

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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor, 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and
5 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:

- (4R)-1-[(2S)-2-(4-{4-[(6-Cyclopropyl-4-[(1S,4S)-2,5-
10 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-
15 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-
20 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-
25 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-
30 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-
35 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.

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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), 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.

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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), 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 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and prodrugs thereof, or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable excipient for use in the treatment of cancer.

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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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and prodrugs thereof, or a pharmaceutically acceptable salt thereof.

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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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and prodrugs thereof, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of cancer.

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A seventh aspect of the invention is 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, 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and prodrugs thereof, or a pharmaceutically

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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,

5 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and prodrugs thereof, or a pharmaceutically acceptable salt thereof for the treatment of cancer.

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Detailed description of the invention

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.

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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.

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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.

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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 increase longevity in the patient being treated.

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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).

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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 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.

20 Compounds for use

As described here, 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), 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:

(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.
- 35 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 CDK4/6

inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), 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.

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.

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.

- 10 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
15 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
20 compound of the formula (I) or mixtures thereof.

- 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).

- 25 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
30 relevant points of chirality).

- 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%,
35 for example at least 99.9%).

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.

5 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).

10 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).

15 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).

20 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.

25 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, 30 p.163-198. Prodrugs include ester and carbamate derivatives.

35 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
5 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
10 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,
15 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.

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

Furthermore, the present invention also includes various hydrates, solvates, crystal
25 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 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.

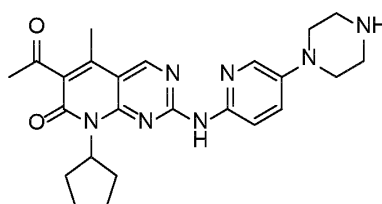
30 The anti-cancer agents

As described herein, the anti-cancer agent is selected from the group consisting of a
CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune
35 checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and prodrugs thereof.

The term "CDK4/6 inhibitor" refers to cyclin-dependent kinase 4 and 6 inhibitors and includes Palbociclib, ribociclib and abemaciclib.

In one embodiment, the anti-cancer agent is a CDK4/6 inhibitor. In a particular embodiment, the CDK4/6 agonist is Palbociclib.

Palbociclib refers to the compound having the name 6-acetyl-8-cyclopentyl-5-methyl-2-[(5-piperazin-1-ylpyridin-2-yl)amino]pyrido[2,3-d]pyrimidin-7-one, and the following structure.



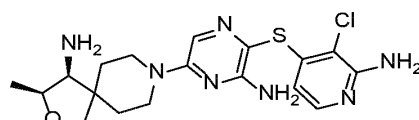
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The term "SHP2 inhibitor" refers to inhibitors of the protein tyrosine phosphatase SHP2, encoded by PTPN11, and includes TNO155, JAB-3068, RMC-4630 and RLY-1971.

In one embodiment, the anti-cancer agent is an SHP2 inhibitor. In a particular embodiment, the SHP2 inhibitor is TNO155.

TNO155 refers to the compound having the name (3S,4S)-8-[6-amino-5-[(2-amino-3-chloro-4-pyridinyl)thio]-2-pyrazinyl]-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine, and the following structure:

20

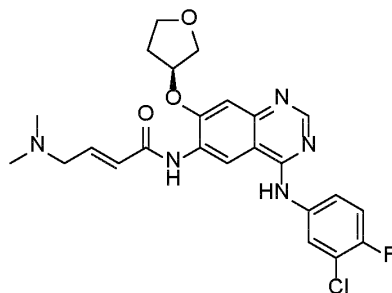


The term "EGFR inhibitor" refers to inhibitors of the epidermal growth factor receptor (EGFR) and includes both tyrosine kinase inhibitors (TKI) (such as afatinib, erlotinib or gefitinib) and monoclonal antibodies (such as cetuximab or necitumumab). The tyrosine kinase inhibitors bind to the tyrosine kinase domain in the EGFR and inhibit the activity of the EGFR; while monoclonal antibodies bind to the extracellular component of the EGFR and prevent the epidermal growth factor from binding to its own receptor, therefore preventing cell division.

30

In one embodiment, the anti-cancer agent is an EGFR inhibitor. In a particular embodiment, the EGFR inhibitor is a tyrosine kinase inhibitor. In a more particular embodiment, the tyrosine kinase inhibitor is afatinib.

- 5 Afatinib refers to the compound having the name (E)-N-[4-(3-chloro-4-fluoroanilino)-7-[(3S)-oxolan-3-yl]oxyquinazolin-6-yl]-4-(dimethylamino)but-2-enamide, and the following structure:

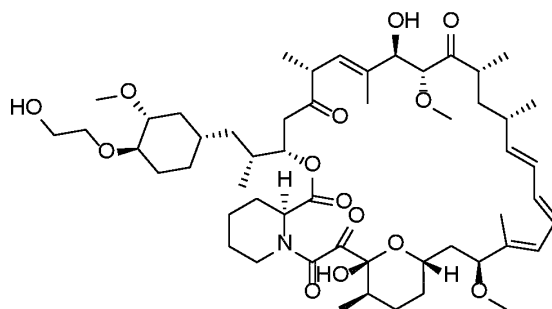


- 10 In a particular embodiment, the EGFR inhibitor is cetuximab.

The term "mTOR inhibitor" refers to a class of drugs that inhibit the mechanistic target of rapamycin (mTOR), which is a serine/threonine-specific protein kinase that belongs to the family of phosphatidylinositol-3 kinase (PI3K) related kinases (PIKKs). mTOR regulates cellular metabolism, growth, and proliferation by forming and signaling through two protein complexes, mTORC1 and mTORC2. The term "mTOR" inhibitor includes Everolimus, Sirolimus, Temsirolimus, Ridaforolimus, Umirolimus, and Zotarolimus.

- 20 In one embodiment, the anti-cancer agent is an mTOR inhibitor. In a particular embodiment, the mTOR inhibitor is Everolimus.

Everolimus refers to the compound having the name (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-[(2R)-1-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]propan-2-yl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone, and the following structure:



The term "immune checkpoint inhibitor" refers to inhibitors of immune checkpoint signaling that restricts immune system functions. Thus, immune checkpoint inhibitors may lead to activation, proliferation and/or increase in signaling of T cells. "Immune checkpoint inhibitors" include anti-PD-1 antibodies (such as nivolumab (OPDIVO; BMS-936558), pembrolizumab (KEYTRUDA™; MK-3475), pidilizumab (CT-011), cemiplimab (LIBTAYO, REGN2810), spartalizumab (PDR001), MEDI0680 (AMP- 514), dostarlimab (TSR-042), cetrelimab (JNJ 63723283), toripalimab (JS001), AMP-224 (GSK-2661380), PF-06801591, tislelizumab (BGB-A317), ABBV-181, BI 754091, or SHR-1210), and anti-PD-L1 antibodies (such as TECENTRIQ; RG7446; MPDL3280A; R05541267), durvalumab (MEDI4736), BMS-936559, avelumab (bavencio), lodapolimab (LY3300054), CX-072 (Proclaim-CX-072), FAZ053, KN035, or MDX-1105).

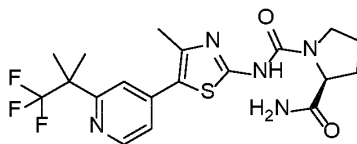
In one embodiment, the anti-cancer agent is an immune checkpoint inhibitor. In a particular embodiment, the immune checkpoint inhibitor is an anti-PD-1 antibody. In a more particular embodiment, the anti-PD-1 antibody is Nivolumab.

Nivolumab is a human immunoglobulin G4 monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and has the following CAS number: 946414-94-4.

The term "PI3K inhibitor" refers to a class of drugs that inhibit phosphatidylinositol-3-kinase. PI3K inhibitors include idelalisib, copanlisib, duvelisib, alpelisib, umbralisib, leniolisib.

In one embodiment, the anti-cancer agent is a PI3K inhibitor. In a particular embodiment, the PI3K inhibitor is Alpelisib.

