed mainly in Europe and America have revealed that a combination chemotherapy in which several types of anticancer agents are combined is efficacious for colorectal cancer and contributes to regression of a tumor and prolongation of the prognosis (J. Clin. Oncol., 22, p.229-237, 2004). In addition to the chemotherapy, a molecular target drug, such as an anti-VEGF (vascular endothelial growth factor) antibody or an anti-EGFR (epidermal growth factor receptor) antibody, is used as a first-choice drug in combination with the chemotherapy. Regarding an EGFR antibody drug, it has been apparent that mutation in a RAS gene is a negative predictive factor for the effect (Cancer Res., 66, p.3992-3995, 2006), and in colorectal cancer, EGFR antibody drugs are applicable only to patients with wild type RAS genes in the current situation.

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In addition, the number of deaths due to lung cancer accounts for 19% of that due to all cancers which is the highest value, and about 1.8 million new patients are reported per year in the world (World Cancer Report 2014). In particular, patients of non-small

cell lung cancer (NSCLC) are reported to account for 80 to 85% of those of lung cancer (American Cancer Society, Cancer Facts and Figures, 2016). Surgical therapy is considered until a certain stage, but surgery is rarely adopted after that stage and chemotherapy or radiotherapy then become a main therapy. Based on the
5 cytomorphology, adenocarcinoma and squamous cell cancer are classified as the most typical type of NSCLC. These tumors follow a similar clinical course, but adenocarcinoma is characterized by localization in the lung periphery.

Pancreatic cancer mainly including pancreatic ductal adenocarcinoma is a cancer with
10 a very poor prognosis having a five years survival rate of 10% or less (CA Cancer J. Clin., 2016, 66, p.7-30), and about 340,000 new cases are reported per year in the world (GLOBOCAN 2012). The most effective therapy for treating pancreatic cancer is a surgery. However, the cancer has often metastasized since early detection is difficult, and the cancer is often not operable. If not operable, chemotherapy or radiotherapy
15 is adopted but the survival rate is not so good. Today, the FOLFIRINOX therapy (multidrug treatment of three chemotherapy agents of 5-FU, irinotecan, and oxaliplatin, plus levofolinate) is used as a standard therapy of pancreatic cancer. However, due to the strong toxicity, the subject patient has to be cautiously selected, for example, the therapy is to be applied only to patients of an ECOG performance
20 status of 1 or less (J. Clin. Oncol., 2018, 36, p.2545-2556). As a molecular target drug, an epidermal growth factor receptor (EGFR) inhibitor, Erlotinib, has been approved in a combination therapy with Gemcitabine. However, the extension of the overall survival is only about two weeks as compared with Gemcitabine alone and no satisfying therapeutic effect has been achieved.

25 RAS proteins are low molecular weight guanosine triphosphate (GTP)-binding proteins of about 21 kDa constituted of 188-189 amino acids, and include four main types of proteins (KRAS (KRAS 4A and KRAS 4B), NRAS, and HRAS) produced by three genes of a KRAS gene, an NRAS gene, and an HRAS gene. RAS proteins are divided into an
30 active GTP-binding type and an inactive GDP-binding type. A RAS protein is activated by replacement of guanosine diphosphate (GDP) with GTP due to, for example, ligand stimulation to a membrane receptor, such as EGFR. The active RAS binds to effector proteins as much as twenty, such as RAF, PI3K, and RALGDS, to activate the downstream signal cascade. On the other hand, the active RAS is converted to the
35 inactive type by replacement of GTP with GDP due to the intrinsic GTP hydrolysis (GTPase) activity. The GTPase activity is enhanced by a GTPase-activating protein (GAP). As can be seen from the above statement, RAS bears an important function of "molecular switch" in an intracellular signal transduction pathway for EGFR or the like,

and plays a critical role in the processes of cell growth, proliferation, angiogenesis, and the like (Nature Rev. Cancer, 2011, 11, p.761-774, Nature Rev. Drug Discov., 2014, 13, p.828-851, Nature Rev. Drug Discov., 2016, 15, p.771-785).

- 5 Substitution of an amino acid by spontaneous mutation of the RAS gene results in a constant activated state due to hypofunction of RAS as GTPase or hyporeactivity to GAP, and then, signals are continuously sent downstream. The excessive signalling may cause carcinogenesis or cancer growth acceleration.
- 10 For instance, it has been found that pancreatic ductal adenocarcinoma occurs through a weakly heteromorphic stage and a subsequent highly heteromorphic stage in the pancreatic intraepithelial neoplasia (PanIN), and mutation of the KRAS gene has already been recognized in an initial stage of PanIN. Subsequently, abnormality occurs in INK4A, p53, and SMAD4 which are tumor suppression genes, leading to malignancy
- 15 (Nature Rev. Cancer, 2010, 10, p.683-695). Furthermore, in 90% or more of the cases of pancreatic ductal adenocarcinoma, mutation is seen in the KRAS gene, and a majority of them are a spontaneous point mutation in the codon 12 located in the KRAS exon 2 (Cancer Cell 2017, 32, p.185-203). As can be seen from the above statement, KRAS plays a critical role in the processes of carcinogenesis and development of
- 20 pancreatic cancer.

As a mutation of a KRAS gene, KRAS G12C mutation, KRAS G12D mutation, and the like are known. G12C mutant KRAS frequently occurs in non-small-cell lung cancer, but occurs few percent in pancreatic cancer (Cancer Cell 2014, 25, p.272-281), and a

25 therapeutic agent against another KRAS mutation is desired. G12D mutant KRAS is seen in about 34% of the cases of pancreatic cancer, and this rate is reported to be the highest in KRAS mutations (Nat. Rev. Cancer, 2018, 18, p.767-777).

WO 2016/049565, WO 2016/049568 and WO 2017/172979 disclose certain KRAS

30 inhibitors and state that the agents are useful for a cancer with a mutation in the codon 12 of KRAS. The G12D mutation is one of such mutations, but any effect on the G12D mutant KRAS cancer is not described.

In recent years, as a technique for inducing degradation of a target protein, bifunctional

35 compounds collectively called as PROTAC (proteolysis-targeting chimera) or SNIPER (specific and nongenetic IAP-dependent protein eraser) are found and are expected as one novel technique of drug development modality (Drug. Discov. Today Technol., 2019, 31, p15-27). Such a bifunctional compound promotes formation of a composite

of the target protein and an E3 ligase in a cell, and degradation of the target protein is induced by using the ubiquitin-proteasome system. The ubiquitin-proteasome system is one of intercellular protein degradation mechanisms. A protein called E3 ligase recognizes a protein to be degraded to convert the protein into ubiquitin, whereby degradation by proteasome is promoted.

Six hundred (600) or more E3 ligases are present in an organism, and are roughly divided into four types of HECT-domain E3s, U-box E3s, monomeric RING E3s, and multi-subunit E3s. E3 ligases used as a bifunctional degradation inducer which are called PROTAC, SNIPER, or the like are currently limited, and typical examples thereof include Von Hippel-Lindau (VHL), celeberron (CRBN), inhibitor of apoptosis protein (IAP), and mouse double minute 2 homolog (MDM2). In particular, VHL is reported in WO 2013/106643 and CRBN is reported in WO 2015/160845.

The bifunctional compounds are compounds in which a ligand of a target protein and a ligand of an E3 ligase are bound via a linker, and some bifunctional compounds for degrading a KRAS protein have been reported (Cell. Chem. Biol., 2020, 27, p19-31, ACS Cent. Sci., 2020, 6, p1367-1375, US 2018/0015087, WO 2019/195609, WO 2020/018788).

Summary of the invention

It has now been surprisingly found that a combination of a compound of formula (I) as defined herein and certain additional anti-cancer agents as defined herein represents a promising strategy for the treatment of cancer.

Without wishing to be bound by theory, it is believed that the compound of the formula (I) as defined herein is a bifunctional compound, and it has a degradation-inducing action on a G12D mutant KRAS protein and a G12D mutant KRAS inhibition activity, and can be used with an anti-cancer agent in the treatment of cancer. In particular, it is believed that the combination of a compound of formula (I) and an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof allows for a potent synergistic effect in the treatment of cancer.

Accordingly, in a first aspect of the invention there is provided a combination of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an anti-

cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the compound of formula (I)

5 is selected from the group consisting of:

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-(hydroxymethyl)-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]ethyl}-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(1-methyl-1H-pyrazol-5-yl)phenyl]ethyl}-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-

methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide, and

- (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl}-L-prolinamide.

- 10 A second aspect of the invention is a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention, for use in the treatment of cancer, wherein the treatment further comprises administration of an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a
15 fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof.

- An alternative second aspect of the invention is an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum
20 compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the treatment further comprises administration of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention.

- 25 A third aspect of the invention is a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention and an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an
30 analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable excipient.

- A fourth aspect of the invention is a pharmaceutical composition comprising a
35 compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention and an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs

thereof, or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable excipient for use in the treatment of cancer.

5 A fifth aspect of the invention is a method of treating cancer comprising administering, to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention, and a therapeutically effective amount of an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine
10 compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof.

A sixth aspect of the invention is the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention, and an anti-cancer agent selected from the group consisting of a taxane compound, a
15 fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of cancer.

A seventh aspect of the invention is a kit-of-parts comprising:
20 (A) a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention, and optionally one or more pharmaceutically acceptable excipient, and
(B) a pharmaceutical composition comprising an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum
25 compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable excipient,
which components (A) and (B) are each provided in a form that is suitable for administration in conjunction with the other,
30 for use in the treatment of cancer.

An eighth aspect of the invention is the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention, and an anti-cancer agent selected from the group consisting of a taxane compound, a
35 fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof for the treatment of cancer.

Detailed description of the invention

5 Unless indicated otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains.

10 Preferences and options for a given aspect, embodiment, feature or parameter of the invention should, unless the context indicates otherwise, be regarded as having been disclosed in combination with any and all preferences and options for all other aspects, features and parameters of the invention.

15 Wherever the word "about" is employed herein (for example, in the context of doses of active ingredients) it will be appreciated that such variables are approximate and as such may vary by $\pm 10\%$, for example $\pm 5\%$ and preferably $\pm 2\%$ (e.g. $\pm 1\%$) from the numbers specified herein.

20 The skilled person will understand that references to the "treatment of" a particular condition (and similarly "treating") take their normal meanings in the field of medicine. In particular, the terms may refer to achieving a reduction in the severity of one or more clinical symptom associated with the condition or to increasing longevity in the patient being treated.

25 As used herein, references to patients will refer to a living subject being treated, including mammalian (e.g. human) patients. In particular embodiments of the relevant aspects of the invention (e.g. the first, second, fourth, fifth, sixth and eighth aspects of the invention), the treatment is in a mammal (e.g. a human).

30 As used herein, the term therapeutically effective amount will refer to an amount of a compound that confers a therapeutic effect on the treated patient. The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of and/or feels an effect). For example, in relation to cancers formed as one or more solid tumour, said therapeutic effect may be observed as a reduction in
35 the volume of one or more of those tumours.

For the avoidance of doubt, compounds of formula (I) and the anti-cancer agents as described herein may exist as solids, and thus the scope of the invention includes all

amorphous, crystalline and part crystalline forms thereof, and may also exist as oils. Where such compounds exist in crystalline and part crystalline forms, such forms may include hydrates and solvates, which are included in the scope of the invention. The compounds may also exist in solution.

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Compounds for use

As described herein, in a first aspect of the invention there is provided a combination of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-
10 containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the compound of formula (I) is selected from the group consisting of:

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(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide,

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(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-(hydroxymethyl)-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide,

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(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]ethyl}-L-prolinamide,

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(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(1-methyl-1H-pyrazol-5-yl)phenyl]ethyl}-L-prolinamide,

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(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-

methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide, and

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl}-L-prolinamide.

In a second aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention, for use in the treatment of cancer, wherein the treatment further comprises administration of an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof.

In an alternative second aspect of the invention there is provided an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the treatment further comprises administration of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention.

35 Compounds of formula (I)

The compound of formula (I) as referred to herein is a compound selected from the group consisting of:

- (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-(hydroxymethyl)-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]ethyl}-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(1-methyl-1H-pyrazol-5-yl)phenyl]ethyl}-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide, and
- (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-

methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl}-L-prolinamide.

- 5 For the avoidance of doubt, the structures of the compounds of formula (I) correspond to the structures provided in Examples 1 to 8.

In an embodiment, the compound of formula (I) is (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide.

In an embodiment, the compound of formula (I) is (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-{4-[4-(hydroxymethyl)-1,3-thiazol-5-yl]phenyl}ethyl]-L-prolinamide.

In an embodiment, the compound of formula (I) is (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]ethyl}-L-prolinamide.

In an embodiment, the compound of formula (I) is (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(1-methyl-1H-pyrazol-5-yl)phenyl]ethyl}-L-prolinamide.

In an embodiment, the compound of formula (I) is (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide.

In an embodiment, the compound of formula (I) is (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]-L-prolinamide.

In an embodiment, the compound of formula (I) is (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-[(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl]-4-hydroxy-L-prolinamide.

In an embodiment, the compound of formula (I) is (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl]-L-prolinamide.

In particular embodiments, the compound of formula (I) is selected from the group consisting of:

(4R)-1-[(2S)-2-(4-{4-[(7M)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[(7M)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(4-(hydroxymethyl)-1,3-thiazol-5-yl)phenyl]ethyl]-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[(7M)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]ethyl]-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[(7M)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-

- methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(1-methyl-1H-pyrazol-5-yl)phenyl]ethyl]-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(7M)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl)-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-[(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl]-4-hydroxy-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(7M)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl)-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(7M)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl)-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-[(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl]-4-hydroxy-L-prolinamide, and
- (4R)-1-[(2S)-2-(4-{4-[(7M)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl)-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl]-L-prolinamide.

In certain embodiments, the compound of formula (I) is selected from the group consisting of:

- (4R)-1-[(2S)-2-(4-{4-[(7P)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl)-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(7P)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl)-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(4-(hydroxymethyl)-1,3-thiazol-5-yl)phenyl]ethyl]-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(7P)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-

- yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]ethyl}-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(7P)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(1-methyl-1H-pyrazol-5-yl)phenyl]ethyl}-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(7P)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(7P)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide,
- (4R)-1-[(2S)-2-(4-{4-[(7P)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide, and
- (4R)-1-[(2S)-2-(4-{4-[(7P)-6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl}-L-prolinamide.
- 30 The compound of formula (I) and the anti-cancer agent may have tautomers or geometrical isomers depending on the type of the substituent. In this specification, the compound of the formula (I) and the anti-cancer agent may sometimes be described only as one of the isomers, but the present invention includes tautomers or geometrical isomers other than the one described, and includes separated isomers or
- 35 mixtures thereof.

The compound of formula (I) may have one or more asymmetric carbon atom and, accordingly, may exist in the form of specific enantiomers and diastereomers thereof.

The present invention includes separated enantiomers and diastereomers of the compound of the formula (I) or mixtures thereof.

5 The enantiomers of chiral compounds having one or more asymmetric carbon atom may be given "(R)" and "(S)" labels in respect of each point of chirality based on methods known in the art (e.g. using Cahn-Ingold-Prelog priority rules).

10 In certain embodiments, references to a specific stereoisomer of the compound of formula (I) may refer to the specific stereoisomer (e.g. the specific enantiomer or diastereoisomer indicated) being present in the substantial absence of other stereoisomers (i.e. stereoisomers have a different configuration at one or more of the relevant points of chirality).

15 In such instances, the compound in the relevant configuration may be present in an enantiomeric excess (e.e.) or diastereomeric excess (d.e.), as appropriate, of at least 60% (such as at least 70%, 80%, 90%, 95%, or 98% or, particularly, at least 99%, for example at least 99.9%).

