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(54) **FGFR3 FUSION GENE AND PHARMACEUTICAL DRUG TARGETING SAME**

FGFR3-FUSIONSGEN UND DARAUF GERICHTETER PHARMAZEUTISCHER WIRKSTOFF

GÈNE DE FUSION FGFR3 ET MÉDICAMENT PHARMACEUTIQUE CIBLANT CELUI-CI

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Description

Technical Field

[0001] The disclosure relates to novel fusion polypeptides expressed in abnormal cells such as cancer cells; polynucleotides encoding the polypeptides; vectors comprising the polynucleotides; cells comprising the vectors; antibodies and fragments thereof which specifically bind to the polypeptides; oligonucleotide primers that hybridize to the polynucleotides; oligonucleotides that cleave the polynucleotides; pharmaceutical compositions comprising the antibodies or oligonucleotides; methods and kits for detecting the polynucleotides or fusion polypeptides; methods for testing cancer susceptibility, whether a subject is affected with cancer, or whether cancer has progressed based on the presence or absence of the polynucleotides or fusion polypeptides; methods for selecting cancer patients to which an FGFR inhibitor is applicable; pharmaceutical compositions for treating cancer wherein compounds having FGFR inhibitory activity or pharmaceutically acceptable salts thereof are used for administration to patients expressing the fusion polypeptides or carrying the polynucleotides; methods for treating or preventing cancer which comprise the step of administering an effective amount of compounds having FGFR inhibitory activity or pharmaceutically acceptable salts thereof to patients expressing the fusion polypeptides or carrying the polynucleotides; use of compounds having FGFR inhibitory activity or pharmaceutically acceptable salts thereof in the production of pharmaceutical compositions for cancer treatment for administration to patients expressing the fusion polypeptides or carrying the polynucleotides; compounds having FGFR inhibitory activity or pharmaceutically acceptable salts thereof for use in treating or preventing patients expressing the fusion polypeptides or carrying the polynucleotides; as well as methods for identifying FGFR inhibitors, and such.

Background Art

[0002] Cancer can develop in any organ or tissue, and is highly refractory and lethal. It goes with saying that cancer is a very troublesome disease. Recent statistical data showed that one out of every two persons is diagnosed with cancer during life, and one out of four men and one out of six women die of cancer. Thus, cancer remains an extremely severe disease.

[0003] To date, a number of anticancer agents have been developed and prescribed to many cancer patients, and certain therapeutic outcome has been achieved. However, anticancer agents are well known to cause serious side effects as well. Meanwhile, it has long been known that there are individual differences in the response to anticancer agents, *i.e.*, therapeutic effects and side effects, although the cause remains undissolved.

[0004] Recent advances in science and technology, in particular, rapid progress of pharmacogenomics (PGx), has enabled us to understand various diseases including cancer (such as cancer, diabetes, and hypertension) at the molecular level. It has been revealed that among patients showing similar symptoms; there are cases where genetic polymorphism (including gene mutation) is involved in the various individual differences observed, for example, differences in the absorption, distribution, metabolism, and excretion of administered pharmaceutical agents, as well as differences in the response at sites of action, differences in pathological conditions, and differences in disease susceptibility.

[0005] This suggests that for patients who are already affected with cancer, therapeutic effects can be enhanced and side effects can be reduced, for example, by analyzing the patients' genomic information in advance before administration of anticancer agents, and selecting an agent to be administered and determining the mode of prescription based on the presence or absence of specific genetic polymorphisms.

[0006] Likewise, for healthy persons also, genomic information of an individual can be analyzed using pharmacogenomics to predict the person's susceptibility to a disease (likelihood of being affected with a disease) as well as the person's responsiveness to pharmaceutical agents, based on the presence or absence of specific genetic polymorphisms.

[0007] This novel type of therapeutic method, which uses specific genetic polymorphisms thus identified or mutant polypeptides resulting from such polymorphisms as a biomarker, is referred to as order-made medicine, tailor-made medicine, personalized medicine, or custom-made medicine, and has been adopted for the clinical development of pharmaceutical products and clinical practice in various countries.

[0008] Similarly, agents that target the specific genetic polymorphisms identified as described above or mutant polypeptides resulting from such polymorphisms are referred to as molecularly targeted drugs, and their development is setting off actively.

[0009] Fibroblast growth factor receptors (FGFRs) are kinases belonging to the receptor tyrosine kinase family. FGFR1, FGFR2, FGFR3, and FGFR4 constitute the FGFR family. The ligand is fibroblast growth factor (FGF), and 22 types of structurally similar proteins form the family.

[0010] Signals transmitted *via* FGFR are conveyed to the MAPK pathway or PI3K/AKT pathway. It has been reported that in cancer, signal transduction is involved in cell growth, angiogenesis, cell migration, invasion, metastasis, etc.; and FGFR is activated as a result of overexpression, gene hyper-amplification, mutation, or translocation (Non-patent Document 1). For example, it is known that for FGFR3, genetic translocation is observed in multiple myeloma (Non-patent

Document 2); gene mutation is observed in bladder cancer (Non-patent Document 3); and overexpression is observed in ovarian cancer, non-small cell lung carcinoma, and hepatocellular carcinoma.

[0011] The findings described above suggest a connection between FGFR and cancer. Thus, attempts have been made to develop compounds with FGFR inhibitory activity as anticancer agents (Non-patent Documents 4 and 5).

[0012] While it has been reported very recently that genetic translocation that suggests the presence of a fusion polypeptide of FGFR3 and transforming acidic coiled-coil protein 3 (TACC3) or a fusion polypeptide of FGFR1 and TACC1 was found in very few cases of brain tumor glioblastoma multiforme (GBM) (three of 97 samples, 3.1 %) (Non-patent Document 6), the connection between fusion polypeptides of FGFR with other proteins and other types of cancer remains unclear.

Prior Art Documents

[Non-patent Documents]

[0013]

[Non-patent Document 1] Cytokine & Growth Factor Reviews, 2005, 16: 139-149
[Non-patent Document 2] Blood, 2003, 101: 4569-4575
[Non-patent Document 3] Nature Genetics, 1999 Sep., 23(1): 18-20
[Non-patent Document 4] Cancer Research, 2012, 72: 2045-2056
[Non-patent Document 5] J. Med. Chem., 2011, 54: 7066-7083
[Non-patent Document 6] Science, Vol. 337, Issue 6099, 7 September 2012: 1231-1235

Summary of the Invention

[Problems to be Solved by the Invention]

[0014] In view of the above circumstances, the present invention aims to identify and provide cancer cell-specific molecules that can be used as a biomarker to enable personalized medicine for FGFR inhibitor-based cancer therapy, and cancer cell-specific molecules that are useful in development of molecularly targeted drugs targeting FGFR, as well as to provide various materials and methods to be used in personalized medicine and development of molecularly targeted drugs that utilize such molecules as a biomarker or molecular target.

[Means for Solving the Problems]

[0015] As mentioned above, a connection between FGFR and cancer has been suggested; however, connections between fusion proteins of FGFR with other proteins and various types of cancer remain unrevealed.

[0016] To achieve the above-described objective, the present inventors conducted dedicated studies on expression, hyper-amplification, mutation, translocation, and such of FGFR-encoding genes in various cancer cells. As a result, the present inventors discovered in multiple bladder cancer cells and lung cancer cells, novel fusion polypeptide genes between an FGFR3 polypeptide gene and other polypeptide genes, in particular, fusion polypeptide genes between an FGFR3 polypeptide gene and a BAIAP2L1 polypeptide gene, and fusion polypeptide genes between an FGFR3 polypeptide gene and a TACC3 polypeptide gene

[0017] Therefore, the present invention concerns:

[1] a compound having FGFR inhibitory activity or a pharmaceutically acceptable salt thereof for use in a method of treating or preventing cancer in a patient who has been identified to express a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide or carrying a polynucleotide encoding the fusion polypeptide,

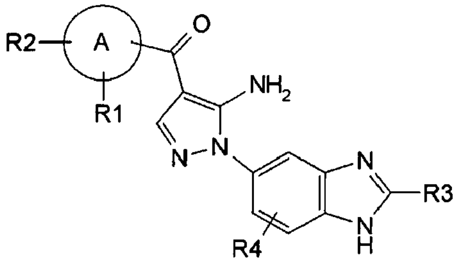
wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7,

wherein the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8, and

wherein the compound or a pharmaceutically acceptable salt thereof is capable of inhibiting a growth of a cancer cell expressing the fusion polypeptide or having a nucleotide encoding the fusion polypeptide, in particular wherein the cancer is bladder cancer, brain tumor, head and neck squamous cell carcinoma, lung cancer, lung adenocarcinoma, lung squamous cell carcinoma, skin melanoma, esophageal cancer, gastric cancer, or liver cancer, preferably bladder cancer.

In another preferred embodiment, said compound or its pharmaceutically acceptable salt is represented by:

[Compound 1]



(I)

wherein R_1, R_2, R_3, and R_4 each independently represents the group listed below:

R_1 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, - $(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, - $C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

R_2 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, - $(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, - $C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$; or

R_1 and R_2, together with an atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein the heterocyclyl or heteroaryl is optionally substituted by halogen;

R_3 represents hydrogen, C_{1-5} alkyl, C_{6-10} aryl C_{1-6} alkyl, or C_{1-4} haloalkyl;

R_4 represents hydrogen, halogen, C_{1-3} alkyl, C_{1-4} haloalkyl, hydroxy, cyano, nitro, C_{1-4} alkoxy, $-(CH_2)_nZ_1$, $-NR_6R_7$, $-OR_5$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $NR_{17}SO_2R_{18}$, COOH, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$,

$-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

A represents a 5- to 10-membered heteroaryl ring or C_{6-10} aryl ring;

R_5 represents C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{1-3} alkoxy C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{6-10} aryl, C_{6-10} aryl C_{1-3} alkyl, or 3- to 10-membered heterocyclyl C_{1-3} alkyl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, or C_{1-6} trihydroxy alkyl which is optionally substituted by one or more groups independently selected from group Q;

R_6 and R_7, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl C_{1-3} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, or cyano(C_{1-3}

alkyl); or alternatively R_6 and R_7, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

n represents 1 to 3;

R_8 and R_9, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, or halogen; or alternatively R_8 and R_9, together with a carbon atom linked thereto, form a cycloaliphatic ring;

Z_1 represents hydrogen, $NR_{10}R_{11}$, -OH, or 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{10} and R_{11}, which can be the same or different, each represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, cyano(C_{1-3} alkyl), or C_{1-3} alkylsulfonyl C_{1-4} alkyl; or alternatively R_{10} and R_{11}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{12} and R_{13}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3-to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, 3- to 10-membered cycloaliphatic ring, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; or alternatively R_{12} and R_{13}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{14} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{15} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{16} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{17} represents hydrogen or C_{1-4} alkyl;

R_{18} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{19} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, or 5-to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{20} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{21} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{22} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{23} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{24} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{25} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{26} and R_{27}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3-to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively R_{26} and R_{27}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{28} and R_{29}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3-to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively R_{28} and R_{29}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{30} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

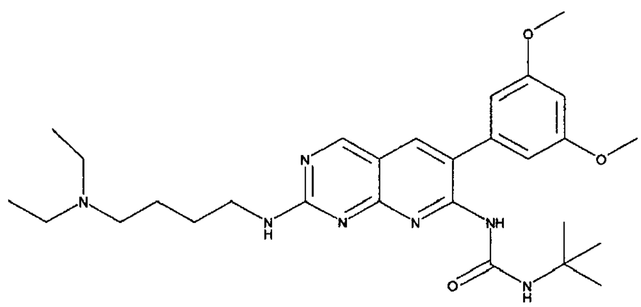
R_{31} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{32} represents C_{1-4} alkyl or C_{6-10} aryl;

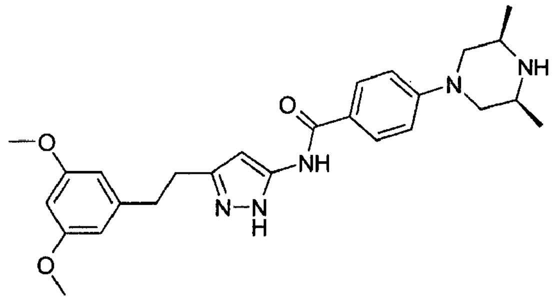
<group P>
halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, 3- to 10-membered heterocyclylamino, $-SO_2R_{16}$, -CN, $-NO_2$, and 3- to 10-membered heterocyclyl;

<group Q>
halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl amine, - SO_2R_{16}, -CN, $-NO_2$, C_{3-7} cycloalkyl, $-COR_{19}$, and 3- to 10-membered heterocyclyl which is optionally substituted by C_{1-4} alkyl;

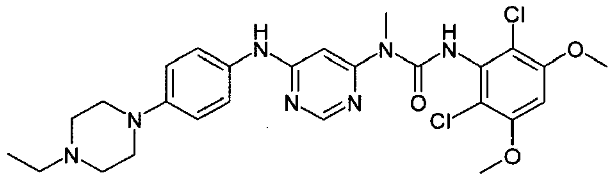
[Compound 2]



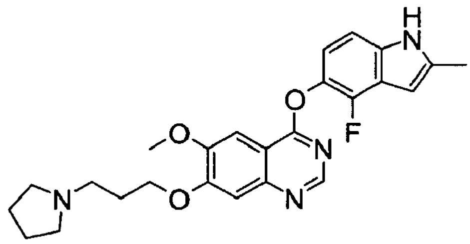
[Compound 3]



[Compound 4]



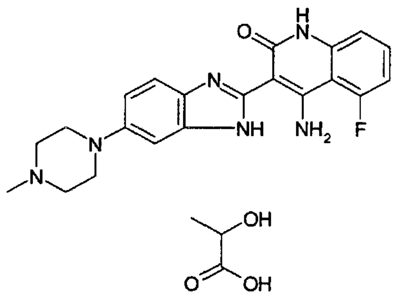
[Compound 5]



,

or

[Compound 6]



;

[2] Another embodiment of the present invention concerns:

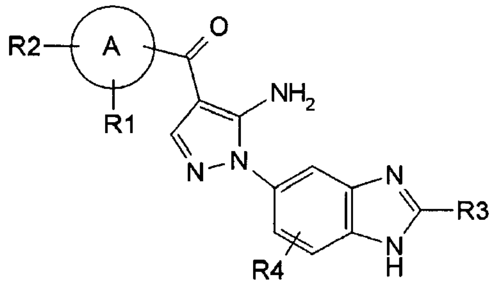
a method for selecting a patient, in particular a patient having bladder cancer, brain tumor, head and neck squamous cell carcinoma, lung cancer, lung adenocarcinoma, lung squamous cell carcinoma, skin melanoma, esophageal cancer, gastric cancer, or liver cancer, to which an anticancer agent comprising a compound having FGFR inhibitory activity or a pharmaceutically acceptable salt thereof is applicable, which comprises the steps of:

(a) determining the presence or absence of a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide or a polynucleotide encoding a fusion polypeptide comprising an FGFR3 polypeptide

and a BAIAP2L1 polypeptide in a sample isolated from a subject,
wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7, and
wherein the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8; and

(b) selecting a patient confirmed to have the fusion polypeptide or the polynucleotide as a patient to which the anticancer agent is applicable,
wherein the compound or a pharmaceutically acceptable salt thereof is capable of inhibiting a growth of a cancer cell expressing the fusion polypeptide or having a nucleotide encoding the fusion polypeptide, in particular wherein said compound or its pharmaceutically acceptable salt is represented by:

[Compound 1]



(I)

wherein R_1, R_2, R_3, and R_4 each independently represents the group listed below:

R_1 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$,$-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

R_2 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$; or

R_1 and R_2, together with an atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein the heterocyclyl or heteroaryl is optionally substituted by halogen;

R_3 represents hydrogen, C_{1-5} alkyl, C_{6-10} aryl C_{1-6} alkyl, or C_{1-4} haloalkyl;

R_4 represents hydrogen, halogen, C_{1-3} alkyl, C_{1-4} haloalkyl, hydroxy, cyano, nitro, C_{1-4} alkoxy, $-(CH_2)_nZ_1$, $-NR_6R_7$, $-OR_5$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $NR_{17}SO_2R_{18}$, COOH, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$,

$-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

A represents a 5- to 10-membered heteroaryl ring or C_{6-10} aryl ring;

R_5 represents C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4}

haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{1-3} alkoxy C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{6-10} aryl, C_{6-10} aryl C_{1-3} alkyl, or 3- to 10-membered heterocyclyl C_{1-3} alkyl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, or C_{1-6} trihydroxy alkyl which is optionally substituted by one or more groups independently selected from group Q;

R_6 and R_7, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl C_{1-3} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, or cyano(C_{1-3} alkyl); or alternatively R_6 and R_7, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

n represents 1 to 3;

R_8 and R_9, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, or halogen; or alternatively R_8 and R_9, together with a carbon atom linked thereto, form a cycloaliphatic ring;

Z_1 represents hydrogen, $NR_{10}R_{11}$, -OH, or 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{10} and R_{11}, which can be the same or different, each represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, cyano(C_{1-3} alkyl), or C_{1-3} alkylsulfonyl C_{1-4} alkyl; or alternatively R_{10} and R_{11}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{12} and R_{13}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3-to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, 3- to 10-membered cycloaliphatic ring, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; or alternatively R_{12} and R_{13}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{14} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{15} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{16} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{17} represents hydrogen or C_{1-4} alkyl;

R_{18} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{19} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, or 5-to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{20} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{21} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{22} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{23} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{24} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{25} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{26} and R_{27}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3-to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively R_{26} and R_{27}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{28} and R_{29}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3-to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively R_{28} and R_{29}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{30} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

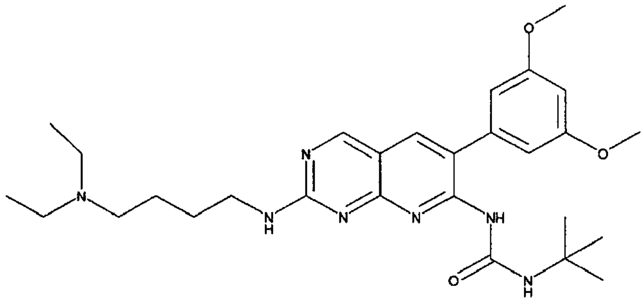
R_{31} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{32} represents C_{1-4} alkyl or C_{6-10} aryl;

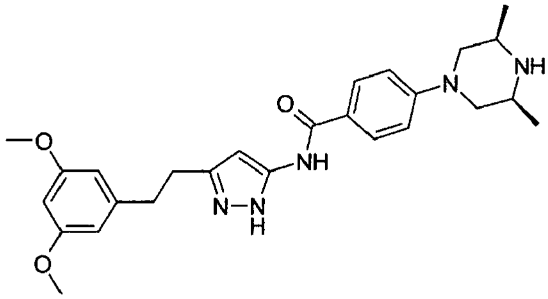
<group P>
halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, 3- to 10-membered heterocyclylamino, $-SO_2R_{16}$, -CN, $-NO_2$, and 3- to 10-membered heterocyclyl;

<group Q>
halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl amine, - SO_2R_{16}, -CN, $-NO_2$, C_{3-7} cycloalkyl, $-COR_{19}$, and 3- to 10-membered heterocyclyl which is optionally substituted by C_{1-4} alkyl.

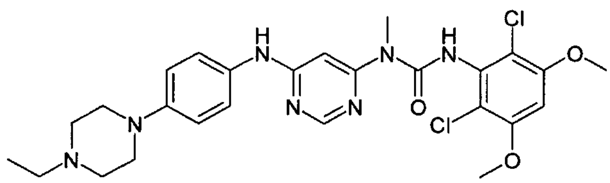
[Compound 2]



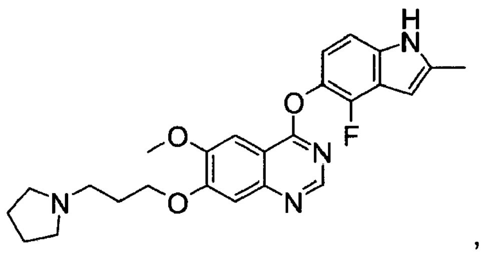
[Compound 3]



[Compound 4]

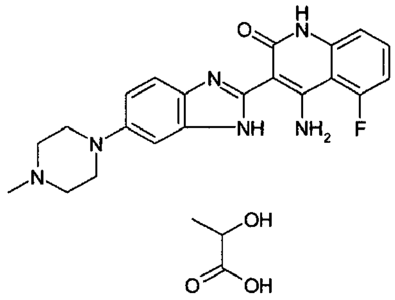


[Compound 5]



or

[Compound 6]



;

[3] A further embodiment of the present invention concerns:

a method for testing cancer susceptibility of a subject, whether a subject is affected with cancer, or whether cancer has progressed in a subject, in particular wherein the cancer is bladder cancer, brain tumor, head and neck squamous cell carcinoma, lung cancer, lung adenocarcinoma, lung squamous cell carcinoma, skin melanoma, esophageal cancer, gastric cancer, or liver cancer, by determining the presence or absence of a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide or determining the presence or absence of a polynucleotide encoding a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide in a sample isolated from the subject,

wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7,

wherein the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8; and

wherein the method is based on the criterion that a subject is more likely to develop cancer, is affected with cancer, or has progressed cancer when the fusion polypeptide or polynucleotide encoding the fusion polypeptide is detected.

[4] An additional embodiment of the present invention concerns:

a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide:

wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7, and

the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8, in particular wherein the fusion polypeptide is derived from bladder cancer or lung cancer, more particularly wherein the fusion polypeptide consists of the amino acid sequence of SEQ ID NO: 32 or 38, and

a polynucleotide encoding said fusion polypeptide, in particular wherein the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 16, more particularly wherein the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 31 or 37, or a vector comprising said polynucleotide, as well as

a recombinant cell comprising said vector.

[5] Finally, the present invention concerns:

A method for detecting

(a) a fusion polypeptide that comprises an FGFR3 polypeptide and a BAIAP2L1 polypeptide, which comprises the step of detecting the fusion polypeptide in a sample isolated from a subject by using an antibody or antigen-binding fragment thereof that binds to the fusion polypeptide of the present invention, or

(b) a polynucleotide encoding a fusion polypeptide that comprises an FGFR3 polypeptide and a BAIAP2L1 polypeptide, which comprises the step of detecting a polynucleotide encoding the fusion polypeptide in a sample isolated from a subject by using a pair of oligonucleotide primers consisting of sense and antisense primers each hybridizing to a polynucleotide encoding the fusion polypeptide of the present invention for detecting or amplifying the polynucleotide.

[Effects of the Invention]

[0018] Fusion polypeptides of the present invention comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide are expressed specifically in various types of cancer cells including bladder cancer cells. The proliferation of cells expressing such fusion polypeptides is significantly inhibited by compounds having FGFR inhibitory activity. Thus, use of a fusion polypeptide of the present invention as a biomarker for FGFR inhibitor-based cancer therapy enables one to assess the applicability and mode of use of an FGFR inhibitor for individual patients, and enables one to avoid side effects and control the mode of treatment to produce the best therapeutic effect in the FGFR inhibitor-based therapy. This enables personalized medicine.

[0019] In addition, the use of fusion polypeptides of the present invention as a target in developing cancer therapeutic agents targeting FGFR, *i.e.,* molecularly targeted drugs, makes it possible to provide FGFR inhibitors with high levels of specificity and antitumor activity against target cancer cells as well as cancer therapeutic agents comprising the inhibitors.

[0020] FGFR inhibitors obtained as described above have high specificity towards target cancer cells, and it becomes possible to provide cancer therapeutic agents with great antitumor activity and few side effects.

[0021] Furthermore, fusion polypeptides of the present invention have a close correlation to various types of cancers, and thus the likelihood of developing cancer (cancer susceptibility) of a subject, whether a subject is affected with cancer, or whether cancer has progressed in a subject can be tested by determining whether samples from the subject, which is not limited to cancer patients but also includes healthy persons, contain the fusion polypeptide of the present invention or a polynucleotide encoding the fusion polypeptide.

[0022] In addition, fusion polypeptides of the present invention have a close correlation to various types of cancers. Thus, by identifying a test compound that suppresses proliferation of cells (such as cancer cells) which express the fusion polypeptides of the present invention, it becomes possible to provide FGFR inhibitors with high FGFR specificity, and this can be done by comparing the level of cell proliferation between in the presence and absence of the test compound.

Brief Description of the Drawings

[0023]

Fig. 1 is a photograph showing results on amplification of a polynucleotide v1 encoding the FGFR3-TACC3 fusion polypeptide, as tested by polymerase chain reaction (PCR) using cDNAs derived from bladder cancer samples collected from bladder cancer patients (20 patients) and cDNAs synthesized from RT112/84 RNA.

Fig. 2 is a photograph showing results on amplification of a polynucleotide v2 encoding the FGFR3-TACC3 fusion polypeptide, as tested by polymerase chain reaction (PCR) using cDNAs derived from bladder cancer samples collected from bladder cancer patients (20 patients) and cDNAs synthesized from RT4 RNA.

Fig. 3 is a photograph showing results on amplification of a polynucleotide encoding the FGFR3-BAIAP2L1 polypeptide, as tested by polymerase chain reaction (PCR) using cDNAs derived from bladder cancer samples collected from bladder cancer patients (20 patients) and cDNAs synthesized from SW780 RNA.

Fig. 4 is a photograph showing results on amplification of a polynucleotide encoding the FGFR3-BAIAP2L1 polypeptide, as tested by polymerase chain reaction (PCR) using cDNAs derived from lung cancer samples collected from lung cancer patients (40 patients) and cDNA synthesized from SW780 RNA.
View A shows a result of the test using a pair of oligonucleotide primers (SEQ ID NOs: 3 and 4).
The leftmost lanes on the top and bottom gels show the results for molecular-weight markers.
View B shows a result of the test using a pair of oligonucleotide primers (SEQ ID NOs: 17 and 18).
The leftmost lanes on the top and bottom gels show the results for molecular-weight markers.

Fig. 5 is a photograph showing results of detecting a polynucleotide encoding a FGFR3-BAIAP2L1 polypeptide in various types of bladder cancer cell lines tested by FISH analysis.

View A1 shows a test result of the RT112/84 cell line using a split-signal probe.
View A2 shows a test result of the SW780 cell line using a split-signal probe.
View B1 shows a test result of the RT112/84 cell line using a fusion-signal probe.
View B2 shows a test result of the SW780 cell line using a fusion-signal probe.

Fig. 6 shows results of testing the presence or absence of FGFR3 dependency in the proliferation of various bladder cancer cell lines using siRNA against FGFR3 or BAIAP2L1.
View A shows a result of the test using the BFTC-905 cell line.
View B shows a result of the test using the UM-UC-14 cell line.
View C shows a result of the test using the RT4 cell line.
View D shows a result of the test using the SW780 cell line.