Alpelisib refers to the compound having the name "(2S)-N1-{4-Methyl-5-[2-(1,1,1-trifluoro-2-methyl-2-propanyl)-4-pyridinyl]-1,3-thiazol-2-yl}-1,2-pyrrolidinedicarboxamide", and the following structure:



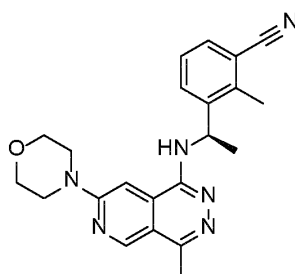
5

The term "SOS1 inhibitor" refers to inhibitors of the RAS guanine nucleotide exchange factor SOS1. SOS1 inhibitors include BI-3406 and MRTX0902.

10 In one embodiment, the anti-cancer agent is an SOS1 inhibitor. In a particular embodiment, the SOS1 inhibitor is MRTX0902.

MRTX0902 refers to the compound having the name "(R)-2-Methyl-3-(1-((4-methyl-7-morpholinopyrido-[3,4-d]pyridazin-1-yl)amino)ethyl)benzonitrile", CAS number: 2654743-22-1, and the following structure:

15

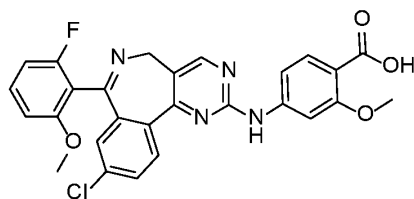


20 The term "AURK inhibitor" refers to inhibitors of Aurora kinase. AUK inhibitors include Aurora kinase A inhibitors and Aurora kinase B inhibitors. AURK inhibitors include Alisertib, Barasertib, Danusertib, AT9283, PF-03814735, AMG 900.

In one embodiment, the anti-cancer agent is an AURK inhibitor. In a particular embodiment, the AURK inhibitor is a AURK A inhibitor. In a more particular embodiment, the AURK A inhibitor is Alisertib.

25

Alisertib refers to the compound having the name "4-{[9-Chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoic acid", and the following structure:



In some embodiments, the anti-cancer agent is selected from the group consisting of a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, and prodrugs thereof.

In some embodiments, the anti-cancer agent is selected from the group consisting of a PI3K inhibitor, an SOS1 inhibitor, an AURK inhibitor, and prodrugs thereof.

10 The cancers

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

“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”.

“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.

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

“Lung cancer” is a malignant tumor occurring in the lung.

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

5

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 first aspect of the invention) for the relevant condition and has failed to respond or has not responded adequately to that treatment.

10

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 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).

15

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 selected from a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor, and prodrugs thereof.

25

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

30

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.

35

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 alternative embodiment, the G12D mutant KRAS-positive cancer is a G12D mutant
5 KRAS-positive lung cancer.

According to a second aspect of the invention is an anti-cancer agent selected from the group consisting of a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an
10 AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), 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.

15 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.

20 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
25 selected from the group consisting of a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and prodrugs thereof, or a pharmaceutically acceptable salt thereof, and optionally one or more
30 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
35 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
5 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
10 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.

15 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
20 described herein).

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

25 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR
30 inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and prodrugs thereof, or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable excipient for use in the treatment of cancer.

35 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

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.

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 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 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 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.

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 hours, 8 hours, 12 hours, 24 hours, 2 days, 3 days, 4 days, 5 days or 6 days) of each other.

5

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

10 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 salt thereof (or pharmaceutical composition comprising the same).

15 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 pharmaceutical composition comprising the same) are administered sequentially, such as wherein the second drug is administered after confirming that the treatment with
20 the first drug is effective. Methods for determining the effectiveness of the first drug are known to the skilled person.

The skilled person will understand that compounds and pharmaceutical formulations as defined herein may be administered either by oral administration with a tablet, pill,
25 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.

As a solid composition for oral administration, a tablet, powder, granular, or other
30 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.

35

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 preservative.

- 5 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 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
- 10 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 is dissolved or suspended in sterile water or a sterile solvent for injection before use.
- 15 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 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
- 20 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 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
- 25 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 chlorofluoroalkane or carbon dioxide.
- 30 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.
- 35 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.

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).

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).

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.

Dosages

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.

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).

5

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).

- 10 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

15

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
20 amount of an anti-cancer agent selected from the group consisting of a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and prodrugs thereof, or a pharmaceutically acceptable salt
25 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.

30

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,
35 and an anti-cancer agent selected from the group consisting of a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor),

and prodrugs thereof, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of cancer.

- 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

- 10 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, and optionally one or more pharmaceutically acceptable excipient, and
- 15 (B) a pharmaceutical composition comprising an anti-cancer agent selected from the group consisting of a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and prodrugs thereof, or a pharmaceutically
- 20 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,
- for use in the treatment of cancer.

- 25 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.

- 30 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
- 35 (II) instructions to use that component in conjunction with the other of the two components,
- for use in the treatment of cancer.

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.

5

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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor (e.g., a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor), and prodrugs thereof, or a pharmaceutically acceptable salt thereof for the treatment of cancer.

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

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

25

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:

- 5 (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.

10

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

15 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.

20

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

25 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

30 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

35 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 compound or can be separated using a difference in physiochemical properties between
10 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 appropriate optically active raw material compound.

15 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 example, octadecylsilyl (ODS) column chromatography or silica gel column
20 chromatography.

Advantages of the invention

Treatments as described herein may have the advantage that they may be more
25 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.

Without wishing to be bound by theory, it is believed that the compound of the formula
30 (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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor, and prodrugs thereof, to act synergistically in the treatment of
35 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.
- 10 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).
- 15 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

20

The following abbreviations may be used herein.

- DMF: N,N-dimethylformamide
DMAC: N,N-dimethylacetamide
- 25 THF: tetrahydrofuran
MeCN: acetonitrile
MeOH: methanol
EtOH: ethanol
DOX: 1,4-dioxane
- 30 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
- 35 hexafluorophosphate
DABCO: 1,4-diazabicyclo[2.2.2]octane
PdCl₂(dppf)·CH₂Cl₂: [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride-dichloromethane adduct

Pd/C: palladium on carbon

Production examples

5 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
10 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
15 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.

20 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
25 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
30 solid.

Production Example 3

35 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.

10 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.

25

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.

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.

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}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 (5.62 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.

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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]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 (173 mg) as a solid.

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Production Example 14

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.

15 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.

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 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.

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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

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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-dimethylimidazolium 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 CHCl₃ were added, and the mixture was stirred overnight. The mixture was divided into layers, the aqueous layer was extracted with CHCl₃, 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

10

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.

20 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

35 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 CH_2Cl_2 (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.

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.

Production Example 52

5

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.

35

Production Example 58

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 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 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, 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 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.

Production Example 60

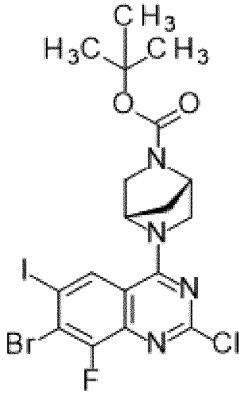
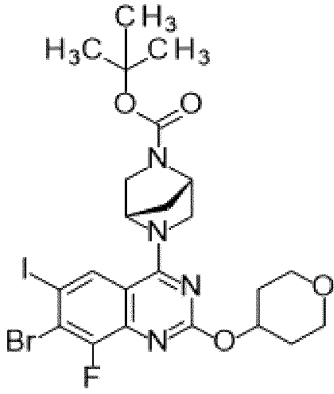
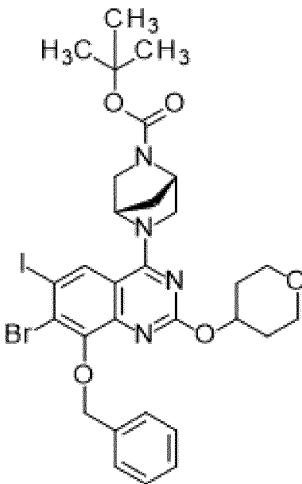
Under an argon atmosphere, bis(tri-tert-butylphosphine)palladium(0) (18 mg) was added to a mixture of 4-methyl-1,3-oxazole-5-carboxylic acid (178 mg), tetra-n-butylammonium chloride (195 mg), tert-butyl (4R)-4-(4-bromophenyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (250 mg), cesium carbonate (344 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,