20 The compound of formula (I) may have axial chirality, which may refer to compounds having one or more axis about which a set of substituents is held in a spatial arrangement that is not superposable on its mirror image. For the avoidance of doubt, all axial arrangements of such compounds are within the scope of the invention.

25 The enantiomers of axially chiral compounds may be given "M" and "P" labels based on methods known in the art (e.g. using Cahn-Ingold-Prelog priority rules, with the added rule that the two "near" substituents have higher priority than the far ones).

30 In certain embodiments, references to a specific axial stereoisomer of the compound of formula (I) may refer to the specific stereoisomer (e.g. the isomer with M-axial chirality) being present in the substantial absence of the corresponding opposite stereoisomer (e.g. the isomer with P-chirality).

35 In such instances, the compound of formula (I) the axial stereoisomer (e.g. the M-axial isomer) have a purity of at least 70% (e.g. at least 80%, 90%, 95%, or 99%) relative to the other axial stereoisomers (e.g. relative to the P-axially chiral isomer).

For the avoidance of doubt, compounds referred to as having a specific stereochemistry at a defined position (e.g. axial chirality) may also have stereochemistry at one or

more other positions, and so may exist as mixtures of enantiomers or diastereoisomers in relation to the stereochemistry at those positions.

- Furthermore, the present invention includes pharmaceutically acceptable prodrugs (which may be referred to as precursors) of the compound represented by the formula (I) and the anti-cancer agent. A pharmaceutically acceptable prodrug will include compounds having a group that can be converted into an amino group, a hydroxy group, a carboxy group, or the like by solvolysis or under physiological conditions. Examples of groups that may be used to form a prodrug include groups described in Prog. Med., 1985, 5, p.2157-2161 or in "Iyakuhin no Kaihatsu (development of pharmaceuticals)", Vol.7, Bunshi-sekkei (molecular design), Hirokawa Shoten, 1990, p.163-198. Prodrugs include ester and carbamate derivatives, or derivatives such as conjugates (e.g. conjugates of albumin-bound paclitaxel).
- Prodrugs may be referred to as precursors of the active compounds (i.e. compounds of formula (I) and the anti-cancer agent), which may refer to compounds that are metabolised to form active compounds *in vivo*.

- Pharmaceutically acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound comprised in the formulations of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. by rotary evaporation under reduced pressure, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound comprised in the formulations of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

- Example salts include salts shown in P. Heinrich Stahl, Handbook of Pharmaceutical Salts Properties, Selection, and Use, Wiley-VCH, 2008. Specific examples include an acid addition salt with an inorganic acid, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, or phosphoric acid, or with an organic acid, such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, mandelic acid, tartaric acid, dibenzoiltartaric acid, ditoluoyltartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, aspartic acid, or glutamic acid, a salt with an inorganic metal, such as sodium, potassium, magnesium, calcium, or aluminum, a salt with an organic base, such as methylamine, ethylamine,

or ethanolamine, a salt with various amino acids and amino acid derivatives, such as acetylleucine, lysine, and ornithine, and an ammonium salt.

In an embodiment, the pharmaceutically acceptable salt of the compound of formula
5 (I) and/or of the anti-cancer agent is a hydrochloride (HCl) salt.

Furthermore, the present invention also includes various hydrates, solvates, crystal polymorphism substances, and amorphous solid forms of the compound of the formula (I) and the anticancer agents, and salts thereof. In addition, the present invention
10 also includes compounds labeled with various radioactive or non-radioactive isotopes. The "amorphous solid forms" include both a form showing no peak in the powder X-ray diffraction (XRD) pattern and a form having a low crystallinity.

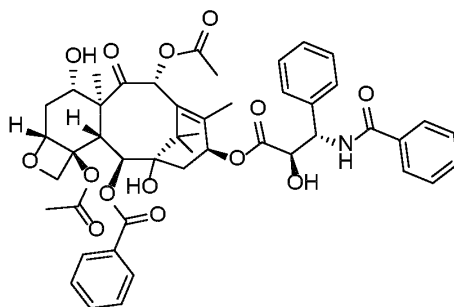
The anti-cancer agents

15 As described herein, the anti-cancer agent is selected from the group comprising a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin and a fluoropyrimidine compound, and prodrugs thereof.

20 The term "taxane" refers to a class of diterpene compounds that were first derived from natural sources such as plants of the genus *Taxus*, but some have been synthesised artificially. Taxanes feature a taxadiene core. As used herein, taxanes include paclitaxel, docetaxel, cabazitaxel, and baccatin III.

25 In one embodiment, the anti-cancer is a taxane. In a particular embodiment, the taxane is paclitaxel.

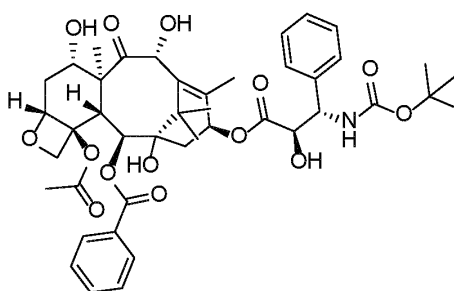
Paclitaxel refers to the compound having the name
30 [(1S,2S,3R,4S,7R,9S,10S,12R,15S)-4,12-diacetyloxy-15-[(2R,3S)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy-1,9-dihydroxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.0³.10.0⁴,7]heptadec-13-en-2-yl] benzoate, and the following structure:



In a particular embodiment, the taxane is docetaxel.

- 5 Docetaxel refers to the compound having the name [(1S,2S,3R,4S,7R,9S,10S,12R,15S)-4-acetyloxy-1,9,12-trihydroxy-15-[(2R,3S)-2-hydroxy-3-[(2-methylpropan-2-yl)oxycarbonylamino]-3-phenylpropanoyl]oxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.0^{3,10}.0^{4,7}]heptadec-13-en-2-yl] benzoate, and the following structure:

10



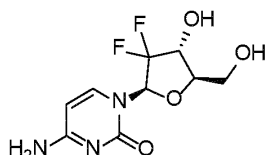
- 15 Nucleosides are the structural subunit of nucleic acids such as DNA and RNA, and consist of a nucleobase (also termed a nitrogenous base) and a five-carbon sugar (ribose or 2'-deoxyribose).

- 20 "Fluorine-containing nucleosides" refer to a class of chemotherapeutics. As used herein, "fluorine-containing nucleosides" include nucleosides wherein at least one of the hydrogen substituents on the nucleoside has been replaced with one or more fluorine substituents. "Fluorine-containing nucleosides" include gemcitabine and fludarabine.

- 25 In one embodiment, the anti-cancer is a fluorine-containing nucleoside. In particular embodiments, the fluorine-containing nucleoside contains at least one fluorine substituent on the sugar unit of the nucleoside.

In particular embodiments, the fluorine-containing nucleoside is gemcitabine.

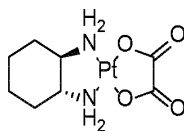
Gemcitabine refers to the compound having the name 4-amino-1-[(2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2-one, and the following structure:



10 As used herein, a "platinum compound" refers to platinum-based chemotherapeutic agents. "Platinum compounds" are coordination complexes of platinum, such as cis-platin, oxaliplatin, carboplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin and satraplatin.

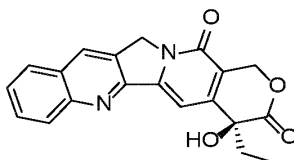
15 In one embodiment, the anti-cancer is a platinum compound. In particular embodiments, the platinum compound is oxaliplatin.

Oxaliplatin refers to the compound having the name [(1R,2R)-cyclohexane-1,2-diamine](ethanedioato-O,O')platinum(II), and the following structure:



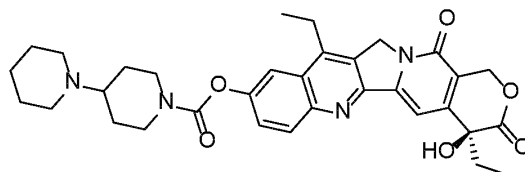
20

An analogue of camptothecin refers to a compound which is related in structure to camptothecin, such as irinotecan, aminocamptothecin, 9-nitrocamptothecin (rubitecan), gimatecan, topotecan, silatecan, cositecan, exatecan, lurtotecan and belotecan. The term "analogue of camptothecin" may include compounds comprising the following sub-structure:



In one embodiment, the anti-cancer is an analogue of camptothecin. In a particular embodiment, the analogue of camptothecin is irinotecan.

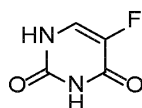
Irinotecan refers to the compound having the name [(19S)-10,19-diethyl-19-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.0.02,11.04,9.015,20]henicosa-1(21),2,4(9),5,7,10,15(20)-heptaen-7-yl]4-piperidin-1-ylpiperidine-1-carboxylate, and the following structure:



10 A "fluoropyrimidine" compound refers to a pyrimidine substituted with at least one fluoro substituent, and includes capecitabine, floxuridine, and fluorouracil (5-FU). The skilled person will understand that capecitabine is a prodrug of 5-FU.

In one embodiment, the anti-cancer is a fluoropyrimidine compound. In a particular
15 embodiment, fluoropyrimidine compound is 5-fluorouracil, also known as 5-FU.

The terms "5-fluorouracil" and "5-FU" refer to the compound having the name 5-fluoro-1H-pyrimidine-2,4-dione, and the following structure:



20

The cancers

As used herein, the following terms may be understood to have meanings as indicated.

25 "G12D Mutation" represents a mutation in which the amino acid residue corresponding to the codon 12 in a wild type protein is converted from glycine to aspartic acid.

"G12D Mutant KRAS" represents KRAS having the "G12D mutation".

30 "G12D mutant KRAS-positive cancer" is a G12D mutant KRAS-positive cancer, and, for example, is a cancer in which KRAS G12D mutation occurs and a cancer which has a high positive rate for G12D mutant KRAS.

"Pancreatic cancer" is a malignant tumor occurring in the pancreas. Examples thereof include pancreatic ductal carcinoma and pancreatic ductal adenocarcinoma. In an embodiment, "pancreatic cancer" is pancreatic ductal carcinoma, and in an embodiment, "pancreatic cancer" is pancreatic ductal adenocarcinoma.

5

"Colorectal cancer" is a malignant tumor occurring in the large intestine.

"Lung cancer" is a malignant tumor occurring in the lung.

10 In one embodiment, the cancer is a metastatic, locally advanced, recurrent, and/or refractory cancer.

In a certain embodiment, the cancer is a cancer of a patient who is previously untreated in respect of the relevant condition (i.e. has no medical history of previous treatment
15 for the condition), which patient (or, specifically, the relevant cancer) may be referred to as being treatment naïve.

In a further embodiment, the cancer is a cancer of a patient who has received treatment (i.e. a different treatment, being a treatment other than that defined in the
20 first aspect of the invention) for the relevant condition and has failed to respond or has not responded adequately to that treatment.

In one embodiment, the cancer is defined as being refractory to treatment (i.e. a treatment resistant cancer, being a cancer that does not respond or does not respond
25 adequately to other medical treatments, which will refer to medical treatments other than those defined in the first aspect of the invention). The refractory cancer may present resistance to treatment from the start of the medical treatment, or resistance by the cancer cells may be acquired during the course of the previous medical treatment(s).

30

In a particular embodiment, the cancer is a refractory cancer with respect to therapy with a compound of formula (I) absent the combination as defined in the first aspect of the invention (i.e. wherein previous therapy included a compound of formula (I)) but wherein the treatment did not comprise treatment with an anti-cancer agent
35 selected from a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, and a fluoropyrimidine compound).

In an embodiment, the cancer is pancreatic cancer. In particular embodiments, the pancreatic cancer is pancreatic ductal carcinoma or pancreatic ductal adenocarcinoma.

5 In an embodiment, the cancer is colorectal cancer. In particular embodiments, the colorectal cancer is colon cancer or rectal cancer.

In an embodiment, the cancer is lung cancer. In a particular embodiment, the lung cancer is small cell lung cancer or non-small cell lung cancer.

10 In one embodiment, the cancer is a G12D mutant KRAS-positive cancer.

In a particular embodiment, the G12D mutant KRAS-positive cancer is G12D mutant KRAS-positive pancreatic cancer. In an alternative embodiment, the G12D mutant KRAS-positive cancer is a G12D mutant KRAS-positive colorectal cancer. In an
15 alternative embodiment, the G12D mutant KRAS-positive cancer is a G12D mutant KRAS-positive lung cancer.

According to a second aspect of the invention is an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum
20 compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the treatment further comprises administration of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention.

25 For the avoidance of doubt, the second aspect of the invention may have any of the particular features and embodiments described herein for the first aspect of the invention, including all combinations thereof.

30 Pharmaceutical compositions

According to a third aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention and an anti-cancer agent
35 selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable excipient.

For the avoidance of doubt, the pharmaceutical compositions of the third aspect of the invention may have any of the particular features and embodiments described herein for the other (e.g. the first and second) aspects of the invention, including all combinations thereof.

Suitable pharmaceutical compositions may be commercially available or otherwise are described in the literature, such as, Remington, *The Science and Practice of Pharmacy*, 19th ed., Mack Printing Company, Easton, Pennsylvania (1995), and *Martindale – The Complete Drug Reference* (35th Edition), and the documents referred to therein, the relevant disclosures in all of which documents are hereby incorporated by reference in their entirety. Otherwise, the preparation of suitable compositions, and in particular combined preparations including both a compound of formula (I) and an anti-cancer agent, or pharmaceutically acceptable salts thereof, may be achieved by the skilled person using routine techniques.

References to pharmaceutically acceptable excipient(s) may be understood to include pharmaceutically acceptable, diluents, carriers and/or adjuvants, as known to those skilled in the art.

In particular embodiments, the pharmaceutical composition may be for administration in accordance with one or more of the modes of administration as described herein.

For the avoidance of doubt, pharmaceutical compositions as described herein may comprise one or more dose of the compound of formula (I) and/or the anti-cancer agent as described herein, or may comprise partial doses of such components (in which case multiple such compositions may be administered in the course of treatments as described herein).

For the avoidance of doubt, pharmaceutical compositions as described herein may also be referred to as pharmaceutical formulations.

According to a fourth aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention and an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, and

optionally one or more pharmaceutically acceptable excipient for use in the treatment of cancer.

For the avoidance of doubt, the pharmaceutical compositions of the fourth aspect of the invention may have any of the particular features and embodiments described herein for the other (e.g. the first to third) aspects of the invention, including all combinations thereof.

Administration

10

As used herein, by referring to methods and treatments involving a compound of formula (I), or pharmaceutically acceptable salt thereof, and an anti-cancer agent, or pharmaceutically acceptable salt thereof (both as defined in the first aspect of the invention), we include that the compound of formula (I), or pharmaceutically acceptable salt thereof, and an anti-cancer agent, or pharmaceutically acceptable salt thereof (including pharmaceutical compositions comprising each respective component) are administered, sequentially, separately or simultaneously, as part of a medical intervention directed towards treatment of the relevant disease or disorder.

20 Thus, in certain embodiments, the two active ingredients (i.e. the compound of formula (I), or pharmaceutically acceptable salt thereof, and the anti-cancer agent, or pharmaceutically acceptable salt thereof) are administered (optionally repeatedly) either together, or sufficiently closely in time, to enable a beneficial effect for the patient, that is greater, over the course of the treatment of the relevant condition, than
25 if either a formulation comprising a compound of formula (I), or pharmaceutically acceptable salt, or a formulation comprising an anti-cancer agent (as defined in the first aspect of the invention), or pharmaceutically acceptable salt are administered (optionally repeatedly) alone, in the absence of the other component, over the same course of treatment. Determination of whether a combination provides a greater
30 beneficial effect in respect of, and over the course, of treatment of a particular cancer may be achieved routinely by the skilled person.