Fig. 7 shows results of testing the effect of FGFR inhibitors in inducing apoptosis in various cancer cells expressing the FGFR3-BAIAP2L1 fusion polypeptide.

Fig. 8 shows results of examining the ability of the FGFR3-BAIAP2L1 fusion polypeptide to transform normal cells by testing the cells in monolayer culture. The upper figure shows a result of wild-type FGFR3-expressing cells in monolayer culture.
The lower figure shows a result of FGFR3-BAIAP2L1 fusion polypeptide-expressing cells in monolayer culture.

Fig. 9 shows results of examining the transforming ability and tumorigenic ability of the FGFR3-BAIAP2L1 fusion polypeptide in normal cells by testing the cells in spheroid culture.
The upper row photographs show results of culturing the untreated parent cells.
The middle row photographs show results of culturing the wild-type FGFR3-expressing cells.
The lower row photographs show results of culturing the FGFR3-BAIAP2L1 fusion polypeptide-expressing cells.

Fig. 10 presents photographs showing results of examining the ability of the FGFR3-BAIAP2L1 fusion polypeptide to transform normal cells and the contribution of BAIAP2L1 to the transforming ability, by performing tests using the autophosphorylation ability of FGFR3 as an indicator.

Fig. 11 shows a result of examining the ability of the FGFR3-BAIAP2L1 fusion polypeptide to transform normal cells and the contribution of BAIAP2L1 to the transforming ability, by performing tests using scaffold-independent cell proliferation as an indicator.

Fig. 12 shows results of examining the *in vivo* tumorigenic ability of the FGFR3-BAIAP2L1 fusion polypeptide by performing tests using nude mice. In order from the left, the states 15 days after inoculating subcutaneously to the inguinal region of nude mice, wild-type FGFR3-expressing cells, wild-type BAIAP2L1-expressing cells, FGFR3-BAIAP2L1 fusion polypeptide-expressing cells, and cells expressing a fusion polypeptide of FGFR3 and a BAR-domain-deficient BAIAP2L1, respectively, are shown.

Fig. 13 shows a result of examining the tumor-growth-inhibiting effect of the FGFR inhibitor on the *in vivo* tumor formation by a FGFR3-BAIAP2L1 fusion polypeptide by using nude mice for tests.

Mode for Carrying Out the Invention

[0024] The present invention is as illustrated in [1] to [5] described above.

[0025] In the present invention, "FGFR" refers to any FGFR belonging to the FGFR family comprising FGFR1, FGFR2, FGFR3, and FGFR4, which are fibroblast growth factor receptors (FGFRs) belonging to the receptor tyrosine kinase family (Cytokine & Growth Factor Reviews, 2005, 16: 139-149). FGFRs may be of any origin, and are preferably FGFRs derived from mammals (humans, mice, rats, guinea pigs, rabbits, sheep, monkeys, goats, donkeys, bovines, horses, pigs, etc.), more preferably human FGFRs, and still more preferably human FGFR3 comprising the amino acid sequence of SEQ ID NO: 6 or 7 (cDNA sequences, SEQ ID NOs: 10 and 11, respectively / GenBank Accession Nos. NM_001163213.1 and NM_000142.4, respectively). The human FGFR3 gene locus is 4p16.3.

[0026] In the present invention, "human FGFR3" refers to a wild-type human FGFR3 polypeptide comprising the amino acid sequence of SEQ ID NO: 6 or 7. Also described is a mutant polypeptide with a substitution, deletion, or insertion of one or more amino acids (preferably one to ten amino acids, and more preferably one to five amino acids) in the wild-type polypeptide.

[0027] The mutant polypeptide also includes polypeptides having 70% or higher homology, preferably 80% or higher homology, more preferably 90% or higher homology, and still more preferably 95% or higher homology to the amino acid sequence of the wild-type polypeptide.

[0028] In the present invention, "BAIAP2L1" refers to brain-specific angiogenesis inhibitor 1-associated protein 2-like protein 1 (BAIAP2L1; also referred to as "insulin receptor tyrosine kinase substrate" (IRTKS)) (Journal of Cell Science, 2007, 120: 1663-1672). BAIAP2L1 may be of any origin, and is preferably a mammalian BAIAP2L1, more preferably a human BAIAP2L1, and still more preferably a human BAIAP2L1 comprising the amino acid sequence of SEQ ID NO: 8 (cDNA sequence, SEQ ID NO: 12 / GenBank Accession No. NM_018842.4). The human BAIAP2L1 gene locus is 7q22.1, and it is located on a chromosome different from the one that carries the FGFR3 gene.

[0029] In the present invention, "human BAIAP2L1" refers to a wild-type human BAIAP2L1 polypeptide comprising the amino acid sequence of SEQ ID NO: 8. Also described is a mutant polypeptide with a substitution, deletion, or insertion of one or more amino acids (preferably one to ten amino acids, and more preferably one to five amino acids) in the wild-type polypeptide.

[0030] The mutant polypeptide also includes polypeptides having 70% or higher homology, preferably 80% or higher homology, more preferably 90% or higher homology, and still more preferably 95% or higher homology to the amino acid sequence of the wild-type polypeptide.

[0031] Also described is "TACC3" which refers to transforming acidic coiled-coil protein 3 (TACC3) (Genomics. 1999 Jun 1; 58(2): 165-70). TACC3 is preferably a mammalian TACC3, more preferably a human TACC3, and still more preferably a human TACC3 comprising the amino acid sequence of SEQ ID NO: 9 (cDNA sequence, SEQ ID NO: 13 / GenBank Accession No. NM_006342.2). The human TACC3 gene locus is 4p16.3, and it is located upstream of the FGFR3 gene on the same chromosome.

[0032] Generally, "human TACC3" refers to a wild-type human TACC3 polypeptide comprising the amino acid sequence of SEQ ID NO: 9, or a mutant polypeptide with a substitution, deletion, or insertion of one or more amino acids (preferably one to ten amino acids, and more preferably one to five amino acids) in the wild-type polypeptide.

[0033] The mutant polypeptide also includes polypeptides having 70% or higher homology, preferably 80% or higher homology, more preferably 90% or higher homology, and still more preferably 95% or higher homology to the amino acid sequence of the wild-type polypeptide.

[0034] Amino acid sequence (or nucleotide sequence) identity can be determined using the BLAST algorithm by Karlin and Altschul (Proc. Natl. Acad. Sci. USA (1993) 90, 5873-7). Programs such as BLASTN and BLASTX were developed based on this algorithm (Altschul et al., J. Mol. Biol. (1990) 215, 403-10). To analyze nucleotide sequences according to BLASTN based on BLAST, the parameters are set to, for example, score = 100 and wordlength = 12. On the other hand, parameters used for the analysis of amino acid sequences by BLASTX based on BLAST include, for example, score = 50 and wordlength = 3. Default parameters for each program are used when using the BLAST and Gapped BLAST programs. Specific techniques for such analyses are known in the art (one can refer to the information on the website of the National Center for Biotechnology Information (NCBI), Basic Local Alignment Search Tool (BLAST)).

[0035] In the present invention, "fusion polypeptide" refers to a polypeptide in which the whole or a part of the wild-type or mutant FGFR3 polypeptide described above is fused to the whole or a part of the wild-type BAIA2P2L1 described above.

[0036] Furthermore, the fusion polypeptides of the present invention include fusion polypeptides in which the fusion site formed between the whole or a part of each of the two types of polypeptides comprises an amino acid sequence encoded by a portion of the intron sequence in the genomic DNA (including exons and introns) encoding the wild-type FGFR3 polypeptide or a mutant FGFR3 polypeptide.

[0037] Examples of such fusion polypeptides include polypeptides comprising the amino acid sequences of SEQ ID NOs: 30 and 36. The amino acid sequence of positions 761 to 793 and the amino acid sequence of positions 759 to 791 are encoded by portions of the intron sequence of the FGFR3 gene, respectively (the nucleotide sequence of positions 2,281 to 2,379 in SEQ ID NO: 29, and the nucleotide sequence of positions 2,275 to 2,373 in SEQ ID NO: 35, respectively).

[0038] Herein, "a part of a polypeptide" refers to a polypeptide consisting of an arbitrary partial sequence from the full-length amino acid sequence of a wild-type or mutant polypeptide.

[0039] Examples of specific embodiments include a fusion polypeptide of FGFR3 and BAIAP2L1 comprising the amino acid sequence of SEQ ID NO: 32, and a fusion polypeptide of FGFR3 and BAIAP2L1 comprising the amino acid sequence of SEQ ID NO: 38. Also described is a fusion polypeptide of FGFR3 and TACC3 comprising the amino acid sequence of SEQ ID NO: 28, a fusion polypeptide of FGFR3 and TACC3 comprising the amino acid sequence of SEQ ID NO: 30, a fusion polypeptide of FGFR3 and TACC3 comprising the amino acid sequence of SEQ ID NO: 34, and a fusion polypeptide of FGFR3 and TACC3 comprising the amino acid sequence of SEQ ID NO: 36.

[0040] As described above, the fusion polypeptides comprising the amino acid sequences of SEQ ID NOs: 30 and 36 comprise in their fusion site an amino acid sequence encoded by a portion of the FGFR3 gene intron sequence.

[0041] Polynucleotides of the present invention include polynucleotides encoding a fusion polypeptide of the present invention described above, which include any polynucleotides that can encode a fusion polypeptide of the present invention. The polynucleotides include genomic DNAs and cDNAs. Genomic DNAs include exons and introns. Furthermore, the cDNAs may include nucleic acid sequences derived from a portion of an intron sequence that encodes amino acid sequence.

[0042] The polynucleotides also include degenerate polynucleotides constituted with any codons as long as the codons encode the same amino acids.

[0043] The polynucleotides of the present invention also include polynucleotides encoding fusion polypeptides derived from mammals. In a preferred embodiment, the polynucleotides of the present invention include polynucleotides encoding fusion polypeptides derived from humans.

[0044] In a specific embodiment, the polynucleotides of the present invention are polynucleotides encoding a fusion polypeptide in which the whole or a part of the wild-type FGFR3 polypeptide (SEQ ID NO: 6 or 7) is fused to the whole or a part of the wild-type BAIA2P2L1 polypeptide (SEQ ID NO: 8) described above. Also described is a fusion polypeptide in which the whole or a part of the wild-type FGFR3 polypeptide (SEQ ID NO: 6 or 7)-is fused to the whole or a part of the wild-type TACC3 polypeptide (SEQ ID NO: 9) described above.

[0045] Examples of more specific embodiments include a polynucleotide comprising a nucleotide sequence corresponding to the junction site of two polypeptides in the fusion polypeptide of SEQ ID NOs: 14, 15, or 16.

[0046] Examples of even more specific embodiments include a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 31 which encodes the fusion polypeptide of FGFR3 and BAIAP2L1 comprising the amino acid sequence of SEQ ID NO: 32, and a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 37 which encodes the fusion polypeptide of FGFR3 and BAIAP2L1 comprising the amino acid sequence of SEQ ID NO: 38. Also described is a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 27 which encodes the fusion polypeptide of FGFR3 and TACC3 comprising the amino acid sequence of SEQ ID NO: 28, a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 29 which encodes the fusion polypeptide of FGFR3 and TACC3 comprising the amino acid sequence of SEQ ID NO: 30, a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 33 which encodes the fusion polypeptide of FGFR3 and TACC3 comprising the amino acid sequence of SEQ ID NO: 34, a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 35 which encodes the fusion polypeptide of FGFR3 and TACC3 comprising the amino acid sequence of SEQ ID NO: 36.

[0047] As described above, the nucleotide sequence at positions 2,281 to 2,379 of SEQ ID NO: 29 is a nucleic acid sequence derived from an FGFR3 gene intron, and encodes the amino acid sequence of positions 761 to 793 in the polypeptide comprising the amino acid sequence of SEQ ID NO: 30.

[0048] Similarly, the nucleotide sequence at positions 2,275 to 2,373 of SEQ ID NO: 35 is a nucleic acid sequence derived from an FGFR3 gene intron, and encodes the amino acid sequence of positions 759 to 791 in the polypeptide comprising the amino acid sequence of SEQ ID NO: 36.

[0049] The polynucleotides of the present invention may be obtained by any methods. The polynucleotides of the present invention include, for example, all complementary DNAs (cDNAs) prepared from mRNAs, DNAs prepared from genomic DNA, DNAs obtained by chemical synthesis, DNAs obtained by PCR amplification using RNA or DNA as template, and DNAs constructed by appropriately combining these methods.

[0050] Polynucleotides encoding fusion polypeptides of the present invention can be obtained using routine methods by cloning cDNA from mRNA encoding a fusion polypeptide of the present invention or isolating genomic DNA and subjecting it to splicing treatment, or by chemical synthesis.

[0051] For example, in a method that clones cDNA from mRNA encoding a fusion polypeptide of the present invention, first, mRNA encoding a fusion polypeptide of the present invention is prepared from arbitrary tissues or cells expressing and producing the fusion polypeptide of the present invention according to routine methods. This may be achieved, for example, by preparing total RNA using a method such as the guanidine-thiocyanate method, hot phenol method, or AGPC method, and treating the total RNA with affinity chromatography using oligo(dT) cellulose, poly U-Sepharose, or the like.

[0052] Then, cDNA strand synthesis is carried out using the prepared mRNA as template by a known method that uses, for example, reverse transcriptase (Mol. Cell. Biol., Vol.2, p.161, 1982; Mol. Cell. Biol., Vol.3, p.280, 1983; Gene, Vol.25, p.263, 1983). The cDNA is converted to double-stranded cDNA, and inserted into a plasmid vector, phage vector, cosmid vector, or such. To prepare a cDNA library, the resulting vector is transformed into *E. coli,* or transfected into *E. coli* after *in vitro* packaging.

[0053] The present invention also relates to vectors (recombinant vectors) carrying the above-described polynucleotide encoding a fusion polypeptide of the present invention.

[0054] The vectors of the present invention are not particularly limited as long as they can replicate and maintain or self-propagate in various prokaryotic and/or eukaryotic cells as a host. The vectors of the present invention include plasmid vectors and phage vectors.

[0055] Cloning vectors include, for example, pUC19, λgt10, and λgt11. When isolating host cells capable of expressing a fusion polypeptide of the present invention, preferably the vector is one that has a promoter which enables expression of the polynucleotide of the present invention.

[0056] Recombinant vectors of the present invention can be prepared using routine methods simply by ligating a polynucleotide encoding a fusion polypeptide of the present invention to a recombinant vector available in the art (plasmid DNA and bacteriophage DNA).

[0057] Recombinant vectors for use in the present invention include, for example, *E. coli*-derived plasmids (pBR322, pBR325, pUC12, pUC13, pUC19, etc.), yeast-derived plasmids (pSH19, pSH15, etc.), and *Bacillus subtilis*-derived plasmids (pUB110, pTP5, pC194, etc.).

[0058] Examples of phages are bacteriophages such as λ phage, and animal or insect viruses (pVL1393, Invitrogen) such as retrovirus, vaccinia virus, nuclear polyhedrosis virus, and lentivirus.

[0059] Expression vectors are useful for the purpose of producing a fusion polypeptide of the present invention by expressing a polynucleotide encoding the fusion polypeptide of the present invention. Expression vectors are not particular limited as long as they have the function of producing fusion polypeptides of the present invention by expressing polynucleotides encoding the polypeptides in various prokaryotic and/or eukaryotic cells as a host.

[0060] Such expression vectors include, for example, pMAL C2, pEF-BOS (Nucleic Acid Research, Vol.18, 1990, p. 5322) and pME18S (Jikken Igaku Bessatsu (Experimental Medicine: SUPPLEMENT), "Idenshi Kougaku Handbook (Handbook of Genetic Engineering)" (1992)).

[0061] Alternatively, fusion polypeptides of the present invention may be produced as fusion proteins with other proteins. For example, when preparing as a fusion protein with glutathione S-transferase (GST), cDNA encoding a fusion polypeptide of the present invention can be subcloned into, for example, plasmid pGEX4T1 (Pharmacia). *E. coli* DH5α is transformed with the resulting plasmid, and the transformants are cultured to prepare the fusion protein.

[0062] Alternatively, fusion polypeptides of the present invention may be produced as fusions with influenza hemagglutinin (HA), immunoglobulin constant region, β-galactosidase, maltose-binding protein (MBP), or such. Furthermore, fusion polypeptides of the present invention may be produced as fusions with known peptides, for example, FLAG (Hopp, T. P. et al., BioTechnology (1988) 6, 1204-1210), 6x His consisting of 6 histidine (His) residues, 10x His, influenza hemagglutinin (HA), fragments of human c-myc, fragments of VSV-GP, fragments of p18HIV, T7-tag, HSV-tag, E-tag, fragments of SV40T antigen, lck tag, fragments of α-tubulin, B-tag, fragments of Protein C, Stag, StrepTag, and HaloTag.

[0063] When using bacteria, in particular *E. coli,* as a host cell, vectors of the present invention preferably contain at least a promoter-operator region, a start codon, a polynucleotide encoding a fusion polypeptide of the present invention, a stop codon, a terminator region, and a replicon.

[0064] When yeast, animal cells, or insect cells are used as a host, expression vectors preferably contain a promoter, a start codon, a polynucleotide encoding a fusion polypeptide of the present invention, and a stop codon.

[0065] The vectors may also contain DNA encoding a signal peptide, an enhancer sequence, 5' and 3' untranslated regions of the gene encoding a protein of the present invention, splice junctions, polyadenylation sites, a selection marker region, a replicon, and such.

[0066] Furthermore, if necessary, the vectors may contain marker genes (genes for gene amplification, drug resistance genes, etc.) that enable selection of transformed hosts or hosts with gene amplification.

[0067] Marker genes include, for example, the dihydrofolate reductase (DHFR) gene, thymidine kinase gene, neomycin resistance gene, glutamate synthase gene, adenosine deaminase gene, ornithine decarboxylase gene, hygromycin-B-phosphotransferase gene, and aspartate transcarbamylase gene.

[0068] A promoter-operator region for expressing the fusion polypeptide of the present invention in bacteria comprises a promoter, an operator, and a Shine-Dalgarno (SD) sequence (for example, AAGG).

[0069] For example, when the host is the genus *Escherichia,* it comprises, for example, the Trp promoter, lac promoter, recA promoter, λPL promoter, lpp promoter, tac promoter, or such.

[0070] Examples of a promoter for expressing the fusion polypeptide of the present invention in yeast are the PH05 promoter, PGK promoter, GAP promoter, ADH promoter, and such.

[0071] When the host is *Bacillus,* examples are the SL01 promoter, SP02 promoter, penP promoter, and such.

[0072] When the host is a eukaryotic cell such as a mammalian cell, examples are an SV40-derived promoter, retrovirus promoter, heat shock promoter, and such; and SV40 and retrovirus are preferred. Nevertheless, the promoter is not limited to the above examples. In addition, use of an enhancer is effective for expression.

[0073] A preferable initiation codon is, for example, a methionine codon (ATG). A commonly used termination codon (for example, TAG, TAA, TGA) is exemplified as a termination codon. Commonly used natural or synthetic terminators are used as a terminator region.

[0074] A replicon refers to a DNA capable of replicating the whole DNA sequence in host cells, and includes a natural plasmid, an artificially modified plasmid (DNA fragment prepared from a natural plasmid), a synthetic plasmid, and such. Examples of preferable plasmids for *E. coli* are pBR322 or its artificial derivatives (DNA fragment obtained by treating pBR322 with appropriate restriction enzymes), for yeast are yeast 2 μ plasmid or yeast chromosomal DNA, and pRSVneo ATCC 37198, and for mammalian cells are plasmid pSV2dhfr ATCC 37145, plasmid pdBPV-MMTneo ATCC 37224, plasmid pSV2neo ATCC 37149, and such.

[0075] An enhancer sequence, polyadenylation site, and splicing junction that are usually used in the art, such as those derived from SV40 can also be used.

[0076] The expression vector of the present invention can be prepared by continuously and circularly linking at least the above-mentioned promoter, initiation codon, polynucleotide encoding the fusion polypeptide of the present invention, termination codon, and terminator region, to an appropriate replicon. If desired, appropriate DNA fragments (for example, linkers, restriction sites, and such), can be used by a common method such as restriction enzyme digestion or ligation using T4 DNA ligase.

[0077] The present invention also relates to recombinant cells transformed with the above-mentioned vectors of the present invention, and recombinant cells of the present invention can be prepared by introducing the expression vector mentioned above into host cells.

[0078] Host cells used in the present invention are not particularly limited as long as they are compatible with an expression vector mentioned above and can be transformed. Examples thereof include various cells such as wild-type cells or artificially established recombinant cells commonly used in the technical field of the present invention (for example, bacteria (the genera *Escherichia* and *Bacillus*), yeast (the genus *Saccharomyces,* the genus *Pichia,* and such), animal cells, or insect cells).

[0079] *E. coli* or animal cells are preferred. Specific examples are *E. coli* (DH5α, TB1, HB101, and such), mouse-derived cells (COP, L, C127, Sp2/0, NS-1, NIH3T3, and such), rat-derived cells (PC12, PC12h), hamster-derived cells (BHK, CHO, and such), monkey-derived cells (COS1, COS3, COS7, CV1, Velo, and such), and human-derived cells (Hela, diploid fibroblast-derived cells, myeloma cells, and HepG2, and such).

[0080] An expression vector can be introduced (transformed (transfected)) into host cells according to routine methods

[when the host is E. coli, Bacillus subtilis, or such]: Proc. Natl. Acad. Sci. USA, Vol.69, p.2110 (1972); Mol. Gen. Genet., Vol.168, p.111 (1979); J. Mol. Biol., Vol.56, p.209 (1971);
[when the host is Saccharomyces cerevisiae]: Proc. Natl. Acad. Sci. USA, Vol.75, p.1927 (1978); J. Bacteriol., Vol.153, p.163 (1983);
[when the host is an animal cell]: Virology, Vol.52, p.456 (1973);
[when the host is an insect cell]: Mol. Cell. Biol., Vol.3, pp.2156-2165 (1983).

[0081] Fusion polypeptides of the present invention can be produced by culturing transformed recombinant cells (hereinafter, the term also refers to inclusion bodies) comprising an expression vector prepared as described above in nutritive media according to routine methods.

[0082] Fusion polypeptides of the present invention can be produced by culturing the above-described recombinant cells, in particular animal cells, and allowing them to secrete into culture supernatants.

[0083] The resulting culture is filtered or centrifuged to obtain a culture filtrate (supernatant). Fusion polypeptides of the present invention are purified and isolated from the culture filtrate by routine methods commonly used to purify and isolate natural or synthetic proteins. Examples of an isolation and purification method are methods that utilize solubility such as the salting out and solvent precipitation methods; methods that utilize difference in molecular weight such as dialysis, ultrafiltration, gel filtration, and sodium dodecyl sulfate-polyacrylamide gel electrophoresis; methods that utilize charge such as ion exchange chromatography and hydroxylapatite chromatography; method that utilize specific affinity such as affinity column chromatography; methods that utilize difference in hydrophobicity such as reverse phase high performance liquid chromatography; and methods that utilize difference in the isoelectric point such as isoelectric focusing.

[0084] Meanwhile, when a fusion polypeptide of the present invention is in the periplasm or cytoplasm of cultured recombinant cells (such as *E. coli*), the cells are collected by routine methods such as filtration and centrifugation of the culture, and then suspended in an appropriate buffer. After the cell wall and/or cell membrane of the cells are disrupted using methods such as sonication, lysozyme, and cryolysis, a membrane fraction containing the protein of the present invention is obtained using methods such as centrifugation and filtration. The membrane fraction is solubilized with a detergent such as Triton-X100 to obtain the crude solution. Then, the protein of the present invention can be isolated and purified from the crude solution using routine methods such as those exemplified above.

[0085] The present disclosure also relates to arbitrary oligonucleotides that hybridize to polynucleotides (cDNAs and genomic DNAs) encoding the above-described fusion polypeptides of the present invention.

[0086] Oligonucleotides have nucleotide sequences that are complementary to arbitrary partial nucleotide sequences of the cDNAs and genomic DNAs, and which are useful as a pair of oligonucleotide primers consisting of sense and antisense primers in polymerase chain reaction (PCR). The whole nucleotide sequence of a polynucleotide encoding a fusion polypeptide of the present invention or an arbitrary portion of the nucleotide sequence can be amplified by PCR using the pair of oligonucleotide primers.

[0087] Oligonucleotide primers include oligonucleotides of any length that are complementary to the nucleotide sequence of a polynucleotide of the present invention. The oligonucleotide primers preferably include those having a sequence of at least 12 consecutive nucleotides, more preferably 12 to 50 nucleotides, and still more preferably 12 to

20 nucleotides.

[0088] Oligonucleotides are also useful as a probe when handling DNA or RNA hybridization. When used as a probe, the DNAs include a partial nucleotide sequence of 20 or more consecutive nucleotides, preferably a partial nucleotide sequence of 50 or more consecutive nucleotides, more preferably a partial nucleotide sequence of 100 or more consecutive nucleotides, even more preferably a partial nucleotide sequence of 200 or more consecutive nucleotides, and still more preferably a partial nucleotide sequence of 300 or more consecutive nucleotides, which hybridize to a polynucleotide of the present invention.

[0089] The present description also relates to oligonucleotides that bind to mRNA polynucleotides encoding fusion polypeptides of the present invention and have an activity of inhibiting translation of the mRNAs into proteins. It is particularly preferable that the oligonucleotides include siRNAs that cleave the mRNAs by binding to the mRNA polynucleotides encoding fusion polypeptides of the present invention.

[0090] The oligonucleotides refer to those which bind to mRNAs encoding fusion polypeptides of the present invention and thereby inhibit their expression and include, for example, antisense oligonucleotides, ribozymes, and short interfering RNAs (siRNA). They bind to the mRNAs and then inhibit their translation into proteins.

[0091] An antisense oligonucleotide refers to an oligonucleotide that specifically hybridizes to genomic DNA and/or mRNA, and inhibits their protein expression by inhibiting the transcription and/or translation.

[0092] The binding to a target polynucleotide (mRNA, etc.) may be a result of common base pair complementarity. Alternatively, when an antisense oligonucleotide binds to, for example, a DNA duplex, the binding may be a result of specific interaction at the major grooves in double helix. Target sites for an antisense oligonucleotide include the 5' end of an mRNA, for example, 5' untranslated sequences up to or including the AUG start codon, and 3' untranslated sequences of an mRNA, as well as coding region sequences.