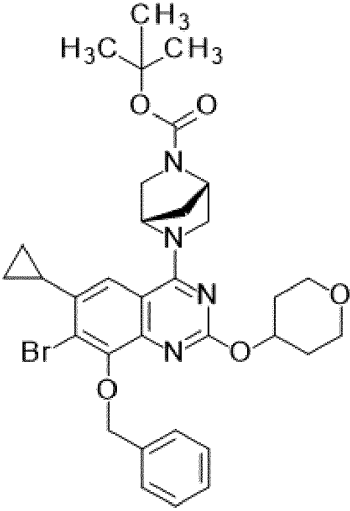
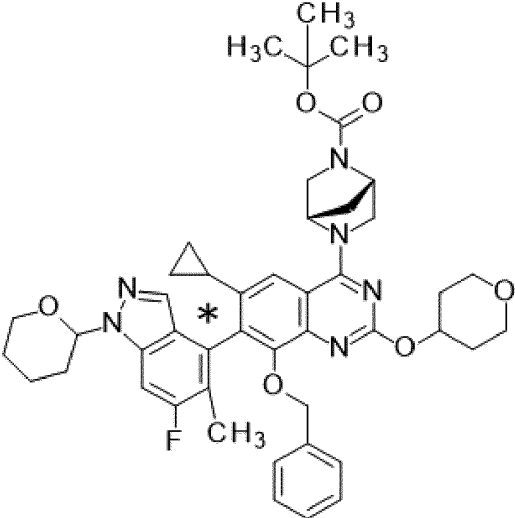
and the insoluble materials were removed by filtration through celite pad. The filtrate was washed with water and saturated aqueous sodium chloride solution and was dried over anhydrous magnesium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting
5 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.

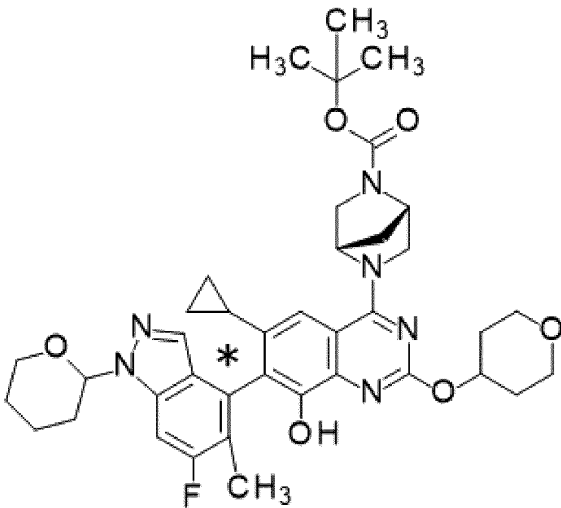
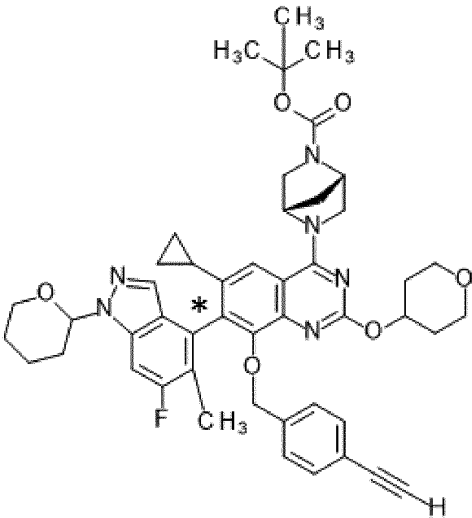
In the following tables, "PEx" represents "production example" and "PSyn" indicates
10 which other production example was also prepared using the same method as the "PEx" in the same row of the table (i.e. the "PEx" was prepared using the same method as the method used to prepare the production example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

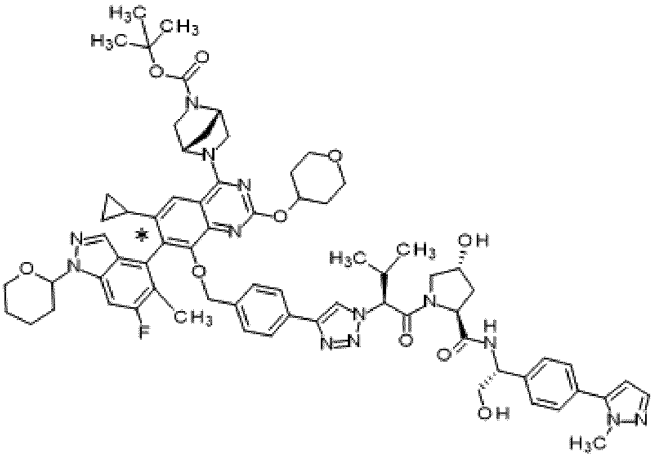
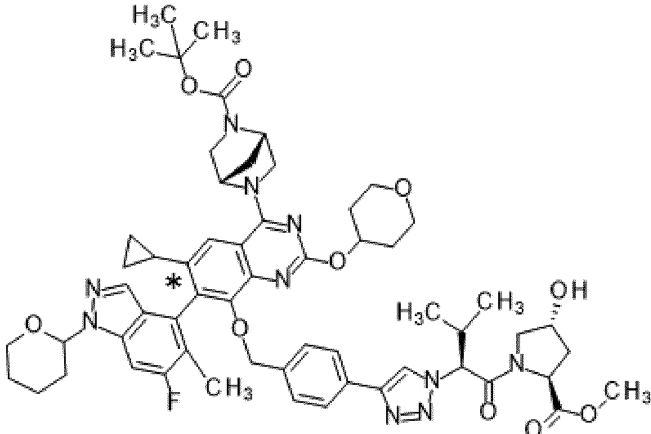
15 Structure: chemical structural formula (a compound with "*" in the chemical structural formula represents that the compound is a single axial stereoisomer). n HCl: n hydrochloride ("n HCl" shows that the compound is monohydrochloride to trihydrochloride), Data: physiochemical data, ESI+: m/z value in mass spectrometry (ionization method ESI, [M+H]⁺ unless otherwise specified), ESI-: m/z value in mass
20 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).

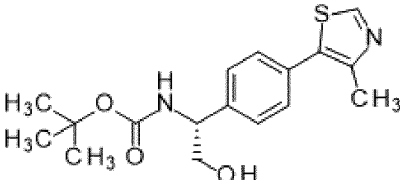
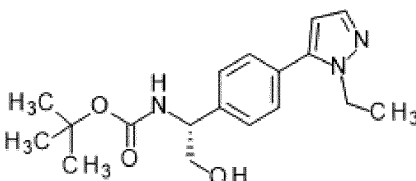
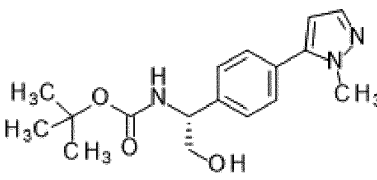
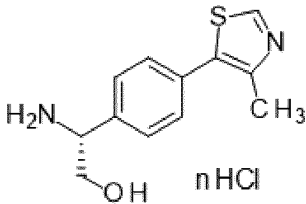
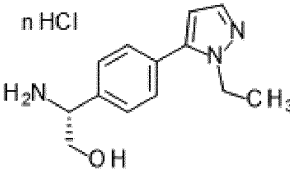
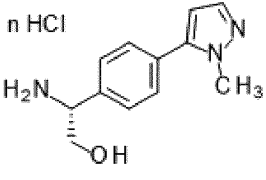
Table 1