In further embodiments, the two compounds or compositions are administered (optionally repeatedly) prior to, after, and/or at the same time as, administration of
35 the other component. When used in this context, the terms "administered simultaneously" and "administered at the same time as" include that individual doses of a compound of formula (I), or pharmaceutically acceptable salt thereof, and an anti-cancer agent (as defined in the first aspect of the invention), or pharmaceutically

acceptable salt thereof, are administered within 2 hours (e.g. within 60 minutes, 45 minutes, 30 minutes, 20 minutes or 10 minutes) of each other.

5 In certain embodiments, the two compounds or compositions are administered (optionally repeatedly) sequentially. When used in this context, the terms "administered sequentially" include that individual doses of a compound of formula (I), or pharmaceutically acceptable salt thereof, and an anti-cancer agent (as defined in the first aspect of the invention), or pharmaceutically acceptable salt thereof, are administered at a time interval between 2 hour and 7 days (e.g. 3 hours, 4 hours, 6
10 hours, 8 hours, 12 hours, 24 hours, 2 days, 3 days, 4 days, 5 days or 6 days) of each other.

For the avoidance of doubt, the compound of formula (I), or pharmaceutically acceptable salt thereof (or pharmaceutical composition comprising the same) may be
15 administered before administration of the anti-cancer agent, or pharmaceutically acceptable salt thereof (or pharmaceutical composition comprising the same). Alternatively, the anti-cancer agent or pharmaceutically acceptable salt thereof (or pharmaceutical composition comprising the same) may be administered before the formulation comprising the compound of formula (I), or pharmaceutically acceptable
20 salt thereof (or pharmaceutical composition comprising the same).

In one embodiment, the compound of formula (I), or pharmaceutically acceptable salt thereof (or pharmaceutical composition comprising the same) and the formulation comprising the anti-cancer agent, or pharmaceutically acceptable salt thereof (or
25 pharmaceutical composition comprising the same) are administered sequentially, such as wherein the second drug is administered after confirming that the treatment with the first drug is effective. Methods for determining the effectiveness of the first drug are known to the skilled person.

30 The skilled person will understand that compounds and pharmaceutical formulations as defined herein may be administered either by oral administration with a tablet, pill, capsule, granule, powder, liquid, or other agent or by parenteral administration with an intraarticular, intravenous, intramuscular, or other injection, a transmucosal agent, or an inhalant.

35 As a solid composition for oral administration, a tablet, powder, granular, or other agent is used. In such a solid composition, one or two or more active ingredients are mixed with at least one inactive excipient. The composition may contain an inactive

additive, for example, a lubricant, a disintegrator, a stabilizer, a dissolution aid according to an ordinary method. A tablet or pill may be coated with a sugar coating or a film soluble in the stomach or intestine, as needed.

- 5 Liquid compositions for oral administration include a pharmaceutically acceptable emulsion, solution, suspension, syrup, or elixir agent, and contain a generally used inactive diluent, for example, purified water or EtOH (ethanol). The liquid composition may contain, in addition to the inactive diluent, an adjuvant, such as a solubilizer, a wetting agent, or a suspending agent, a sweetening agent, a flavor, a fragrant, or a
10 preservative.

- The injection agents for parenteral administration include a sterile aqueous or nonaqueous solution, suspension, or emulsion agent. Examples of the aqueous solvent include distilled water for injection or physiological saline. An example of the
15 nonaqueous solvent is an alcohol, such as EtOH. Such a composition may further contain an isotonicizing agent, a preservative, a wetting agent, an emulsifier, a dispersant, a stabilizer, or a dissolution aid. These are sterilized, for example, by filtration through a bacteria keeping filter, incorporation of a microbicide, or irradiation. In addition, such a composition can be produced as a sterile solid composition, which
20 is dissolved or suspended in sterile water or a sterile solvent for injection before use.

- The transmucosal agent, such as an inhalant or a transnasal agent, is used in a solid, liquid, or semi-solid form, and can be produced according to a conventionally known method. For example, a known excipient, and in addition, a pH modifier, a
25 preservative, a surfactant, a lubricant, a stabilizer, a thickener, or the like may be appropriately added. The administration can be performed by using an appropriate device for inhalation or insufflation. For example, the agent can be administered using a known device, such as a metering and administering inhalation device, or an atomizer, as a compound alone or a powder of a mixture formulated, or as a solution
30 or a suspension in combination with a pharmaceutically acceptable carrier. A dry powder inhaler or the like may be for a single administration or multiple administrations, and dry powder or powder-containing capsule can be used. Alternatively, the agent may be used in a form of a pressurized aerosol spray or the like using an appropriate ejection agent, for example, a suitable gas, such as a
35 chlorofluoroalkane or carbon dioxide.

In one embodiment, the compounds and compositions as described herein are administered orally, intraarticularly, intravenously, intramuscularly, transmucosally, or

by inhalation. In a particular embodiment, the compounds and compositions as described herein are administered intravenously.

5 In one embodiment, the compound of formula (I) or pharmaceutically acceptable salt thereof (or pharmaceutical composition comprising the same) is administered orally, intraarticularly, intravenously, intramuscularly, transmucosally or by inhalation, such as intravenously.

10 In one embodiment, the anti-cancer agent, or pharmaceutically acceptable salt thereof (or pharmaceutical composition comprising the same) is administered orally, intraarticularly, intravenously, intramuscularly, transmucosally or by inhalation, such as orally or intravenously (as determined by the anti-cancer agent used).

15 In one embodiment, the compound of formula (I), or pharmaceutically acceptable salt thereof, and the anti-cancer agent, or pharmaceutically acceptable salt thereof, are administered simultaneous or sequentially, via the same administration route (e.g. intravenously).

20 In alternative embodiments, the compound of formula (I), or pharmaceutically acceptable salt thereof, and the anti-cancer agent, or pharmaceutically acceptable salt thereof, are administered sequentially, via different administration routes. For example, the compound of formula (I), or pharmaceutically acceptable salt thereof, may be administered intravenously and the anti-cancer agent, or pharmaceutically acceptable salt thereof, administered orally.

25

Dosages

30 The skilled person will be able to determine suitable (i.e. therapeutically effective) doses of the compounds of formula (I) and the anti-cancer agents as described herein using routine techniques and by reference to relevant literature concerning the same, such as relevant marketing authorizations and/or drug formularies.

35 For the avoidance of doubt, references herein to uses, compounds for use, methods, combinations, compositions and kits-of parts shall include references to agents used therein being in a therapeutically effective amount thereof.

Exemplary doses of the compounds of formula (I) and the anti-cancer agents as described herein are as follows.

In the case of oral administration, the daily dose of the compound of formula (I) and/or the anti-cancer agent may be appropriately about 0.001 to 100 mg/kg body weight, preferably 0.1 to 30 mg/kg body weight, further preferably 0.1 to 10 mg/kg body weight, and the dose is given at once or is divided into two to four times in a day (e.g. two, three, or four times a day).

In the case of intravenous administration, the daily dose of the compound of formula (I) and/or the anti-cancer agent may be appropriately about 0.0001 to 10 mg/kg body weight, and is given at once or is divided into multiple times in a day (e.g. two, three, or four times a day).

In addition, the daily dose of a transmucosal agent is about 0.001 to 100 mg/kg body weight, and is given at once or is divided into multiple times in a day (e.g. two, three, or four times a day).

The skilled person will understand that the use dose is appropriately decided depending on the individual case, taking the symptoms, age, sex, and the like of the patient into account.

Method of treatment

According to a fifth aspect of the invention is a method of treating cancer comprising administering, to a patient in need thereof, a therapeutically effective amount of a compound of the first aspect of the invention, or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention, and a therapeutically effective amount of an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof.

For the avoidance of doubt, the method of the fifth aspect of the invention may have any of the particular features and embodiments described above for the other (e.g. the first to fourth) aspects of the invention, including all combinations thereof.

Use in the manufacture of a medicament

A sixth aspect of the invention is the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention,
5 and an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of cancer.

10 For the avoidance of doubt, the use of the sixth aspect of the invention may have any of the particular features and embodiments described above for the other (e.g. the first to fifth) aspects of the invention, including all combinations thereof.

Kit-of-parts

15 According to the seventh aspect of the invention, there is provided a kit-of-parts comprising:

(A) a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention,
20 and optionally one or more pharmaceutically acceptable excipient, and

(B) a pharmaceutical composition comprising an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, and optionally one or more
25 pharmaceutically acceptable excipient,

which components (A) and (B) are each provided in a form that is suitable for administration in conjunction with the other,
for use in the treatment of cancer.

30 As used herein, by referring to components being administered in conjunction with each other, we include that such components are administered, sequentially, separately or simultaneously, as part of a medical intervention directed towards treatment of the relevant disease or disorder, as described herein.

35 In an alternative seventh aspect of the invention, there is provided a kit-of-parts comprising:

(I) one of components (A) or (B) as described in the seventh aspect of the invention,
and

(II) instructions to use that component in conjunction with the other of the two components,
for use in the treatment of cancer.

- 5 For the avoidance of doubt, the kits-of-parts of the seventh aspect of the invention may have any of the particular features and embodiments described above for the other (e.g. the first to sixth) aspects of the invention, including all combinations thereof.

10 Use for treatment

- In an eighth aspect of the invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to the first aspect of the invention, and an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof for the treatment of cancer.
- 15

- For the avoidance of doubt, the use of the eighth aspect of the invention may have any of the particular features and embodiments described above for the other (e.g. the first to seventh) aspects of the invention, including all combinations thereof.
- 20

Preparation of compounds/compositions

- 25 Pharmaceutical compositions, combination products and kits as described herein may be prepared in accordance with standard and/or accepted pharmaceutical practice.

- Thus, in a further aspect of the invention there is provided a process for the preparation of a pharmaceutical composition as described herein, which process comprises bringing into association a compound of formula (I) or a pharmaceutically acceptable salt thereof and an anti-cancer agent, both as described herein, with one or more pharmaceutically-acceptable excipient.
- 30

- In further aspects of the invention, there is provided a process for the preparation of a combination product or kit-of-parts as hereinbefore defined, which process comprises bringing into association a compound of formula (I) or a pharmaceutically acceptable salt thereof and an anti-cancer agent, both as described herein.
- 35

As used herein, references to bringing into association will mean that the two components are rendered suitable for administration in conjunction with each other.

Thus, in relation to the process for the preparation of a kit-of-parts as hereinbefore defined, by bringing the two components "into association with" each other, we include

- that the two components of the kit-of-parts may be:
- (i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or
 - (ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

Compounds as described herein, including compounds of formula (I) and pharmaceutically acceptable salts thereof and anti-cancer agents as described herein, may be prepared in accordance with techniques that are well known to those skilled in the art, such as those described in the examples provided hereinafter and/or as provided in the published literature pertain to each such compound.

Certain compounds as described herein, such as anti-cancer agents as described herein, and pharmaceutical compositions comprising the same, may be commercially available from sources known to those skilled in the art.

The compound of the formula (I) and a salt thereof can be produced by applying various known synthetic methods using characteristics based on the basic structure or the type of substituent thereof. Here, depending on the type of functional group, it is sometimes effective as a production technique to substitute the functional group with an appropriate protective group (a group that can be easily converted to the functional group) in the process from a raw material to an intermediate. Examples of the protective group include protective groups described in P. G. M. Wuts and T. W. Greene, "Greene's Protective Groups in Organic Synthesis", 5th edition, John Wiley & Sons Inc., 2014, and a group appropriately selected from the protective groups is used depending on the reaction conditions. In such a method, a reaction is carried out with the protective group introduced, and then the protective group is removed, as required, whereby a desired compound can be obtained.

In addition, a prodrug of the compound of the formula (I) can be produced by introducing a special group in a process from a raw material to an intermediate as for the above protective group, or by further carrying out a reaction using the compound

of the formula (I) obtained. This reaction can be carried out by applying a method known to a person skilled in the art, such as common esterification, amidation, or dehydration.

- 5 The isolation and purification are performed by applying a common chemical operation, such as extraction, fractional crystallization or various types of fraction chromatography.

- Various types of isomers can be produced by selecting an appropriate raw material
10 compound or can be separated using a difference in physiochemical properties between the isomers. For example, an optical isomer can be obtained by a general optical resolution method of a racemate (for example, fractional crystallization for inducing a racemate to a diastereomer salt with an optically active base or acid, chromatography using a chiral column or the like or the like) and can also be produced from an
15 appropriate optically active raw material compound.

- In addition, the compound of the formula (I) or an intermediate thereof sometimes has an axial chirality and is obtained as a mixture of axial stereoisomers, and each axial stereoisomer can be isolated by separation using a common separation operation, for
20 example, octadecylsilyl (ODS) column chromatography or silica gel column chromatography.

Advantages of the invention

- 25 Treatments as described herein may have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than and/or have a better treatment profile than treatments for the same conditions as known in the prior art.
- 30 Without wishing to be bound by theory, it is believed that the compound of the formula (I) has a degradation-inducing action on a G12D mutant KRAS protein and a G12D mutant KRAS inhibition activity, and can be used with an anticancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and
35 prodrugs thereof, to act synergistically in the treatment of cancer, and in particular a G12D mutant KRAS-positive cancer.

Examples

The production method of the compound of the formula (I) will be described in further detail below based on Examples. Note that the present invention is not to be limited to the compounds described in the following Examples. The production methods of raw material compounds are also shown in the Production Examples. The production method of the compound of the formula (I) is not limited only to the production methods of specific Examples described below, and the compound of the formula (I) can also be produced by a combination of the production methods or a method that is obvious to a person skilled in the art.

In the event that there is a discrepancy between nomenclature and the structure of compounds as depicted graphically, it is the latter that presides (unless contradicted by any experimental details that may be given and/or unless it is clear from the context).

For the purpose of convenience, the concentration mol/L is shown as M. For example, 1 M aqueous sodium hydroxide solution means an aqueous sodium hydroxide solution of 1 mol/L.

Abbreviations

The following abbreviations may be used herein.

DMF: N,N-dimethylformamide
DMAc: N,N-dimethylacetamide
THF: tetrahydrofuran
MeCN: acetonitrile
MeOH: methanol
EtOH: ethanol
DOX: 1,4-dioxane
DMSO: dimethyl sulfoxide
TEA: triethylamine
DIPEA: N,N-diisopropylethylamine
tBuOK: potassium tert-butoxide
HATU: 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
DABCO: 1,4-diazabicyclo[2.2.2]octane

$\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$: [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride-dichloromethane adduct

Pd/C: palladium on carbon

5 Production examples

Production Example 1

A mixture of 7-bromo-2,4-dichloro-8-fluoro-6-iodoquinazoline (100 g), DOX (1000 mL), and THF (500 mL) was cooled with ice bath, then DIPEA (240 mL) and tert-butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (48 g) were added, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure until the total volume of the solution became about 400 mL. A mixed solvent (hexane/ethyl acetate = 4/1, 1000 mL) was added to the resulting solution, and the mixture was stirred at room temperature. The precipitated solid was filtered to give tert-butyl (1S,4S)-5-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (123 g) as a solid.

Production Example 2

To a mixture of tert-butyl (1S,4S)-5-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (30 g), tetrahydro-2H-pyran-4-ol (15.0 mL), DMF (150 mL), THF (100 mL), and DABCO (1.15 g) was added cesium carbonate (50.3 g) with stirring at room temperature, under an argon atmosphere, the mixture was stirred at room temperature overnight. About 1 kg of ice water was added to the reaction mixture, and the mixture was stirred at room temperature for 6 hours. The precipitated solid was filtered, washed with water, and dried under reduced pressure overnight to give tert-butyl (1S,4S)-5-{7-bromo-8-fluoro-6-iodo-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (32.8 g) as a solid.