[0093] When using as an antisense oligonucleotide, antisense oligonucleotides include partial nucleotide sequences of 5 to 100 consecutive nucleotides, preferably partial nucleotide sequences of 5 to 70 consecutive nucleotides, more preferably partial nucleotide sequences of 5 to 50 consecutive nucleotides, and still more preferably partial nucleotide sequences of 5 to 30 consecutive nucleotides.

[0094] Furthermore, antisense oligonucleotides can be partially modified by chemical modification to prolong their half-life in blood (to stabilize them) or increase their intracellular membrane permeability when administered to patients, or to enhance their resistance to degradation or absorption in the digestive organs in oral administration. Such chemical modification includes, for example, chemical modification of a phosphate bond, ribose, nucleobase, sugar moiety in oligonucleotides, and 3' and/or 5' ends of oligonucleotides.

[0095] The modification of phosphate bonds includes, for example, conversion of one or more of the bonds to phosphodiester bonds (D-oligo), phosphorothioate bonds, phosphorodithioate bonds (S-oligo), methyl phosphonate (MP-oligo), phosphoroamidate bonds, non-phosphate bonds and methyl phosphonothioate bonds, and combinations thereof. The modification of ribose includes, for example, conversion to 2'-fluororibose or 2'-O-methylribose. The modification of nucleotide base includes, for example, conversion to 5-propynyluracil or 2-aminoadenine.

[0096] Ribozyme refers to oligonucleotides having a catalytic activity of cleaving mRNA. In general, ribozymes have endonuclease, ligase, or polymerase activity. Ribozymes include various types of trans-acting ribozymes, for example, hammerhead ribozymes and hairpin ribozymes.

[0097] siRNA refers to double-stranded oligonucleotides capable of carrying out RNA interference (for example, Bass, 2001, Nature, 411, 428-429; Elbashir et al., 2001, Nature, 411, 494-498).

[0098] siRNA cleaves mRNA in a sequence-specific manner, and as a result inhibits translation of the mRNA into protein. siRNA includes double-stranded RNAs that are 20 to 25 base pairs long and comprise a sequence complementary to the target polynucleotide sequence. siRNAs also include oligonucleotides comprising chemically modified nucleotides and non-nucleotides.

[0099] The present description also relates to antibodies which bind to the above-described fusion polypeptide of the present invention, and antigen-binding fragments thereof.

[0100] Antibodies are not limited by their origin, form, function, etc. Antibodies may be any antibodies, monoclonal or polyclonal antibodies. However, preferred antibodies are monoclonal antibodies. Antibodies may be those derived from any animal, such as human antibodies, mouse antibodies, and rat antibodies. Antibodies may also be recombinant antibodies such as chimeric antibodies and humanized antibodies. Preferred antibodies include chimeric antibodies, human antibodies, and humanized antibodies.

[0101] The humanized antibodies can be prepared by methods known to those skilled in the art. The variable region of an antibody is typically composed of three complementarity-determining regions (CDRs) sandwiched by four frames (FRs). The CDRs practically determine the binding specificity of an antibody. The amino acid sequences of CDRs are highly diverse. On the other hand, amino acid sequences that constitute FRs often exhibit high homology among antibodies having different binding specificities. Therefore, it is said that in general the binding specificity of an antibody can be transplanted to a different antibody by grafting the CDRs.

[0102] Humanized antibodies are also referred to as reshaped human antibodies, and they are prepared by transferring the CDRs of an antibody derived from a non-human mammal such as a mouse, to the complementarity determining regions of a human antibody. General genetic recombination techniques for their preparation are also known (see European Patent Application Publication No. 125023 and WO 96/02576).

[0103] Specifically, for example, when the CDRs are derived from a mouse antibody, a DNA sequence is designed such that the CDRs of the mouse antibody are linked with the framework regions (FRs) of a human antibody, and it is synthesized by PCR using, as primers, several oligonucleotides that have portions overlapping the ends of both CDRs and FRs (see the method described in WO 98/13388). The resulting DNA is then ligated to a DNA encoding a human antibody constant region, inserted into an expression vector, and introduced into a host to produce the antibody (see European Patent Application Publication No. EP 239400 and International Patent Application Publication No. WO 96/02576).

[0104] Human antibody framework regions to be linked with CDRs are selected so that the complementarity determining regions form a favorable antigen-binding site. If needed, amino acids of the framework region in an antibody variable region may be substituted, deleted, added, and/or inserted so that the complementarity determining regions of the reshaped human antibody form a proper antigen-binding site. For example, mutations can be introduced into the amino acid sequence of the FR by applying the PCR method used to graft mouse CDRs to human FRs. Specifically, mutations can be introduced into a portion of the nucleotide sequences of primers that anneal to the FRs. The mutations are introduced into FRs synthesized using such primers. Mutant FR sequences having desired properties can be selected by assessing and determining the antigen-binding activity of amino acid-substituted mutant antibodies by the method described above and (Sato, K. et al., Cancer Res. (1993) 53, 851-856).

[0105] In general, constant regions from human antibodies are used for those of humanized antibodies.

[0106] There are no particular limitations to the human antibody constant regions to be used in the present invention; and for example, when using a heavy-chain constant region, it may be a human IgG1 constant region, human IgG2 constant region, human IgG3 constant region, human IgG4 constant region, or human IgM, IgA, IgE, or IgD constant region. Alternatively, when using a light-chain constant region, it may be a human κ chain constant region or human λ chain constant region. Furthermore, constant regions derived from a human antibody may have a naturally-occurring sequence or may be a constant region having a sequence with modification (substitution, deletion, addition, and/or insertion) of one or more amino acids in the naturally-occurring sequence.

[0107] Moreover, after a humanized antibody is prepared, amino acids in the variable region (for example, CDR and FR) and constant region of the humanized antibody may be deleted, added, inserted, and/or substituted with other amino acids. The humanized antibodies also include such humanized antibodies with amino acid substitutions and such.

[0108] The origin of the CDRs of a humanized antibody is not particularly limited, and may be any animal. For example, it is possible to use sequences of mouse antibodies, rat antibodies, rabbit antibodies, camel antibodies, and such. CDR sequences of mouse antibodies are preferred.

[0109] When administered to humans for therapeutic purposes, humanized antibodies are useful because their immunogenicity in the human body is reduced.

[0110] Chimeric antibodies comprise, for example, heavy and light chain constant regions of a human antibody, and heavy and light chain variable regions of an antibody of a non-human mammal, such as mouse. Chimeric antibodies can be prepared using known methods. For example, antibodies can be produced by cloning an antibody gene from hybridomas, inserting it into an appropriate vector, and introducing the construct into hosts (see, for example, Carl, A. K. Borrebaeck, James, W. Larrick, THERAPEUTIC MONOCLONAL ANTIBODIES, Published in the United Kingdom by MACMILLAN PUBLISHERS LTD, 1990). Specifically, cDNAs of the antibody variable regions (V regions) are synthesized from the hybridoma mRNAs using reverse transcriptase. Once DNAs encoding the V regions of an antibody of interest are obtained, they are linked with DNAs encoding the constant regions (C regions) of a desired human antibody. The resulting constructs are inserted into expression vectors. Alternatively, DNAs encoding the antibody V regions may be inserted into an expression vector comprising DNAs encoding the C regions of a human antibody. The DNAs are inserted into an expression vector so that they are expressed under the regulation of expression regulatory regions, for example, enhancers and promoters. In the next step, host cells can be transformed with the expression vector to allow expression of chimeric antibodies.

[0111] Human antibodies can be obtained using methods known to those skilled in the art. For example, desired human antibodies with antigen-binding activity can be obtained by sensitizing human lymphocytes with an antigen of interest or cells expressing an antigen of interest *in vitro*; and fusing the sensitized lymphocytes with human myeloma cells such as U266 (see Japanese Patent Application Kokoku Publication No. (JP-B) H01-59878 (examined, approved Japanese patent application published for opposition)). Alternatively, the desired human antibody can also be obtained by immunizing a transgenic animal having an entire repertoire of human antibody genes with a desired antigen (see International Patent Application Publication Nos. WO 93/12227, WO 92/03918, WO 94/02602, WO 94/25585, WO 96/34096, and WO 96/33735).

[0112] Alternatively, B cells expressing antibodies that have antigen-binding activity are isolated from a pool of human lymphocytes by flow cytometry, cell array, or such. The antibody genes from selected B cells can be analyzed, and DNA sequences of the human antibodies that bind to the antigen can be determined (Jin, A. et al., Nature Medicine (2009) 15, 1088-92; Scheid, J.F. et al., Nature (2009) 458, 636-640; Wrammert, J. et al., Nature (2008) 453, 667-672; Tiller, T. et al., Journal of Immunological Methods (2008) 329, 112-124). When DNA sequences of the antigen-binding antibodies are revealed, human antibodies can be prepared by constructing appropriate expression vectors carrying the sequences. Such methods are known, and WO 92/01047, WO 92/20791, WO 93/06213, WO 93/11236, WO 93/19172, WO 95/01438, and WO 95/15388 can be used as references.

[0113] Furthermore, techniques for obtaining human antibodies by panning with a human antibody phage library are known. For example, the variable region of a human antibody is expressed as a single chain antibody (scFv) on the phage surface using a phage display method, and phages that bind to the antigen can be selected. By analyzing the genes of selected phages, DNA sequences encoding the variable regions of human antibodies that bind to the antigen can be determined. If the DNA sequences of scFvs that bind to the antigen are identified, appropriate expression vectors comprising these sequences can be constructed to obtain human antibodies. Such methods are well known. Reference can be made to WO 92/01047, WO 92/20791, WO 93/06213, WO 93/11236, WO 93/19172, WO 95/01438, WO 95/15388, and such.

[0114] The antibodies include not only divalent antibodies as represented by IgG, but also monovalent antibodies, multivalent antibodies as represented by IgM. In addition, the antibodies also include bispecific antibodies capable of binding to different antigens.

[0115] Antibodies include not only whole antibody molecules but also any antigen-binding fragments such as low-molecular-weight antibodies.

[0116] Antibodies also include modified antibodies that are linked to cytotoxic substances. Antibodies also include those with altered sugar chains.

[0117] Low-molecular-weight antibodies (minibodies) included in antigen-binding fragments are antibodies comprising an antibody fragment that lacks part of a whole antibody (for example, whole IgG, etc.). The minibodies are not particularly limited, as long as they have the activity to bind to a fusion polypeptide of the present invention.

[0118] Minibodies are not particularly limited, as long as they comprise a portion of a whole antibody. It is however preferable that the minibodies comprise an antigen-binding domain. In general, the antigen-binding domain is antibody CDR, and is preferably six CDRs of an antibody. Thus, the preferred antigen-binding domains include, for example, six CDRs of an antibody and antibody variable regions (heavy chain and/or light chain variable regions).

[0119] The minibodies preferably have a smaller molecular weight than whole antibodies. However, the minibodies may form multimers, for example, dimers, trimers, or tetramers, and thus their molecular weights can be greater than those of whole antibodies.

[0120] Other specific examples of the antigen-binding molecule fragments include, for example, Fab, Fab', F(ab')2, and Fv. Meanwhile, specific examples of low-molecular-weight antibodies include, for example, Fab, Fab', F(ab')2, Fv, scFv (single chain Fv), diabodies, and sc(Fv)2 (single chain (Fv)2). Multimers (for example, dimers, trimers, tetramers, and polymers) of these antibodies are also included in the low-molecular-weight antibodies.

[0121] Antigen-binding fragments can be obtained, for example, by treating antibodies with enzymes to produce antibody fragments. Enzymes known to generate antibody fragments include, for example, papain, pepsin, and plasmin. Alternatively, a gene encoding such an antibody fragment can be constructed, introduced into an expression vector, and expressed in appropriate host cells (see, for example, Co, M.S. et al., J. Immunol. (1994) 152, 2968-2976; Better, M. & Horwitz, A. H. Methods in Enzymology (1989) 178, 476-496; Plueckthun, A. & Skerra, A. Methods in Enzymology (1989) 178, 476-496; Lamoyi, E., Methods in Enzymology (1989) 121, 652-663; Rousseaux, J. et al., Methods in Enzymology(1989) 121, 663-669; Bird, R. E. et al., TIBTECH (1991) 9, 132-137).

[0122] Digestive enzymes cleave at a specific site in an antibody fragment, yielding antibody fragments of specific structures shown below. Genetic engineering techniques can be applied to such enzymatically-obtained antibody fragments to delete an arbitrary portion of the antibody.

[0123] Antibody fragments obtained by using the above-described digestive enzymes are as follows:

Papain digestion: F(ab)2 or Fab

Pepsin digestion: F(ab')2 or Fab'

Plasmin digestion: Facb

[0124] The minibodies include antibody fragments lacking an arbitrary region, as long as they have the activity to bind to a fusion polypeptide.

[0125] "Diabody" refers to a bivalent antibody fragment constructed by gene fusion (Holliger P et al., Proc. Natl. Acad. Sci. USA 90: 6444-6448 (1993); EP 404,097; WO 93/11161, etc.). Diabodies are dimers composed of two polypeptide chains. In each of the polypeptide chains forming a dimer, a VL and a VH are usually linked by a linker in the same chain. In general, the linker in a diabody is short enough such that the VL and VH cannot bind to each other. Specifically, the number of amino acid residues constituting the linker is, for example, about five residues. Thus, the VL and VH encoded on the same polypeptide cannot form a single-chain variable region fragment, and will form a dimer with another single-chain variable region fragment. As a result, the diabody has two antigen binding sites.

[0126] scFv antibodies are single-chain polypeptides produced by linking a heavy chain variable region ([VH]) to a light chain variable region ([VL]) *via* a linker or such (Huston, J. S. et al., Proc. Natl. Acad. Sci. U.S.A. (1988) 85, 5879-5883; Plickthun "The Pharmacology of Monoclonal Antibodies" Vol. 113, eds., Resenburg and Moore, Springer Verlag, New York, pp. 269-315, (1994)). The H-chain V region and L-chain V region of scFv may be derived from any antibody described herein. The peptide linker for linking the V regions is not particularly limited. For example, an arbitrary single-chain peptide containing about three to 25 residues can be used as a linker. Specifically, it is possible to use the peptide linkers or such described below.

[0127] The V regions of both chains can be linked, for example, by PCR as described above. To link the V regions by PCR, first, a DNA from the DNAs below that encodes a complete or desired partial amino acid sequence is used as a template:

DNA sequence encoding an H chain or H-chain V region of an antibody, and

DNA sequence encoding an L chain or L-chain V region of an antibody.

[0128] DNAs encoding the H-chain and L-chain V regions are amplified by PCR using a pair of primers having sequences corresponding to sequences at both ends of the DNA to be amplified. Then, a DNA encoding the peptide linker portion is prepared. The peptide linker-encoding DNA can also be synthesized by PCR. Here, nucleotide sequences that can be ligated to the amplification products of V regions synthesized separately are added to the 5' end of the primers to be used. Then, PCR is carried out using each DNA of the [H chain V region DNA] - [peptide linker DNA] - [L chain V region DNA], and assembly PCR primers.

[0129] The assembly PCR primers are composed of a combination of a primer that anneals to the 5' end of the [H chain V region DNA] and a primer that anneals to the 3' end of the [L chain V region DNA]. In other words, the assembly PCR primers are a set of primers that can be used to amplify DNA encoding the full-length sequence of an scFv to be synthesized. Meanwhile, nucleotide sequences that can be ligated to the V-region DNAs have been added to the [peptide linker DNA]. Thus, these DNAs are linked together, and then the whole scFv is ultimately generated as an amplification product by the assembly PCR primers. Once the scFv-encoding DNAs are generated, expression vectors carrying these DNAs and recombinant cells transformed with these expression vectors can be obtained by conventional methods. Furthermore, the scFv can be obtained by culturing the resulting recombinant cells to express the scFv-encoding DNAs.

[0130] The order of the heavy chain and light chain variable regions to be linked together is not particularly limited, and they may be arranged in any order. Examples of the arrangement are listed below.

[VH] linker [VL]

[VL] linker [VH]

[0131] sc(Fv)2 is a single-chain low-molecular-weight antibody produced by linking two VHs and two VLs using linkers and such (Hudson et al., J Immunol. Methods 1999; 231: 177-189). For example, sc(Fv)2 can be produced by linking scFvs *via* a linker.

[0132] Antibodies in which two VHs and two VLs are arranged in the order of VH, VL, VH, and VL ([VH] linker [VL] linker [VH] linker [VL]) from the N terminus of the single-chain polypeptide are preferred. However, the order of the two VHs and two VLs is not limited to the above arrangement, and they may be arranged in any order. Examples of the arrangement are listed below:

[VL] linker [VH] linker [VH] linker [VL]

[VH] linker [VL] linker [VL] linker [VH]

[VH] linker [VH] linker [VL] linker [VL]

[VL] linker [VL] linker [VH] linker [VH]

[VL] linker [VH] linker [VL] linker [VH]

[0133] The amino acid sequence of the heavy chain variable region or light chain variable region in a low-molecular-weight antibody may contain a substitution, deletion, addition, and/or insertion. Furthermore, the heavy chain variable region and light chain variable region may also lack some portions or be added with other polypeptides, as long as they have antigen binding ability when linked together. Alternatively, the variable regions may be chimerized or humanized.

[0134] Linkers which bind the variable regions of the antibody include arbitrary peptide linkers that can be introduced using genetic engineering, or synthetic linkers such as those disclosed in Protein Engineering, 9(3), 299-305, 1996.

[0135] The preferred linkers are peptide linkers. The length of the peptide linkers is not particularly limited, and those skilled in the art can appropriately select the length depending on the purpose. A typical length is one to 100 amino acids, preferably 3 to 50 amino acids, more preferably 5 to 30 amino acids, and particularly preferably 12 to 18 amino acids (for example, 15 amino acids).

[0136] Amino acid sequences of such peptide linkers include, for example:

Ser;

Gly·Ser;

Gly·Gly·Ser;

Ser·Gly·Gly;

Gly·Gly·Gly·Ser (SEQ ID NO: 19);

Ser·Gly·Gly·Gly (SEQ ID NO: 20);

Gly·Gly·Gly·Gly·Ser (SEQ ID NO: 21);

Ser·Gly·Gly·Gly·Gly (SEQ ID NO: 22);

Gly·Gly·Gly·Gly·Gly·Ser (SEQ ID NO: 23);

Ser·Gly-Gly·Gly·Gly·Gly (SEQ ID NO: 24);

Gly·Gly·Gly·Gly·Gly·Gly·Ser (SEQ ID NO: 25);

Ser·Gly·Gly·Gly·Gly·Gly·Gly (SEQ ID NO: 26);

(Gly·Gly·Gly·Gly·Ser (SEQ ID NO: 21))n; and

(Ser·Gly·Gly·Gly·Gly (SEQ ID NO: 22))n,

where n is an integer of 1 or larger.

[0137] The amino acid sequence of a peptide linker can be appropriately selected by those skilled in the art according to the purpose. For example, the above-mentioned "n", which determines the length of the peptide linker, is usually 1 to 5, preferably 1 to 3, and more preferably 1 or 2.

[0138] Synthetic linkers (chemical crosslinking agents) include crosslinking agents that are routinely used to crosslink peptides, for example, N-hydroxy succinimide (NHS), disuccinimidyl suberate (DSS), bis(sulfosuccinimidyl) suberate (BS3), dithiobis(succinimidyl propionate) (DSP), dithiobis(sulfosuccinimidyl propionate) (DTSSP), ethylene glycol bis(succinimidyl succinate) (EGS), ethylene glycol bis(sulfosuccinimidyl succinate) (sulfo-EGS), disuccinimidyl tartrate (DST), disulfosuccinimidyl tartrate (sulfo-DST), bis[2-(succinimidoxycarbonyloxy)ethyl] sulfone (BSOCOES), and bis[2-(sulfosuccinimidoxycarbonyloxy)ethyl] sulfone (sulfo-BSOCOES). These crosslinking agents are commercially available.

[0139] When four antibody variable regions are linked, three linkers are usually required. Such multiple linkers may be the same or different.

[0140] The antibodies include antibodies in which one or more amino acid residues have been added to the amino acid sequence of an antibody. Further, fusion proteins which result from a fusion between one of the above antibodies and a second peptide or protein is included in the present description. The fusion proteins can be prepared by ligating a polynucleotide encoding an antibody with a polynucleotide encoding a second peptide or polypeptide in frame, inserting this into an expression vector, and expressing the fusion construct in a host. Some techniques known to those skilled in the art are available for this purpose. The partner peptide or polypeptide to be fused with an antibody may be a known peptide, for example, FLAG (Hopp, T. P. et al., BioTechnology 6, 1204-1210 (1988)), 6x His consisting of six His (histidine) residues, 10x His, influenza hemagglutinin (HA), human c-myc fragment, VSV-GP fragment, p18HIV fragment, T7-tag, HSV-tag, E-tag, SV40 T antigen fragment, lck tag, α-tubulin fragment, B-tag, Protein C fragment, Stag, StrepTag, HaloTag. Other partner polypeptides to be fused with the antibodies include, for example, GST (glutathione-S-transferase), HA (influenza hemagglutinin), immunoglobulin constant region, β-galactosidase, and MBP (maltose-binding protein). A polynucleotide encoding one of these commercially available peptides or polypeptides can be fused with a polynucleotide encoding an antibody. The fusion polypeptide can be prepared by expressing the fusion construct.

[0141] Furthermore, the antibodies may be conjugated antibodies which are linked to any of various molecules including polymeric substances such as polyethylene glycol (PEG) and hyaluronic acid, radioactive substances, fluorescent substances, luminescent substances, enzymes, and toxins. Such conjugated antibodies can be obtained by chemically modifying the obtained antibodies. Methods for modifying antibodies have been established in this field (for example, US 5057313 and US 5156840). The "antibodies" also include such conjugated antibodies.

[0142] Furthermore, the antibodies used in the present invention may be bispecific antibodies. The bispecific antibody refers to an antibody that has variable regions recognizing different epitopes in the same antibody molecule. The bispecific antibodies may recognize different epitopes on the fusion polypeptide molecule of the present invention, or recognize the fusion polypeptide of the present invention with one antigen-binding site and a different substance with the other antigen-binding site.

[0143] Methods for producing bispecific antibodies are known. Bispecific antibodies can be prepared, for example, by linking two antibodies that recognize different antigens. Antibodies to be linked together may be half molecules each of which contains an H chain and an L chain, or quarter molecules that consist of only one H chain. Alternatively, hybridomas producing different monoclonal antibodies can be fused to produce a bispecific antibody-producing fused cell. Furthermore, bispecific antibodies can be produced by genetic engineering techniques.

[0144] The antibodies may differ in amino acid sequence, molecular weight, isoelectric point, presence/absence of sugar chains, and conformation depending on the cell or host producing the antibody or the purification method as described below. However, a resulting antibody is included, as long as it is functionally equivalent to a described antibody. For example, when an antibody is expressed in prokaryotic cells, for example *E. coli,* a methionine residue is added to the N terminus of the original antibody amino acid sequence. Such antibodies are included in the present description.

[0145] Antibodies may be antibodies with altered sugar chains. Methods for modifying antibody sugar chains are known to those skilled in the art, and include, for example, methods for improving ADCC by modifying antibody glycosylation, methods for adjusting ADCC by the presence or absence of fucose in antibody sugar chains, methods for preparing antibodies having sugar chains that do not contain α-1,6 core fucose by producing antibodies in YB2/0 cells, and methods for adding sugar chains having bisecting GlcNAc (WO 99/54342; WO 00/61739; WO 02/31140; WO 02/79255, etc.).

[0146] Antibodies can be produced by known methods using as an immunogen a fusion polypeptide of the present invention (derived from mammals such as humans and mice) or a fragment thereof. Specifically, non-human mammals are immunized by a known immunization method, using as a sensitizing antigen a desired antigen or cells expressing a desired antigen. Immune cells prepared from the immunized animals are fused with known parental cells by a general cell fusion method. The resulting monoclonal antibody-producing cells (hybridomas) are sorted by general screening methods, and monoclonal antibodies are prepared by culturing the cells.

[0147] Non-human mammals to be immunized include, for example, animals such as mice, rats, rabbits, sheep, monkeys, goats, donkeys, cows, horses, and pigs. The antigen can be prepared using a polynucleotide encoding the fusion polypeptide of the present invention according to known methods, for example, by methods using baculovirus (for example, WO 98/46777) or such.

[0148] Hybridomas can be prepared, for example, according to the method of Milstein *et al.* (Kohler, G. and Milstein, C., Methods Enzymol. (1981) 73: 3-46) or such. When the immunogenicity of an antigen is low, immunization may be performed after linking the antigen with a macromolecule having immunogenicity, such as albumin.

[0149] In an embodiment, antibodies that bind to the fusion polypeptides of the present invention include monoclonal antibodies that bind to the fusion polypeptides of the present invention. Immunogens for preparing monoclonal antibodies having binding activity to a fusion polypeptide of the present invention are not particularly limited, as long as antibodies having binding activity to the fusion polypeptide of the present invention can be prepared. It is possible to use as an immunogen, for example, a wild-type fusion polypeptide or a fragment peptide thereof, or a polypeptide obtained by adding an artificial mutation into a wild-type fusion polypeptide.

[0150] Meanwhile, the activity of an antibody to bind to a fusion polypeptide of the present invention can be assayed by methods known to those skilled in the art.

[0151] Meanwhile, monoclonal antibodies can also be obtained by DNA immunization. DNA immunization is a method in which a vector DNA constructed such that an antigen protein-encoding gene can be expressed in an animal to be immunized is administered to the animal, and the immunogen is expressed within the body of the animal to provide immunostimulation. As compared to common immunization methods based on the administration of protein antigens, DNA immunization is expected to be advantageous in that:

- it enables immunostimulation while retaining the structure of a membrane protein; and
- the immunogen does not need to be purified.