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

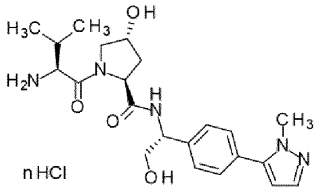
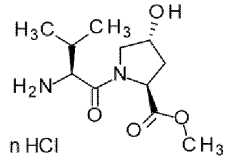
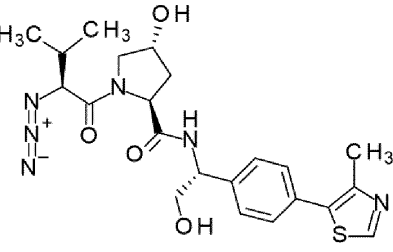
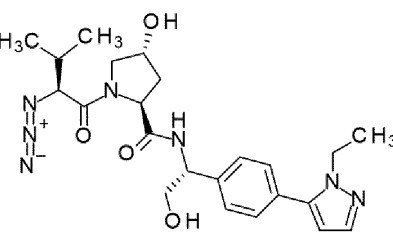
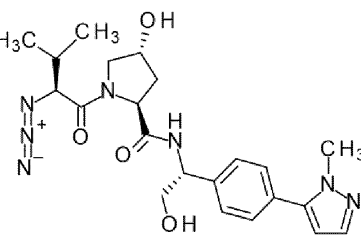
PEx	PSyn	Structure	Data
6	6		ESI+: 715.4
7	7		ESI+: 829.5

PEx	PSyn	Structure	Data
10	8	 Chemical structure of compound 10. It features a central benzimidazole core with a cyclopropyl group at position 2, a 4-fluorophenyl group at position 3, and a 4-methoxyphenyl group at position 4. The benzimidazole ring is substituted with a 4-(tert-butoxycarbonyl)piperidin-1-yl group at position 5 and a 4-(tert-butoxycarbonyl)piperidin-1-yl group at position 6. The structure also includes a 4-(tert-butoxycarbonyl)piperidin-1-yl group at position 7 and a 4-(tert-butoxycarbonyl)piperidin-1-yl group at position 8. The structure is marked with an asterisk (*) on the benzimidazole ring.	ESI+: 1284.4
11	8	 Chemical structure of compound 11. It features a central benzimidazole core with a cyclopropyl group at position 2, a 4-fluorophenyl group at position 3, and a 4-methoxyphenyl group at position 4. The benzimidazole ring is substituted with a 4-(tert-butoxycarbonyl)piperidin-1-yl group at position 5 and a 4-(tert-butoxycarbonyl)piperidin-1-yl group at position 6. The structure also includes a 4-(tert-butoxycarbonyl)piperidin-1-yl group at position 7 and a 4-(tert-butoxycarbonyl)piperidin-1-yl group at position 8. The structure is marked with an asterisk (*) on the benzimidazole ring.	ESI+: 1099.4

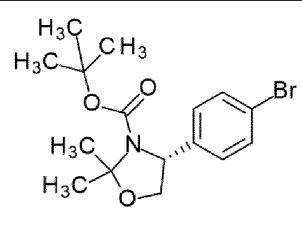
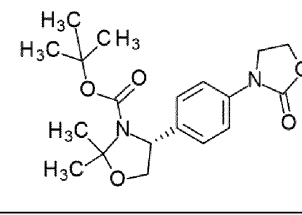
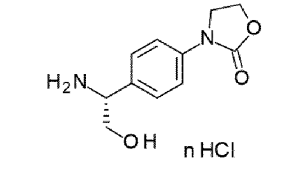
PEx	PSyn	Structure	Data
14	14		ESI+: 335.2
15	15		ESI+: 332.2
16	15		ESI+: 318.2
17	17		ESI+: 235.2
18	18		ESI+: 232.2
19	18		ESI+: 218.1

PEx Output	PSyn Output	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

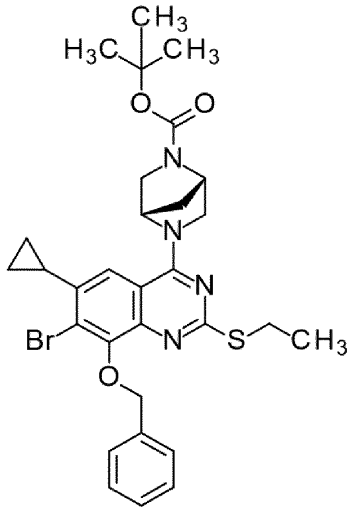
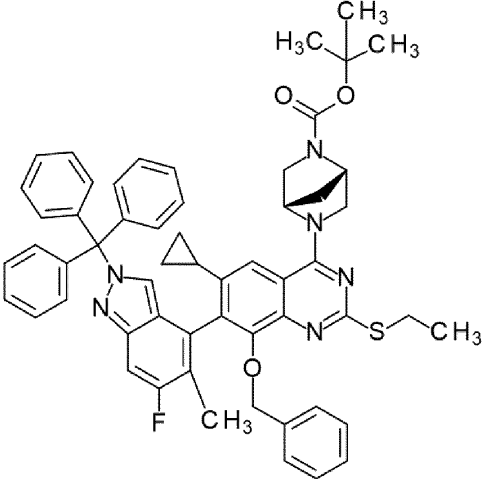
PEx	PSyn	Structure	Data
26	26		ESI+: 547.4
27	26		ESI+: 544.3
28	26		ESI+: 530.4
29	29	nHCl	ESI+: 447.3
30	29	nHCl	ESI+: 444.3

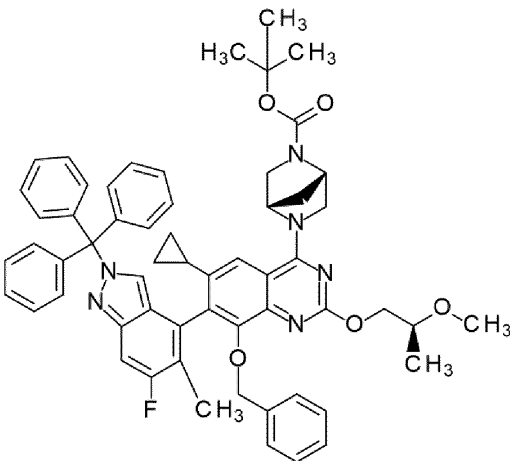
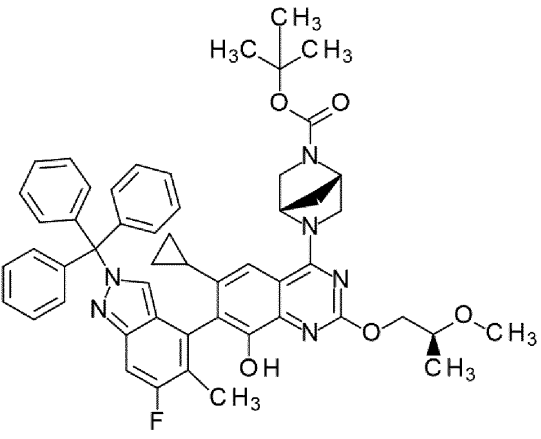
PEx	PSyn	Structure	Data
31	29	 <chem>CC1(C)C(C(C)(C)N1C(=O)C(C)(C)N)C(=O)N[C@@H](O)Cc2ccc(cc2-c3c[nH]c3)C</chem> $n\text{HCl}$	ESI+: 430.3
32	29	 <chem>CC1(C)C(C(C)(C)N1C(=O)C(C)(C)N)C(=O)OC</chem> $n\text{HCl}$	ESI+: 245.2
33	33	 <chem>CC1(C)C(C(C)(C)N1C(=O)C(C)(C)N)C(=O)N[C@@H](O)Cc2ccc(cc2-c3c[nH]s3)C</chem> $n\text{HCl}$	ESI+: 473.3
34	33	 <chem>CC1(C)C(C(C)(C)N1C(=O)C(C)(C)N)C(=O)N[C@@H](O)Cc2ccc(cc2-c3c[nH]c3)CC</chem> $n\text{HCl}$	ESI+: 470.3
35	33	 <chem>CC1(C)C(C(C)(C)N1C(=O)C(C)(C)N)C(=O)N[C@@H](O)Cc2ccc(cc2-c3c[nH]c3)C</chem> $n\text{HCl}$	ESI+: 456.3