35 Production Example 3

Under argon flow, to a mixture of tert-butyl (1S,4S)-5-{7-bromo-8-fluoro-6-iodo-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (11.9

g), benzyl alcohol (2.37 g), and THF (40 mL) was added tBuOK (2.54 g) under ice-bath cooling, and the mixture was stirred at the same temperature for 1.5 hours. Ice water and saturated aqueous ammonium chloride solution were added to the reaction mixture, the mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure, and a mixed solvent of hexane/ethyl acetate (6/1) was added to the resulting residue. The mixture was stirred for a while, and the precipitated solid was filtered, and dried to give tert-butyl (1S,4S)-5-{8-(benzyloxy)-7-bromo-6-iodo-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (11.8 g) as a solid.

Production Example 4

Under an argon atmosphere, a mixture of tert-butyl (1S,4S)-5-{8-(benzyloxy)-7-bromo-6-iodo-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5.47 g), MeCN (88 mL), DOX (10 mL), water (22 mL), cyclopropylboronic acid (1.27 g), tripotassium phosphate (5.67 g), and PdCl₂(dppf)·CH₂Cl₂ (600 mg) was stirred at 100°C for 3 hours. After the reaction mixture was allowed to cool to room temperature, the solution was concentrated under reduced pressure. Saturated aqueous sodium chloride solution was added to the resulting residue, and the mixture was extracted with CHCl₃. The organic layer was dried over anhydrous magnesium sulfate, and the solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give tert-butyl (1S,4S)-5-{8-(benzyloxy)-7-bromo-6-cyclopropyl-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (3.8 g) as a foam-like solid.

Production Example 5

A mixture of tert-butyl (1S,4S)-5-{8-(benzyloxy)-7-bromo-6-cyclopropyl-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (3.15 g), 6-fluoro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol (1.92 g), tripotassium phosphate (4.1 g), dicyclohexyl(2',6'-diisopropoxy-[1,1'-biphenyl]-2-yl)phosphine (0.12 g), (2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (0.2 g), DOX (40 mL), and water (8 mL) was degassed and substituted with argon with stirring at room temperature, and then, the mixture was stirred at 100°C for 2.5 hours under an argon atmosphere. Water

(about 150 mL) was added to the reaction mixture which was cooled to room temperature, and the mixture was extracted with ethyl acetate. After the organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (basic silica gel, hexane/ethyl acetate), and fractions respectively containing (1) low-polar diastereomeric mixture (peak-1 and peak-2; peak-1 and peak-2 had the same axial chirality) and (2) high-polar diastereomeric mixture (peak-3 and peak-4; peak-3 and peak-4 had the same axial chirality) were obtained. Of these fractions, the fractions containing the low-polar diastereomeric mixture (peak-1 and peak-2, the same axial chirality) were collected to give tert-butyl (1S,4S)-5-{8-(benzyloxy)-6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (1.42 g) as a foam-like solid. In addition, the fractions containing the high-polar diastereomeric mixture (peak-3 and peak-4, the same axial chirality) were collected to give tert-butyl (1S,4S)-5-{8-(benzyloxy)-6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (1.37 g) as a foam-like solid. The low-polar diastereomeric mixture was used for the subsequent reaction.

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Production Example 6

To a MeOH (200 mL) solution of tert-butyl (1S,4S)-5-{8-(benzyloxy)-6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (10 g) which was the low-polar diastereomeric mixture obtained in Production Example 11 was added 10% Pd/C (50% wet, 2 g), and the reaction mixture was stirred under hydrogen atmosphere at room temperature for 2 hours. The resulting reaction mixture was filtered through celite pad and washed with MeOH. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give tert-butyl (1S,4S)-5-{6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-8-hydroxy-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (8.11 g) as a foam-like solid.

35 Production Example 7

To a mixture of tert-butyl (1S,4S)-5-{6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-8-hydroxy-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-

diazabicyclo[2.2.1]heptane-2-carboxylate (7.48 g), DMF (70 mL), and 1-(chloromethyl)-4-ethynylbenzene (1.9 g), was added cesium carbonate (6.2 g) with stirring at room temperature, and the mixture was stirred under an argon atmosphere at 60°C for 2 hours. To the reaction mixture which was allowed to cool to room temperature, ice water and saturated aqueous ammonium chloride solution were added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. Then, the insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (basic silica gel, hexane/ethyl acetate), and the resulting solid was filtered to give tert-butyl (1S,4S)-5-{6-cyclopropyl-8-[(4-ethynylphenyl)methoxy]-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (8.12 g) as a foam-like solid.

Production Example 8

To a mixture of tert-butyl (1S,4S)-5-{6-cyclopropyl-8-[(4-ethynylphenyl)methoxy]-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (4.24 g), (4R)-1-[(2S)-2-azido-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]-L-prolinamide (2.30 g), sodium ascorbate (1.45 g), tert-butyl alcohol (35 mL), THF (35 mL), and water (35 mL), was added anhydrous copper(II) sulfate (389 mg) at room temperature, and the mixture was stirred at room temperature for 2.5 hours. Ethyl acetate and water were added, and the aqueous layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl₃/MeOH) to give tert-butyl (1S,4S)-5-{6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-8-{[4-(1-{(2S)-1-[(2S,4R)-4-hydroxy-2-[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]carbonyl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}-1H-1,2,3-triazol-4-yl)phenyl]methoxy}-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5.62 g) as a solid.

Production Example 12

To a 1, 2-dichloroethane (60 mL) solution of tert-butyl (1S,4S)-5-{6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-8-{[4-(1-{(2S)-1-[(2S,4R)-4-hydroxy-2-(methoxycarbonyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]-1H-1,2,3-triazol-4-yl)phenyl]methoxy}-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (3.97 g) was added trimethyltin(IV) hydroxide (3.35 g) at room temperature, and the mixture was stirred at 80°C for 18 hours. After the mixture was allowed to cool to room temperature, hydrochloric acid (1M, 60 mL) was added, and the mixture was extracted with CHCl₃/MeOH (9/1). The organic layer was washed with 1M hydrochloric acid, and dried over anhydrous sodium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl₃/MeOH) to give (4R)-1-[(2S)-2-(4-{4-[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-L-proline (3.26 g) as a solid.

20 Production Example 13

To a mixture of (4R)-1-[(2S)-2-(4-{4-[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-L-proline (150 mg), 3-{4-[(1R)-1-amino-2-hydroxyethyl]phenyl}-1,3-oxazolidin-2-one monohydrochloride (60 mg), DIPEA (70 µL), and DMF (3 mL) was added HATU (70 mg) under ice-bath cooling, and the mixture was stirred under ice-bath cooling for 1 hour. Water, saturated aqueous sodium chloride solution, and ethyl acetate were added to the mixture, and the aqueous layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with water and saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl₃/MeOH) to give tert-butyl (1S,4S)-5-{6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-8-{[4-(1-{(2S)-1-[(2S,4R)-4-hydroxy-2-[(1R)-2-hydroxy-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]ethyl]carbamoyl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]-1H-1,2,3-

triazol-4-yl)phenyl]methoxy}-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (173 mg) as a solid.

Production Example 14

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To a solution of tert-butyl N-[(1R)-1-(4-bromophenyl)-2-hydroxyethyl]carbamate (5.01 g) in DMAc (80 mL) were added 4-Methyl-1,3-thiazole (2.88 mL) and potassium acetate (3.11 g) at room temperature, and the mixture was degassed and filled with argon three times. Palladium acetate (356 mg) was added at room temperature and the mixture was stirred at 100°C for 16 hours. After the mixture was cooled to room temperature, ethyl acetate and water were added, and the insoluble materials were removed by filtration with celite pad. Water was added to the filtrate, and the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (basic silica gel, hexane/ethyl acetate) to give tert-Butyl {(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}carbamate (4.66 g) as a solid.

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Production Example 15

Under an argon atmosphere, to a mixture of tert-butyl N-[(1R)-1-(4-bromophenyl)-2-hydroxyethyl]carbamate (4.43 g), 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (4.67 g), potassium carbonate (3.87 g), DOX (80 mL), and water (8 mL) was added PdCl₂(dppf)·CH₂Cl₂ (1.14 g), and the mixture was stirred at 100°C for 16 hours. After the mixture was allowed to cool to room temperature, ethyl acetate was added, and the mixture was filtered through celite pad and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (basic silica gel, hexane/ethyl acetate) to give tert-butyl {(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}carbamate (3.74 g) as a solid.

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Production Example 17

To a solution in CH₂Cl₂ (50 mL) and MeOH (50 mL) of tert-Butyl {(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}carbamate (4.41 g), was added hydrogen chloride (4M DOX solution, 20 mL) dropwise under ice-bath cooling, and the mixture was stirred at room temperature for 6 hours. Diethyl ether was added to the reaction

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mixture, and the resulting solid was filtered, washed with diethyl ether, and dried under reduced pressure to give (2R)-2-Amino-2-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethan-1-ol n-hydrochloride (2.12 g) as a solid. The filtrate was concentrated and dried under reduced pressure to give (2R)-2-Amino-2-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethan-1-ol n-hydrochloride (2.01 g) as a solid.

Production Example 18

To a solution in CH₂Cl₂ (25 mL) and MeOH (25 mL) of tert-butyl {(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}carbamate (3.34 g), hydrogen chloride (4M DOX solution, 25.6 mL) was added at -20 to -10°C, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure to give (2R)-2-amino-2-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]ethan-1-ol n-hydrochloride (3.06 g) as a solid.

Production Example 20

To a mixture of (2R)-2-Amino-2-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethan-1-ol n-hydrochloride (2.12 g), (4R)-1-(tert-butoxycarbonyl)-4-hydroxy-L-proline (1.76 g), and DMF (22 mL) was added DIPEA (4.7 mL) under ice-bath cooling, and then HATU (3.02 g) was added portionwise under ice-bath cooling to maintain internal temperature below 5°C. The mixture was stirred for 1 hour under ice-bath cooling and 1 hour at room temperature. Under ice-bath cooling, water (120 mL), saturated aqueous sodium chloride solution (50 mL), and ethyl acetate were added, and the aqueous layer was extracted three times with ethyl acetate, and then extracted three times with ethyl acetate/isopropyl alcohol (9/1). The combined organic layer was washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl₃/MeOH) to give tert-Butyl (2S,4R)-4-hydroxy-2-({(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}carbamoyl)pyrrolidine-1-carboxylate (3.09 g) as an oil.

Production Example 21

To a mixture of (2R)-2-amino-2-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]ethan-1-ol n-hydrochloride (3.43 g), (4R)-1-(tert-butoxycarbonyl)-4-hydroxy-L-proline (2.81 g), and DMF (40 mL) was added DIPEA (7.8 mL) under ice-bath cooling, and then HATU

(4.5 g) was added portionwise under ice-bath cooling. The mixture was stirred for 1 hour under ice-bath cooling and 1 hour at room temperature. Under ice-bath cooling, water, saturated aqueous sodium chloride solution, and ethyl acetate were added, and the aqueous layer was extracted with ethyl acetate, and then extracted with ethyl acetate/isopropyl alcohol (9/1). The combined organic layer was washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl₃/MeOH) to give tert-butyl (2S,4R)-2-({(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (5.01 g) as an oil.

Production Example 23

To a solution in CH₂Cl₂ (18 mL) and MeOH (18 mL) of tert-Butyl (2S,4R)-4-hydroxy-2-({(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}carbamoyl)pyrrolidine-1-carboxylate (3.09 g) was added hydrogen chloride (4M DOX solution, 17 mL) under ice-bath cooling, and the mixture was stirred for 1 hour under ice-bath cooling, for 5 hours at room temperature. The reaction mixture was concentrated and dried under reduced pressure to give (4R)-4-Hydroxy-N-{{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}}-L-prolinamide n-hydrochloride (2.92 g) as a solid.

Production Example 24

To a solution in CH₂Cl₂ (35 mL) and MeOH (30 mL) of tert-butyl (2S,4R)-2-({(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (5.01 g) was added hydrogen chloride (4M DOX solution, 28 mL) at -20 to -10°C, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure to give (4R)-N-{{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}}-4-hydroxy-L-prolinamide n-hydrochloride (4.71 g) as a solid.

Production Example 26

To a mixture of (4R)-4-hydroxy-N-{{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}}-L-prolinamide n-hydrochloride (3.81 g), N-(tert-butoxycarbonyl)-L-valine (2.16 g), and DMF (45 mL) was added DIPEA (6.2 mL), then HATU (3.61 g) was

added portionwise under ice-bath cooling. The mixture was stirred for 1 hour under ice-bath cooling and for 1 hour at room temperature. Under ice-bath cooling, water, saturated aqueous sodium chloride solution, and ethyl acetate were added, and the aqueous layer was extracted with ethyl acetate, then extracted with ethyl acetate/isopropyl alcohol (9/1). The combined organic layer was washed with saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl₃/MeOH) to give N-(tert-butoxycarbonyl)-L-valyl-(4R)-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide (4.43 g) as a solid.

Production Example 29

To a solution in CH₂Cl₂ (35 mL) and MeOH (35 mL) of N-(tert-butoxycarbonyl)-L-valyl-(4R)-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide (4.43 g) was added hydrogen chloride (4M DOX solution, 20 mL) at -20 to -15°C, and the mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure to give L-valyl-(4R)-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide n-hydrochloride (4.21 g) as a solid.

Production Example 33

To a mixture of L-valyl-(4R)-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide n-hydrochloride (1.71 g), TEA (3.2 mL), THF (20 mL), and MeCN (20 mL) was added a MeCN (5 mL) solution of 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (1.06 g) dropwise over 10 minutes or more under ice-bath cooling, and the mixture was stirred under ice-bath cooling for 5 hours. Water, saturated aqueous sodium chloride solution, and ethyl acetate were added, and the aqueous layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was dried over anhydrous sodium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl₃/MeOH) to give (4R)-1-[(2S)-2-azido-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide (1.07 g) as a solid.

Production Example 37

A mixture of tert-butyl N-[(1R)-1-(4-bromophenyl)-2-hydroxyethyl]carbamate (2.04 g), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (2.05 g), potassium acetate (1.91 g), DOX (40 mL), and bis(triphenylphosphine)palladium(II) dichloride (460 mg) was stirred under an argon atmosphere at 100°C overnight. The reaction solution which was cooled to room temperature was diluted with ethyl acetate, and the mixture was filtered through celite pad. The filtrate was washed with water and saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give tert-butyl {(1R)-2-hydroxy-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}carbamate (3.21 g) as an oil.

Production Example 38

Under an argon atmosphere, to a mixture of tert-butyl {(1R)-2-hydroxy-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}carbamate (3.21 g), 5-bromo-1,3-thiazol-4-carboxylic acid methyl ester (2.6 g), tripotassium phosphate (3.8 g), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (730 mg), DOX (30 mL), and water (6 mL) was added palladium(II) acetate (200 mg) at room temperature, and the mixture was stirred at 100°C for 3 hours. After the mixture was allowed to cool to room temperature, ethyl acetate was added, and the mixture was washed with water and saturated aqueous sodium chloride solution. After the organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give methyl 5-(4-{(1R)-1-[(tert-butoxycarbonyl)amino]-2-hydroxyethyl}phenyl)-1,3-thiazol-4-carboxylate (1.48 g) as a solid.