[0152] In order to obtain monoclonal antibodies by DNA immunization, first, a polynucleotide encoding a fusion polypeptide of the present invention is administered to an animal to be immunized. The polynucleotide encoding a fusion polypeptide of the present invention can be synthesized according to an above-described method by known techniques such as PCR. The resulting DNA (polynucleotide) is inserted into an appropriate expression vector and then administered to an animal to be immunized. The expression vector includes any vectors described above (for example, commercially available expression vectors such as pcDNA3.1). Vectors can be administered to a living body by commonly used methods. For example, DNA immunization can be performed, for example, by using a gene gun to inject gold particles immobilized with an expression vector into cells. A preferred method for obtaining monoclonal antibodies is to perform booster immunization with cells expressing the fusion polypeptide of the present invention after DNA immunization.
[0153] Once the mammal is immunized as described above and the serum level of a desired antibody is confirmed to be increased, immune cells are collected from the mammal and subjected to cell fusion. Preferred immune cells are spleen cells in particular.
[0154] Mammalian myeloma cells are used for fusion with the above immune cells. It is preferred that myeloma cells have appropriate selection markers for screening. The selection marker refers to a phenotype that allows (or does not allow) survival under particular culture conditions. Known selection markers include hypoxanthine-guanine-phosphoribosyltransferase deficiency (hereinafter abbreviated as "HGPRT deficiency") and thymidine kinase deficiency (hereinafter abbreviated as "TK deficiency"). HGPRT- or TK-deficient cells exhibit hypoxanthine-aminopterin-thymidine sensitivity (hereinafter abbreviated as "HAT sensitivity"). In HAT selection medium, HAT-sensitive cells cannot synthesize DNA and thus will die. However, when fused with normal cells, they can continue to synthesize DNA *via* the salvage pathway of the normal cells and thus can grow even in HAT selection medium.
[0155] HGPRT- or TK-deficient cells can be selected using a medium containing 6-thioguanine, 8-azaguanine (hereinafter abbreviated as "8AG"), or 5'-bromodeoxyuridine. While normal cells are killed due to incorporation of these pyrimidine analogs into DNA, cells lacking these enzymes can survive in the selection medium because they cannot incorporate these pyrimidine analogs. Another selection marker called G418 resistance confers resistance to 2-deoxystreptamine antibiotics (gentamicin analogs) due to the neomycin resistance gene. Various myeloma cells suitable for cell fusion are known.
[0156] Cell fusion between immune cells and myeloma cells can be essentially carried out according to known methods, for example, the method by Kohler and Milstein *et al.* (Kohler. G. and Milstein, C., Methods Enzymol. (1981) 73, 3-46).
[0157] More specifically, cell fusion can be carried out, for example, in a common culture medium in the presence of a cell fusion-promoting agent. The fusion-promoting agent includes, for example, polyethylene glycol (PEG) and Sendai virus (HVJ). If required, an auxiliary agent such as dimethyl sulfoxide may also be added to improve fusion efficiency.
[0158] The immune cells and myeloma cells may be used at an arbitrarily determined ratio. For example, the ratio of immune cells to myeloma cells is preferably from 1 to 10. Culture media to be used for cell fusion include, for example, media that are suitable for the cell growth of myeloma cell line, such as RPMI1640 and MEM, and other common culture media used for this type of cell culture. In addition, the culture media may also be supplemented with serum supplement such as fetal calf serum (FCS).
[0159] Predetermined amounts of immune cells and myeloma cells are mixed well in the culture medium, and then mixed with a PEG solution pre-heated to about 37°C to produce fused cells (hybridomas). In the cell fusion method, for example, PEG with mean molecular weight of about 1,000-6,000 can be added to the cells typically at a concentration of 30% to 60% (w/v). Then, successive addition of the appropriate culture medium listed above and removal of supernatant by centrifugation are repeated to eliminate the cell fusion agent and such, which are unfavorable to the growth of hybridomas.
[0160] The resulting hybridomas can be screened using a selection medium according to the selection marker possessed by myeloma cells used in the cell fusion. For example, HGPRT- or TK-deficient cells can be screened by culturing them in a HAT medium (a medium containing hypoxanthine, aminopterin, and thymidine). Specifically, when HAT-sensitive myeloma cells are used in cell fusion, cells successfully fused with normal cells can be selectively grown in the HAT medium. The cell culture using the above HAT medium is continued for a sufficient period of time to allow all cells except the desired hybridomas (non-fused cells) to die. Specifically, in general, the desired hybridomas can be selected by culturing the cells for several days to several weeks. Then, screening and single cloning of hybridomas that produce an antibody of interest can be carried out by performing ordinary limiting dilution methods.
[0161] Screening and single cloning of an antibody of interest can be suitably carried out by known screening methods

based on antigen-antibody reaction. For example, an antigen is bound to a carrier such as beads made of polystyrene or such and commercially available 96-well microtiter plates, and then reacted with the culture supernatant of hybridoma. Next, the carrier is washed and then reacted with an enzyme-labeled secondary antibody or such. When the culture supernatant contains an antibody of interest reactive to the sensitizing antigen, the secondary antibody binds to the carrier *via* this antibody. Finally, the secondary antibody bound to the carrier is detected to determine whether the culture supernatant contains the antibody of interest. Hybridomas producing a desired antibody capable of binding to the antigen can be cloned by the limiting dilution method or such.

[0162] In addition to the above-described method for preparing hybridomas through immunization of a nonhuman animal with an antigen, antibodies of interest can also be obtained by sensitizing human lymphocytes with an antigen. Specifically, first, human lymphocytes are sensitized with the fusion polypeptide of the present invention *in vitro.* Then, the sensitized lymphocytes are fused with an appropriate fusion partner. For example, human-derived myeloma cells with the ability to divide permanently can be used as the fusion partner (see JP-B (Kokoku) H01-59878). Antibodies obtained by this method are human antibodies having an activity of binding to the fusion polypeptide of the present invention.

[0163] The nucleotide sequence encoding an antibody that binds to the fusion polypeptide of the present invention obtained by the above-described method or such, and its amino acid sequence can be obtained by methods known to those skilled in the art.

[0164] Based on the obtained sequence of the antibody that binds to the fusion polypeptide of the present invention, the antibody that binds to the fusion polypeptide of the present invention can be prepared by genetic recombination techniques known to those skilled in the art. Specifically, a polynucleotide encoding an antibody can be constructed based on the sequence of the antibody that recognizes the fusion polypeptides of the present invention, inserted into an expression vector, and then expressed in appropriate host cells (see for example, Co, M. S. et al., J. Immunol. (1994) 152, 2968-2976; Better, M. and Horwitz, A. H., Methods Enzymol. (1989) 178, 476-496; Pluckthun, A. and Skerra, A., Methods Enzymol. (1989) 178, 497-515; Lamoyi, E., Methods Enzymol. (1986) 121, 652-663; Rousseaux, J. et al., Methods Enzymol. (1986) 121, 663-669; Bird, R. E. and Walker, B. W., Trends Biotechnol. (1991) 9, 132-137).

[0165] The vectors include M13 vectors, pUC vectors, pBR322, pBluescript, and pCR-Script. Alternatively, when aiming to subclone and excise cDNA, the vectors include, for example, pGEM-T, pDIRECT, and pT7, in addition to the vectors described above. Expression vectors are particularly useful when using vectors for producing the antibodies. For example, when aiming for expression in *E. coli* such as JM109, DH5α, HB101, and XL1-Blue, the expression vectors not only have the above-described characteristics that allow vector amplification in *E. coli,* but must also carry a promoter that allows efficient expression in *E. coli,* for example, lacZ promoter (Ward et al., Nature (1989) 341, 544-546; FASEB J. (1992) 6, 2422-2427), araB promoter (Better et al., Science (1988) 240, 1041-1043), T7 promoter or such. Such vectors include pGEX-5X-1 (Pharmacia), "QIAexpress system" (Qiagen), pEGFP, or pET (in this case, the host is preferably BL21 that expresses T7 RNA polymerase) in addition to the vectors described above.

[0166] The vectors may contain signal sequences for antibody secretion. As a signal sequence for antibody secretion, a pelB signal sequence (Lei, S. P. et al J. Bacteriol. (1987) 169, 4379) may be used when a protein is secreted into the *E. coli* periplasm. The vector can be introduced into host cells by calcium chloride or electroporation methods, for example.

[0167] In addition to vectors for *E. coli,* the vectors for producing the antibodies include mammalian expression vectors (for example, pcDNA3 (Invitrogen), pEF-BOS (Nucleic Acids. Res. 1990, 18(17), p5322), pEF, and pCDM8), insect cell-derived expression vectors (for example, the "Bac-to-BAC baculovirus expression system" (Gibco-BRL) and pBacPAK8), plant-derived expression vectors (for example, pMH1 and pMH2), animal virus-derived expression vectors (for example, pHSV, pMV, and pAdexLcw), retroviral expression vectors (for example, pZIPneo), yeast expression vectors (for example, "Pichia Expression Kit" (Invitrogen), pNV11, and SP-Q01), and *Bacillus subtilis* expression vectors (for example, pPL608 and pKTH50), for example.

[0168] When aiming for expression in animal cells such as CHO, COS, and NIH3T3 cells, the vectors must have a promoter essential for expression in cells, for example, SV40 promoter (Mulligan et al., Nature (1979) 277, 108), MMLV-LTR promoter, EF1α promoter (Mizushima et al., Nucleic Acids Res. (1990) 18, 5322), and CMV promoter, and more preferably they have a gene for selecting transformed cells (for example, a drug resistance gene that allows evaluation using an agent (neomycin, G418, or such)). Vectors with such characteristics include pMAM, pDR2, pBK-RSV, pBK-CMV, pOPRSV, and pOP13, for example.

[0169] In addition, the following method can be used for stable gene expression and gene amplification in cells: CHO cells deficient in a nucleic acid synthesis pathway are introduced with a vector (for example, pSV2-dhfr ("Molecular Cloning 2nd edition", Cold Spring Harbor Laboratory Press, 1989)) that carries a DHFR gene which compensates for the deficiency, and the vector is amplified using methotrexate (MTX). Alternatively, the following method can be used for transient gene expression: COS cells with a gene expressing SV40 T antigen on their chromosome are transformed with a vector (pcD and such) with an SV40 replication origin. Replication origins derived from polyoma virus, adenovirus, bovine papilloma virus (BPV), and such can also be used. To amplify gene copy number in host cells, the expression vectors may further carry selection markers such as aminoglycoside transferase (APH) gene, thymidine kinase (TK) gene, *E. coli* xanthine-guanine phosphoribosyltransferase (Ecogpt) gene, and dihydrofolate reductase (dhfr) gene.

[0170] The antibodies obtained by the methods described above can be isolated from inside host cells or from outside the cells (the medium, or such), and purified to homogeneity. The antibodies can be isolated and purified by methods routinely used for isolating and purifying antibodies, and the type of method is not limited. For example, the antibodies can be isolated and purified by appropriately selecting and combining column chromatography, filtration, ultrafiltration, salting out, solvent precipitation, solvent extraction, distillation, immunoprecipitation, SDS-polyacrylamide gel electrophoresis, isoelectrofocusing, dialysis, recrystallization, and such.

[0171] The chromatographies include, for example, affinity chromatography, ion exchange chromatography, hydrophobic chromatography, gel filtration, reverse phase chromatography, and adsorption chromatography (Strategies for Protein Purification and Characterization: A Laboratory Course Manual. Ed Daniel R. Marshak et al., Cold Spring Harbor Laboratory Press, 1996). The chromatographic methods described above can be conducted using liquid chromatography, for example, HPLC and FPLC. Columns that can be used for affinity chromatography include protein A columns and protein G columns. Columns using protein A include, for example, Hyper D, POROS, and Sepharose FF (GE Amersham Biosciences). The present description includes antibodies that are highly purified using these purification methods.

[0172] The binding activity to the fusion polypeptide of the present invention of the obtained antibodies can be determined by methods known to those skilled in the art. Methods for determining the antigen-binding activity of an antibody include, for example, ELISA (enzyme-linked immunosorbent assay), EIA (enzyme immunoassay), RIA (radioimmunoassay), and fluorescent antibody method. For example, when enzyme immunoassay is used, antibody-containing samples, such as purified antibodies and culture supernatants of antibody-producing cells, are added to antigen-coated plates. A secondary antibody labeled with an enzyme, such as alkaline phosphatase, is added and the plates are incubated. After washing, an enzyme substrate, such as p-nitrophenyl phosphate, is added, and the absorbance is measured to evaluate the antigen-binding activity.

[0173] In the present invention, "cancer" generally refers to malignant neoplasm which may be metastatic or non-metastatic. For instance, non-limiting examples of cancer that develops from epithelial tissues such as gastrointestinal tract and skin include brain tumor, skin cancer, head and neck cancer, esophageal cancer, lung cancer, gastric cancer, duodenal cancer, breast cancer, prostate cancer, cervical cancer, cancer of uterine body, pancreatic cancer, liver cancer, colorectal cancer, colon cancer, bladder cancer, and ovarian cancer. Meanwhile, non-limiting examples of sarcoma that develops from non-epithelial tissues (stroma) such as muscles include osteosarcoma, chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, and angiosarcoma. Furthermore, non-limiting examples of hematological cancer derived from hematopoietic organs include malignant lymphoma including Hodgkin's lymphoma and non-Hodgkin's lymphoma, leukemia including acute myelocytic leukemia, chronic myelocytic leukemia, acute lymphatic leukemia, and chronic lymphatic leukemia, and multiple myeloma.

[0174] In the present invention, cancer includes any newly developed pathological tissue tumor (neoplasm). In the present invention, neoplasm leads to tumor formation which is characterized by partial neovascularization. Neoplasm can be benign, for example, angioma, glioma, and teratoma, or malignant, for example, cancer, sarcoma, glial tumor, astrocytoma, neuroblastoma, and retinoblastoma.

[0175] In the present invention, preferred examples of cancer include bladder cancer, brain tumor, head and neck squamous cell carcinoma, lung cancer, lung adenocarcinoma, lung squamous cell carcinoma, skin melanoma, esophageal cancer, gastric cancer, and liver cancer.

[0176] In the present invention, "cancer tissue" refers to a tissue containing at least one cancer cell. For example, as cancer tissues contain cancer cells and blood vessels, cancer tissue refers to all cell types that contribute to the formation of tumor mass containing cancer cells and endothelial cells. Herein, tumor mass refers to foci of tumor tissue. The term "tumor" is generally used to refer to benign or malignant neoplasm.

[0177] In the present invention, the pharmaceutical composition generally refers to a pharmaceutical agent for treating, preventing, or examining/diagnosing diseases.

[0178] The pharmaceutical compositions can be formulated by methods known to those skilled in the art. For example, they can be used parenterally, in an injectable form of sterile solutions or suspensions including water or other pharmaceutically acceptable liquid. For example, such compositions may be formulated by mixing in a unit dose form required by the generally approved pharmaceutical manufacturing practice, by appropriately combining with pharmacologically acceptable carriers or media, specifically sterile water, physiological saline, vegetable oil, emulsifier, suspension, surfactant, stabilizer, flavoring agent, excipient, vehicle, preservative, binder, or such. The amount of active ingredient in such formulations is adjusted so that an appropriate amount can be obtained within a specified range.

[0179] Sterile compositions for injection can be formulated according to general formulation practice using vehicles such as distilled water for injection. Aqueous solutions for injection include, for example, physiological saline, and isotonic solutions containing glucose or other adjuvants (e.g., D-sorbitol, D-mannnose, D-mannitol, and sodium chloride). These can be used in combination with appropriate solubilizers, for example, alcohol (ethanol, etc.), polyalcohol (propylene glycol, polyethylene glycol, etc.), and non-ionic detergents (Polysorbate 80™, HCO-50, etc.).

[0180] Oils include sesame oil and soybean oils. Benzyl benzoate and/or benzyl alcohol can be used in combination as solubilizers. It is also possible to combine buffers (for example, phosphate buffer and sodium acetate buffer), soothing agents (for example, procaine hydrochloride), stabilizers (for example, benzyl alcohol and phenol), and/or antioxidants. Appropriate ampules are filled with the prepared injections.

[0181] The pharmaceutical compositions are preferably administered parenterally. For example, compositions are administered in an injectable form, or in a form for transnasal administration, transpulmonary administration, or transdermal administration. For example, they can be administered systemically or locally by intravenous injection, intramuscular injection, intraperitoneal injection, subcutaneous injection, or such.

[0182] Administration methods can be appropriately selected in consideration of the patient's age and symptoms. The dose of a pharmaceutical composition containing an antigen-binding molecule may be, for example, 0.0001 mg to 1,000 mg/kg for each administration. Alternatively, the dose may be, for example, 0.001 to 100,000 mg per patient. However, the present invention is not limited by the numeric values described above. The dosage and administration method vary according to the patient's weight, age, symptoms, and such. Those skilled in the art can set an appropriate dosage and administration method in consideration of the factors described above.

[0183] Amino acids in the amino acid sequences described herein may be modified after translation (for example, modification of N-terminal glutamine into pyroglutamic acid by pyroglutamylation is well known to those skilled in the art). As a matter of course, such posttranslationally modified amino acids are also included in the amino acid sequences of the present invention.

[0184] The present invention also relates to methods for detecting a fusion polypeptide of the present invention or a polynucleotide encoding the fusion polypeptide in samples from subjects (including cancer patients and healthy persons).

[0185] The presence or absence of a fusion polypeptide of the present invention in a sample from a subject can be tested and determined, for example, using antigen-antibody reaction which is performed by contacting an above-described antibody or antigen-binding fragment thereof that binds to a fusion polypeptide of the present invention with a sample (tumor tissue, normal tissue, and various body fluid specimens containing cancer or normal cells (blood, serum, urine, saliva, ascites, pleural effusion, etc.)) collected from a subject (cancer patient, person who may be affected with cancer, person with the risk of getting cancer, or healthy person; however, it is not limited to human).

[0186] The antigen (*i.e.,* a fusion polypeptide of the present invention) in an antigen-antibody reaction can be detected, for example, by using conventional immunoassay.

[0187] In the present invention, immunoassay refers to a method for detecting a fusion polypeptide of the present invention in a sample (tumor tissue, normal tissue, and various body fluid specimens containing cancer or normal cells (blood, serum, urine, saliva, ascites, pleural effusion, etc.)) based on the reaction mechanism between an antigen (*i.e.,* a fusion polypeptide of the present invention) and an antibody that binds to the antigen or antigen-binding fragment thereof. Any immunoassay is included in the present invention as long as it is a method that can detect the fusion polypeptides of the present invention.

[0188] For immunoassay in the present invention, for example, the principles of various methods such as those described in "Kouso Men-eki Sokutei Hou (Enzyme immunoassay)" (3rd Ed., eds., Eiji Ishikawa et al., Igakushoin, 1987) can be applied. Specifically, these various methods can be carried out using one or more antibodies that bind to an antigen of interest to capture (trap) the antigen to be detected in a sample.

[0189] Applicable principles preferably include, for example, single antibody solid phase methods, double antibody liquid phase methods, double antibody solid phase methods, sandwich methods, and one-pot methods such as described in JP-B (Kokoku) H02-39747. Meanwhile, assays based on antigen-antibody reaction also include enzyme multiplied immunoassay technique (EMIT), enzyme channeling immunoassay, enzyme modulator mediated enzyme immunoassay (EMMIA), enzyme inhibitor immunoassay, immunoenzymometric assay, enzyme enhanced immunoassay, and proximal linkage immunoassay.

[0190] In the present invention, it is possible to select and use any appropriate immunoassay principle such as those described above depending on the objective of the test.

[0191] The immunoassays of the present invention also include sandwich methods using a biotin- or enzyme-labeled antibody, and multi-well microtiter plates having a number of wells including 96-well microplate, as well as one-pot methods using beads and antibodies labeled with biotin or enzyme such as peroxidase.

[0192] As described above, antibodies that bind to a fusion polypeptide of the present invention or antigen-binding fragments thereof, which are used in immunoassays of the present invention, may be labeled with a labeling substance that can provide a detectable signal by itself or upon reaction with other substances.

[0193] Such labeling substances include, for example, enzymes, fluorescent substances, chemiluminescent substances, biotin, avidin, and radioisotopes. More specifically, the substances include enzymes such as peroxidase (*e.g.,* horseradish peroxidase), alkaline phosphatase, β-D-galactosidase, glucose oxidase, glucose-6-phosphate dehydrogenase, alcohol dehydrogenase, malate dehydrogenase, penicillinase, catalase, apoglucoseoxidase, urease, luciferase, and acetylcholinesterase; fluorescent substances such as fluorescein isothiocyanate, phycobiliprotein, rare earth metal chelates, dansyl chloride, and tetramethylrhodamine isothiocyanate; radioisotopes such as ^{3}H, ^{14}C, ^{125}I, and ^{131}I; biotin; avidin; and chemiluminescent substances.

[0194] Such radioisotopes and fluorescent substances can provide a detectable signal by themselves.

[0195] Meanwhile, enzymes, chemiluminescent substances, biotin, and avidin cannot provide any detectable signal by themselves, but provide a detectable signal when reacting with one or more different substances.

[0196] For example, when an enzyme is used, at least a substrate is necessary. Various substrates are used according to the type of enzymatic activity assay method (colorimetric assay, fluorescent assay, bioluminescence assay, chemiluminescent assay, etc.). For example, hydrogen peroxide is used as a substrate for peroxidase. Meanwhile, biotin is generally reacted with at least avidin or enzyme-modified avidin, but substrates are not limited thereto. If needed, it is also possible to use various chromogenic substances according to the substrates.

[0197] The presence or absence of a polynucleotide encoding a fusion polypeptide of the present invention in a sample from a subject can be tested and determined, for example, according to routine methods using various oligonucleotides (a pair of oligonucleotide primers, oligonucleotide probes, etc.) described above, and mRNA, cDNA prepared using mRNA as a template, genomic DNA, or such in a sample (tumor tissue, normal tissue, and various body fluid specimens containing cancer or normal cells (blood, serum, urine, saliva, ascites, pleural effusion, etc.)) collected from a subject (cancer patient, person who may be affected with cancer, person with the risk of getting cancer, or healthy person; however, it is not limited to human) by using various gene analysis methods. Such gene analysis methods include, for example, Northern blotting, polymerase chain reaction (PCR), Southern blotting, ligase chain reaction (LCR), strand displacement amplification (SDA), nucleic acid sequence-based amplification (NASBA), isothermal and chimeric primer-initiated amplification of nucleic acids (ICAN), loop-mediated isothermal amplification (LAMP), TMA method (Gen-Probe's TMA system), microarray, and next-generation sequencing method.

[0198] In these assays, oligonucleotides are hybridized to a polynucleotide encoding a fusion polypeptide of the present invention derived from a sample. Desired stringent conditions for such hybridization include, for example, the conditions of 6 M urea, 0.4% SDS, 0.5x SSC, and 37°C; and hybridization conditions of equivalent stringency. Depending on the objective, it is possible to use more stringent conditions, for example, 6 M urea, 0.4% SDS, and 0.1 x SSC, and 42°C.

[0199] The present description also relates to kits for detecting a fusion polypeptide of the present invention or a polynucleotide encoding the fusion polypeptide in samples from subjects described above (including cancer patients and healthy persons).

[0200] Specifically, detection kits may contain an above-described antibody or antigen-binding fragment thereof that binds to a fusion polypeptide of the present invention (including antibodies or antigen-binding fragments thereof labeled with above-described various labeling substances). Depending on the objective of each immunoassay described above, the kits may also contain various detection reagents (enzymes, substrates, etc.) and instruction manuals.

[0201] Specifically, detection kits may contain various oligonucleotides described above (a pair of oligonucleotide primers, oligonucleotide probes, etc.) that hybridize to mRNA derived from a polynucleotide encoding a fusion polypeptide of the present invention, cDNA prepared using the mRNA as template, or genomic DNA. According to the objective of each gene analysis, the kits may also contain various reagents (enzymes, other oligonucleotides, nucleic acid, reaction buffer, etc.) and instruction manuals.

[0202] The present invention also relates to methods for testing cancer susceptibility of a subject, whether a subject is affected with cancer, or whether cancer has progressed in a subject based on the presence or absence of a fusion polypeptide of the present invention or a polynucleotide encoding the fusion polypeptide in a sample isolated from the subject.

[0203] Specifically, the methods of the present invention include methods for testing cancer susceptibility of a subject, whether a subject is affected with cancer, or whether cancer has progressed in a subject by testing/determining the presence or absence of a fusion polypeptide of the present invention in a sample (tumor tissue, normal tissue, and various body fluid specimens containing cancer or normal cells (blood, serum, urine, saliva, etc.)) collected from the subject (cancer patient, person who may be affected with cancer, person with the risk of getting cancer, or healthy person; however, it is not limited to human) using the above-described methods and kits for detecting the fusion polypeptide of the present invention, wherein the method is based on the criterion that a subject is more likely to develop cancer, is affected with cancer, or has progressed cancer when the fusion polypeptide is detected.

[0204] In addition, the methods of the present invention include methods of testing cancer susceptibility of a subject, whether a subject is affected with cancer, or whether cancer has progressed in a subject by testing/determining the presence or absence of a polynucleotide encoding a fusion polypeptide of the present invention in a sample (tumor tissue, normal tissue, and various body fluid specimens containing cancer or normal cells (blood, serum, urine, saliva, etc.)) collected from the subject (cancer patient, person who may be affected with cancer, person with the risk of getting cancer, or healthy person; however, it is not limited to human) using the above-described methods and kits for detecting the polynucleotide encoding the fusion polypeptide of the present invention, wherein the method is based on the criterion that a subject is more likely to develop cancer, is affected with cancer, or has progressed cancer when the polynucleotide encoding the fusion polypeptide is detected.

[0205] The present invention also relates to methods for selecting a patient to which an anticancer agent (as described below) comprising a compound having FGFR inhibitory activity is applicable, based on the presence or absence of a fusion polypeptide of the present invention or a polynucleotide encoding a fusion polypeptide in a sample isolated from a subject.

[0206] Specifically, the methods of the present invention include methods that test/determine the presence or absence of a fusion polypeptide of the present invention in a sample (tumor tissue, normal tissue, and various body fluid specimens containing cancer or normal cells (blood, serum, urine, saliva, etc.)) collected from the subject (cancer patient or person who may be affected with cancer; however, it is not limited to human) using the above-described methods and kits for detecting the fusion polypeptide of the present invention, and select a subject as a patient to which an anticancer agent (as described below) comprising a compound having FGFR inhibitory activity is applicable when the fusion polypeptide of the present invention is detected.

[0207] The methods of the present invention further include methods that test/determine the presence or absence of a polynucleotide encoding a fusion polypeptide of the present invention in a sample (tumor tissue, normal tissue, and various body fluid specimens containing cancer or normal cells (blood, serum, urine, saliva, etc.)) collected from a subject (cancer patient or person who may be affected with cancer; however, it is not limited to human) using the above-described methods and kits for detecting the polynucleotide encoding the fusion polypeptide of the present invention, and select a subject as a patient to which an anticancer agent (as described below) comprising a compound having FGFR inhibitory activity is applicable when a polynucleotide encoding the fusion polypeptide of the present invention is detected.

[0208] In the present invention, "FGFR inhibitor" and "compound having FGFR inhibitory activity" are used interchangeably, and refer to a compound having the activity of inhibiting the activity of the above-mentioned FGFR, specifically, one or more arbitrary FGFRs belonging to the FGFR family comprising FGFR1, FGFR2, FGFR3, and FGFR4, which are fibroblast growth factor receptors (FGFRs) belonging to the receptor tyrosine kinase family. Preferably, they refer to a compound having the activity of inhibiting human FGFR activity, and more preferably a compound having the activity of inhibiting the activity of human FGFR3 comprising the amino acid sequence of SEQ ID NO: 6 or 7 (cDNA sequences, SEQ ID NOs: 10 and 11, respectively / GenBank Accession Nos. NM_001163213.1 and NM_000142.4, respectively).