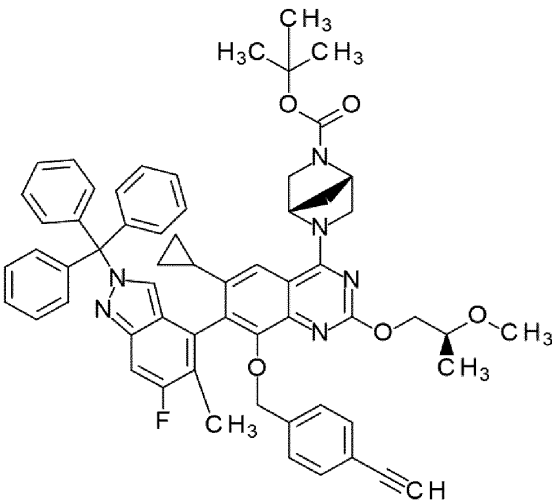
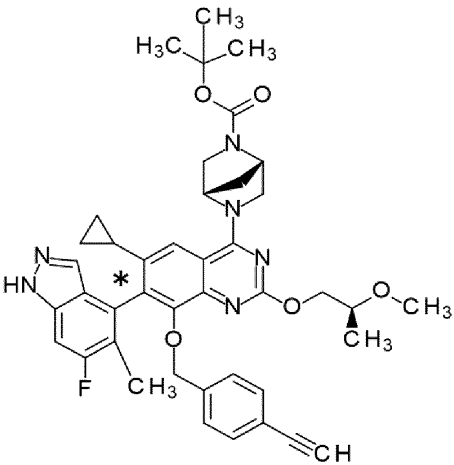
PEx	PSyn	Structure	Data
36	33		ESI+: 271.2
37	37		ESI+: 386.3 [M+Na]+
38	38		ESI+: 379.3
39	39		ESI+: 351.2
40	17		ESI+: 251.1

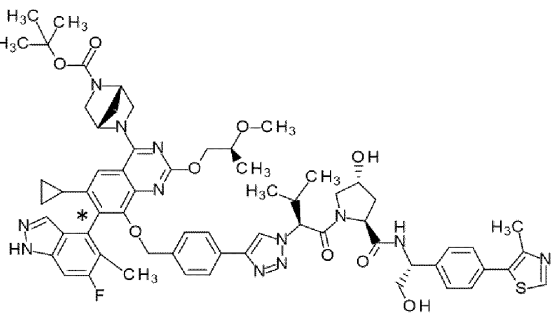
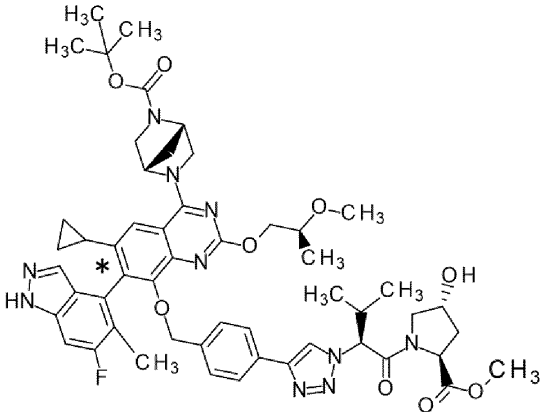
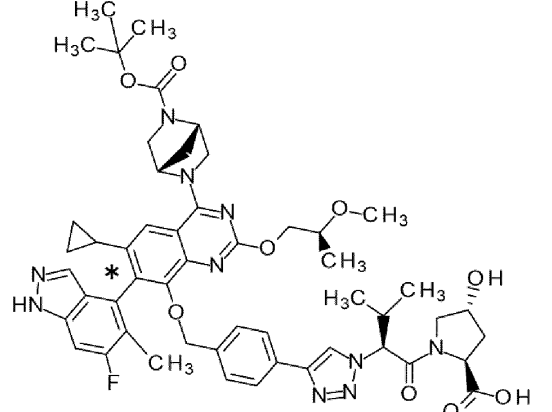
PEX	PSyn	Structure	Data
41	41		ESI+: 378.2 [M+Na] ⁺
42	42		ESI+: 385.2 [M+Na] ⁺
43	17		ESI+: 245.1 [M+Na] ⁺

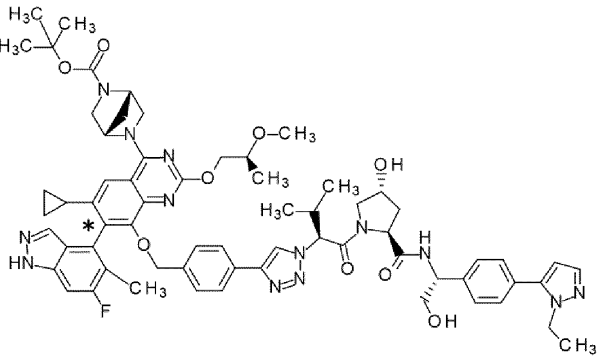
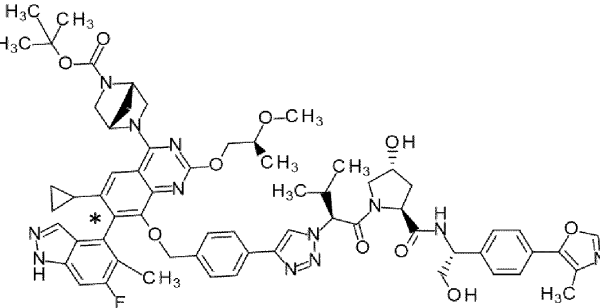
PEX	PSyn	Structure	Data
44	2		ESI+: 610.9
45	3		ESI+: 698.9

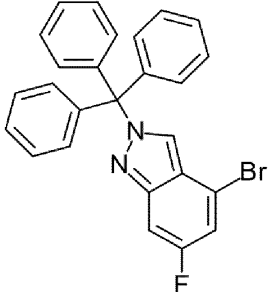
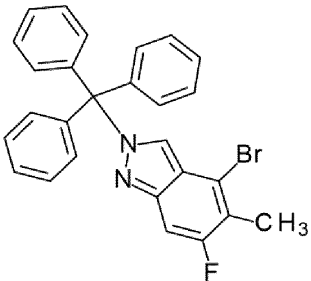
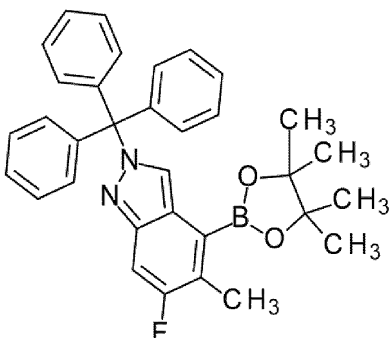
PEx	PSyn	Structure	Data
46	4		ESI+: 613.3
47	5		ESI+: 923.3

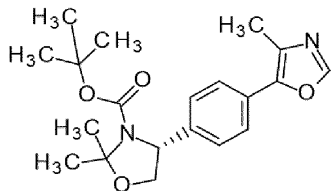
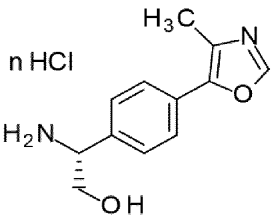
PEx	PSyn	Structure	Data
48	48	 Chemical structure of compound 48: A complex molecule featuring a central benzene ring substituted with a fluorine atom (F) and a methyl group (CH₃). This central ring is part of a larger system including a pyrazole ring, a cyclopropane ring, and a piperidine ring. The piperidine ring is substituted with a tert-butyl ester group (H₃C-C(CH₃)₂-COO-) and a methoxy group (OCH₃). The pyrazole ring is substituted with a methoxy group (OCH₃) and a methyl group (CH₃). The cyclopropane ring is substituted with a phenyl group (C₆H₅).	ESI+: 951.8
49	6	 Chemical structure of compound 49: A complex molecule featuring a central benzene ring substituted with a fluorine atom (F) and a methyl group (CH₃). This central ring is part of a larger system including a pyrazole ring, a cyclopropane ring, and a piperidine ring. The piperidine ring is substituted with a tert-butyl ester group (H₃C-C(CH₃)₂-COO-) and a methoxy group (OCH₃). The pyrazole ring is substituted with a methoxy group (OCH₃) and a methyl group (CH₃). The cyclopropane ring is substituted with a phenyl group (C₆H₅). The structure is identical to compound 48, but the central benzene ring is substituted with a hydroxyl group (OH) instead of a fluorine atom (F).	ESI+: 861.7

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

PEx	PSyn	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

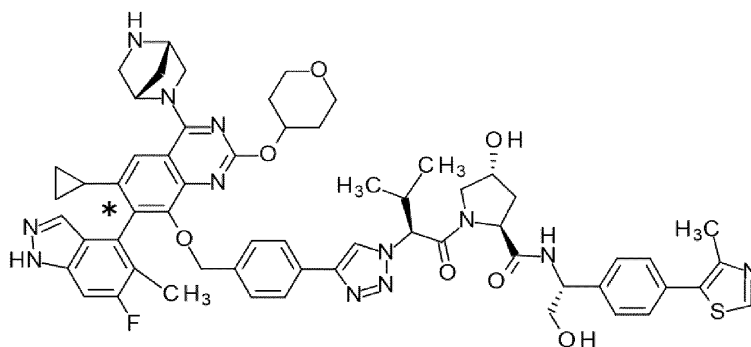
- 5 The following are examples of compounds of formula (I) and the characterization thereof.