Production Example 39

Under nitrogen atmosphere, to a CH₂Cl₂ (20 mL) solution of methyl 5-(4-{(1R)-1-[(tert-butoxycarbonyl)amino]-2-hydroxyethyl}phenyl)-1,3-thiazol-4-carboxylate (1.01 g) was added diisobutylaluminum hydride (1M toluene solution, 11 mL) dropwise under ice-bath cooling, and the mixture was stirred under ice-bath cooling for 1 hour. Under ice-bath cooling, the reaction was quenched with MeOH, and 10% aqueous

sodium potassium tartrate solution (60 mL) and CHCl_3 were added, and the mixture was stirred overnight. The mixture was divided into layers, the aqueous layer was extracted with CHCl_3 , and the organic layer was dried over anhydrous sodium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL), and sodium borohydride (350 mg) was added under ice-bath cooling. The mixture was stirred under ice-bath cooling for 1 hour. Water was added and the mixture was extracted with CHCl_3 . The organic layer was dried over anhydrous sodium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($\text{CHCl}_3/\text{MeOH}$) to give tert-butyl [(1R)-2-hydroxy-1-{4-[4-(hydroxymethyl)-1,3-thiazol-5-yl]phenyl}ethyl]carbamate (588 mg) as a solid.

Production Example 41

To a mixture of tert-butyl N-[(1R)-1-(4-bromophenyl)-2-hydroxyethyl]carbamate (1 g), 2,2-dimethoxypropane (3.3 mL), and acetone (15 mL) was added a boron trifluoride-diethyl ether complex (26 μL), and the mixture was stirred at room temperature for 1 hour. TEA (66 μL) was added to the mixture, and the mixture was stirred at room temperature for 10 minutes. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give tert-butyl (4R)-4-(4-bromophenyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (1.09 g) as a solid.

Production Example 42

To a DOX (1.69 mL) solution of tert-butyl (4R)-4-(4-bromophenyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (300 mg) and 1,3-oxazolidin-2-one (183 mg) were added copper(I) iodide (32 mg), racemic-(1R,2R)-cyclohexane-1,2-diamine (20 μL), and potassium carbonate (290 mg) at room temperature. Under microwave irradiation, the mixture was stirred for 2 hours at 140°C and for 1 hour at 150°C . Ethyl acetate and water were added, and the mixture was filtered through celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give tert-butyl (4R)-2,2-dimethyl-4-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]-1,3-oxazolidine-3-carboxylate (120 mg) as a solid.

Production Example 48

To a mixture of tert-butyl (1S,4S)-5-{8-(benzyloxy)-6-cyclopropyl-2-(ethylsulfanyl)-7-[6-fluoro-5-methyl-2-(triphenylmethyl)-2H-indazol-4-yl]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (350 mg) and CH₂Cl₂ (7 mL) was added m-chloroperbenzoic acid (about 30% water content, 100 mg) under ice-bath cooling with stirring. The reaction mixture was stirred for 1.5 hours under ice-bath cooling, and diluted with CH₂Cl₂, washed with saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium thiosulfate solution. The organic layer was dried over anhydrous magnesium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure to give sulfoxide. The obtained sulfoxide was mixed with (S)-2-methoxypropanol (45 mg) and THF (4 mL). To the mixture was added KOtBu (80 mg) under ice-methanol bath cooling, and the mixture was stirred at room temperature for 1 hour under an argon atmosphere. Ice water and aqueous ammonium chloride solution was added to the reaction mixture, and products were extracted with ethyl acetate twice. The combined organic layers were washed with saturated aqueous sodium chloride solution and was dried over anhydrous magnesium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (basic silica gel, hexane/ethyl acetate) to give tert-butyl (1S,4S)-5-{8-(benzyloxy)-6-cyclopropyl-7-[6-fluoro-5-methyl-2-(triphenylmethyl)-2H-indazol-4-yl]-2-[(2S)-2-methoxypropoxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (280 mg) as a form-like solid.

25 Production Example 51

MeOH (3 mL) was added to tert-butyl (1S,4S)-5-{6-cyclopropyl-8-[(4-ethynylphenyl)methoxy]-7-[6-fluoro-5-methyl-2-(triphenylmethyl)-2H-indazol-4-yl]-2-[(2S)-2-methoxypropoxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (211 mg), and 4-methylbenzene-1-sulfonic acid monohydrate (48 mg) was added at room temperature with stirring. Then, the mixture was stirred at room temperature for 1 hour under an argon atmosphere. Ice and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted with ethyl acetate twice. The combined organic layer was washed with saturated aqueous sodium chloride solution and was dried over anhydrous magnesium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (basic silica gel, hexane/ethyl acetate) to give tert-butyl

(1S,4S)-5-{6-cyclopropyl-8-[(4-ethynylphenyl)methoxy]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (a single axial stereoisomer, 87 mg) which was a low-polar diastereomer as a solid, and tert-butyl (1S,4S)-5-{6-cyclopropyl-8-[(4-ethynylphenyl)methoxy]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (a single axial stereoisomer, 59 mg) which was a high-polar diastereomer as a solid. The low-polar diastereomer was used for the subsequent reaction.

10 Production Example 52

To a solution of tert-butyl (1S,4S)-5-{6-cyclopropyl-8-[(4-ethynylphenyl)methoxy]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (80 mg) in t-BuOH (0.7 mL), THF (0.7 mL), water (0.7 mL) were added (4R)-1-[(2S)-2-azido-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide (53 mg), sodium ascorbate (33 mg) and CuI (12 mg) at room temperature, and the mixture was stirred at 50°C for 3 hours. After cooling to room temperature, a solution of EDTA disodium salt in water was added. The mixture was extracted three times with CH₂Cl₂, and the organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (basic silica gel, CHCl₃/MeOH) to give tert-butyl (1S,4S)-5-{6-cyclopropyl-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-8-{[4-(1-{(2S)-1-[(2S,4R)-4-hydroxy-2-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}carbamoyl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}-1H-1,2,3-triazol-4-yl)phenyl]methoxy}-2-[(2S)-2-methoxypropoxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (102 mg) as a form-like solid.

Production Example 57

To a mixture of 4-bromo-6-fluoro-1H-indazole (235 g), TEA (183 mL) and CH₂Cl₂ (1880 mL) was added 1,1',1''-(chloromethanetriyl)tribenzene (335 g) at room temperature, and the mixture was stirred at 25°C for 16 hours. The reaction mixture was poured into ice water (1.5 L), and the organic layer and the aqueous layer were separated. The aqueous layer was extracted with CH₂Cl₂ (400 mL) three times. The combined organic layer was dried over anhydrous sodium sulfate. Then, the insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. Petroleum ether (550 mL) was added to the resulting residue for trituration (0°C, 2

hours), and then 4-bromo-6-fluoro-2-(triphenylmethyl)-2H-indazole (508.98 g) was obtained as a solid by collecting by filtration and drying under reduced pressure.

Production Example 58

5

To a mixture of 4-bromo-6-fluoro-2-(triphenylmethyl)-2H-indazole (100 g) and 2-methyltetrahydrofuran (1000 mL) was added lithium diisopropylamide (2 M THF solution, 214.28 mL) at -78°C under nitrogen atmosphere, and the mixture was stirred at -78°C for 2.5 hours. Methyl iodide (26.68 mL) was added at -78°C, and the mixture
10 was stirred at 25°C for 2.5 hours. Water (2000 mL) was added to quench the reaction, and the mixture was extracted with ethyl acetate (800 mL) twice. The combined organic layer was dried over anhydrous sodium sulfate. Then, the insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. Ethyl acetate (50 mL)/petroleum ether (50 mL) were added to the resulting residue
15 for trituration, and then 4-bromo-6-fluoro-5-methyl-2-(triphenylmethyl)-2H-indazole (81 g) was obtained as a solid by filtration and drying under reduced pressure.

Production Example 59

To a mixture of 4-bromo-6-fluoro-5-methyl-2-(triphenylmethyl)-2H-indazole (100 g), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (61.42 g), triphenylphosphine (10.57 g), potassium acetate (59.34 g) and DOX (1000 mL) was added palladium acetate (4.52 g) under nitrogen atmosphere at room temperature. After the reaction mixture was degassed and filled with nitrogen gas three times each,
25 the mixture was stirred at 100°C for 12 hours under nitrogen atmosphere. After cooling to ambient temperature, water (1500 mL) was added, and the mixture was extracted with ethyl acetate (900 mL) three times. The combined organic layer was dried over anhydrous sodium sulfate, and then the insoluble materials were removed by filtration. Activated carbon (50 g) was added to the resulting solution, and the solution was
30 stirred at 20°C for 1 hour and filtered while washing with ethyl acetate (50 mL) three times. The filtrate was concentrated. Methanol (200 mL) was added to the resulting residue for trituration, and the resulting solid was filtered and dried under reduced pressure to give 6-fluoro-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(triphenylmethyl)-2H-indazole (110 g) as a solid.

35

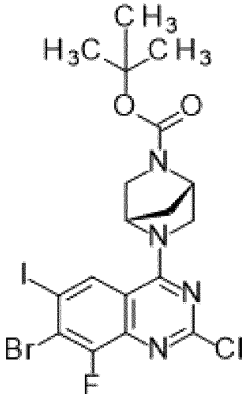
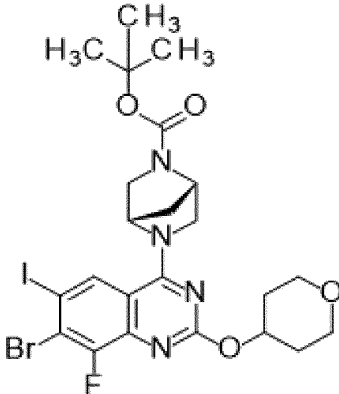
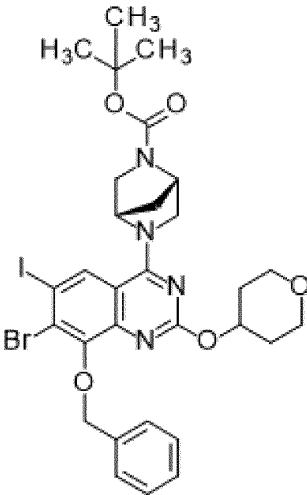
Production Example 60

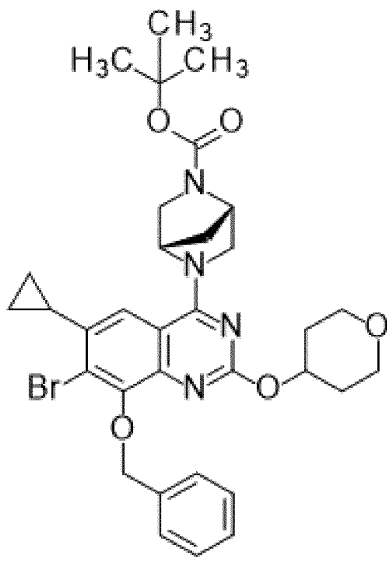
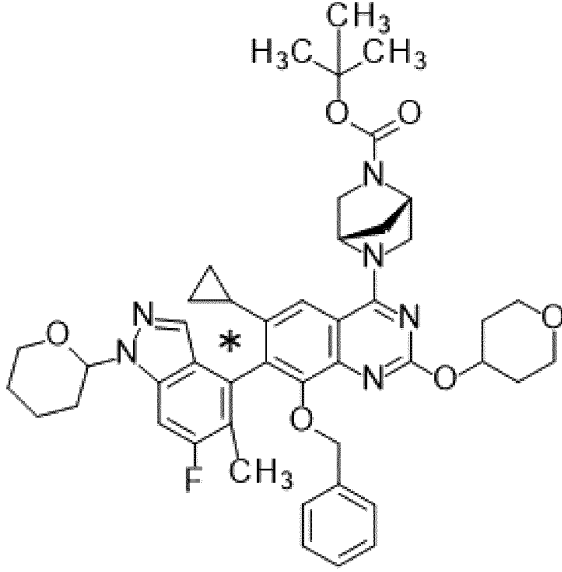
Under an argon atmosphere, bis(tri-tert-butylphosphine)palladium(0) (18 mg) was added to a mixture of 4-methyl-1,3-oxazole-5-carboxylic acid (178 mg), tetra-n-butylammonium chloride (195 mg), tert-butyl (4R)-4-(4-bromophenyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (250 mg), cesium carbonate (344 mg) and DMF (2.5 mL), and the mixture was stirred at 170°C for 30 minutes under microwave irradiation. The mixture was cooled to room temperature and was then diluted with ethyl acetate, and the insoluble materials were removed by filtration through celite pad. The filtrate was washed with water and saturated aqueous sodium chloride solution and was dried over anhydrous magnesium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (CHCl₃/MeOH) to give tert-butyl (4R)-2,2-dimethyl-4-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]-1,3-oxazolidine-3-carboxylate (215 mg) as a solid.

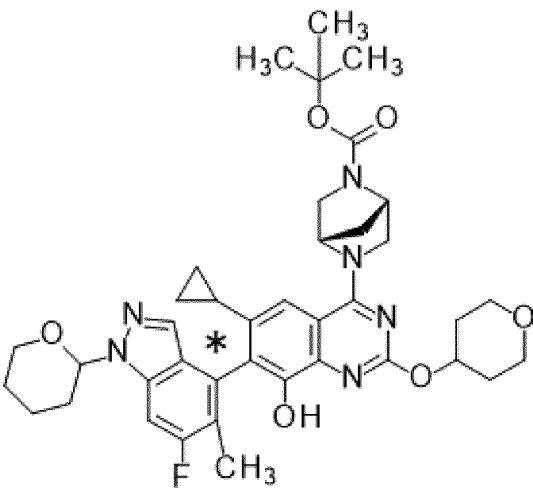
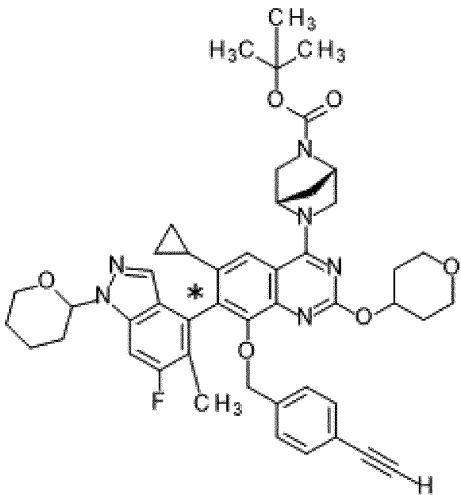
In the following tables, "PEX" represents "production example" and "PSyn" indicates which other production example was also prepared using the same method as the "PEX" in the same row of the table (i.e. the "PEX" was prepared using the same method as the method used to prepare the production example number indicated in the "PSyn" column).

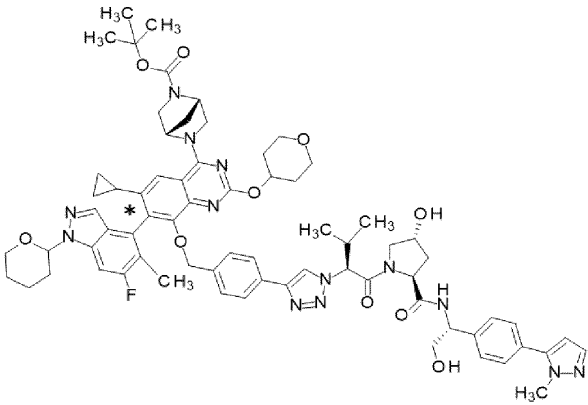
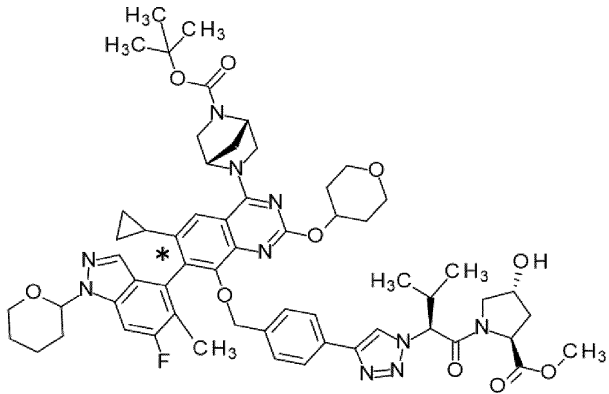
Structure: chemical structural formula (a compound with "*" in the chemical structural formula represents that the compound is a single axial stereoisomer). n HCl: n hydrochloride ("n HCl" shows that the compound is monohydrochloride to trihydrochloride), Data: physiochemical data, ESI+: m/z value in mass spectrometry (ionization method ESI, [M+H]⁺ unless otherwise specified), ESI-: m/z value in mass spectrometry (ionization method ESI, [M-H]⁻ unless otherwise specified), NMR: δ value (ppm) of peak in ¹H-NMR (500 MHz) in DMSO-d₆, NMR (100°C): δ value (ppm) of peak in ¹H-NMR (500 MHz) in DMSO-d₆ at 100°C, s: singlet (spectrum), d: doublet (spectrum), dd: double doublet (spectrum), t: triplet (spectrum), q: quartet (spectrum), m: multiplet (spectrum), br: broad (spectrum) (example: br s).