[0209] Any FGFR inhibitors are included in the FGFR inhibitors of the present invention as long as the compounds have the activity of inhibiting FGFR activity.

[0210] Specifically, the FGFR inhibitors of the present invention include any compounds, antibodies, nucleic acid pharmaceuticals (siRNA, antisense nucleic acids, ribozymes, and such) having an action mechanism of:

(1) inhibiting the FGFR kinase activity;

(2) inhibiting dimerization between FGFR, TACC3, and BAIAP2L1;

(3) inhibiting FGFR-mediated signaling (MAPK pathway and PI3K/AKT pathway) (for example, MEK inhibitors, RAF inhibitors, ERK inhibitors, PI3K inhibitors, mTOR inhibitors, AKT inhibitors, PDK inhibitors, S6K inhibitors, etc.); or

(4) inhibiting FGFR expression (for example, siRNA, HSP90 inhibitors, etc.).

[0211] Antibodies having the activity of inhibiting FGFR activity, which are included as FGFR inhibitors of the present invention, comprise antibodies identified by the following code names: RG7444, FP-1039, AV370, and PRO-001.

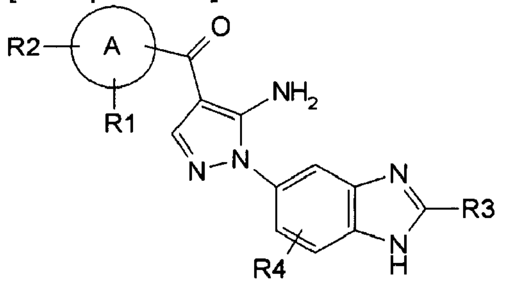
[0212] Low-molecular-weight compounds having the activity of inhibiting FGFR activity, which are included as FGFR inhibitors of the present invention, include, for example:

(1) compounds disclosed in the following Patent Document and Non-patent Documents: Cancer Research, 2012, 72: 2045-2056; J. Med. Chem., 2011, 54: 7066-7083; International Publication WO 2011/016528;

(2) compounds identified by the following generic names or code names: AZD-4547 (compound C in Table 2-1 described below), BGJ-398 (compound D in Table 2-2 described below), LY-2874455, cediranib (AZD2171; compound E in Table 2-2 described below), PD173074 (compound B in Table 2-1 described below), regorafenib, ponatinib, orantinib, nintedanib, masitinib, lenvatinib, dovitinib (TKI258; compound F in Table 2-2 described below), brivanib, volasertib, golvatinib, ENMD-2076, E-3810, XL-999, XL-228, ARQ087, Tivozanib, motesanib, and regorafenib; and

(3) compounds exemplified below; however, FGFR inhibitors are not limited thereto:

[Compound 1]



wherein R_1, R_2, R_3, and R_4 each independently represents the group listed below:

R_1 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$,$-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$,$-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

R_2 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$,$-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$,$-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$; or

R_1 and R_2, together with an atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein the heterocyclyl or heteroaryl is optionally substituted by halogen;

R_3 represents hydrogen, C_{1-5} alkyl, C_{6-10} aryl C_{1-6} alkyl, or C_{1-4} haloalkyl;

R_4 represents hydrogen, halogen, C_{1-3} alkyl, C_{1-4} haloalkyl, hydroxy, cyano, nitro, C_{1-4} alkoxy, $-(CH_2)_nZ_1$, $-NR_6R_7$, $-OR_5$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $NR_{17}SO_2R_{18}$, COOH, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$,

$-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

A represents a 5- to 10-membered heteroaryl ring or C_{6-10} aryl ring;

R_5 represents C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{1-3} alkoxy C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{6-10} aryl, C_{6-10} aryl C_{1-3} alkyl, or 3- to 10-membered heterocyclyl C_{1-3} alkyl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, or C_{1-6} trihydroxy alkyl which is optionally substituted by one or more groups independently selected from group Q;

R_6 and R_7, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl C_{1-3} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, or cyano(C_{1-3} alkyl); or alternatively R_6 and R_7, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

n represents 1 to 3;

R_8 and R_9, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, or halogen; or alternatively

R_8 and R_9, together with a carbon atom linked thereto, form a cycloaliphatic ring;

Z_1 represents hydrogen, $NR_{10}R_{11}$, -OH, or 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{10} and R_{11}, which can be the same or different, each represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, cyano(C_{1-3} alkyl), or C_{1-3} alkylsulfonyl C_{1-4} alkyl; or alternatively R_{10} and R_{11}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{12} and R_{13}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3-to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, 3- to 10-membered cycloaliphatic ring, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; or alternatively R_{12} and R_{13}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{14} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{15} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{16} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{17} represents hydrogen or C_{1-4} alkyl;

R_{18} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{19} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, or 5-to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{20} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{21} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{22} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{23} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{24} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{25} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{26} and R_{27}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl,

C_{6-10} aryl C_{1-4} alkyl, 3-to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively R_{26} and R_{27}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{28} and R_{29}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3-to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively R_{28} and R_{29}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{30} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

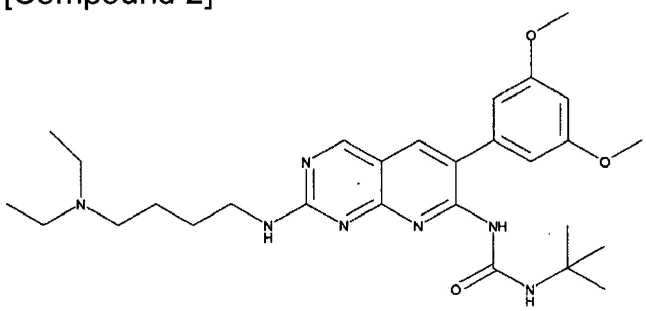
R_{31} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{32} represents C_{1-4} alkyl or C_{6-10} aryl;

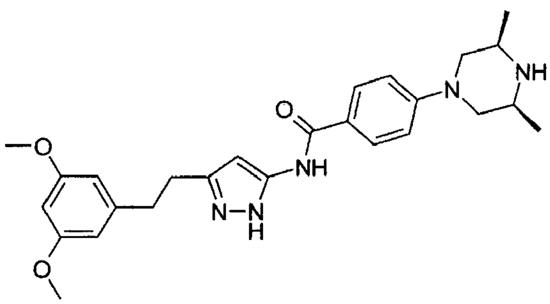
<group P>
halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, 3- to 10-membered heterocyclylamino, $-SO_2R_{16}$, -CN, $-NO_2$, and 3- to 10-membered heterocyclyl;

<group Q>
halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl amine, - SO_2R_{16}, -CN, $-NO_2$, C_{3-7} cycloalkyl, $-COR_{19}$, and 3- to 10-membered heterocyclyl which is optionally substituted by C_{1-4} alkyl.

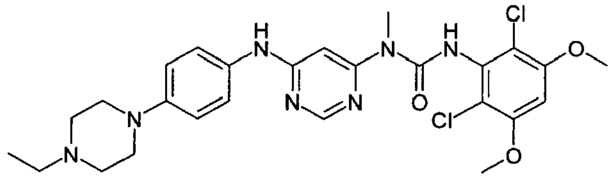
[Compound 2]



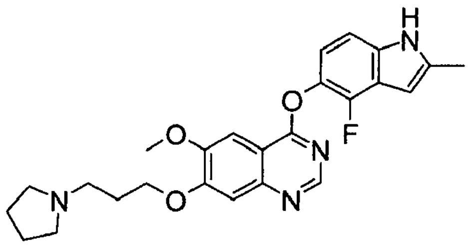
[Compound 3]



[Compound 4]



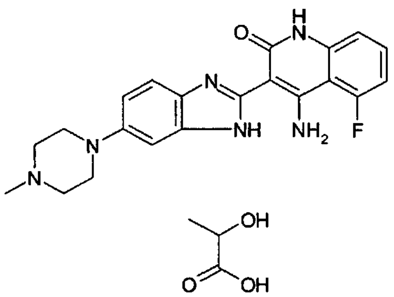
[Compound 5]



,

or

[Compound 6]



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[0213] Herein, the "alkyl" refers to a monovalent group derived from an aliphatic hydrocarbon by removing an arbitrary hydrogen atom. It contains no heteroatom or unsaturated carbon-carbon bond in the backbone, and has a subset of hydrocarbyl or hydrocarbon group structures which contain hydrogen and carbon atoms. The alkyl group includes linear and branched structures. Preferred alkyl groups include alkyl groups with one to six carbon atoms (C_{1-6}; hereinafter, "C_{p-q}" means that the number of carbon atoms is p to q), C_{1-5} alkyl groups, C_{1-4} alkyl groups, and C_{1-3} alkyl groups.

[0214] Specifically, the alkyl includes, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, s-butyl group, t-butyl group, pentyl group, isopentyl group, 2,3-dimethylpropyl group, 3,3-dimethylbutyl group, and hexyl group.

[0215] Herein, "alkenyl" refers to a monovalent hydrocarbon group having at least one double bond (two adjacent SP2 carbon atoms), and includes those of linear and branched forms. Depending on the configuration of the double bond and substituents (if any), the geometry of the double bond can be of entgegen (E) or zusammen (Z), or cis or trans configuration. Preferred alkenyl groups include C_{2-6} alkenyl groups.

[0216] Specifically, the alkenyl includes, for example, vinyl group, allyl group, 1-propenyl group, 2-propenyl group, 1-butenyl group, 2-butenyl group (including cis and trans), 3-butenyl group, pentenyl group, and hexenyl group.

[0217] Herein, "alkynyl" refers to a monovalent hydrocarbon group having at least one triple bond (two adjacent SP carbon atoms), and includes those of linear and branched forms. Preferred alkynyl groups include C_{2-6} alkynyl groups.

[0218] Specifically, the alkynyl includes, for example, ethynyl group, 1-propynyl group, propargyl group, 3-butynyl group, pentynyl group, and hexynyl group.

[0219] The alkenyl and alkynyl may each have one, two or more double bonds or triple bonds.

[0220] Herein, "cycloalkyl" refers to a saturated or partially saturated cyclic monovalent aliphatic hydrocarbon group, and includes monocyclic groups, bicyclo rings, and spiro rings. Preferred cycloalkyl includes C_{3-7} cycloalkyl groups. Specifically, the cycloalkyl group includes, for example, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, and cycloheptyl group.

[0221] Herein, "cycloalkylalkyl" refers to a group in which an arbitrary hydrogen atom of an "alkyl" defined above is substituted with a "cycloalkyl" defined above. Preferred cycloalkylalkyl groups include C_{3-7} cycloalkylC_{1-3} alkyl, and specifically include, for example, cyclopropylmethyl group and cyclopropylethyl group.

[0222] Herein, "hetero atom" refers to a nitrogen atom (N), oxygen atom (O), or sulfur atom (S).

[0223] Herein, "halogen" refers to a fluorine atom, chlorine atom, bromine atom, or iodine atom.

[0224] Herein, "haloalkyl" refers to a group in which preferably one to nine, more preferably one to five identical or different "halogen atoms" defined above are linked to an "alkyl" defined above.

[0225] Specifically, the haloalkyl includes, for example, chloromethyl group, dichloromethyl group, trichloromethyl group, fluoromethyl group, difluoromethyl group, perfluoroalkyl group (such as trifluoromethyl group and $-CF_2CF_3$), and 2,2,2-trifluoroethyl group.

[0226] Herein, "alkoxy" refers to an oxy group linked with an "alkyl" defined above. Preferred alkoxy includes C_{1-4} alkoxy groups and C_{1-3} alkoxy groups. Specifically, alkoxy includes, for example, methoxy group, ethoxy group, 1-propoxy group, 2-propoxy group, n-butoxy group, i-butoxy group, sec-butoxy group, and *tert*-butoxy group.

[0227] Herein, "haloalkoxy" refers to a group in which preferably one to nine, more preferably one to five identical or different halogen atoms defined above are linked to an "alkoxy" defined above.

[0228] Specifically, the haloalkoxy includes, for example, chloromethoxy group, trichloromethoxy group, and trifluoromethoxy group.

[0229] Herein, "aryl" refers to a monovalent aromatic hydrocarbon ring. The aryl preferably includes C_{6-10} aryl. Specifically, the aryl includes, for example, phenyl group and naphthyl groups (for example, 1-naphthyl group and 2-naphthyl group).

[0230] Herein, "alicyclic ring" refers to a monovalent non-aromatic hydrocarbon ring. The alicyclic ring may have unsaturated bonds within its ring, and may be a multicyclic group having two or more rings. The carbon atoms constituting the ring may be oxidized to form a carbonyl. The number of atoms constituting an alicyclic ring preferably ranges from three to ten (3- to 10-membered aliphatic ring). The alicyclic ring includes, for example, cycloalkyl rings, cycloalkenyl rings, and cycloalkynyl rings.

[0231] Herein, "heteroaryl" refers to a monovalent aromatic heterocyclic group in which the ring-constituting atoms include preferably one to five hetero atoms. The heteroaryl may be partially saturated, and may be a monocyclic or condensed ring (for example, a bicyclic heteroaryl condensed with a benzene ring or monocyclic heteroaryl ring). The number of ring-constituting atoms preferably ranges from five to ten (5- to 10-membered heteroaryl).

[0232] Specifically, the heteroaryl includes, for example, furyl group, thienyl group, pyrrolyl group, imidazolyl group, pyrazolyl group, thiazolyl group, isothiazolyl group, oxazolyl group, isooxazolyl group, oxadiazolyl group, thiadiazolyl group, triazolyl group, tetrazolyl group, pyridyl group, pyrimidyl group, pyridazinyl group, pyrazinyl group, triazinyl group, benzofuranyl group, benzothienyl group, benzothiadiazolyl group, benzothiazolyl group, benzoxazolyl group, benzoxadiazolyl group, benzoimidazolyl group, indolyl group, isoindolyl group, azaindolyl group, indazolyl group, quinolyl group, isoquinolyl group, cinnolinyl group, quinazolinyl group, quinoxalinyl group, benzodioxolyl group, indolidinyl group, and imidazopyridyl group.

[0233] Herein, "heterocyclyl" refers to a non-aromatic monovalent heterocyclic group in which the ring-constituting atoms include preferably one to five hetero atoms. The heterocyclyl may contain double or triple bonds in its ring. The carbon atoms may be oxidized to form carbonyl. The ring may be a monocyclic or condensed ring. The number of the ring-constituting atoms preferably ranges from three to ten (3- to 10-membered heterocyclyl).

[0234] Specifically, the heterocyclyl includes, for example, oxetanyl group, dihydrofuryl group, tetrahydrofuryl group, dihydropyranyl group, tetrahydropyranyl group, tetrahydropyridyl group, morpholinyl group, thiomorpholinyl group, pyrrolidinyl group, piperidinyl group, piperazinyl group, pyrazolidinyl group, imidazolinyl group, imidazolidinyl group, oxazolidinyl group, isooxazolidinyl group, thiazolidinyl group, isothiazolidinyl group, thiadiazolidinyl group, azetidinyl group, oxazolidone group, benzodioxanyl group, benzoxazolyl group, dioxolanyl group, and dioxanyl group.

[0235] Herein, "arylalkyl" refers to a group in which an arbitrary hydrogen atom in an "alkyl" defined above is substituted with an "aryl" defined above. The arylalkyl preferably includes C_{6-10} aryl C_{1-4} alkyl and C_{6-10} aryl C_{1-3} alkyl. Specifically, the arylalkyl includes, for example, benzyl group, phenethyl group, and naphthylmethyl group.

[0236] Herein, "heteroarylalkyl" refers to a group in which an arbitrary hydrogen atom in an alkyl defined above is substituted with a "heteroaryl" defined above. The heteroarylalkyl preferably includes 5- to 10-membered heteroaryl C_{1-3} alkyl. Specifically, the heteroarylalkyl includes, for example, pyrrolylmethyl group, imidazolylmethyl group, thienylmethyl group, pyridylmethyl group, pyrimidylmethyl group, quinolylmethyl group, and pyridylethyl group.

[0237] Herein, "heterocyclylalkyl" refers to a group in which an arbitrary hydrogen atom in an "alkyl" defined above is substituted with a "heterocyclyl" defined above. The heterocyclylalkyl preferably includes 3- to 10-membered heterocyclyl C_{1-3} alkyl. Specifically, the heterocyclylalkyl includes, for example, morpholinylmethyl group, morpholinylethyl group, thiomorpholinylmethyl group, pyrrolidinylmethyl group, piperidinylmethyl group, piperazinylmethyl group, piperazinylethyl group, and oxetanylmethyl group.

[0238] Herein, "monohydroxyalkyl" refers to a group in which an arbitrary hydrogen atom in an "alkyl" defined above is substituted with a hydroxyl group. The monohydroxyalkyl preferably includes C_{1-6} monohydroxyalkyl and C_{2-6} monohydroxyalkyl. Specifically, the monohydroxyalkyl includes, for example, hydroxymethyl group, 1-hydroxyethyl group, and 2-hydroxyethyl group.

[0239] Herein, "dihydroxyalkyl" refers to a group in which two arbitrary hydrogen atoms in an "alkyl" defined above are substituted with two hydroxyl groups. The dihydroxyalkyl preferably includes C_{1-6} dihydroxyalkyl and C_{2-6} dihydroxyalkyl. Specifically, the dihydroxyalkyl includes, for example, 1,2-dihydroxyethyl group, 1,2-dihydroxypropyl group, and 1,3-dihydroxypropyl group.

[0240] Herein, "trihydroxyalkyl" refers to a group in which three arbitrary hydrogen atoms in an "alkyl" defined above are substituted with three hydroxyl groups. The trihydroxyalkyl preferably includes C_{1-6} trihydroxyalkyl and C_{2-6} trihydroxyalkyl.

[0241] Herein, "alkoxyalkyl" refers to a group in which an arbitrary hydrogen atom in an "alkyl" defined above is substituted with an "alkoxy" defined above. The alkoxyalkyl preferably includes C_{1-3} alkoxy C_{1-4} alkyl and C_{1-3} alkoxy C_{2-4} alkyl. Specifically, the alkoxyalkyl includes, for example, methoxyethyl.

[0242] Herein, "alkoxyalkoxyalkyl" refers to a group in which an arbitrary hydrogen atom in the terminal alkyl of an "alkoxyalkyl" defined above is substituted with an "alkoxy" defined above. The alkoxyalkoxyalkyl preferably includes C_{1-3} alkoxy C_{1-4} alkoxy C_{1-4} alkyl and C_{1-3} alkoxy C_{2-4} alkoxy C_{2-4} alkyl.

[0243] Herein, "aminoalkyl" refers to a group in which an arbitrary hydrogen atom in an "alkyl" defined above is substituted with an amino group. The aminoalkyl group preferably includes C_{1-4} aminoalkyl and C_{2-4} aminoalkyl.

[0244] Herein, "alkylamino" refers to an amino group linked with an "alkyl" defined above. The alkylamino preferably includes C_{1-4} alkylamino.

[0245] Herein, "dialkylamino" refers to an amino group linked with two "alkyls" defined above. The two alkyl groups may be same or different. The dialkylamino preferably includes di(C_{1-4} alkyl)amino.

[0246] Herein, "alkylaminoalkyl" refers to a group in which an arbitrary hydrogen atom in an "alkyl" defined above is substituted with an "alkylamino" defined above. The alkylaminoalkyl preferably includes C_{1-4} alkylamino C_{1-4} alkyl and C_{1-4} alkylamino C_{2-4} alkyl.

[0247] Herein, "dialkylaminoalkyl" refers to a group in which an arbitrary hydrogen atom in an "alkyl" defined above is substituted with a "dialkylamino" defined above. The dialkylaminoalkyl preferably includes di(C_{1-4} alkyl)amino C_{1-4} alkyl and di(C_{1-4} alkyl)amino C_{2-4} alkyl.

[0248] Herein, "heterocyclylamino" refers to an amino group linked with a "heterocyclyl" defined above. The heterocyclylamino preferably includes 3- to 10-membered heterocyclylamino.

[0249] Herein, "cyanoalkyl" refers to a group in which an arbitrary hydrogen atom in an "alkyl" defined above is substituted with a cyano group. The cyanoalkyl preferably includes cyano(C_{1-3} alkyl).

[0250] Herein, "alkylsulfonyl" refers to a sulfonyl group linked with an "alkyl" defined above (i.e. alkyl-SO_2-). The alkylsulfonyl preferably includes C_{1-3} alkylsulfonyl. Specifically, the alkylsulfonyl includes methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, and i-propylsulfonyl.

[0251] Herein, "alkylsulfonylalkyl" refers to a group in which an arbitrary hydrogen atom in an "alkyl" defined above is substituted with an "alkylsulfonyl" defined above. The alkylsulfonylalkyl preferably includes C_{1-3} alkylsulfonyl C_{1-4} alkyl and C_{1-3} alkylsulfonyl C_{2-4} alkyl.

[0252] Preferably, the compounds represented by formula (I) shown above are as follows:

R_1 shown above preferably represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$,$-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted with one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3-to 10-membered heterocyclyl each of which is optionally substituted with one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$.

[0253] R_1 shown above more preferably represents hydrogen, hydroxy, halogen, cyano, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl,$-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_8$, COOH, C_{6-10} aryl which is optionally substituted with one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl each of which is optionally substituted with one or more groups independently selected from group Q. Specifically, the above 5- to 10-membered heteroaryl is particularly preferably an imidazolyl group, thienyl group, pyridyl group, pyridazinyl group, or pyrazolyl group. The above 3- to 10-membered heterocyclyl is particularly preferably a morpholinyl group, tetrahydropyridyl group, or piperidinyl group.

[0254] R_2 shown above preferably represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$,$-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted with one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3-to 10-membered heterocyclyl each of which is optionally substituted with one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$.

[0255] R_2 shown above more preferably represents hydrogen, halogen, C_{1-4} haloalkyl, C_{1-6} alkyl, $-OR_5$, C_{6-10} aryl which is optionally substituted with one or more groups independently selected from group P, or 5- to 10-membered heteroaryl which is optionally substituted with one or more groups independently selected from group Q. Specifically, this 5- to 10-membered heteroaryl is particularly preferably a pyridyl group.

[0256] R_1 and R_2 shown above can preferably be taken together with the atoms to which they are attached to form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl. The heterocyclyl or heteroaryl may have a halogen atom as a substituent. Specifically, the 3- to 10-membered heterocyclyl formed together with the atoms to which R_1 and R_2 are attached, is particularly preferably a dioxolanyl group or dioxanyl group.

[0257] R_3 shown above preferably represents hydrogen, C_{1-5} alkyl, C_{6-10} aryl C_{1-6} alkyl, or C_{1-4} haloalkyl, more preferably hydrogen, C_{1-4} alkyl, C_{6-10} aryl C_{1-4} alkyl, or C_{1-3}perfluoroalkyl, and particularly preferably C_1 alkyl.

[0258] R_4 shown above preferably represents hydrogen, halogen, C_{1-3} alkyl, C_{1-4} haloalkyl, hydroxy, cyano, nitro, C_{1-4} alkoxy, $-(CH_2)_nZ_1$, $-NR_6R_7$, $-OR_5$,$-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $NR_{17}SO_2R_{18}$, COOH, $-COR_{19}$, $-COOR_{20}$,$-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$-SO_3R_{31}, or $-Si(R_{32})_3$.

[0259] R_4 shown above more preferably represents hydrogen, halogen, C_{1-3} alkyl, C_{1-3} perfluoroalkyl, cyano, methanesulfonyl, hydroxyl, alkoxy, or amino, and particularly preferably hydrogen or halogen.

[0260] Ring A mentioned above is preferably a 5- to 10-membered heteroaryl ring or C_{6-10} aryl ring, more preferably benzene, indole, azaindole, benzofuran, benzothiophene, benzothiazole, quinoline, or pyrrole, and particularly preferably indole or pyrrole.

[0261] R_5 shown above preferably represents C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{1-3} alkoxy C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} amino alkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{6-10} aryl, C_{6-10} aryl C_{1-3} alkyl, or 3- to 10-membered heterocyclyl C_{1-3} alkyl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or 5- to 10-membered heteroaryl C_{1-3} alkyl, each of which is optionally substituted with one or more groups independently selected from group Q, C_{1-6} monohydroxyalkyl, C_{1-6} dihydroxyalkyl, or C_{1-6} trihydroxyalkyl.

[0262] R_5 shown above more preferably represents C_{1-5} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl, C_{6-10} aryl C_{1-3} alkyl, or 3- to 10-membered heterocyclyl C_{1-3} alkyl or 3- to 10-membered heterocyclyl each of which is optionally substituted with one or more groups independently selected from group Q. Specifically, the above 3- to 10-membered heterocyclylalkyl is particularly preferably a piperazinylethyl group, oxetanylmethyl group, or morpholinylethyl group. The above 3- to 10-membered heterocyclyl is particularly preferably an oxetanyl group or tetrahydropyranyl group.

[0263] R_6 and R_7 shown above may be the same or different, and each preferably represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{2-4} alkyl, C_{6-10} aryl C_{1-3} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5-to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxyalkyl, C_{1-6} dihydroxyalkyl, C_{1-6} trihydroxyalkyl, 3- to 10-membered heterocyclyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, or cyano(C_{1-3} alkyl).

[0264] R_6 and R_7 shown above more preferably each independently represent hydrogen, C_{1-3} alkoxy C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, or C_{1-6} dihydroxyalkyl. Specifically, the 3- to 10-membered heterocyclylalkyl is particularly preferably a morpholinylethyl group, and the 5- to 10-membered heteroarylalkyl is particularly preferably a pyridylethyl group.

[0265] Alternatively, R_6 and R_7 shown above can preferably be taken together with the nitrogen atoms to which they are attached to form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl.

[0266] "n" shown above represents an integer from 1 to 3. Preferably, n is 1.

[0267] R_8 and R_9 shown above preferably may be the same or different, and each represents hydrogen, C_{1-4} alkyl, or halogen, and more preferably hydrogen.

[0268] Alternatively, R_8 and R_9 shown above can preferably be taken together with the carbon atoms to which they are attached to form an alicyclic ring.

[0269] Z_1 shown above preferably represents hydrogen, $NR_{10}R_{11}$, -OH, or 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl each of which is optionally substituted with one or more groups independently selected from group Q, more preferably $NR_{10}R_{11}$ or -OH, or 3- to 10-membered heterocyclyl which is optionally substituted with one or more groups independently selected from group Q. Specifically, the above 3- to 10-membered heterocyclyl is particularly preferably a pyrrolidinyl group, piperazinyl group, piperidinyl group, or morpholinyl group.