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

10

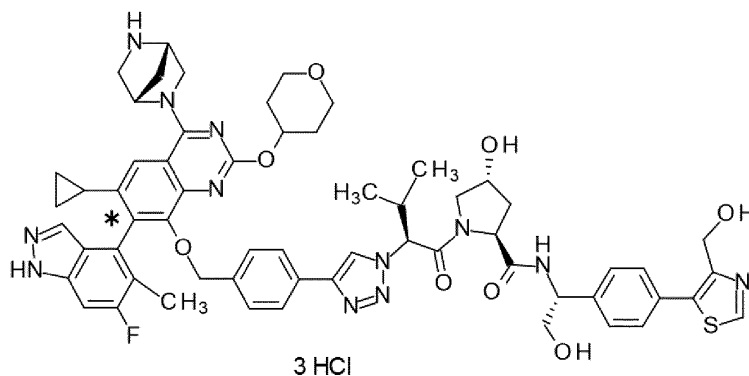
Example 1: (4R)-1-[(2S)-2-(4-{4-[(6-cyclopropyl-4-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-[(oxan-4-yl)oxy]quinazolin-8-yl}oxy)methyl]phenyl}-1H-1,2,3-triazol-1-yl)-3-methylbutanoyl]-4-hydroxy-N-[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]-L-prolinamide

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



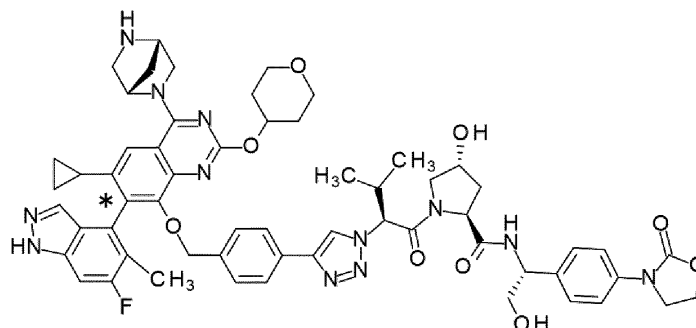
5

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
 10 (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,
 15 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
 20 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.

25 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

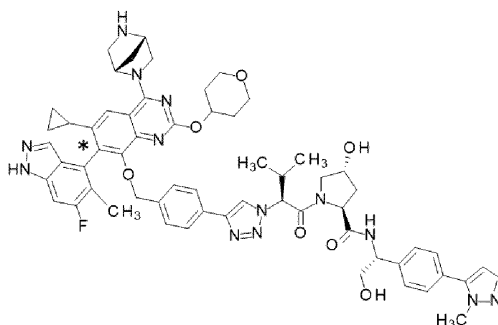


- 5 To a mixture of tert-butyl (1S,4S)-5-{6-cyclopropyl-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-8-{[4-(1-{(2S)-1-[(2S,4R)-4-hydroxy-2-[(1R)-2-hydroxy-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]ethyl]carbamoyl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]-1H-1,2,3-triazol-4-yl)phenyl]methoxy}-2-[(oxan-4-yl)oxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (170 mg),
 10 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),
 15 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
 20 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
 25 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-
- 30

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

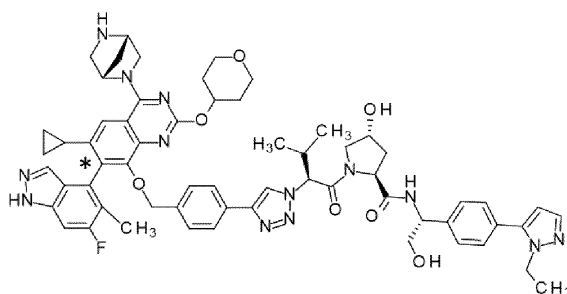


- 5 This compound was prepared using a method analogous to the method provided for Example 5 below.

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), 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).

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



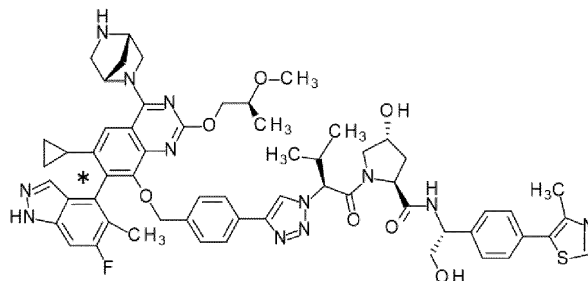
To a solution of tert-Butyl (1S,4S)-5-(6-cyclopropyl-8-{[4-(1-{(2S)-1-[(2S,4R)-2-
 5 hydroxypyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}-1H-1,2,3-triazol-4-
 yl)phenyl]methoxy}-7-[6-fluoro-5-methyl-1-(oxan-2-yl)-1H-indazol-4-yl]-2-[(oxan-
 4-yl)oxy]quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (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
 10 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
 15 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
 20 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.

25 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),
 30 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).

35

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



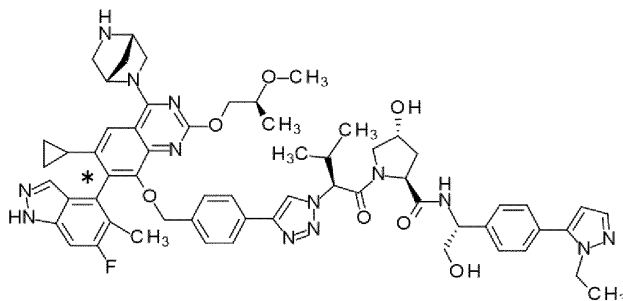
To a mixture of tert-butyl (1S,4S)-5-{6-cyclopropyl-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-8-{[4-(1-{(2S)-1-[(2S,4R)-4-hydroxy-2-({(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl}carbamoyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}-1H-1,2,3-triazol-4-yl)phenyl]methoxy}-2-[(2S)-2-methoxypropoxy]quinazolin-4-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (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.

20 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).

30 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

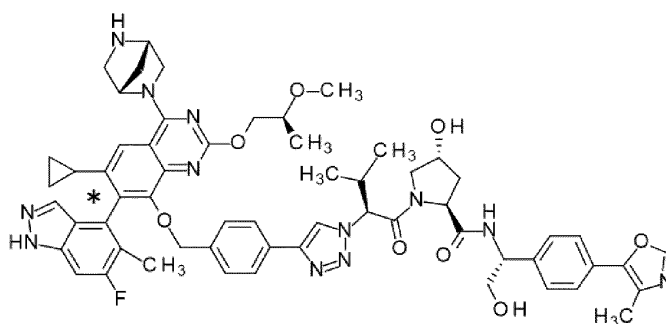


- 5 This compound was prepared using a method analogous to the method provided for Example 6 above.

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
 10 (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
 15 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).

- 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-
 20 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



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

ESI+: 1089.9.