Table 1

PEx	PSyn	Structure	Data
1	1		ESI+: 583.1, 585.1
2	2		ESI+: 651.0
3	3		ESI+: 739.2

PEx	PSyn	Structure	Data
4	4		ESI+: 653.4
5	5		ESI+: 805.6

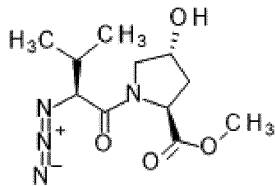
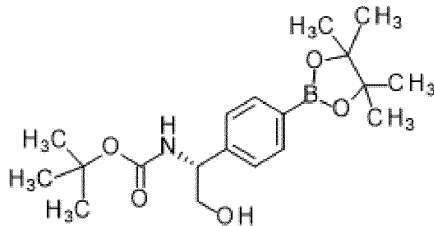
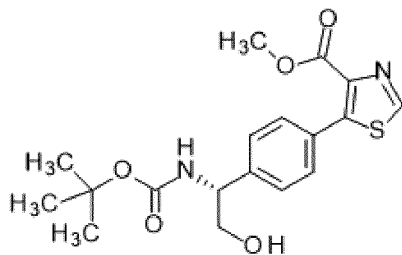
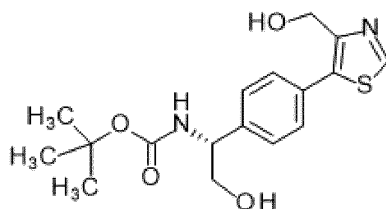
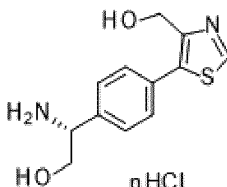
PEx	PSyn	Structure	Data
6	6		ESI+: 715.4
7	7		ESI+: 829.5

PEx	PSyn	Structure	Data
10	8	 Chemical structure of compound 10. It features a central benzimidazole core with a tert-butyl ester group, a morpholine ring, a cyclopropyl group, a fluorine atom, and a methyl group. It is linked via an ether bridge to a phenyl ring, which is further connected to a triazole ring. This triazole is linked to a chiral center with a methyl group and a hydroxyl group, which is part of a morpholine ring. This morpholine is linked to another chiral center with a hydroxyl group, which is part of a morpholine ring. This morpholine is linked to a phenyl ring, which is further connected to a pyrazole ring.	ESI+: 1284.4
11	8	 Chemical structure of compound 11. It features a central benzimidazole core with a tert-butyl ester group, a morpholine ring, a cyclopropyl group, a fluorine atom, and a methyl group. It is linked via an ether bridge to a phenyl ring, which is further connected to a triazole ring. This triazole is linked to a chiral center with a methyl group and a hydroxyl group, which is part of a morpholine ring. This morpholine is linked to another chiral center with a hydroxyl group, which is part of a morpholine ring. This morpholine is linked to a phenyl ring, which is further connected to a pyrazole ring.	ESI+: 1099.4

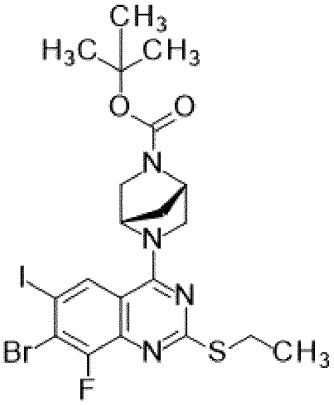
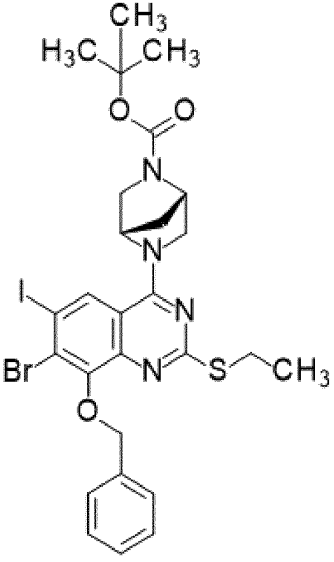
PEX	PSyn	Structure	Data
14	14		ESI+: 335.2
15	15		ESI+: 332.2
16	15		ESI+: 318.2
17	17		ESI+: 235.2
18	18		ESI+: 232.2
19	18		ESI+: 218.1

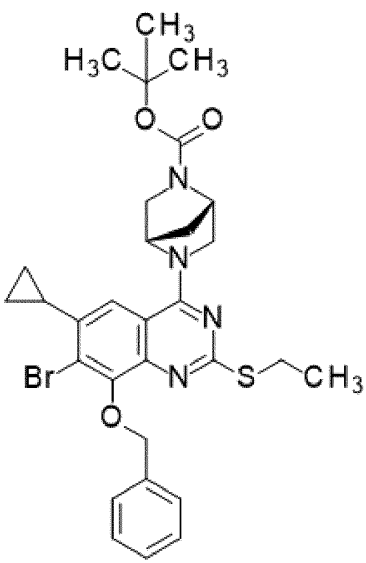
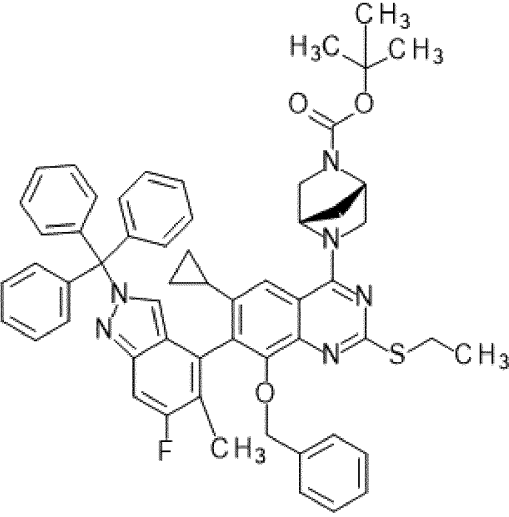
PEX	PSyn	Structure	Data
20	20		ESI+: 448.3
21	21		ESI+: 445.3
22	21		ESI+: 431.3
23	23		ESI+: 348.2
24	24		ESI+: 345.2
25	24		ESI+: 331.2

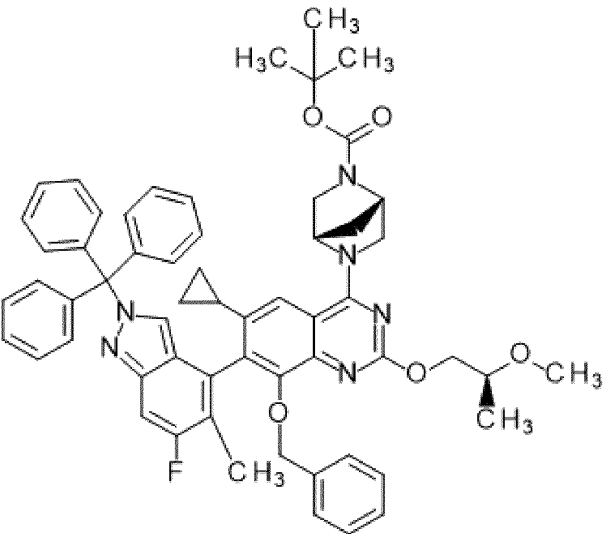
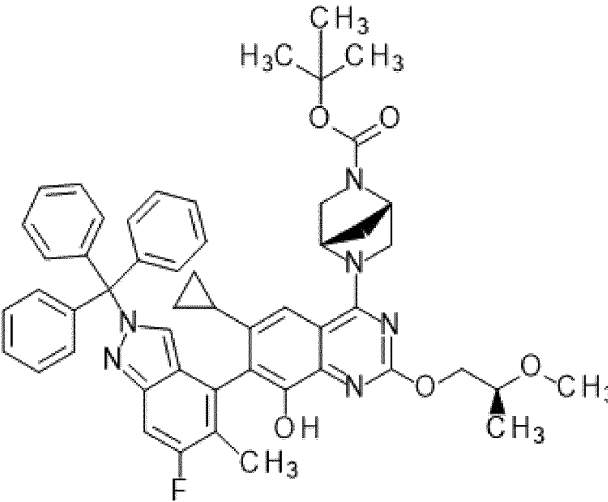
PEx	PSyn	Structure	Data
26	26		ESI+: 547.4
27	26		ESI+: 544.3
28	26		ESI+: 530.4
29	29		ESI+: 447.3
30	29		ESI+: 444.3

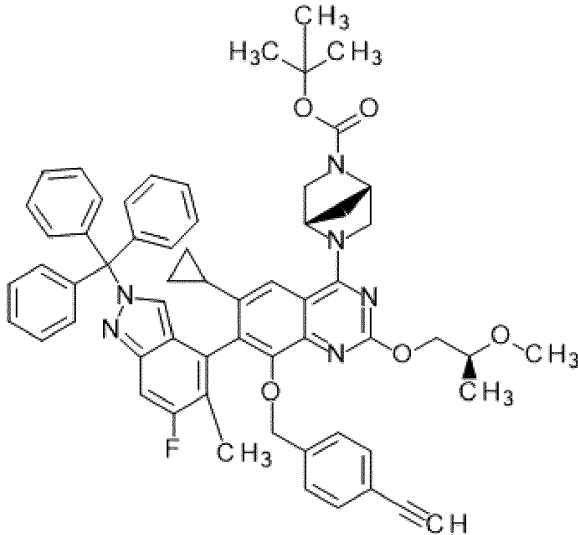
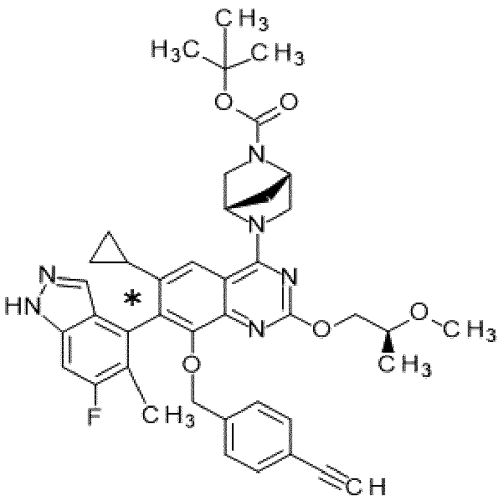
PEx Structure	PSyn Structure	Structure	Data
36	33		ESI+: 271.2
37	37		ESI+: 386.3 [M+Na] ⁺
38	38		ESI+: 379.3
39	39		ESI+: 351.2
40	17	 nHCl	ESI+: 251.1

PEx Product Example	PSyn Process Synthesis	Structure	Data
41	41		ESI+: 378.2 [M+Na] ⁺
42	42		ESI+: 385.2 [M+Na] ⁺
43	17		ESI+: 245.1 [M+Na] ⁺

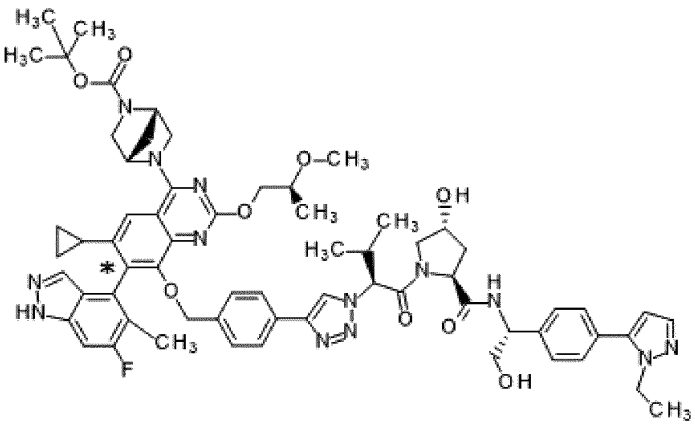
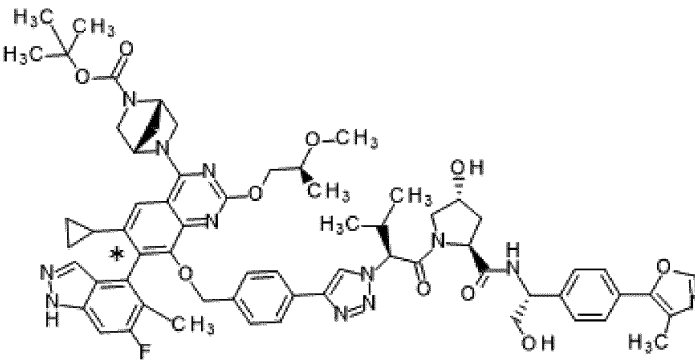
PEx	PSyn	Structure	Data
44	2		ESI+: 610.9
45	3		ESI+: 698.9

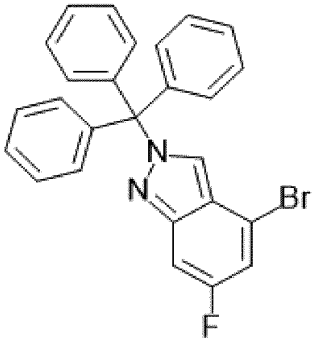
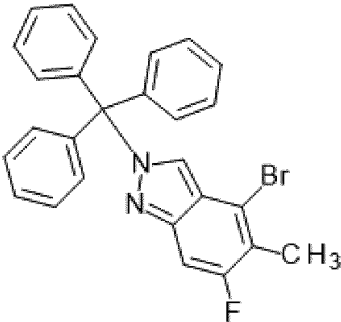
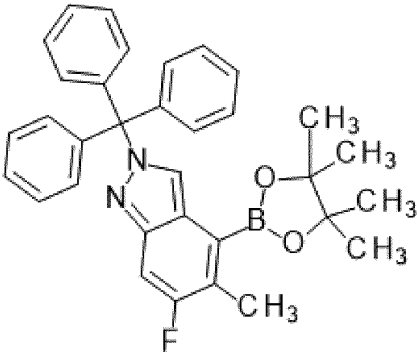
PEx	PSyn	Structure	Data
46	4		ESI+: 613.3
47	5		ESI+: 923.3

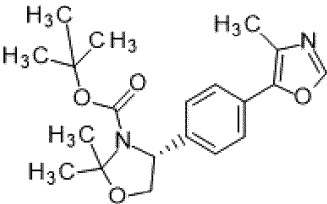
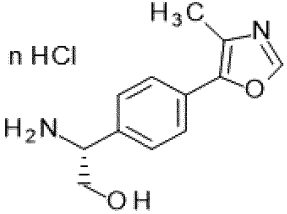
PEx	PSyn	Structure	Data
48	48		ESI+: 951.8
49	6		ESI+: 861.7

PEX	PSyn	Structure	Data
50	7		ESI+: 975.7
51	51		ESI+: 733.4

PEx OUTCOME	PSyn OUTCOME	Structure	Data
52	52		ESI+: 1205.4
53	52		ESI+: 1003.7
54	12		ESI+: 989.5

PEx	PSyn	Structure	Data
55	13		ESI+: 1203.5
56	13		ESI+: 1189.8

PEx	PSyn	Structure	Data
57	57		NMR: 7.08-7.15 (6H, m), 7.36-7.44 (10H, m), 7.49-7.54 (1H, m), 7.89 (1H, d)
58	58		NMR: 2.34 (3H, d), 7.07-7.13 (6H, m), 7.36-7.43 (9H, m), 7.51 (1H, d), 7.79 (1H, d)
59	59		NMR: 1.21 (12H, s), 2.44 (3H, d), 7.04-7.11 (6H, m), 7.34-7.44 (9H, m), 7.49 (1H, d), 8.09 (1H, d)

PEx	PSyn	Structure	Data
60	60		ESI+: 359.2
61	17		ESI+: 219.1

Examples

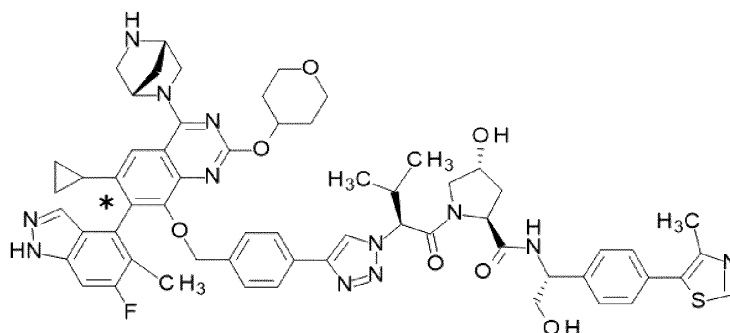
- 5 The following are examples of compounds of formula (I) and the characterization thereof.