[0270] R_{10} and R_{11} shown above preferably may be the same or different, and each preferably represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, cyano(C_{1-3} alkyl), or C_{1-3} alkylsulfonyl C_{1-4} alkyl, more preferably C_{1-4} alkyl, C_{2-6} alkynyl, or C_{1-3} alkoxy C_{2-4} alkyl.

[0271] Alternatively, R_{10} and R_{11} shown above can preferably be taken together with the nitrogen atoms to which they are attached to form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl.

[0272] R_{12} and R_{13} shown above preferably may be the same or different, and each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-

membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered alicyclic ring, more preferably hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl.

[0273] Alternatively, R_{12} and R_{13} shown above preferably can be taken together with the nitrogen atoms to which they are attached to form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl each of which is optionally substituted with one or more groups independently selected from group Q, and particularly preferably 3- to 10-membered heterocyclylalkyl. Specifically, piperazinyl group, morpholinyl group, pyrrolidinyl group, and piperidinyl group are more preferred.

[0274] R_{14} shown above preferably represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted with one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl each of which is optionally substituted with one or more groups independently selected from group Q, and more preferably represents C_{1-4} alkyl or C_{1-4} haloalkyl.

[0275] R_{15} shown above preferably represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted with one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl each of which is optionally substituted with one or more groups independently selected from group Q.

[0276] R_{16} shown above preferably represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted with one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl each of which is optionally substituted with one or more groups independently selected from group Q, and more preferably represents C_{1-4} alkyl.

[0277] R_{17} shown above preferably represents hydrogen or C_{1-4} alkyl, and more preferably hydrogen.

[0278] R_{18} shown above preferably represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted with one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl each of which is optionally substituted with one or more groups independently selected from group Q, and more preferably represents C_{1-4} alkyl.

[0279] R_{19} shown above preferably represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl each of which is optionally substituted with one or more groups independently selected from group Q, and more preferably represents hydrogen, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl each of which is optionally substituted with one or more groups independently selected from group Q. Specifically, this 3- to 10-membered heterocyclyl is more preferably a piperazinyl group, morpholinyl group, pyrrolidinyl group, or piperidinyl group.

[0280] R_{20} shown above preferably represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl.

[0281] R_{21} shown above preferably represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl.

[0282] R_{22} shown above preferably represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl.

[0283] R_{23} shown above preferably represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl.

[0284] R_{24} shown above preferably represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl.

[0285] R_{25} shown above preferably represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl.

[0286] R_{26} and R_{27} shown above preferably may be the same or different, and each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered alicyclic ring.

[0287] Alternatively, R_{26} and R_{27} shown above can preferably be taken together with the nitrogen atoms to which they are attached to form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl.

[0288] R_{28} and R_{29} shown above preferably may be the same or different, and each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered alicyclic ring.

[0289] Alternatively, R_{28} and R_{29} shown above preferably can be taken together with the nitrogen atoms to which they are attached to form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl.

[0290] R_{30} shown above preferably represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl.

[0291] R_{31} shown above preferably represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl.

[0292] R_{32} shown above preferably represents C_{1-4} alkyl, or C_{6-10} aryl.

[0293] Preferred substituents included in group P defined above are halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, 3- to 10-membered heterocyclylamino, $-SO_2R$, -CN, $-NO_2$, and 3- to 10-membered heterocyclyl; and more preferably halogen, C_{1-4} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, and 3- to 10-membered heterocyclyl. Specifically, this 3- to 10-membered heterocyclyl is particularly preferably a morpholinyl group.

[0294] Preferred substituents included in group Q defined above are halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-6} monohydroxyalkyl, C_{1-6} dihydroxyalkyl, C_{1-6} trihydroxyalkyl, 3- to 10-membered heterocyclylamino, $-SO_2R$ -CN, $-NO_2$, C_{3-7} cycloalkyl, $-COR_{19}$, and 3- to 10-membered heterocyclyl which is optionally substituted with C_{1-4} alkyl; and more preferably halogen, C_{1-4} alkyl, C_{1-4} haloalkyl,-OH, C_{1-3} alkoxy, C_{1-6} monohydroxyalkyl, $-SO_2R_{16}$, C_{3-7} cycloalkyl, $-COR_{19}$, and 3-to 10-membered heterocyclyl which is optionally substituted with C_{1-4} alkyl. Specifically, this 3- to 10-membered heterocyclyl is more preferably a piperazinyl group, piperidinyl group, or morpholinyl group.

[0295] Specific examples of the compounds include:

(1) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone;

(2) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-pyrrolidin-1-ylmethyl-1H-indol-2-yl)-methanone;

(3) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(4-hydroxy-piperidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(4) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-pyrrolo[3,2-c]pyridin-2-yl)-methanone;

(5) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-piperazin-1-ylmethyl-1H-indol-2-yl)-methanone;

(6) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2-morpholin-4-yl-ethoxy)-1H-indol-2-yl]-methanone;

(7) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(tetrahydropyran-4-yloxy)-1H-indol-2-yl]-methanone;

(8) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-chloro-1H-indol-2-yl)-methanone;

(9) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-bromo-1H-indol-2-yl)-methanone;

(10) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-iodo-1H-indol-2-yl)-methanone;

(11) 2-[5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazole-4-carbonyl]-1H-indole-5-carbonitrile;

(12) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-bromo-5-fluoro-1H-indol-2-yl)-methanone;

(13) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-ethynyl-1H-indol-2-yl)-methanone;

(14) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2-fluorophenyl)-1H-indol-2-yl]-methanone;

(15) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3-fluorophenyl)-1H-indol-2-yl]-methanone;

(16) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(4-fluorophenyl)-1H-indol-2-yl]-methanone;

(17) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2-chlorophenyl)-1H-indol-2-yl]-methanone;

(18) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3-chlorophenyl)-1H-indol-2-yl]-methanone;

(19) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(4-chlorophenyl)-1H-indol-2-yl]-methanone;

(20) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2-trifluoromethyl-phenyl)-1H-indol-2-yl]-methanone;

(21) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3-trifluoromethyl-phenyl)-1H-indol-2-yl]-methanone;

(22) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(4-trifluoromethyl-phenyl)-1H-indol-2-yl]-methanone;

(23) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-bromo-1H-indol-2-yl)-methanone;

(24) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3-fluoro-pyridin-2-yl)-1H-indol-2-yl]-methanone;

(25) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-methyl-1H-indol-2-yl)-methanone;

(26) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(4,4-difluoro-piperidine-1-carbonyl)-1H-indol-2-yl]-methanone;

(27) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(3,3-difluoro-piperidine-1-carbonyl)-1H-indol-2-yl]-methanone;

(28) 2-[5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazole-4-carbonyl]-1H-indole-5-carboxylic acid (2,2,2-trifluoro-ethyl)-amide;

(29) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(5-trifluoromethyl-pyridin-2-yl)-1H-indol-2-yl]-methanone;

(30) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(6-trifluoromethyl-pyridin-2-yl)-1H-indol-2-yl]-methanone;

(31) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(5-chloro-pyridin-2-yl)-1H-indol-2-yl]-methanone;

(32) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(4-methyl-pyridin-2-yl)-1H-indol-2-yl] methanone;

(33) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3-chloro-4-fluoro-phenyl)-1H-indol-2-yl]-methanone;

(34) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3-trifluoromethyl-pyridin-2-yl)-1H-indol-2-yl]-methanone;

(35) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(4-trifluoromethyl-pyridin-2-yl)-1H-indol-2-yl] methanone;

(36) [5-amino-1-(6-fluoro-2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone;

(37) 2-[5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazole-4-carbonyl]-1H-indole-6-carboxylic acid;

(38) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-hydroxymethyl-1H-indol-2-yl)-methanone;

(39) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-{6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-1H-indol-2-yl}-methanone;

(40) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3-methyl-oxetan-3-ylmethoxy)-1H-indol-2-yl]-methanone;

(41) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3-fluoro-piperidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(42) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-{[bis(2-methoxy-ethyl)-amino]-methyl}-1H-indol-2-yl)-methanone;

(43) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-{6-[(methyl-prop-2-ynyl-amino)-methyl]-1H-indol-2-yl}-methanone;

(44) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3,3-difluoro-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(45) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2,5-dimethyl-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(46) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3,3-difluoro-piperidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(47) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-((S)-3-methyl-morpholin-4-ylmethyl)-1H-indol-2-yl]-methanone;

(48) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-bromo-1H-indol-2-yl)-methanone;

(49) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-iodo-1H-indol-2-yl)-methanone;

(50) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-pyrrolo[3,2-b]pyridin-2-yl)-methanone;

(51) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-bromo-6-trifluoromethyl-1H-indol-2-yl)-methanone;

(52) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-iodo-1H-indol-2-yl)-methanone;

(53) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-methyl-1H-indol-2-yl)-methanone;

(54) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-isopropyl-1H-indol-2-yl)-methanone;

(55) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(2-fluorophenyl)-1H-indol-2-yl]-methanone;

(56) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-benzyl-1H-indol-2-yl)-methanone;

(57) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(2-trifluoromethyl-phenyl)-1H-indol-2-yl]-methanone;

(58) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(3-fluorophenyl)-1H-indol-2-yl]-methanone;

(59) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(3-trifluoromethyl-phenyl)-1H-indol-2-yl]-methanone;

(60) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-ethynyl-1H-indol-2-yl)-methanone;

(61) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5H-[1,3]dioxolo[4,5-f]indol-6-yl)-methanone;

(62) [5-amino-1-(7-fluoro-2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone;

(63) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(4-trifluoromethyl-phenyl)-1H-indol-2-yl]-methanone;

(64) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-butoxy-1H-indol-2-yl)-methanone;

(65) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(1-methyl-piperidin-4-yl)-1H-indol-2-yl] methanone;

(66) N-{2-[5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazole-4-carbonyl]-1H-indol-6-yl}-methanesulfonamide;

(67) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(6-morpholin-4-yl-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(68) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-butyl-1H-indol-2-yl)-methanone;

(69) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(1-methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-methanone;

(70) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(5-methoxy-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(71) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2-methoxy-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(72) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-cyclopropyl-1H-indol-2-yl)-methanone;

(73) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2-methoxyphenyl)-1H-indol-2-yl]-methanone;

(74) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-phenyl-1H-indol-2-yl)-methanone;

(75) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(5-methanesulfonyl-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(76) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-isopropyl-1H-indol-2-yl)-methanone;

(77) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-pyridin-2-yl-1H-indol-2-yl)-methanone;

(78) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-cyclopropyl-1H-indol-2-yl)-methanone;

(79) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-pyridazin-3-yl-1H-indol-2-yl)-methanone;

(80) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-isopropoxy-1H-indol-2-yl)-methanone;

(81) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(2-methoxy-ethoxy)-1H-indol-2-yl]-methanone;

(82) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-cyclopropylmethoxy-1H-indol-2-yl)-methanone;

(83) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(2,2-difluoro-5H-[1,3]dioxolo[4,5-f]indol-6-yl)-methanone;

(84) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3-chloro-pyridin-2-yl)-1H-indol-2-yl]-methanone;

(85) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(5-fluoro-pyridin-2-yl)-1H-indol-2-yl]-methanone;

(86) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(6-morpholin-4-yl-pyridazin-3-yl)-1H-indol-2-yl]-methanone;

(87) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-chloro-6-cyclopropylmethoxy-1H-indol-2-yl)-methanone;

(88) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2,4-difluorophenyl)-1H-indol-2-yl]-methanone;

(89) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-pyridazin-4-yl-1H-indol-2-yl)-methanone;

(90) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(3-fluoro-1H-indol-2-yl)-methanone;

(91) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(1-isopropyl-piperidin-4-yl)-6-trifluoromethyl-1H-indol-2-yl]-methanone;

(92) 2-[5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazole-4-carbonyl]-1H-indole-6-carbonitrile;

(93) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-2-yl]-methanone;

(94) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-piperidin-4-yl-1H-indol-2-yl)-methanone;

(95) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-((R)-3-fluoro-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(96) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-fluoro-5-piperidin-4-yl-1H-indol-2-yl)-methanone;

(97) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-fluoro-5-(1-methyl-piperidin-4-yl)-1H-indol-2-yl]-methanone;

(98) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(1-isopropyl-piperidin-4-yl)-1H-indol-2-yl]-methanone;

(99) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-fluoro-5-(1-isopropyl-piperidin-4-yl)-1H-indol-2-yl]-methanone;

(100) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-pyridin-3-yl-1H-indol-2-yl)-methanone;

(101) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(6-morpholin-4-yl-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(102) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-pyridin-3-yl-1H-indol-2-yl)-methanone;

(103) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(6-piperazin-1-yl-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(104) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(6-hydroxy-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(105) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-fluoro-5-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(106) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-fluoro-5-pyrrolidin-1-ylmethyl-1H-indol-2-yl)-methanone;

(107) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(1-methyl-piperidin-4-yl)-1H-indol-2-yl]-methanone;

(108) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(4-morpholin-4-yl-phenyl)-1H-indol-2-yl]-methanone;

(109) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3,4,5,6-tetrahydro-2H-[1,2']bipyridin-5'-yl)-

1H-indol-2-yl]-methanone;

(110) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(6-piperazin-1-yl-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(111) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(6-methoxy-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(112) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-((S)-3-methyl-morpholin-4-ylmethyl)-1H-indol-2-yl]-methanone;

(113) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-((R)-3-fluoro-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(114) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(2,5-dimethyl-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(115) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(3-fluoro-piperidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(116) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(3,3-difluoro-piperidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(117) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-{6-[2-(4-methyl-piperazin-1-yl)pyridin-4-yl]-1H-indol-2-yl}-methanone;

(118) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-pyridin-4-yl-1H-indol-2-yl)-methanone;

(119) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(4-fluoropiperidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(120) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(4,4-difluoro-piperidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(121) [5-amino-1-(2-difluoromethyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(1-methyl-piperidin-4-yl)-1H-indol-2-yl]-methanone;

(122) [5-amino-1-(2-difluoromethyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone;

(123) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(3,3-difluoro-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(124) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(1-cyclopentyl-piperidin-4-yl)-1H-indol-2-yl]-methanone;

(125) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(1-cyclohexyl-piperidin-4-yl)-1H-indol-2-yl]-methanone;

(126) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-bromo-1H-pyrrol-2-yl)-methanone;

(127) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-pyrrol-2-yl)-methanone;

(128) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-phenyl-1H-pyrrol-2-yl)-methanone;

(129) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4-(3-chlorophenyl)-1H-pyrrol-2-yl]-methanone;

(130) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4-(4-fluorophenyl)-1H-pyrrol-2-yl]-methanone;

(131) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4-(3-fluorophenyl)-1H-pyrrol-2-yl]-methanone;

(132) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-morpholin-4-ylmethyl-1H-indol-2-yl)-methanone;

(133) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4-(2-morpholin-4-yl-ethylamino)-1H-indol-2-yl]-methanone;

(134) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(4-methylpiperazine-1-carbonyl)-1H-indol-2-yl]-methanone;

(135) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2-morpholin-4-yl-ethylamino)-1H-indol-2-yl]-methanone;

(136) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(piperazine-1-carbonyl)-1H-indol-2-yl]-methanone;

(137) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4-(2-methoxy-ethylamino)-1H-indol-2-yl]-methanone;

(138) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4-(2-hydroxy-1-hydroxymethyl-ethylamino)-1H-indol-2-yl]-methanone;

(139) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4-(2-pyridin-4-yl-ethylamino)-1H-indol-2-yl]-methanone;

(140) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2-methoxy-ethylamino)-1H-indol-2-yl]-methanone;

(141) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-morpholin-4-yl-1H-indol-2-yl)-methanone;

(142) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-morpholin-4-yl-1H-indol-2-yl)-methanone;

(143) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-morpholin-4-ylmethyl-1H-indol-2-yl)-methanone;

(144) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-morpholin-4-ylmethyl-1H-indol-2-yl)-methanone;

(145) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(morpholine-4-carbonyl)-1H-indol-2-yl]-methanone;

(146) [5-amino-1-(2-isopropyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone;

(147) [5-amino-1-(2-propyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone;

(148) [5-amino-1-(1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone;

(149) [5-amino-1-(2-trifluoromethyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone;

(150) [5-amino-1-(2-ethyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone;

(151) [5-amino-1-(2-benzyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)methanone;

(152) 1-(4-{2-[5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazole-4-carbonyl]-1H-indol-5-ylmethyl}-piperazin-1-yl)-ethanone;

(153) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-

1H-indol-2-yl]-methanone;

(154) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-piperazin-1-ylmethyl-1H-indol-2-yl)-methanone;

(155) 1-(4-{2-[5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazole-4-carbonyl]-1H-indol-6-ylmethyl}-piperazin-1-yl)-ethanone;

(156) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(157) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(158) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-pyrrolidin-1-ylmethyl-1H-indol-2-yl)-methanone;

(159) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-fluoro-1H-indol-2-yl)-methanone;

(160) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-fluoro-1H-indol-2-yl)-methanone;

(161) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-fluoro-1H-indol-2-yl)-methanone;

(162) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-pyrrolo[2,3-b]pyridin-2-yl)-methanone;

(163) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-fluoro-6-morpholin-4-ylmethyl-1H-indol-2-yl)-methanone;

(164) 2-[5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazole-4-carbonyl]-1H-indole-5-carboxylic acid;

(165) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-methoxy-1H-indol-2-yl)-methanone;

(166) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4,6-dimethoxy-1H-indol-2-yl)-methanone;

(167) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-methoxy-1H-indol-2-yl)-methanone;

(168) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-methoxy-1H-indol-2-yl)-methanone;

(169) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4,6-dimethyl-1H-indol-2-yl)-methanone;

(170) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-*tert*-butyl-1H-indol-2-yl)-methanone;

(171) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-isopropyl-1H-indol-2-yl)-methanone;

(172) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-benzyloxy-1H-indol-2-yl)-methanone;

(173) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-benzyloxy-1H-indol-2-yl)-methanone;

(174) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5,6-dimethoxy-1H-indol-2-yl)-methanone;

(175) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-*tert*-butyl-1H-indol-2-yl)-methanone;

(176) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-fluoro-4-trifluoromethyl-1H-indol-2-yl)-methanone;

(177) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-phenoxy-1H-indol-2-yl)-methanone;

(178) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-methylsulfanyl-1H-indol-2-yl)-methanone;

(179) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-*tert*-butyl-1H-indol-2-yl)-methanone;

(180) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-methyl-1H-indol-2-yl)-methanone;

(181) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-ethyl-1H-indol-2-yl)-methanone;

(182) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-fluoro-6-trifluoromethyl-1H-indol-2-yl)-methanone;

(183) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-fluoro-5-methoxy-1H-indol-2-yl)-methanone;

(184) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-chloro-5-methoxy-1H-indol-2-yl)-methanone;

(185) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-chloro-6-methoxy-1H-indol-2-yl)-methanone;

(186) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-isopropoxy-1H-indol-2-yl)-methanone;

(187) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-benzyloxy-1H-indol-2-yl)-methanone;

(188) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-isopropoxy-1H-indol-2-yl)-methanone;

(189) (5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(2,3-dihydro-6H-[1,4]dioxino[2,3-f]indol-7-yl)-methanone;

(190) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4,6-di-*tert*-butyl-1H-indol-2-yl)-methanone;

(191) 2-[5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazole-4-carbonyl]-1H-indole-4-carbonitrile;

(192) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-imidazol-1-yl-1H-indol-2-yl)-methanone;

(193) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-trifluoromethylsulfanyl-1H-indol-2-yl)-methanone;

(194) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-methylsulfanyl-1H-indol-2-yl)-methanone;

(195) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-methanesulfonyl-1H-indol-2-yl)-methanone;

(196) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(4,4-difluoro-piperidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(197) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(4-fluoro-piperidin-1-ylmethyl)-1H-indol-2-yl]-methanone;

(198) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(oxetan-3-yloxy)-1H-indol-2-yl]-methanone;

(199) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-hydroxy-1H-indol-2-yl)-methanone;

(200) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-methanesulfonyl-1H-indol-2-yl)-methanone;

(201) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4,5-dibromo-1H-pyrrol-2-yl)-methanone;

(202) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4,5-diphenyl-1H-pyrrol-2-yl)-methanone; and

(203) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4,5-dipyridin-3-yl-1H-pyrrol-2-yl)-methanone.

(204) [5-amino-1-(2-methyl-3H- benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-chloro-1H-indol-2-yl)-methanone;

(205) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-chloro-1H-indol-2-yl)-methanone;

(206) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-3-yl)-methanone;

(207) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-6-yl)-methanone;

(208) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-bromo-6-fluoro-1H-indol-2-yl)-methanone;

(209) [5-amino-1-(2-ethyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-bromo-6-fluoro-1H-indol-2-yl)-methanone;

(210) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-trifluoromethyl-1H-indol-2-yl)-methanone;

(211) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-trifluoromethoxy-1H-indol-2-yl)-methanone;

(212) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4,6-dichloro-1H-indol-2-yl)-methanone;

(213) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-bromo-4-fluoro-1H-indol-2-yl)-methanone;

(214) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-trifluoromethoxy-1H-indol-2-yl)-methanone;

(215) [5-amino-1-(2-ethyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-trifluoromethoxy-1H-indol-2-yl)-methanone;

(216) [5-amino-1-(2-ethyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5-trifluoromethyl-1H-indol-2-yl)-methanone;

(217) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(5,6-dichloro-1H-indol-2-yl)-methanone;

(218) [5-amino-1-(2-ethyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-bromo-5-fluoro-1H-indol-2-yl)-methanone;

(219) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4,5-dichloro-1H-indol-2-yl)-methanone;

(220) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4,6-difluoro-1H-indol-2-yl)-methanone;

(221) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3-chloro-pyridin-4-yl)-1H-indol-2-yl]-methanone;

(222) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(6-methylpyridine-3-yl)-1H-indol-2-yl]-methanone;

(223) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(5-fluoro-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(224) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2-trifluoromethyl-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(225) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(5-chloro-2-methoxy-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(226) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(5-chloro-pyridin-3-yl)-1H-indol-2-yl]-methanone;

(227) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-thiophen-3-yl-1H-indol-2-yl)-methanone;

(228) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(4-chloropyridin-3-yl)-1H-indol-2-yl]-methanone;

(229) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(6-thiophen-2-yl-1H-indol-2-yl)-methanone;

(230) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(3-fluoro-pyridin-4-yl)-1H-indol-2-yl]-methanone;

(231) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[6-(2-trifluoromethyl-pyridin-4-yl)-1H-indol-2-yl]-methanone;

(232) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(3,3-difluoro-pyrrolidine-1-carbonyl)-1H-indol-2-yl]-methanone;

(233) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(2,6-dimethyl-morpholine-4-carbonyl)-1H-indol-2-yl]-methanone;

(234) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-([1,4'] bipiperidinyl-1'-carbonyl)-1H-indol-2-yl]-methanone;

(235) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-{5-[4-(2,2,2-trifluoro-ethyl)-piperazine-1-carbonyl]-1H-indol-2-yl}-methanone;

(236) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-{5-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-1H-indol-2-yl}-methanone;

(237) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(3,3,4,4-tetrafluoro-pyrrolidine-1-carbonyl)-1H-indol-2-yl]-methanone;

(238) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-((R)-3-fluoro-pyrrolidine-1-carbonyl)-1H-indol-2-yl]-methanone;

(239) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-((S)-3-fluroro-pyrrolidine-1-carbonyl)-1H-indol-2-yl]-methanone;

(240) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4-(4-methoxyphenyl)-1H-pyrrol-2-yl]-methanone;

(241) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4-(3-methoxyphenyl)-1H-pyrrol-2-yl]-methanone;

(242) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4,5-bis-(3-fluoro-phenyl)-1H-pyrrol-2-yl]-methanone;

(243) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4,5-bis-(4-methoxy-phenyl)-1H-pyrrol-2-yl]-methanone;

(244) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4-(2,4-difluorophenyl)-1H-pyrrol-2-yl]-methanone;

(245) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4-(4-trifluoromethoxy-phenyl)-1H-pyrrol-2-yl]-methanone;

(246) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[4,5-bis-(3-methoxy-phenyl)-1H-pyrrol-2-yl]-methanone;

(247) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-benzofuran-2-yl-methanone;

(248) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-benzo[b] thiophen-2-yl-methanone;

(249) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-benzothiazol-2-yl-methanone;

(250) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(4-fluorophenyl)-methanone;

(251) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(3-chlorophenyl)-methanone;

(252) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-quinolin-3-yl-methanone;

(253) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-quinolin-7-yl-methanone; and

(254) [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-quinolin-6-yl-methanone.

[0296] More specific examples include compounds in which A is indole and R_3 and R_4 are both hydrogen in formula (I) described above, and compounds shown in Tables 1 and 2 in the Examples described later can be included as examples.

[0297] The above-mentioned compounds can be produced according to the production method described in International Publication WO 2011/016528.

[0298] In the present invention, compounds having FGFR inhibitory activity as describe above include not only free forms but also pharmaceutically acceptable salts thereof.

[0299] Such "salts" include, for example, inorganic acid salts, organic salts, inorganic base salts, organic base salts, and acidic or basic amino acid salts.

[0300] Preferred inorganic acid salts include, for example, hydrochloride, hydrobromide, sulfate, nitrate, and phosphate. Preferred organic salts include, for example, acetate, succinate, fumarate, maleate, tartrate, citrate, lactate, malate, stearate, benzoate, methanesulfonate, and p-toluenesulfonate. A particularly preferred salt in the present invention is malate.

[0301] Preferred inorganic base salts include, for example, alkali metal salts such as sodium salts and potassium salts; alkali earth metal salts such as calcium salts and magnesium salts; aluminum salts; and ammonium salts. Preferred organic base salts include, for example, diethylamine salts, diethanolamine salts, meglumine salts, and N,N-dibenzylethylenediamine salts.

[0302] Preferred acidic amino acid salts include, for example, aspartate and glutamate. Preferred basic amino acid salts include, for example, arginine salts, lysine salts, and ornithine salts.

[0303] In the present invention, compounds having FGFR inhibitory activity also include hydrates thereof. Furthermore, in the present invention, compounds having FGFR inhibitory activity may absorb some type of solvents to form solvates. Such solvates are also included.

[0304] In addition, compounds having FGFR inhibitory activity in the present invention include all possible structural isomers (geometric isomers, optical isomers, stereoisomers, tautomers, etc.), and mixtures of isomers.

[0305] Compounds having FGFR inhibitory activity in the present invention also include any crystalline polymorphism thereof.

[0306] In the present invention, compounds having FGFR inhibitory activity also include prodrugs thereof. "Prodrug" refers to derivatives of the compounds of the present invention which have a chemically or metabolically degradable group, and upon administration to the living body, revert to the original compounds and exhibit the original drug efficacy. The prodrugs include non-covalent complexes and salts.