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Biological Examples

Example A1: *In vivo* combination therapy with molecular targeted agents in human KRAS G12D mutation positive KP-4 pancreatic cancer cell line-derived xenograft mice

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KP-4 cells (Japanese Collection of Research Bioresources Cell Bank, Cat# JCRB0182) 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 KP-4 cells (1×10⁷) in 0.2 mL of DPBS (containing 50% BD Matrigel (Corning Incorporated)) for tumor development. Animals were randomized and treatment started on day 8 after tumor inoculation, when average tumor size reached approximately 200 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 oil (HCO-40) in 5% glucose solution. The compound of Example 1 was dissolved in it. Palbociclib (a CDK4/6 inhibitor) and TNO155 (a SHP2 inhibitor) were dissolved in 0.5% methyl cellulose (MC)/0.5% tween 80 solution (Solvent B). The tumor size and the body weight were measured twice to three times a week. The tumor volume was calculated using the following formula.

[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 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 21 days of the first treatment
1	Solvent A	i.v.	-	QW	-
	Solvent B	p.o.	-	QD	
2	Example 1	i.v.	30	QW	65%
	Solvent B	p.o.	-	QD	
3	Solvent A	i.v.	-	QW	89%
	Palbociclib	p.o.	60	QD	
4	Solvent A	i.v.	-	QW	90%
	TNO155	p.o.	10	BID	
5	Example 1 +	i.v.	30	QW	109%
	Palbociclib	p.o.	60	QD	
6	Example 1 +	i.v.	30	QW	108%
	TNO155	p.o.	10	BID	
QW: once weekly, QD: once daily, BID: twice daily					

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 Palbociclib or TNO155, suggesting that the combination with a compound of Example 1 is superior to Palbociclib or TNO155 monotherapy for the treatment of G12D mutant KRAS-positive pancreatic cancer.

Example A2: *In vivo* combination therapy with molecular targeted agents in human KRAS G12D mutation positive KP-4 pancreatic cancer cell line-derived xenograft mice

KP-4 cells (Japanese Collection of Research Bioresources Cell Bank, Cat# JCRB0182) were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum at 37°C in an atmosphere of 5% CO₂ in air. 7-8-week-old female nude mice (BALB/c nude mice, from Beijing Vital River Laboratory Animal Technology Co., Ltd) were inoculated subcutaneously with KP-4 cells (1×10⁷) in 0.2 mL of DPBS (containing 50% BD Matrigel (Corning Incorporated)) for tumor development. Animals were randomized and treatment started on day 6 after tumor inoculation, when average tumor size reached approximately 150-180 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. Alpelisib (a PI3K alpha inhibitor) was dissolved in 0.5% MC / 0.5% tween 80 (Solvent B). MRTX0902 (a SOS1 inhibitor) was dissolved in 10% DMSO/90% (20% SBE- β -CD in saline) (Solvent C). Alisertib (an Aurora A inhibitor) was dissolved in 10% 2-hydroxypropyl- β -cyclodextrin / 1% sodium bicarbonate (Solvent D). The tumor size and the body weight were measured twice to three times a week. The tumor volume was calculated using the following formula.

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

TGI rate (%) by the test compound was calculated for each group using the formula: $\text{TGI (\%)} = [1 - (\text{Ti} - \text{T1}) / (\text{Vi} - \text{V1})] \times 100$; Ti is the average 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 3

Group	Treatment	Route of administration	Dosage (mg/kg)	Dosing Schedule	TGI (%) after 21 days of the first treatment
1	Solvent A	i.v.	-	QW	-
	Solvent B	p.o.	-	QD	
2	Solvent A	i.v.	-	QW	-
	Solvent C	p.o.	-	BID	
3	Solvent A	i.v.	-	QW	-
	Solvent D	p.o.	-	QD	
4	Example 1	i.v.	30	QW	16%
	Solvent B	p.o.	-	QD	
5	Solvent A	i.v.	-	QW	-2%
	Alpelisib	p.o.	15	QD	
6	Solvent A	i.v.	-	QW	13%
	MRTX0902	p.o.	50	BID	
7	Solvent A	i.v.	-	QW	-10%
	Alisertib	p.o.	10	QD	

8	Example 1	i.v.	30	QW	50%
	Alpelisib	p.o.	15	QD	
9	Example 1	i.v.	30	QW	76%
	MRTX0902	p.o.	50	BID	
10	Example 1	i.v.	30	QW	60%
	Alisertib	p.o.	10	QD	
QW: once weekly, QD: once daily、BID: twice daily					

As shown in the test results described in Table 3, a compound of Example 1 showed anti-tumor activity in mice bearing human pancreatic cancer cells with KRAS G12D mutation in combination with Alpelisib, MRTX0902 or Alisertib, suggesting that the combination with a compound of Example 1 is superior to Alpelisib, MRTX0902 or Alisertib monotherapy for the treatment of G12D mutant KRAS-positive pancreatic cancer.

Example B: *In vivo* combination therapy with molecular targeted agents in human KRAS G12D mutation positive AsPC-1 pancreatic cancer cell line-derived xenograft mice

AsPC-1 cells (American Type Culture Collection, Cat# CRL-1682) were cultured in RPMI-1640 medium supplemented with 10% FBS 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 AsPC-1 cells (1×10⁶) in 0.2 mL of DPBS (containing 50% BD Matrigel (Corning Incorporated)) for tumor development. Animals were randomized and treatment started on day 17 after tumor inoculation, when average tumor size reached approximately 200 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 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. Afatinib (an EGFR inhibitor) was dissolved in 0.5% MC/0.5% tween 80 solution (Solvent B). Everolimus (a mTOR inhibitor) was dissolved in 5% tween 80/propylene glycol solution. The tumor size and the body weight were measured twice to three times a week. The tumor volume was calculated using the following formula.

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

TGI rate (%) by the test compound was calculated for each group using the formula:

- 5 TGI (%) = [1-(Ti-T1)/ (Vi-V1)] ×100; Ti is the average 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.

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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	-
	Solvent B	p.o.	-	QD	
2	Example 1	i.v.	30	QW	47%
	Solvent B	p.o.	-	QD	
3	Solvent A	i.v.	-	QW	40%
	Afatinib	p.o.	12.5	QD	
4	Solvent A	i.v.	-	QW	41%
	Everolimus	p.o.	5	QD	
5	Example 1 +	i.v.	30	QW	76%
	Afatinib	p.o.	12.5	QD	
6	Example 1 +	i.v.	30	QW	75%
	Everolimus	p.o.	5	QD	
QW: once weekly, QD: once daily					

- As shown in the test results described in Table 4, a compound of Example 1 showed anti-tumor activity in mice bearing human pancreatic cancer cells with KRAS G12D mutation in combination with Afatinib or Everolimus, suggesting that the combination with a compound of Example 1 is superior to Afatinib or Everolimus monotherapy for the treatment of G12D mutant KRAS-positive pancreatic cancer.

- 20 Example C: *In vivo* combination therapy with immune checkpoint inhibitor in mixed xenograft model from human KRAS G12D mutation positive HPAC pancreatic cancer cell line and human CD3-positive T cells

HPAC cells (ATCC, Cat# CRL-2119) were cultured in RPMI-1640 medium supplemented with 10% FBS at 37°C in an atmosphere of 5% CO₂ in air. CD3-positive T cells were obtained from peripheral blood mononuclear cells using the CD3 MACS isolation procedure according to manufacturer's instructions (Miltenyi Biotec, Bergisch Gladbach, Germany). CD3-positive T cells were expanded by culture with mitomycin C (final 25 µg/mL)-treated HPAC cells for 10 days in total, in RPMI-1640 supplemented with FBS and IL-2 (final 10 ng/mL). 6-week old male NOD-scid mice (NOD/ShiJic-scid mice, from CLEA Japan, Inc) were inoculated subcutaneously with 0.1 mL DPBS containing HPAC cells (5×10⁶) and CD3-positive T cells (1×10⁵) that were previously co-cultured with mitomycin C-treated HPAC cells for tumor development. Animals were randomized and treatment started on 7 days after tumor inoculation, when average tumor size reached approximately 50 mm³. Each group consisted of 13 mice. The testing article was administrated as shown in Table 5. 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. Nivolumab (an anti-programmed death-1 [PD-1]) was dissolved in DPBS. The tumor size and the body weight were measured three times a week. The tumor volume was calculated using the following formula.