In the following examples, the asterisk indicates that the compound is a single axial stereoisomer.

10

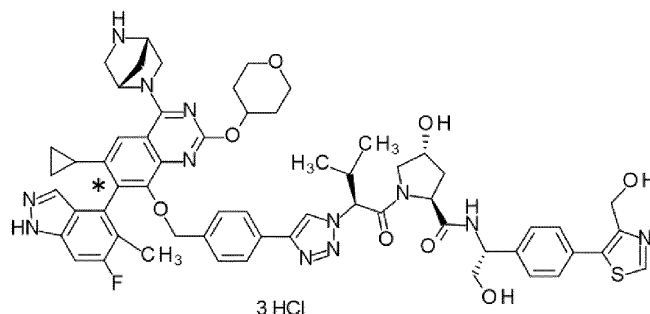
Example 1: (4R)-1-[(2S)-2-(4-{4-[(6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl)oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]-L-prolinamide

15



- To a mixture of tert-butyl (1S,4S)-5-{6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-8-{[4-(1-{(2S)-1-[(2S,4R)-4-hydroxy-2-({(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}carbamoyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}-1H-1,2,3-triazol-4-yl)phenyl]methoxy}-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5.61 g) and CH₂Cl₂ (60 mL) was added trifluoroacetic acid (27 mL) under ice-bath cooling, and then the mixture was stirred at room temperature for 2 hours. The resulting reaction mixture was concentrated under reduced pressure, and saturated aqueous sodium hydrogen carbonate solution was added to the residue. The mixture was extracted three times with CHCl₃/MeOH (5/1), and then, the combined organic layer was dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure, and the resulting crude product was purified by ODS column chromatography (MeCN/0.1% aqueous formic acid solution). Saturated aqueous sodium hydrogen carbonate solution was added to fractions containing the target compound, and the mixture was extracted three times with CHCl₃/MeOH (5/1). The combined organic layer was dried over anhydrous sodium sulfate, and the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (basic silica gel, CHCl₃/MeOH) to give a product. Isopropyl acetate (70 mL) was added to the obtained product, and the mixture was stirred at 80°C for 10 minutes, and was stirred at room temperature overnight. Hexane (70 mL) was added, and the mixture was stirred at room temperature for 1 hour. Then, the resulting solid was filtered, washed with isopropyl acetate/hexane (1/1), and dried under reduced pressure at 40°C overnight to give the title compound (3.01 g) as a solid.
- ESI+: 1117.3;
NMR (100°C): 0.48-0.68 (4H, m), 0.77 (3H, br d), 1.07 (3H, br d), 1.35-1.43 (1H, m), 1.66-1.77 (3H, m), 1.87 (1H, br d), 1.89-1.97 (1H, m), 1.98-2.10 (3H, m), 2.01 (3H, d), 2.10-2.21 (1H, m), 2.45 (3H, s), 2.50-2.59 (1H, m), 3.06 (1H, dd), 3.13 (1H, d), 3.35-3.45 (2H, m), 3.57-3.64 (1H, m), 3.65-3.75 (3H, m), 3.75-3.79 (1H, m), 3.80-3.90 (3H, m), 4.16 (1H, dd), 4.35 (1H, br s), 4.41-4.48 (1H, m), 4.48-4.56 (1H, m), 4.78-4.84 (2H, m), 4.84-4.95 (1H, m), 5.13 (1H, br s), 5.17-5.24 (1H, m), 5.24-5.31 (2H, m), 6.82 (2H, d), 7.30 (1H, d), 7.38-7.44 (4H, m), 7.44-7.48 (2H, m), 7.61 (2H, br d), 8.00 (1H, br d), 8.43 (1H, br s), 8.88 (1H, s), 12.75 (1H, br s).
- Example 2: (4R)-1-[(2S)-2-(4-{4-[(6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-

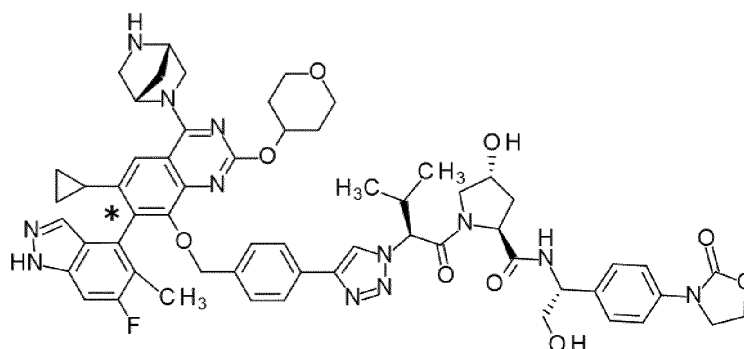
methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-[4-(hydroxymethyl)-1,3-thiazol-5-yl]phenyl]ethyl]-L-prolinamide trihydrochloride



Under nitrogen atmosphere, to a mixture of (4R)-1-[(2S)-2-(4-{4-[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-L-proline (65 mg), (2R)-2-amino-2-{4-[4-(hydroxymethyl)-1,3-thiazol-5-yl]phenyl}ethan-1-ol dihydrochloride (25 mg), and DMF (1 mL) were sequentially added DIPEA (50 μ L) and HATU (35 mg) under ice-bath cooling, and the mixture was stirred at room temperature for 1 hour. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, and then dried over anhydrous sodium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($\text{CHCl}_3/\text{MeOH}$) to give an amide product (59 mg). Subsequently, the obtained compound was dissolved in CH_2Cl_2 (0.5 mL) and MeOH (0.5 mL), and hydrogen chloride (4M DOX solution, 0.5 mL) was added under ice-bath cooling. The mixture was stirred at room temperature for 2 hours, and then concentrated under reduced pressure. Diethyl ether was added to the resulting residue, and the precipitated solid was filtered, washed with diethyl ether, and dried under reduced pressure to give the title compound (43 mg) as a solid.

ESI+: 1133.3.

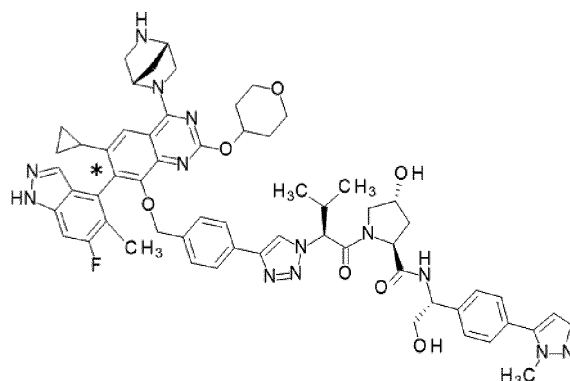
Example 3: (4R)-1-[(2S)-2-(4-{4-[(6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]ethyl}-L-prolinamide



To a mixture of tert-butyl (1S,4S)-5-{6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-8-{{4-[1-{{(2S)-1-[(2S,4R)-4-hydroxy-2-{{(1R)-2-hydroxy-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]ethyl}carbonyl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}-1H-1,2,3-triazol-4-yl)phenyl]methoxy}-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (170 mg), CH₂Cl₂ (2 mL), and MeOH (2 mL) was added hydrogen chloride (4M DOX solution, 0.988 mL) under ice-bath cooling, and the mixture was stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure, CHCl₃ and saturated aqueous sodium hydrogen carbonate solution were added, and the mixture was stirred for a while. Then, the aqueous layer was extracted with CHCl₃/MeOH (5/1), and the combined organic layer was dried over anhydrous sodium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (basic silica gel, CHCl₃/MeOH), and then purified by ODS column chromatography (MeCN/0.1% aqueous formic acid solution). The fractions containing the target compound were combined, basified with saturated aqueous sodium hydrogen carbonate solution, and then extracted twice with CHCl₃/MeOH (5/1). The combined organic layer was dried over anhydrous sodium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting solid was washed with diethyl ether, and dried under reduced pressure to give the title compound (74 mg) as a solid.

ESI+: 1105.7.

Example 4: (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl)oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(1-methyl-1H-pyrazol-5-yl)phenyl]ethyl]-L-prolinamide

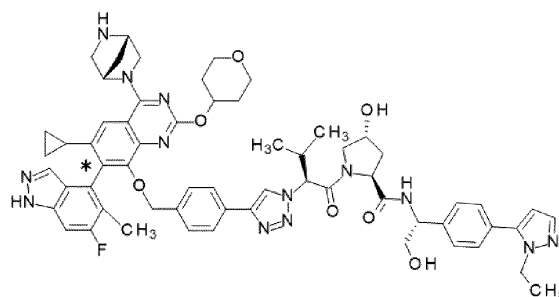


This compound was prepared using a method analogous to the method provided for Example 5 below.

5 ESI+: 1100.4;

NMR (100°C): 0.48-0.68 (4H, m), 0.77 (3H, br d), 1.03-1.10 (3H, m), 1.35-1.44 (1H, m), 1.66-1.77 (3H, m), 1.87 (1H, br d), 1.89-1.97 (1H, m), 1.98-2.10 (3H, m), 2.01 (3H, d), 2.11-2.24 (1H, m), 2.50-2.60 (1H, m), 3.06 (1H, dd), 3.14 (1H, d), 3.36-3.44 (2H, m), 3.56-3.64 (1H, m), 3.65-3.75 (3H, m), 3.77 (1H, br s), 3.80-3.92 (6H, m),
 10 4.16 (1H, dd), 4.36 (1H, br s), 4.41-4.48 (1H, m), 4.49-4.57 (1H, m), 4.73-4.84 (2H, m), 4.87-4.96 (1H, m), 5.13 (1H, br s), 5.17-5.24 (1H, m), 5.24-5.32 (2H, m), 6.31 (1H, d), 6.82 (2H, d), 7.30 (1H, d), 7.38-7.45 (5H, m), 7.45 (1H, d), 7.47 (1H, br s), 7.61 (2H, br d), 8.01 (1H, br d), 8.43 (1H, s), 12.75 (1H, br s).

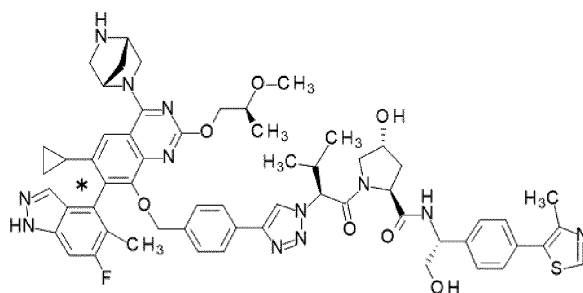
15 Example 5: (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl)oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide



20

To a solution of tert-Butyl (1S,4S)-5-(6-cyclopropyl-8-{[4-(1-{(2S)-1-[(2S,4R)-2-((1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl)carbamoyl]-4-hydroxypyrrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}-1H-1,2,3-triazol-4-

- yl)phenyl]methoxy}-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-2-[(oxan-4-yl)oxy]quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5.72 g) in CH₂Cl₂ (55 mL) was added trifluoroacetic acid (27 mL) dropwise over 20 minutes under ice-bath cooling, and the mixture was stirred at room temperature for 2 hours. The
- 5 resulting reaction mixture was concentrated under reduced pressure, and saturated aqueous sodium hydrogen carbonate solution and CHCl₃/MeOH (9/1) were added to the residue. The mixture was extracted three times with CHCl₃/MeOH (9/1), and then, the combined organic layer was dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure, and the resulting crude product was purified
- 10 by ODS column chromatography (MeCN/0.1% aqueous formic acid solution). Saturated aqueous sodium hydrogen carbonate solution was added to fractions containing the target compound, and the mixture was extracted three times with CHCl₃/MeOH (9/1). The combined organic layer was dried over anhydrous sodium sulfate, and the solution was concentrated under reduced pressure. The residue was purified by silica gel column
- 15 chromatography (basic silica gel, CHCl₃/MeOH) to give a product. EtOH was added to the obtained product, and the mixture was concentrated under reduced pressure. Diethyl ether was added to the residue and the resulting precipitate was filtered, washed with diethyl ether, and dried under reduced pressure to (2.98 g) as a solid.
- 20 ESI+:1114.5;
NMR (100°C): 0.48-0.68 (4H, m), 0.77 (3H, br d), 1.03-1.10 (3H, m), 1.30 (3H, t), 1.35-1.43 (1H, m), 1.66-1.77 (3H, m), 1.87 (1H, br d), 1.89-1.97 (1H, m), 1.98-2.10 (3H, m), 2.01 (3H, d), 2.11-2.20 (1H, m), 2.50-2.60 (1H, m), 3.06 (1H, dd), 3.13 (1H, d), 3.35-3.45 (2H, m), 3.57-3.64 (1H, m), 3.65-3.75 (3H, m), 3.75-3.79 (1H, m),
- 25 3.80-3.93 (3H, m), 4.11 (2H, q), 4.16 (1H, dd), 4.35 (1H, br s), 4.41-4.48 (1H, m), 4.49-4.57 (1H, m), 4.78-4.84 (2H, m), 4.87-4.96 (1H, m), 5.12 (1H, br s), 5.17-5.24 (1H, m), 5.24-5.32 (2H, m), 6.27 (1H, d), 6.82 (2H, d), 7.30 (1H, d), 7.35-7.40 (2H, m), 7.40-7.48 (5H, m), 7.61 (2H, br d), 8.01 (1H, br d), 8.43 (1H, s), 12.75 (1H, br s).
- 30
- Example 6: (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide
- 35

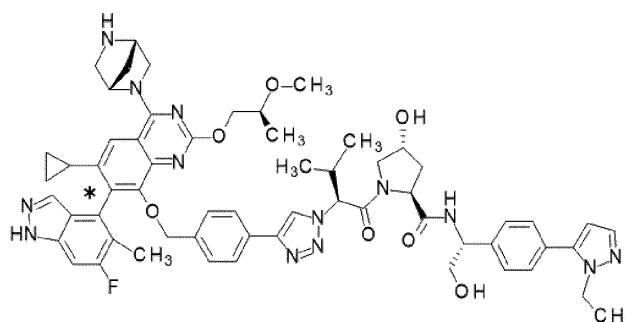


To a mixture of tert-butyl (1S,4S)-5-{6-cyclopropyl-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-8-{[4-(1-{(2S)-1-[(2S,4R)-4-hydroxy-2-({(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}carbamoyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl]phenyl]methoxy}-2-[(2S)-2-methoxypropoxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (98 mg) and CH₂Cl₂ (3 mL) was added trifluoroacetic acid (1 mL) under ice-methanol bath cooling, and then the mixture was stirred at room temperature for 2 hours under an argon atmosphere. The resulting reaction mixture was concentrated under reduced pressure, and ice, saturated aqueous sodium hydrogen carbonate solution, and CHCl₃/MeOH (10/1) were added to the residue. The mixture was stirred for 10 minutes, and then extracted with CHCl₃/MeOH (10/1), and then, the combined organic layer was dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure, and the resulting product was dissolved in MeOH and concentrated, dried under reduced pressure to give the title compound (73 mg) as a solid.