[0307] In the present invention, compounds having FGFR inhibitory activity include those in which one or more atoms within the molecule have been replaced with isotopes. Herein, "isotope" refers to an atom which has the same atomic number (proton number) but different mass number (sum of protons and neutrons). The target atoms to be replaced with an isotope in the compounds of the present invention include, for example, hydrogen atom, carbon atom, nitrogen atom, oxygen atom, phosphorus atom, sulfur atom, fluorine atom, and chlorine atom. Their isotopes include ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl. In particular, radioisotopes such as ^{3}H and ^{14}C, which emit radiation and decay, are useful in *in vivo* tissue distribution studies or such of pharmaceuticals or compounds. Stable isotopes do not decay, and thus their quantity rarely changes; and since there is no emission of radiation, stable isotopes can be used safely. The compounds of the present invention can be converted into isotope-substituted compounds according to routine methods by replacing reagents used in synthesis with reagents containing corresponding isotopes.

[0308] Herein, "anticancer agent" or "pharmaceutical composition for treating cancer" which comprises an FGFR inhibitor are used interchangeably, and refers to a cancer therapeutic composition that comprises an above-described compound having FGFR inhibitory activity and pharmaceutically acceptable carriers.

[0309] The compounds having FGFR inhibitory activity of the present invention can be formulated into tablets, powders, fine granules, granules, coated tablets, capsules, syrups, troches, inhalants, suppositories, injections, ointments, eye ointments, eye drops, nasal drops, ear drops, cataplasms, lotions, and such by routine methods. For the formulation, conventional excipients, binders, lubricants, colorants, flavoring agents, and if needed, stabilizers, emulsifiers, absorbefacients, surfactants, pH adjusting agents, preservatives, antioxidants, and such can be used. The compounds of the present invention are formulated using routine methods, by combining ingredients that are generally used as materials for pharmaceutical preparations.

[0310] For example, to produce oral formulations, the compounds of the present invention or pharmacologically acceptable salts thereof are combined with excipients, and if needed, binders, disintegrating agents, lubricants, coloring agents, flavoring agents, and the like; and then formulated into powders, fine granules, granules, tablets, coated tablets, capsules, and such by routine methods.

[0311] The ingredients include, for example, animal and vegetable oils such as soybean oils, beef tallow, and synthetic glycerides; hydrocarbons such as liquid paraffin, squalane, and solid paraffin; ester oils such as octyldodecyl myristate and isopropyl myristate; higher alcohols such as cetostearyl alcohol and behenyl alcohol; silicon resins; silicon oils; surfactants such as polyoxyethylene fatty acid esters, sorbitan fatty acid esters, glycerin fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene hydrogenated castor oils, and polyoxyethylene/polyoxypropylene block copolymers; water-soluble polymers such as hydroxyethyl cellulose, polyacrylic acids, carboxyvinyl polymers, polyethylene glycol, polyvinylpyrrolidone, and methyl cellulose; lower alcohols such as ethanol and isopropanol; polyalcohols such as glycerin, propylene glycol, dipropylene glycol, and sorbitol; saccharides such as glucose and sucrose; inorganic powders such as silicic anhydride, magnesium aluminum silicate, and aluminum silicate; and purified water.

[0312] Excipients include, for example, lactose, cornstarch, sucrose, glucose, mannitol, sorbit, crystalline cellulose, and silicon dioxide.

[0313] Binders include, for example, polyvinyl alcohol, polyvinyl ether, methyl cellulose, ethyl cellulose, Arabic gum, tragacanth, gelatin, shellac, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, polypropylene glycol/polyoxyethylene block polymer, and meglumine.

[0314] Disintegrating agents include, for example, starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, dextran, pectin, and calcium carboxymethyl cellulose.

[0315] Lubricants include, for example, magnesium stearate, talc, polyethylene glycol, silica, and hardened vegetable oil.

[0316] Coloring agents approved for use as additives for pharmaceuticals are used. Flavoring agents used include, for example, cacao powder, menthol, aromatic powder, peppermint oil, borneol, and cinnamon powder.

[0317] Of course, these tablets and granules may be coated with sugar, or if needed, other appropriate coatings. Alternatively, when liquid preparations such as syrups and injections are produced, the compounds of the present invention or pharmacologically acceptable salts thereof are combined with pH adjusting agents, solubilizers, isotonizing agents, or such, and if needed, solubilizing agents, stabilizers, and such, and then formulated using routine methods.

[0318] Methods for producing external preparations are not limited, and they can be produced by conventional methods. Various conventional materials for pharmaceuticals, quasi-drugs, cosmetics, and such can be used as base materials in the production. Specifically, the base materials used include, for example, animal and vegetable oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicon oils, surfactants, phospholipids, alcohols, polyalcohols, water-soluble polymers, clay minerals, and purified water. Furthermore, as necessary, it is possible to add pH-adjusting agents, antioxidants, chelating agents, preservatives, colorants, flavoring agents, and such. However, the base materials for external preparations of the present invention are not limited thereto.

[0319] Furthermore, if needed, the preparations may be combined with components that have an activity of inducing differentiation, or components such as blood flow-enhancing agents, antimicrobial agents, antiphlogistic agents, cell-activating agents, vitamins, amino acids, humectants, and keratolytic agents. The amount of above-described base materials added is a quantity that provides a concentration typically selected in the production of external preparations.

[0320] The anticancer agents (granular pharmaceutical compositions for treating cancer) for administering a compound having FGFR inhibitory activity in the present invention are not particularly limited in their dosage form; and the agents may be administered orally or parenterally by commonly used methods. They can be formulated and administered as, for example, tablets, powders, granules, capsules, syrups, troches, inhalants, suppositories, injections, ointments, eye ointments, eye drops, nose drops, ear drops, cataplasms, lotions, etc.

[0321] In the present invention, the dosage of an FGFR inhibitor contained in an anticancer agent or a pharmaceutical composition for treating cancer can be appropriately selected according to the severity of symptoms, age, sex, weight, dosage form, salt type, specific type of disease, and such.

[0322] The dosage varies considerably depending on the patient's disease type, symptom severity, age, sex, sensitivity to the agent, and such. Typically, the agent is administered to an adult once or several times a day at a daily dose of about 0.03 to 1,000 mg, preferably 0.1 to 500 mg, and more preferably 0.1 to 100 mg. The agents or compositions of the present invention are administered once or several times a day. When an injection is used, the daily dose is generally about 1 μg/kg to 3,000 μg/kg, and preferably about 3 μg/kg to 1,000 μg/kg.

[0323] The present invention also relates to pharmaceutical compositions for treating cancer which comprise an above-described compound having FGFR inhibitory activity, and are characterized by their use of being administered to patients expressing a fusion polypeptide of the present invention or carrying a polynucleotide encoding the fusion polypeptide.

[0324] The present invention further relates to methods for treating or preventing cancer which comprise administering an effective amount of the above-mentioned compounds having FGFR inhibitory activity or pharmaceutically acceptable salts thereof to patients expressing the fusion polypeptides or carrying the polynucleotides; use of compounds having

FGFR inhibitory activity or pharmaceutically acceptable salts thereof in the production of pharmaceutical compositions for cancer treatment for administration to patients expressing the fusion polypeptides or carrying the polynucleotides; compounds having FGFR inhibitory activity or pharmaceutically acceptable salts thereof for use in treatment or prevention for patients expressing the fusion polypeptides or carrying the polynucleotides; and such.

[0325] Specifically, use of the pharmaceutical compositions for treating cancer is characterized in that whether a patient expresses the fusion polypeptide or carries a polynucleotide encoding the fusion polypeptide is tested using a fusion polypeptide of the present invention as a biomarker before an above-described anticancer agent comprising an FGFR inhibitor is administered to the patient, and the anticancer agent containing an FGFR inhibitor is administered to the patient only if the patient expresses the fusion polypeptide or carries a polynucleotide encoding the fusion polypeptide. This enables one to avoid side effects in therapies using the agent and control the therapeutic condition to produce the best therapeutic effect, thus enabling personalized medicine.

[0326] In the present invention, specifically in the case of bladder cancer, the fusion genes of the present invention are found to be significantly expressed when bladder cancer progresses to stage 3 or later in stage classification.

[0327] Stage classification of bladder cancer is, specifically, classification by TNM classification. TNM classification is composed of a T factor (initial of tumor) showing the extent of tumor, an N factor (initial of lymph node) showing the presence or absence of lymph node metastasis of tumor, and an M factor (initial of metastasis) showing the presence or absence of distal metastasis other than lymph node metastasis. Among them, cancers in which the tumor has infiltrated into the subepithelial connective tissue are classified as stage 1, those in which the tumor has infiltrated into muscularis propria are classified as stage 2, those in which the tumor has infiltrated into the fatty tissue surrounding the bladder to those in which the tumor has infiltrated into any one of prostate interstitium, uterus, or vagina are classified as stage 3, and those in which the tumor has infiltrated into either the pelvic wall or the abdomen wall, or those that show lymph node metastasis or distal metastasis are classified as stage 4.

[0328] Whether a patient expresses a fusion polypeptide of the present invention or carries a polynucleotide encoding the fusion polypeptide can be tested by using methods of the present invention described above.

[0329] The present description also relates to methods for identifying compounds having FGFR inhibitory activity.

[0330] Specifically, methods for identifying compounds having FGFR inhibitory activity include methods comprising the steps of:

(a) culturing cells that express a fusion polypeptide of the present invention in the presence or absence of a test compound and determining the level of cell proliferation;

(b) comparing the proliferation level of cultured cell between in the presence and absence of the test compound; and

(c) judging that the test compound has FGFR inhibitory activity when the proliferation level of the cell cultured in the presence of the test compound is lower than that of the cell cultured in the absence of the test compound.

[0331] Cells used for the above method may be living cells, established cell lines, or recombinant cells, as long as they express a fusion polypeptide of the present invention. Such recombinant cells include those introduced with an above-described vector carrying a polynucleotide encoding a fusion polypeptide of the present invention.

[0332] Meanwhile, the living cells include cells collected from cancer patients. The established cell lines include cancer cell lines established from cancer cells collected from cancer patients.

[0333] Cancer includes any cancer described above.

[0334] Methods for identifying compounds having FGFR inhibitory activity also include those comprising the steps of:

(a) administering a test compound to a non-human mammal transplanted with cells that express an above-described fusion polypeptide of the present invention and determining the proliferation level of the cells;

(b) comparing the cell proliferation level determined in step (a) with that determined using a non-human mammal transplanted with the cells but not administered with the test compound; and

(c) judging that the test compound has FGFR inhibitory activity when the cell proliferation level determined in step (a) is lower than that determined using a non-human mammal transplanted with the cells but not administered with the test compound.

[0335] Cells used for the above method may be living cells, established cell lines, or recombinant cells, as long as they express a fusion polypeptide of the present invention. Such recombinant cells include those introduced with an above-described vector carrying a polynucleotide encoding a fusion polypeptide of the present invention.

[0336] Meanwhile, the living cells include cells collected from cancer patients. The established cell lines include cancer cell lines established from cancer cells collected from cancer patients.

[0337] Cancer includes any cancer described above.

[0338] In the methods of the present invention, the cell proliferation level can be tested according to routine methods, for example, by colorimetric methods that measure the enzyme activity of reducing a dye (MTT, XTT, MTS, WST, etc.) to formazan dye (purple).

[0339] When the above-described cells are cancer cells, the cell proliferation level can also be determined by measuring the volume or weight of tumor formed as a result of cell proliferation.

[0340] Methods for identifying compounds having FGFR inhibitory activity also comprise embodiments that use reporter gene assays.

[0341] Reporter genes include commonly-used genes encoding arbitrary fluorescent proteins, for example, the green fluorescent protein (GFP) derived from *Aequorea coerulescens,* luciferase derived from *Renilla reniformis* or such, reef coral fluorescent proteins (RCFPs) derived from hermatypic coral, fruit fluorescent proteins, and variants thereof.

[0342] Reporter gene assay can be carried out, for example, as follows.

[0343] Recombinant cells are prepared by transforming cells that are typically used for producing recombinant proteins with an expression vector inserted with a polynucleotide encoding the fusion polypeptide of the present invention and a gene encoding a reporter protein, so that the reporter protein-encoding gene is transcribed into mRNA dependently on the signal that transcribes the fusion polypeptide-encoding polynucleotide into mRNA. A test compound is contacted with the obtained transformed cells. Whether the compound affects the expression of the fusion polypeptide is indirectly analyzed by determining the expression level of the fusion polypeptide, which depends on the compound activity, by measuring the intensity of fluorescence emitted by the reporter protein simultaneously expressed with the fusion polypeptide (for example, US Patent No. 5,436,128; US Patent No. 5,401,629).

[0344] Identification of the compounds using the above-described assay can be achieved by manual operation; however, it can also be done readily and simply by so-called "high-throughput screening" using robots automatically (Soshiki Baiyou Kougaku (The Tissue Culture Engineering), Vol. 23, No.13, p.521-524; US Patent No. 5,670,113).

[0345] Hereinbelow, the present invention is specifically described using the Examples, but it is not to be construed as being limited thereto.

[0346] Unless otherwise specified, each assay step can be performed according to known methods.

[0347] Meanwhile, when using commercially available reagents, kits, or such, assays can be performed according to manuals included in the commercial products.

[Example 1]

[0348] Expression of fusion polypeptides between FGFR3 and other polypeptides in various cancer cells

(1) RNA analysis

[0349] RNA was extracted with the miRNeasy Mini Kit (QIAGEN) from each of the four FGFR3-expressing human cell lines derived from bladder cancer, RT112/84 (available from European Collection of Cell Cultures (ECACC); catalog No. 85061106), RT4 (available from American Type Culture Collection (ATCC); catalog No. HTB-2), SW780 (available from ATCC; catalog No. CRL-2169), and BFTC-905 (available from Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ); catalog No. ACC 361). The sequences were determined using paired-end reads (Read Length: 2x75bp) of the HiSeq™ Sequencing system (illumina).

[0350] The determined nucleotide sequences were mapped to Refseq transcripts by referring to an existing method (Maher et al., PNAS, July 28, 2009, 106(30): 12353-12358) to search for candidate fusion genes by looking for pairs of nucleotide sequences that are mapped to different genes. Furthermore, fusion sites were identified using nucleotide sequences that are not mapped to any Refseq transcript, in which one partner of the pair is mapped to one partner in a candidate fusion gene.

[0351] As a result, polynucleotides encoding a fusion polypeptide of FGFR3 and TACC3, a fusion polypeptide of FGFR3 and TACC3, and a fusion polypeptide of FGFR3 and BAIAP2L1 were identified from the three types of bladder cancer cell lines: RT112/84, RT4, and SW780. This suggests that the fusion polypeptides were expressed in these cell lines. Meanwhile, a polynucleotide encoding a wild-type FGFR3 polypeptide was confirmed in BFTC-905 cells.

(2) cDNA analysis

[0352] cDNAs were synthesized by reverse transcription using a reverse transcription kit, Transcriptor Universal cDNA Master (Roche), according to the instruction manual protocol attached to the kit. The RNAs used in Example 1(1), which were extracted from the three types of cells suggested to express a fusion polypeptide of FGFR3 and TACC3 or a fusion polypeptide of FGFR3 and BAIAP2L1, were each used as a template.

[0353] PCR was carried out (35 cycles of 15 seconds at 94°C, 30 seconds at 55°C, and one minute at 68°C) using each of the prepared cDNAs as a template with DNA polymerase KOD-Plus-Ver. 2 (Toyobo), and a pair of oligonucleotide primers (set 1) having the nucleotide sequences of SEQ ID NO: 1 (F3fu-F3: gtgcacaacctcgactactacaag) and SEQ ID NO: 2 (RT112-R3: gtaatcctccacgcacttcttc), a pair of oligonucleotide primers (set 2) having the nucleotide sequences of SEQ ID NO: 1 (F3fu-F3: gtgcacaacctcgactactacaag) and SEQ ID NO: 5 (RT4-R3: gggtgtcactcttctgtctaagga), or a pair of oligonucleotide primers (set 3) having the nucleotide sequences of SEQ ID NO: 3 (F3fu-F2) tgtttgaccgagtctacactcacc) and SEQ ID NO: 4 (SW780-R2: gacatgtcccagttcagttgac). Then, electrophoresis was performed.

[0354] The results showed that with primer set 1, a band of about 670 bp was observed only when the cDNA synthesized from RT112/84 RNA was used as a template. In the amplification with primer set 2, a band of about 610 bp was observed only when the cDNA synthesized from RT4 RNA was used as template. In the amplification with primer set 3, a band of about 450 bp was observed only when the cDNA synthesized from SW780 RNA was used as a template.

[0355] Sequencing was performed by Sanger's sequencing method with BigDye™ Terminator v3.1 Cycle Sequencing Kit (Life Technologies) using each PCR product as a template to determine the nucleotide sequence (SEQ ID NO: 14) of the fusion site in the fusion polynucleotide of FGFR3 and TACC3 (FGFR3-TACC3 polynucleotide v1) expressed in RT112/84, the nucleotide sequence (SEQ ID NO: 15) of the fusion site in the fusion polynucleotide of FGFR3 and TACC3 (FGFR3-TACC3 polynucleotide v2) expressed in RT4, and the nucleotide sequence (SEQ ID NO: 16) of the fusion site in the fusion polynucleotide of FGFR3 and BAIAP2L1 (FGFR3-BAIAP2L1 polynucleotide) expressed in SW780.

[0356] Based on the information obtained as described above, the nucleotide sequences of cDNAs encoding each fusion polypeptide (full-length) were determined by a common method.

[0357] The nucleotide sequence of the cDNA encoding the fusion polypeptide (full-length) of FGFR3 and TACC3 expressed in RT112/84 and its amino acid sequence are shown in SEQ ID NOs: 27 and 28, respectively.

[0358] The nucleotide sequence of the cDNA encoding the fusion polypeptide (full-length) of FGFR3 and TACC3 expressed in RT4 and its amino acid sequence are shown in SEQ ID NOs: 29 and 30, respectively.

[0359] Results of analyzing the nucleotide sequence of the cDNA showed that the nucleotide sequence at positions 2,281 to 2,379 of SEQ ID NO: 29 is an intron-derived nucleic acid sequence of a gene encoding FGFR3, and encodes the amino acid sequence at positions 761 to 793 of SEQ ID NO: 30.

[0360] The nucleotide sequence of the cDNA encoding the fusion polypeptide (full-length) of FGFR3 and BAIAP2L1 expressed in SW780 and its amino acid sequence are shown in SEQ ID NOs: 31 and 32, respectively.

[0361] As described above, while there are two types of wild-type polypeptides for human FGFR3 which comprise the amino acid sequences of SEQ ID NOs: 6 and 7, respectively, the N-terminal FGFR3-derived portions in these fusion polypeptides are those of wild-type FGFR3 that has the amino acid sequence of SEQ ID NO: 6.

[0362] Based on these test results, it is assumed that two types of fusion polypeptides of TACC3 and the other wild-type FGFR3 that has the amino acid sequence of SEQ ID NO: 7, and a fusion polypeptide of BAIAP2L1 and the other wild-type FGFR3 that has the amino acid sequence of SEQ ID NO: 7 are expressed in various types of human-derived cancer cells.

[0363] The nucleotide sequence of the cDNA encoding a fusion polypeptide (full-length) of TACC3 and wild-type FGFR3 that has the amino acid sequence of SEQ ID NO: 7, and its amino acid sequence are shown in SEQ ID NOs: 33 and 34, respectively.

[0364] The nucleotide sequence of the cDNA encoding another fusion polypeptide (full-length) of TACC3 and wild-type FGFR3 that has the amino acid sequence of SEQ ID NO: 7, and its amino acid sequence are shown in SEQ ID NOs: 35 and 36, respectively.

[0365] Here, the nucleotide sequence at positions 2,275 to 2,373 of the cDNA nucleotide sequence of SEQ ID NO: 35 is a nucleic acid sequence derived from an intron of a gene encoding FGFR3, and encodes the amino acid sequence at positions 759 to 791 of SEQ ID NO: 36.

[0366] The nucleotide sequence of the cDNA encoding another fusion polypeptide (full-length) of BAIAP2L1 and wild-type FGFR3 that has the amino acid sequence of SEQ ID NO: 7, and its amino acid sequence are shown in SEQ ID NOs: 37 and 38, respectively.

[0367] Furthermore, the presence of an FGFR3-TACC3 fusion polynucleotide was suspected in head and neck squamous cell carcinoma, lung adenocarcinoma, and lung squamous cell carcinoma, while the presence of an FGFR3-BAIAP2L1 fusion polynucleotide was suspected in head and neck squamous cell carcinoma, lung squamous cell carcinoma, and skin melanoma.

[Example 2]

[0368] Analysis of various FGFR inhibitors for their activities of inhibiting the kinase activity of FGFR1, FGFR2, and FGFR3, and inhibiting the cell proliferation of cell lines expressing the FGFR3-TACC3 fusion polypeptide

1. Analysis of various FGFR inhibitors for their activity of inhibiting the kinase activity of FGFR1, FGFR2, and FGFR3 (*in vitro*)

(1) Inhibitory activity against the FGFR1 enzyme

[0369] The FGFR1 inhibitory activities of compounds listed in Tables 1-1 to 1-5 were measured based on their activity to inhibit phosphorylation of the biotinylated peptide (EGPWLEEEEEAYGWMDF; SEQ ID NO: 39) by a human FGFR1 enzyme (Carna Biosciences, cat 08-133). Phosphorylated biotinylated peptide was detected by time-resolved fluorometry using a europium cryptate-linked anti-phosphotyrosine antibody, and streptavidin linked to an allophycocyanin derivative, XL665. The half maximal inhibitory concentration (IC_{50}) was calculated based on the inhibitory rate against the control group which does not contain the test substance.
[0370] The test result for each compound is shown in Tables 1-1 to 1-5.

(2) Inhibitory activity against the FGFR2 enzyme

[0371] The FGFR2 inhibitory activities of compounds listed in Tables 1-1 to 1-5 were measured based on their activity to inhibit phosphorylation of the biotinylated peptide (EGPWLEEEEEAYGWMDF; SEQ ID NO: 39) by human FGFR2 enzyme prepared using a baculovirus expression system. Phosphorylated biotinylated peptide was detected by time-resolved fluorometry using europium cryptate-linked anti-phosphotyrosine antibody, and streptavidin linked to an allophycocyanin derivative, XL665. The half maximal inhibitory concentration (IC_{50}) was calculated based on the inhibitory rate against the control group which does not contain the test substance.
[0372] The test result for each compound is shown in Tables 1-1 to 1-5.

(3) Inhibitory activity against the FGFR3 enzyme

[0373] The FGFR3 inhibitory activities of compounds listed in Tables 1-1 to 1-5 were measured based on their activity to inhibit phosphorylation of the biotinylated peptide (EGPWLEEEEEAYGWMDF; SEQ ID NO: 39) by human FGFR3 enzyme (Carna Biosciences, cat 08-135). Phosphorylated biotinylated peptide was detected by time-resolved fluorometry using europium cryptate-linked anti-phosphotyrosine antibody, and streptavidin linked to an allophycocyanin derivative, XL665. The half maximal inhibitory concentration (IC_{50}) was calculated based on the inhibitory rate against the control group which does not contain the test substance.
[0374] The test result for each compound is shown in Tables 1-1 to 1-5.

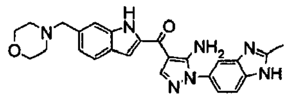
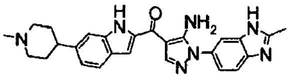
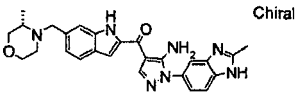
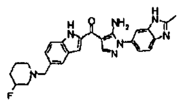
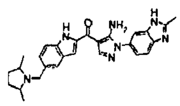
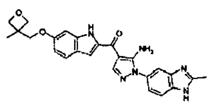
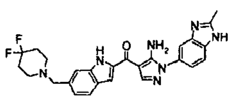
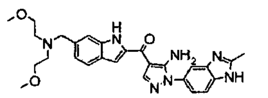
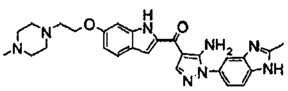
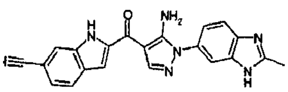
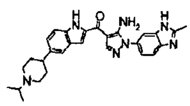
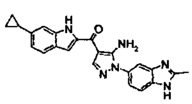
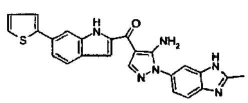
(4) Inhibitory activity of FGFR inhibitors on the cell proliferation of cell lines (*in vitro*)

[0375] Cells of a bladder cancer-derived cell line RT-4 which expresses an FGFR3-TACC3 fusion polypeptide, and cells of a colon cancer-derived cell line HCT116 which does not express an FGFR3 fusion polypeptide, were plated in 96-well plates, and cultured for four days in the presence of DMSO (used as a control) or each of the compounds listed in Tables 1-1 to 1-5 in 2-fold serial dilutions (18 steps) at a maximum concentration of 50 μM. Four days later, the cell proliferation level was determined using WST-8 (DOJINDO LABORATORIES).
[0376] The inhibitory activity of each compound on the cell proliferation of each cell line was calculated according to:

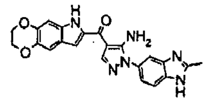
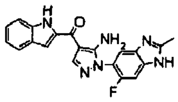
$$(1-T/C) \times 100\ (\%)$$

where T represents absorbance at 450 nM in wells where cells were incubated in the presence of a compound at various concentrations, and C represents absorbance at 450 nM in wells where cells were incubated in the presence of DMSO. IC50 was calculated using the least-square method.
[0377] As shown in Tables 1-1 to 1-5, the result showed that the 50% cell proliferation inhibitory concentration (IC50) for cells expressing the fusion polypeptide was significantly lower than that for cells that do not express the fusion polypeptide.