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

TGI rate (%) by the test compound was calculated for each group using the formula:
$$\text{TGI (\%)} = [1 - (T_i - T_1) / (V_i - V_1)] \times 100;$$
 T_i is the average 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, V_i is the average tumor volume of the vehicle control group on the same day with T_i, and V₁ is the average tumor volume of the vehicle group on the first day of treatment.

Table 5

Group	Treatment	Route of administration	Dosage	Dosing Schedule	TGI (%) after 14 days of the first treatment
1	Solvent A PBS	i.v. i.p.	- -	QW TIW	-
2	Solvent A Nivolumab	i.v. i.p.	- 250 µg/head	QW TIW	26%
3	Example 1 PBS	i.v. i.p.	30 mg/kg -	QW TIW	85%
4	Example 1 + Nivolumab	i.v. i.p.	30 mg/kg 250 µg/head	QW TIW	101%
QW: once weekly, TIW: three times a week					

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

Example D: In vivo combination therapy with molecular targeted agents in human KRAS G12D mutation positive GP5d colorectal cancer cell line-derived xenograft mice

GP5d cells (ECACC, Cat# 95090715) were cultured in DMEM medium supplemented with 2mM glutamine and 10% fetal bovine serum at 37°C in an atmosphere of 5% CO₂ in air. 7-8-week-old female nude mice (BALB/c nude mice, from Beijing Vital River Laboratory Animal Technology Co., Ltd) were inoculated subcutaneously with GP5d 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 10 after tumor inoculation, when average tumor size reached approximately 150-180 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 6. 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. Alpelisib (a PI3K alpha inhibitor) was dissolved in 0.5% MC / 0.5% tween 80 (Solvent B). MRTX0902 (a SOS1 inhibitor) was dissolved in 10% DMSO/90% (20% SBE- β -CD in saline) (Solvent C). Alisertib (an Aurora A inhibitor) was dissolved in 10% 2-hydroxypropyl- β -cyclodextrin / 1% sodium bicarbonate (Solvent D). The tumor size and the body weight were measured twice to three times a week. The tumor volume was calculated using the following formula.

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

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TGI rate (%) by the test compound was calculated for each group using the formula: $\text{TGI (\%)} = [1 - (\text{T}_i - \text{T}_1) / (\text{V}_i - \text{V}_1)] \times 100$; T_i is the average tumor volume of a treatment group on a given day, T_1 is the average tumor volume of the treatment group on the first day of treatment, V_i is the average tumor volume of the vehicle control group on the same day with T_i , and V_1 is the average tumor volume of the vehicle group on the first day of treatment.

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Table 6

Group	Treatment	Route of administration	Dosage (mg/kg)	Dosing Schedule	TGI (%) after 20 days of the first treatment
1	Solvent A	i.v.	-	QW	-
	Solvent B	p.o.	-	QD	
2	Solvent A	i.v.	-	QW	-
	Solvent C	p.o.	-	BID	
3	Solvent A	i.v.	-	QW	-
	Solvent D	p.o.	-	QD	
4	Example 1	i.v.	30	QW	102%
	Solvent B	p.o.	-	QD	
5	Solvent A	i.v.	-	QW	16%
	Alpelisib	p.o.	15	QD	
6	Solvent A	i.v.	-	QW	11%
	MRTX0902	p.o.	50	BID	
7	Solvent A	i.v.	-	QW	-3%
	Alisertib	p.o.	10	QD	
8	Example 1	i.v.	30	QW	105%
	Alpelisib	p.o.	15	QD	

9	Example 1	i.v.	30	QW	106%
	MRTX0902	p.o.	50	BID	
10	Example 1	i.v.	30	QW	103%
	Alisertib	p.o.	10	QD	
QW: once weekly, QD: once daily、BID: twice daily					

As shown in the test results described in Table 6, a compound of Example 1 showed anti-tumor activity in mice bearing human colorectal cancer cells with KRAS G12D mutation in combination with Alpelisib, MRTX0902 or Alisertib, suggesting that the combination with a compound of Example 1 is superior to Alpelisib, MRTX0902 or Alisertib monotherapy for the treatment of G12D mutant KRAS-positive colorectal cancer.

Example E: *In vivo* combination therapy with Cetuximab in human KRAS G12D mutation positive GP5d colorectal cancer cell line-derived xenograft mice

GP5d cells (ECACC, Cat# 95090715) were cultured in DMEM medium supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin solution at 37°C in an atmosphere of 5% CO₂ in air. 5-week-old male nude mice (BALB/c nude mice, from Charles River Laboratories Japan, Inc.) were inoculated subcutaneously with GP5d cells (2.6×10⁶) in 0.1 mL of DPBS (containing 50% Cultrex Basement Membrane Extract (R&D Systems)) for tumor development. Animals were randomized and treatment started on day 10 after tumor inoculation, when average tumor size reached approximately 50-100 mm³. 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 was administered as shown in Table 7. 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. Cetuximab (an anti-EGFR antibody, ERBITUX Injection (Merck Biopharma Co., Ltd)) was administered undiluted. The tumor size and the body weight were measured twice times a week. The tumor volume was calculated using the following formula.

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

TGI rate was calculated using the following formula:

TGI (%) = 100 × (1 – [mean tumor volume on day 21 – mean tumor volume on day 0] in each group/[mean tumor volume on day 21 – mean tumor volume on day 0] in vehicle control group)

5 Table 7

Group	Treatment	Route of administration	Dosage (mg/kg)	Dosing Schedule	TGI (%)
1	Solvent A DPBS	i.v.	-	QW	-
		i.p.	-	BIW	
2	Example 1 DPBS	i.v.	30	QW	55%
		i.p.	-	BIW	
3	Solvent A Cetuximab	i.v.	-	QW	60%
		i.p.	50	BIW	
4	Example 1 Cetuximab	i.v.	30	QW	86%
		i.p.	50	BIW	
QW: once weekly, BIW: twice weekly					

As shown in the test results described in Table 7, a compound of Example 1 showed anti-tumor activity in mice bearing human colorectal cancer cells with KRAS G12D mutation in combination with Cetuximab, suggesting that the combination with a compound of Example 1 is superior to Cetuximab monotherapy for the treatment of G12D mutant KRAS-positive colorectal cancer.

Industrial Applicability

15 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor, 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor, 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor, 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 an anti-cancer agent selected from the group consisting of a CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor, 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor, 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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor, 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:
(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 CDK4/6 inhibitor, an SHP2 inhibitor, an EGFR inhibitor, a mTOR inhibitor, an immune checkpoint inhibitor, a PI3K inhibitor, an SOS1 inhibitor, and an AURK inhibitor, 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,
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 CDK4/6 inhibitor.
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 CDK4/6 inhibitor is Palbociclib.

11. 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 SHP2 inhibitor.
- 5 12. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 11, wherein the SHP2 inhibitor is TNO155.
- 10 13. 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 EGFR inhibitor.
- 15 14. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 13, wherein the EGFR inhibitor is Afatinib.
- 20 15. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 13, wherein the EGFR inhibitor is Cetuximab.
- 25 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 mTOR inhibitor.
- 30 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 mTOR inhibitor is Everolimus.
- 35 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 an immune checkpoint inhibitor.
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 immune checkpoint inhibitor is an anti-PD-1 antibody.

20. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 19, wherein the anti-PD-1 antibody is Nivolumab.
- 5 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 8, wherein the anti-cancer agent is a PI3K inhibitor.
22. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 21, wherein
10 the PI3K inhibitor is Alpelisib.
23. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to any one of Claims
15 1 to 8, wherein the anti-cancer agent is an SOS1 inhibitor.
24. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 23, wherein
20 the SOS1 inhibitor is MRTX0902.
25. 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 AURK inhibitor.
- 25 26. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to Claim 25, wherein
the AURK inhibitor is Alisertib.
27. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to any one of Claims
30 1 to 26, wherein the cancer is pancreatic cancer.
28. The compound for use, pharmaceutical composition, pharmaceutical composition for use, method, use or kit-of-parts for use according to any one of Claims
35 1 to 26, wherein the cancer is colorectal cancer.

29. 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 26, wherein the cancer is lung cancer.