ESI+: 1105.7;

NMR (100°C): 0.48-0.68 (4H, m), 0.77 (3H, br d), 1.04-1.10 (3H, m), 1.14 (3H, d), 1.35-1.43 (1H, m), 1.74 (1H, br d), 1.87 (1H, br d), 1.89-1.97 (1H, m), 2.00 (3H, d), 2.01-2.10 (1H, m), 2.10-2.32 (1H, m), 2.45 (3H, s), 2.45-2.60 (1H, m), 3.06 (1H, dd), 3.14 (1H, d), 3.30 (3H, s), 3.60 (1H, br d), 3.65-3.78 (5H, m), 3.84 (1H, dd), 4.16 (1H, dd), 4.28 (1H, dd), 4.32-4.38 (2H, m), 4.45 (1H, br t), 4.52 (1H, br t), 4.78-4.85 (2H, m), 4.86-4.94 (1H, m), 5.14 (1H, br s), 5.28 (2H, d), 6.83 (2H, d), 7.30 (1H, d), 7.37-7.43 (4H, m), 7.45 (1H, d), 7.47 (1H, s), 7.59 (2H, br d), 8.00 (1H, br d), 8.42 (1H, s), 8.88 (1H, s), 12.75 (1H, br s).

Example 7: (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide



This compound was prepared using a method analogous to the method provided for Example 6 above.

5

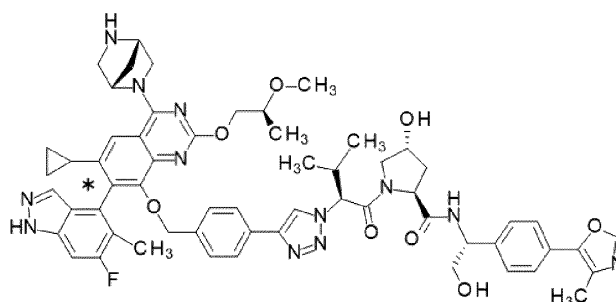
ESI+: 1102.8;

NMR (100°C): 0.48-0.68 (4H, m), 0.77 (3H, br d), 1.07 (3H, d), 1.14 (3H, d), 1.30 (3H, t), 1.35-1.43 (1H, m), 1.75 (1H, br d), 1.85-1.98 (2H, m), 2.00 (3H, d), 2.01-2.10 (1H, m), 2.42-2.51 (1H, m), 2.51-2.60 (1H, m), 3.07 (1H, dd), 3.16 (1H, d), 3.30 (3H, s), 3.60 (1H, br d), 3.65-3.78 (4H, m), 3.80 (1H, br s), 3.84 (1H, br dd), 4.07-4.15 (2H, m), 4.17 (1H, dd), 4.28 (1H, dd), 4.32-4.39 (2H, m), 4.42-4.48 (1H, m), 4.52 (1H, br t), 4.73-4.85 (2H, m), 4.87-4.96 (1H, m), 5.14 (1H, br s), 5.28 (2H, br d), 6.27 (1H, d), 6.83 (2H, d), 7.30 (1H, d), 7.35-7.40 (2H, m), 7.40-7.49 (5H, m), 7.59 (2H, br d), 8.01 (1H, br d), 8.42 (1H, s), 12.75 (1H, br s).

15

Example 8: (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl}-L-prolinamide

20



This compound was prepared using a method analogous to the method provided for Example 6 above.

25

ESI+: 1089.9.

Biological Examples

5

Example A: *In vivo* combination therapy with SOC_s in human KRAS G12D mutation positive PK-59 pancreatic cancer cell line-derived xenograft mice

10 PK-59 cells (RIKEN, Cat# RCB1901) were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum at 37°C in an atmosphere of 5% CO₂ in air. 6-8-week-old female nude mice (BALB/c nude mice, from Beijing Vital River Laboratory Animal Technology Co., Ltd) were inoculated subcutaneously with PK-59 cells (3×10⁶) in 0.2 mL of DPBS (containing 50% BD Matrigel (Corning Incorporated)) for tumor development. Animals were randomized and treatment started on day 7 after
15 tumor inoculation, when average tumor size reached approximately 120 mm³. Animals were assigned into groups using Excel-based randomization software performing stratified randomization based upon their tumor volumes. Each group consisted of 5 mice. The testing article was administrated as shown in Table 2. Solvent A was prepared by mixing 4% by volume of ethanol, 1% by volume of 50% (2-hydroxypropyl)-β-cyclodextrin, 9% by volume of polyoxyethylene hydrogenated castor
20 oil (HCO-40) in 5% glucose solution. The compound of Example 1 was dissolved in it. Gemcitabine and Abraxane™ (nanoparticle albumin-bound (nab) paclitaxel) were dissolved in saline. The tumor size and the body weight were measured twice to three times a week. The tumor volume was calculated using the following formula.
25 [Tumor volume (mm³)] = [long diameter of the tumor (mm)] × [short diameter of the tumor (mm)]² × 0.5

The tumor growth inhibition (TGI) rate (%) by the test compound was calculated for each group using the formula: TGI (%) = [1-(Ti-T1)/ (Vi-V1)] ×100; Ti is the average
30 tumor volume of a treatment group on a given day, T1 is the average tumor volume of the treatment group on the first day of treatment, Vi is the average tumor volume of the vehicle control group on the same day with Ti, and V1 is the average tumor volume of the vehicle group on the first day of treatment.

Table 2

Group	Treatment	Route of administration	Dosage (mg/kg)	Dosing Schedule	TGI (%) after 20 days of the first treatment
1	Solvent A	i.v.	-	BIW	-
	Saline	i.p.	-	BIW	
2	Example 1	i.v.	10	QW	90%
3	Gemcitabine	i.p.	25	BIW	51%
4	Abraxane™	i.v.	10	BIW	81%
5	Example 1 + Gemcitabine	i.v.	10	QW	95%
		i.p.	25	BIW	
6	Example 1 + Abraxane™	i.v.	10	QW	104%
		i.v.	10	BIW	
QW: once weekly, BIW: twice weekly					

As shown in the test results described in Table 2, a compound of Example 1 showed anti-tumor activity in mice bearing human pancreatic cancer cells with KRAS G12D mutation in combination with Gemcitabine or Abraxane™, suggesting that the combination with a compound of Example 1 is superior to Gemcitabine or Abraxane™ monotherapy for the treatment of G12D mutant KRAS-positive pancreatic cancer.

Example B: *In vivo* combination therapy with SOCs in human KRAS G12D mutation positive GP2d colorectal cancer cell line-derived xenograft mice

GP2d cells (European Collection of Authenticated Cell Cultures, Cat#95090714) were cultured in DMEM medium supplemented with 10% fetal bovine serum (2 mM Glutamine) at 37°C in an atmosphere of 5% CO₂ in air. 6-8-week-old female nude mice (BALB/c nude mice, from Beijing Vital River Laboratory Animal Technology Co., Ltd) were inoculated subcutaneously with GP2d cells (3×10⁶) in 0.2 mL of DPBS (containing 50% BD Matrigel (Corning Incorporated)) for tumor development. Animals were randomized and treatment was started 10 days after tumor inoculation when average tumor size reached approximately 150 mm³. Animals were assigned into groups using Excel-based randomization software performing stratified randomization based upon their tumor volumes. Each group consisted of 5 mice. The testing article was administrated as shown in Table 3. Solvent A was prepared by mixing 4% by volume of ethanol, 1% by volume of 50% (2-hydroxypropyl)-β-cyclodextrin, 9% by volume of HCO-40 in 5% glucose solution. The compound of Example 1 was dissolved in it. 5-

FU, Irinotecan were dissolved in saline. Oxaliplatin was dissolved in 5% glucose. The tumor size and the body weight were measured twice to three times a week. The tumor volume was calculated using the following formula.

5 [Tumor volume (mm³)] = [long diameter of the tumor (mm)] x [short diameter of the tumor (mm)]² x 0.5

The TGI rate (%) by the test compound was calculated for each group using the formula: TGI (%) = [1-(Ti-T1)/ (Vi-V1)] x100; Ti is the average tumor volume of a treatment group on a given day, T1 is the average tumor volume of the treatment
10 group on the first day of treatment, Vi is the average tumor volume of the vehicle control group on the same day with Ti, and V1 is the average tumor volume of the vehicle group on the first day of treatment.

Table 3

Group	Treatment	Route of administration	Dosage (mg/kg)	Dosing Schedule	Anti-tumor activity after 23 days of the first treatment
1	Solvent A	i.v.	-	QW	-
	Saline	i.p.	-	TIW	
2	Example 1	i.v.	30	QW	86%
3	5-FU	i.p.	30	TIW	53%
4	Irinotecan	i.p.	30	BIW	85%
5	Oxaliplatin	i.p.	10	QW	35%
6	Example 1 + 5-FU	i.v.	30	QW	90%
		i.p.	30	TIW	
7	Example 1 + Irinotecan	i.v.	30	QW	108%
		i.p.	30	BIW	
8	Example 1 + Oxaliplatin	i.v.	30	QW	94%
		i.p.	10	QW	
QW: once weekly, BIW: twice weekly, TIW: three times weekly					

15 As shown in the test results described in Table 3, a compound of Example 1 showed anti-tumor activity in mice bearing human colorectal cancer cells with KRAS G12D mutation in combination with 5-FU, Irinotecan or Oxaliplatin, suggesting that the combination with a compound of Example 1 is superior to 5-FU, Irinotecan or
20 Oxaliplatin monotherapy for the treatment of G12D mutant KRAS-positive colorectal cancer.

Example C: In vivo combination therapy with Docetaxel in KRAS G12D mutation positive human lung cancer patient-derived xenograft mice

5 4-6 week-old female nude mice (Crl:NMRI-Foxn1nu, from Charles River) were warehoused and subcutaneously inoculated with human lung cancer patient-derived tumor (Model name: LXFA 2204 (from Charles River)). Animals were assigned into groups using Excel-based randomization software performing stratified randomization based upon their tumor volumes. Each group consisted of 8 mice. The testing article
10 was administrated as shown in Table 4. Solvent A was prepared by mixing 4% by volume of ethanol, 1% by volume of 50% (2-hydroxypropyl)- β -cyclodextrin, 9% by volume of HCO-40 in 5% glucose solution. The compound of Example 1 was dissolved in it. Docetaxel was dissolved in 0.9% NaCl Solution. The tumor diameter and the weight volume were measured twice a week. The tumor volume was calculated using
15 the following formula.

$$[\text{Tumor volume (mm}^3\text{)}] = [\text{long diameter of the tumor (mm)}] \times [\text{short diameter of the tumor (mm)}]^2 \times 0.5$$

20 The tumor growth inhibition (TGI) rate (%) by the test compound was calculated as 100% inhibition of the tumor volume of the test compound-treated group on the day before the start of treatment and 0% inhibition of the tumor volume of the vehicle group at the end of 3 weeks after the first treatment.

25 The following results were obtained (Table 4).

Table 4.

Group	Treatment	Route of administration	Dosage (mg/kg)	Dosing Schedule	TGI (%) after 21 days of the first treatment
1	Solvent A	i.v.	-	QW*3	-
2	Example 1	i.v.	30	QW*3	69%
3	Docetaxel	i.v.	10	QD*1	87%
4	Example 1 +	i.v.	30	QW*3	95%
	Docetaxel	i.v.	10	QD*1	
QW: once weekly, QD: once a day					

As shown in the test results described in Table 4, anti-tumor activity of compounds of Example 1 in combination with docetaxel in human G12D mutant KRAS-positive lung cancer cell line tumor-bearing mice suggest that the combination with a compound of Example 1 can be superior to docetaxel monotherapy.

Industrial Applicability

10 The present invention is excellent in anti-tumor activity, and can be used for the treatment of G12D mutant KRAS-positive cancer, in particular, G12D mutant KRAS-positive pancreatic, colorectal and/or lung cancer, and the like.

Claims

1. A combination of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the compound of formula (I) is selected from the group consisting of:
- 10 (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}-L-prolinamide,
- 15 (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-(hydroxymethyl)-1,3-thiazol-5-yl]phenyl}ethyl}-L-prolinamide,
- 20 (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]ethyl}-L-prolinamide,
- 25 (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(1-methyl-1H-pyrazol-5-yl)phenyl]ethyl}-L-prolinamide,
- 30 (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide,
- 35 (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-

yl)phenyl]ethyl}-L-prolinamide,

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-N-{(1R)-1-[4-(1-ethyl-1H-pyrazol-5-yl)phenyl]-2-hydroxyethyl}-4-hydroxy-L-prolinamide, and

(4R)-1-[(2S)-2-(4-{4-[({6-Cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(2S)-2-methoxypropoxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-{(1R)-2-hydroxy-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl}-L-prolinamide.

2. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Claim 1, for use in the treatment of cancer, wherein the treatment further comprises administration of an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Claim 1 and an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutical acceptable excipient.

4. A pharmaceutical composition according to Claim 3 for use in the treatment of cancer.

5. A method of treating cancer comprising administering, to a patient in need thereof, a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Claim 1 and a therapeutically effective amount of an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof.

6. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Claim 1, and an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof for the treatment of cancer.

7. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Claim 1, and an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of cancer.

8. A kit-of-parts comprising:
15 (A) a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Claim 1, and optionally one or more pharmaceutically acceptable excipient, and
(B) a pharmaceutical composition comprising an anti-cancer agent selected from the group consisting of a taxane compound, a fluorine-containing nucleoside, a platinum
20 compound, an analogue of camptothecin, a fluoropyrimidine compound and prodrugs thereof, or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable excipient,
which components (A) and (B) are each provided in a form that is suitable for administration in conjunction with the other,
25 for use in the treatment of cancer.

9. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use, or kit-of-parts for use according to any one of Claims 1 to 8, wherein the anti-cancer agent is a taxane compound.

30 10. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 9, wherein the taxane compound is paclitaxel.

35 11. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 9, wherein the taxane compound is docetaxel.

12. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to any one of Claims 1 to 8, wherein the anti-cancer agent is a fluorine-containing nucleoside.
- 5 13. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 12, wherein the fluorine-containing nucleoside is gemcitabine.
14. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to any one of Claims 1 to 8, wherein the anti-cancer agent is a platinum compound.
- 10 15. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 14, wherein the platinum compound is oxaliplatin.
- 15 16. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to any one of Claims 1 to 8, wherein the anti-cancer agent is an analogue of camptothecin.
- 20 17. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 16, wherein the analogue of camptothecin is irinotecan.
- 25 18. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to any one of Claims 1 to 8, wherein the anti-cancer agent is a fluoropyrimidine compound.
- 30 19. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 18, wherein the fluoropyrimidine compound is 5-FU.
- 35 20. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to any one of Claims 1 to 19 wherein the cancer is pancreatic cancer.

21. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to any one of Claims 1 to 19, wherein the cancer is colorectal cancer.
- 5 22. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to any one of Claims 1 to 19, wherein the cancer is lung cancer.