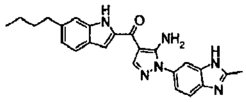
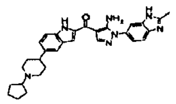
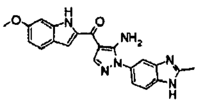
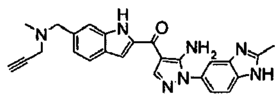
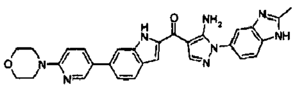
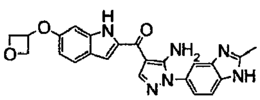
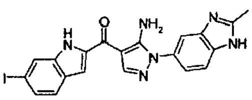
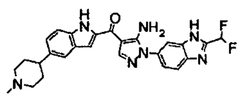
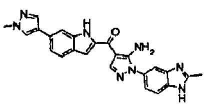
[Table 1-1]

COMPOUND		FGFR1 IC_{50} (μmol/L)	FGFR2 IC_{50} (μmol/L)	FGFR3 IC_{50} (μmol/L)	HCT116 (CRC) IC_{50} (μmol/L)	RT-4 (Bladder) IC_{50} (μmol/L)
1		0.0014	0.0034	0.0035	4.1	0.02
2		0.0069	0.0084	0.018	2.7	0.016
3		0.0027	0.0043	0.0054	2.9	0.018
4		0.00067	0.0085	0.030	9.5	0.018
5		0.00032	0.012	0.012	11	0.021
6		0.00081	0.012	0.0037	12	0.024
7		0.0029	0.0094	0.13	3.2	0.024
8		0.0096	0.023	0.034	11	0.029
9		0.010	0.015	0.046	6.3	0.030
10		0.009	0.0062	0.032	>50	0.039
11		0.011	0.017	0.065	5.7	0.052
12		0.045	0.021	0.082	7.2	0.058
13		0.036	0.010	0.35	0.39	0.065

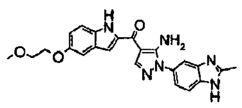
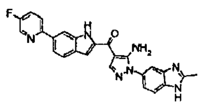
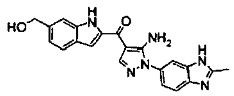
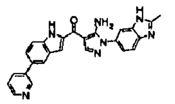
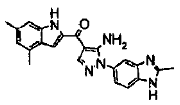
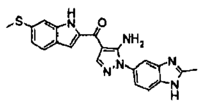
(continued)

COMPOUND		FGFR1 IC_{50} (μmol/L)	FGFR2 IC_{50} (μmol/L)	FGFR3 IC_{50} (μmol/L)	HCT116 (CRC) IC_{50} (μmol/L)	RT-4 (Bladder) IC_{50} (μmol/L)
14		0.038	0.0076	0.10	3.1	0.075
15		0.035	0.016	0.36	19	0.076

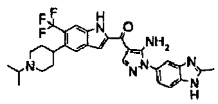
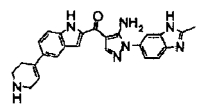
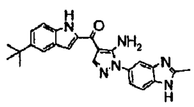
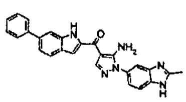
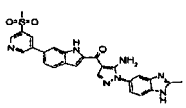
[Table 1-2]

COMPOUND		FGFR1 IC_{50} (μmol/L)	FGFR2 IC_{50} (μmol/L)	FGFR3 IC_{50} (μmol/L)	HCT116 (CRC) IC_{50} (μmol/L)	RT-4 (Bladder) IC_{50} (μmol/L)
16		0.23	0.20	0.40	17	0.076
17		0.011	0.012	0.041	3.8	0.077
18		0.048	0.021	0.079	11	0.082
19		0.017	0.017	0.070	2.5	0.084
20		0.029	0.025	0.082	>50	0.088
21		0.021	0.020	0.090	21	0.088
22		0.016	0.0086	0.21	1.2	0.089
23		0.087	0.11	0.13	10	0.09
24		0.023	0.016	0.060	>50	0.092

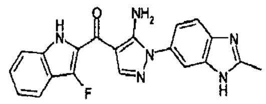
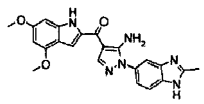
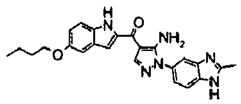
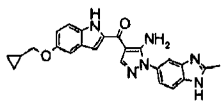
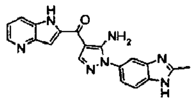
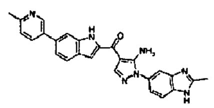
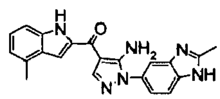
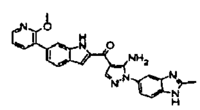
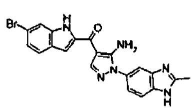
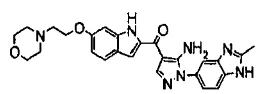
(continued)

COMPOUND		FGFR1 IC_{50} (μmol/L)	FGFR2 IC_{50} (μmol/L)	FGFR3 IC_{50} (μmol/L)	HCT116 (CRC) IC_{50} (μmol/L)	RT-4 (Bladder) IC_{50} (μmol/L)
25		0.018	0.012	0.045	>100	0.098
26		0.022	0.0055	0.094	11	0.13
27		0.015	0.023	0.077	25	0.15
28		0.048	0.039	0.16	21	0.2
29		0.03	0.015	0.14	8.5	0.16
30		0.033	0.020	0.077	13	0.16

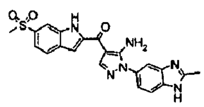
[Table 1-3]

COMPOUND		FGFR1 IC_{50} (μmol/L)	FGFR2 IC_{50} (μmol/L)	FGFR3 IC_{50} (μmol/L)	HCT116 (CRC) IC_{50} (μmol/L)	RT-4 (Bladder) IC_{50} (μmol/L)
31		0.039	0.018	0.077	2	0.17
32		0.043	0.039	0.015	8.7	0.18
33		0.15	0.056	0.95	4.4	0.18
34		0.050	0.026	0.23	3.8	0.19
35		0.043	0.022	0.086	7.8	0.19

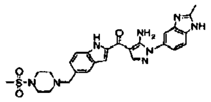
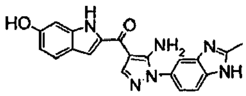
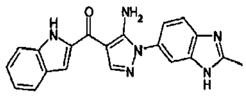
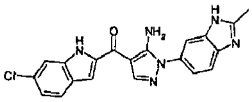
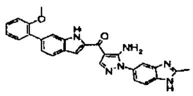
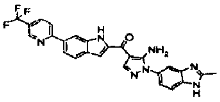
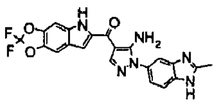
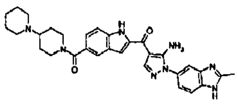
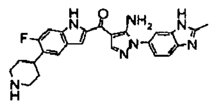
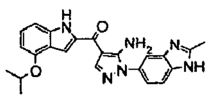
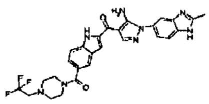
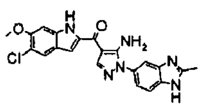
(continued)

COMPOUND		FGFR1 IC_{50} (μmol/L)	FGFR2 IC_{50} (μmol/L)	FGFR3 IC_{50} (μmol/L)	HCT116 (CRC) IC_{50} (μmol/L)	RT-4 (Bladder) IC_{50} (μmol/L)
36		0.075	0.040	0.38	4.8	0.19
37		0.040	0.015	0.080	8.9	0.19
38		0.022	0.012	0.16	6.1	0.21
39		0.024	0.0083	0.37	11	0.21
40		0.042	0.026	0.15	19	0.22
41		0.053	0.017	0.21	>20	0.24
42		0.043	0.021	0.15	15	0.25
43		0.060	0.027	0.13	>50	0.25
44		0.030	0.0089	0.11	10	0.26
45		0.0027	0.0032	0.0054	9.4	0.29

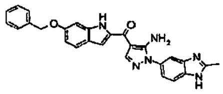
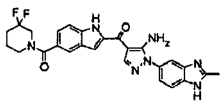
[Table 1-4]

COMPOUND		FGFR1 IC_{50} (μmol/L)	FGFR2 IC_{50} (μmol/L)	FGFR3 IC_{50} (μmol/L)	HCT116(CRC) IC_{50} (μmol/L)	RT-4 (Bladder) IC_{50} (μmol/L)
46		0.056	0.021	0.068	37	0.3

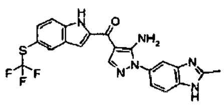
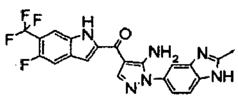
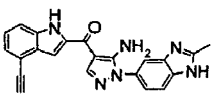
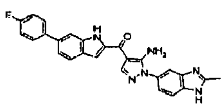
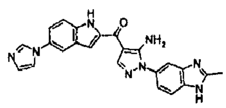
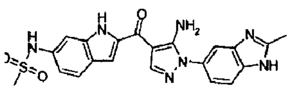
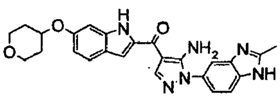
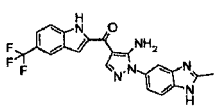
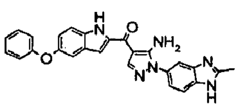
(continued)

COMPOUND		FGFR1 IC_{50} (μmol/L)	FGFR2 IC_{50} (μmol/L)	FGFR3 IC_{50} (μmol/L)	HCT116(CRC) IC_{50} (μmol/L)	RT-4 (Bladder) IC_{50} (μmol/L)
47		0.0079	0.011	0.036	14	0.320
48		0.027	0.018	0.12	37	0.32
49		0.0050	0.023	0.018	13	0.350
50		0.091	0.057	0.37	34	0.39
51		0.076	0.036	0.80	5.1	0.41
52		0.093	0.019	0.35	10	0.44
53		0.057	0.014	0.67	>20	0.44
54		0.038	0.022	0.082	>20	0.46
55		0.033	0.038	0.068	16	0.48
56		0.091	0.026	1.3	19	0.49
57		0.095	0.040	0.32	>20	0.51
58		0.0055	0.0040	0.029	12	0.56

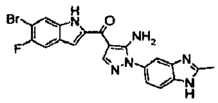
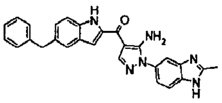
(continued)

COMPOUND		FGFR1 IC_{50} (μmol/L)	FGFR2 IC_{50} (μmol/L)	FGFR3 IC_{50} (μmol/L)	HCT116(CRC) IC_{50} (μmol/L)	RT-4 (Bladder) IC_{50} (μmol/L)
59		0.046	0.016	0.25	3.3	0.58
60		0.030	0.0054	0.0031	17	0.6

[Table 1-5]

COMPOUND		FGFR1 IC_{50} (μmol/L)	FGFR2 IC_{50} (μmol/L)	FGFR3 IC_{50} (μmol/L)	HCT116 (CRC) IC_{50} (μmol/L)	RT-4 (Bladder) IC_{50} (μmol/L)
61		0.14	0.078	0.37	9.1	0.62
62		0.060	0.029	0.18	1.7	0.64
63		0.077	0.022	0.32	13	0.67
64		0.042	0.031	0.36	1.2	0.68
65		0.031	0.020	0.11	23	0.68
66		0.025	0.048	0.043	>50	0.74
67		0.0030	0.0043	0.0067	7.3	0.75
68		0.092	0.037	0.33	>2	0.91
69		0.12	0.11	0.38	4.3	0.92

(continued)

COMPOUND		FGFR1 IC_{50} (μmol/L)	FGFR2 IC_{50} (μmol/L)	FGFR3 IC_{50} (μmol/L)	HCT116 (CRC) IC_{50} (μmol/L)	RT-4 (Bladder) IC_{50} (μmol/L)
70		0.031	0.0085	0.50	9	0.97
71		0.051	0.034	0.18	3.8	0.99

[Example 3]

[0378] Analysis of FGFR inhibitors on their cell proliferation inhibitory activity against various cell lines expressing the FGFR3-TACC3 fusion polypeptide or FGFR3-BAIAP2L1 fusion polypeptide

(1) Cell proliferation inhibitory activity of FGFR inhibitors against various cell lines (*in vitro*)

[0379] Six compounds A to F (Tables 2-1 and 2-2), which are substances that suppress the kinase activity of FGFR, were assessed for their effect on cell proliferation in a total of six types of human bladder cancer-derived cell lines: three types of cell lines expressing an FGFR3-TACC3 or FGFR3-BAIAP2L1 fusion polypeptide: RT112/84 (available from ECACC; catalog No. 85061106), RT4 (available from ATCC; catalog No. HTB-2), and SW780 (available from ATCC; catalog No. CRL-2169); cell line BFTC-905 (available from DSMZ; catalog No. ACC 361) which expresses the wild-type FGFR polypeptide but does not express the fusion polypeptides; cell line UM-UC-14 (available from ECACC; catalog No. 08090509) which expresses the mutated type FGFR polypeptide but does not express the fusion polypeptides; and cell line HT-1376 (available from ATCC; catalog No. CRL-1472) which does not express FGFR3.

[0380] The cells plated in 96-well plates (RT112/84, BFTC-905, and UM-UC-14: 3.0E+03 cells/well; SW780, RT4, and HT-1376: 5.0E+03 cells/well) were cultured for four days in the presence of DMSO (used as a control) or each compound in three-fold serial dilutions (9 steps) at a maximum concentration of 20 μM. Four days later, the cell proliferation level was determined using WST-8 (DOJINDO LABORATORIES).

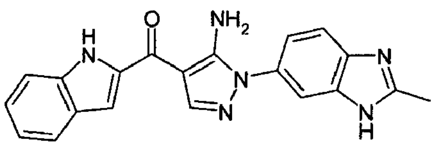
[0381] The cell proliferation inhibitory activity of each compound against each cell line was calculated according to:

$$(1-T/C) \times 100\ (\%)$$

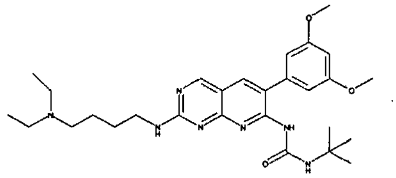
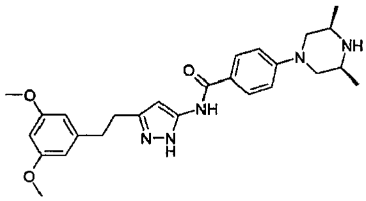
where T represents absorbance at 450 nM in wells where cells were incubated in the presence of a compound at various concentrations, and C represents absorbance at 450 nM in wells where cells were incubated in the presence of DMSO. IC50 was calculated using the least-square method.

[0382] As shown in Table 3, the result showed that the 50% cell proliferation inhibitory concentration (IC50) against cells expressing the fusion polypeptides was significantly lower than that against cells that do not express the fusion polypeptides.

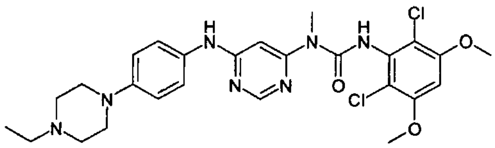
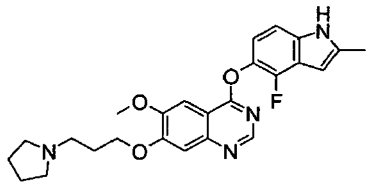
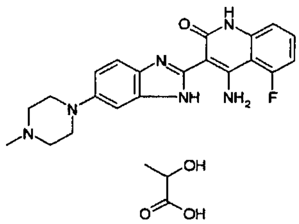
[Table 2-1]

CODE	STRUCTURAL FORMULA/CHEMICAL NAME
A	

(continued)

CODE	STRUCTURAL FORMULA/CHEMICAL NAME
B	COMPOUND REPRESENTED BY [COMPOUND 2] 
C	COMPOUND REPRESENTED BY [COMPOUND 3] 

[Table 2-2]

CODE	STRUCTURAL FORMULA/CHEMICAL NAME
D	COMPOUND REPRESENTED BY [COMPOUND 4] 
E	COMPOUND REPRESENTED BY [COMPOUND 5] 
F	COMPOUND REPRESENTED BY [COMPOUND 6] 

[Table 3]

CELL NAME	IC50 (μmol/L)					
	COMPOUND A	COMPOUND B	COMPOUND C	COMPOUND D	COMPOUND E	COMPOUND F
UM-UC-14	0.11	0.010	0.016	0.017	0.066	0.075
RT112/84	0.018	0.014	0.017	0.018	0.15	0.13
SW780	0.12	0.069	0.16	1.1	0.53	0.57

(continued)

CELL NAME	IC50 (μmol/L)					
	COMPOUND A	COMPOUND B	COMPOUND C	COMPOUND D	COMPOUND E	COMPOUND F
RT4	0.35	0.18	0.25	0.23	0.24	0.25
BFTC-905	>10	14	11	>20	2.5	2.8
HT-1376	>10	11	6.7	10	1.1	0.62

(2) Cell proliferation inhibitory activity of FGFR inhibitors against cells expressing the FGFR3-TACC3 fusion polypeptide (*in vivo*)

[0383] Antitumor effect was assessed using cancer-bearing mice prepared by transplanting cells of the human bladder cancer cell line RT112/84 (ECACC) subcutaneously in the inguinal region of BALB/c nude mice (Charles River Japan, Inc.).
[0384] Nude mice were quarantined for about one week before use, and subjected to subcutaneous transplantation of about 1 x 10^7 RT112/84 cells in the inguinal region. When the tumor size reached about 200 mm^3, the mice were used in experiments.
[0385] Compound A was suspended in a solution containing 10% DMSO, 10% Cremophor EL, 15% PEG400, and 15% HPCD, and orally administered to the mice at a dose of 20 mL/kg once a day.
[0386] Antitumor effect was determined by comparing the tumor growth during 11 days after the first day of administration (Day 10 when the first day of administration is set at Day 0) with that of the control group.

Tumor growth inhibitory effect (TGI) = (1 - [Average tumor growth level of treated group] / [Average tumor growth level of control group]) x 100 (%)

[0387] The result is shown in Table 4.
[0388] FGFR inhibitors exhibited a markedly significant tumor growth inhibitory effect in mice bearing tumor cells expressing the FGFR3-TACC3 fusion polypeptide in a concentration-dependent manner.

[Table 4]

	ANTITUMOR EFFECT	
	DOSE (mg/kg)	TGI AFTER 11 DAYS (%)
Vehicle		-
COMPOUND A	25	61
	50	86
	100	125

[Example 4]

Detection of polynucleotides encoding the FGFR3-TACC3 or FGFR3-BAIAP2L1 fusion polypeptide in clinical specimens

(1) Detection of polynucleotide v1 which encodes the FGFR3-TACC3 fusion polypeptide

[0389] In order to detect the cDNA of polynucleotide v1 encoding the FGFR3-TACC3 fusion polypeptide in clinical samples, PCR was carried out (42 cycles of 10 seconds at 98°C, 15 seconds at 60°C, and one minute at 68°C) with Tks Gflex™ DNA Polymerase (Takara bio) using, as primers, oligonucleotides having the nucleotide sequences of SEQ ID NOs: 1 and 2, and as a substrate, cDNA (Origene) derived from bladder cancer samples collected from bladder cancer patients (20 patients) or cDNA synthesized from RT112/84 (ECACC) RNA. Each of the amplified samples was electrophoresed together with size marker DNAs (Invitrogen).
[0390] As shown in Fig. 1, the result showed that cDNA fragments of polynucleotide v1 encoding the FGFR3-TACC3 fusion polypeptide were not detected in the clinical samples.

(2) Detection of polynucleotide v2 which encodes the FGFR3-TACC3 fusion polypeptide

[0391] In order to detect the cDNA of polynucleotide v2 encoding the FGFR3-TACC3 fusion polypeptide in clinical samples, PCR was carried out (42 cycles of 10 seconds at 98°C, 15 seconds at 60°C, and one minute at 68°C) with Tks Gflex™ DNA Polymerase (Takara bio) using as primers, oligonucleotides having the nucleotide sequences of SEQ ID NOs: 1 and 5, and as a substrate, cDNA (Origene) derived from bladder cancer samples collected from bladder cancer patients (20 patients) or cDNA synthesized from RT4 (ATCC) RNA. Each of the amplified samples was electrophoresed together with size marker DNAs (Invitrogen).

[0392] As shown in Fig. 2, the result showed that a cDNA fragment of polynucleotide v2 encoding the FGFR3-TACC3 fusion polypeptide was detected in a single case.

[0393] The above finding shows that the method described above allows detection of polynucleotide v2 encoding the FGFR3-TACC3 fusion polypeptide in samples derived from clinical specimens of bladder cancer, and thus enables selection of patients who are positive for polynucleotide v2 encoding the FGFR3-TACC3 fusion polypeptide.

(3) Detection of a polynucleotide encoding the FGFR3-BAIAP2L1 fusion polypeptide

[0394] In order to detect cDNA for an FGFR3-BAIAP2L1 polynucleotide in clinical samples, PCR was carried out (42 cycles of 10 seconds at 98°C, 15 seconds at 60°C, and one minute at 68°C) with Tks Gflex™ DNA Polymerase (Takara bio) using, as primers, oligonucleotides having the nucleotide sequences of SEQ ID NOs: 3 and 4, and, as a substrate, cDNA (Origene) derived from bladder cancer samples collected from bladder cancer patients (20 patients) or cDNA synthesized from SW780 (ATCC) RNA. Each of the amplified samples was electrophoresed together with size marker DNAs (Invitrogen).

[0395] As shown in Fig. 3, the result showed that a cDNA fragment of the FGFR3-BAIAP2L1 fusion polynucleotide was detected in a total of two cases.

[0396] The above finding shows that the method described above allows detection of a polynucleotide encoding the FGFR3-BAIAP2L1 fusion polypeptide in samples derived from clinical specimens of bladder cancer, and thus enables selection of patients who are positive for a polynucleotide encoding the FGFR3-BAIAP2L1 fusion polypeptide.

[Example 5]

Detection of polynucleotides encoding the FGFR3-BAIAP2L1 fusion polypeptide and FGFR3-TACC3 fusion polypeptide in clinical specimens of various types of cancers

(1) Detection of a polynucleotide encoding the FGFR3-BAIAP2L1 fusion polypeptide in clinical_specimens of lung cancer (non-bladder cancer) (Test 1)

[0397] In order to detect cDNA for an FGFR3-BAIAP2L1 polynucleotide from clinical specimens of non-bladder cancer, PCR was carried out (42 cycles of 98°C for 10 seconds, 60°C for 15 seconds, and 68°C for one minute) with Tks Gflex(tm) DNA Polymerase (TAKARA BIO INC.) using a pair of oligonucleotide primers having the nucleotide sequences of SEQ ID NO: 3 (F3fu-F2: tgtttgaccgagtctacactcacc) and SEQ ID NO: 4 (SW780-R2: gacatgtcccagttcagttgac), and, as a substrate, 40 samples of cDNAs derived from clinical specimens of lung cancer (OriGene) and cDNA synthesized from SW780 RNA. The amplified samples were electrophoresed together with a size marker DNA (Invitrogen).

[0398] As shown in Fig. 4A, the result showed that a cDNA fragment of a polynucleotide encoding the FGFR3-BAIAP2L1 fusion polypeptide was detected in a total of one case.

[0399] Furthermore, in order to confirm reproducibility, PCR was carried out (42 cycles of 98°C for 10 seconds, 60°C for 15 seconds, and 68°C for one minute) with Tks Gflex(tm) DNA Polymerase (TAKARA BIO INC.) using a pair of oligonucleotide primers having the nucleotide sequences of SEQ ID NO: 17 (F3fu-F1: caactgcacacacgacctgta) and SEQ ID NO: 18 (SW780-R1: ccatcgtagtaggcttttcctg), and, as a substrate, cDNAs derived from the same clinical specimens of lung cancer and cDNA synthesized from SW780 RNA. The amplified samples were electrophoresed together with a size marker DNA (Invitrogen).

[0400] As shown Fig. 4B, the result showed that a cDNA fragment of a polynucleotide encoding the FGFR3-BAIAP2L1 fusion polypeptide was detected in a total of one case. The above finding shows that the method described above allows detection of a polynucleotide encoding the FGFR3-BAIAP2L1 fusion polypeptide in cDNAs derived from clinical specimens of non-bladder cancer with different types of primers, and thus enables selection of patients who are positive for a polynucleotide encoding the FGFR3-BAIAP2L1 fusion polypeptide.

(2) Detection of polynucleotides encoding the FGFR3-BAIAP2L1 fusion polypeptides in clinical specimens of lung cancer (non-bladder cancer) (Test 2)

[0401] PCR was carried out (35 cycles of 98°C for 10 seconds, 60°C for 15 seconds, and 68°C for one minute) with Tks Gflex™ DNA Polymerase (TAKARA BIO INC.) using a pair of oligonucleotide primers (Set 3) having the nucleotide sequences of SEQ ID NO: 3 (F3fu-F2: tgtttgaccgagtctacactcacc) and SEQ ID NO: 4 (SW780-R2: gacatgtcccagttcagttgac), and, as a substrate, 83 samples of cDNAs derived from clinical specimens of lung cancer (OriGene). The presence or absence of DNA amplification was confirmed for each sample by agarose gel electrophoresis. DNA bands having the size of interest were detected in two specimens, and it was determined by DNA sequence analysis (Sanger method) that they are cDNA fragment sequences derived from FGFR3-BAIAP2L1 fusion polynucleotides. Accordingly, the FGFR3-BAIAP2L1 fusion polynucleotide was confirmed to exist in cDNAs derived from clinical cancer specimens.

(3) Detection of polynucleotides encoding the FGFR3-TACC3 fusion polypeptides in clinical specimens of lung cancer, esophageal cancer, gastric cancer, and liver cancer (all are non-bladder cancers)

[0402] PCR was carried out (35 cycles of 98°C for 10 seconds, 60°C for 15 seconds, and 68°C for one minute) with Tks Gflex™ DNA Polymerase (TAKARA BIO INC.) using a pair of oligonucleotide primers (Set 1) having the nucleotide sequences of SEQ ID NO: 1 (F3fu-F3: gtgcacaacctcgactactacaag) and SEQ ID NO: 2 (RT112-R3: gtaatcctccacgcacttcttc), and, as a substrate, 83 samples of cDNAs derived from clinical specimens of lung cancer (OriGene), 18 samples of cDNAs derived from clinical specimens of esophageal cancer (OriGene), five samples of cDNAs derived from clinical specimens of gastric cancer (OriGene), and five samples of cDNAs derived from clinical specimens of liver cancer (OriGene). The presence or absence of DNA amplification was confirmed for each sample by agarose gel electrophoresis. DNA bands having the size of interest were detected in the specimens from two cases of lung cancer, two cases of esophageal cancer, one case of gastric cancer, and one case of liver cancer; and it was determined by DNA sequence analysis (Sanger method) that they are cDNA fragment sequences derived from FGFR3-TACC3 fusion polynucleotides. Accordingly, the FGFR3-TACC3 fusion polynucleotides were confirmed to exist in cDNAs derived from clinical specimens of various types of cancers.

(4) Detection of polynucleotides encoding the FGFR3-BAIAP2L1 fusion polypeptides in bladder cancer cell lines using the FISH method

[0403] In order to detect the FGFR3-BAIAP2L1 fusion genes in bladder cancer cell lines using the fluorescence *in situ* hybridization (FISH) method, an experiment was performed using the following two probe sets and formalin-fixed paraffin-embedded (FFPE) samples of bladder cancer cell lines RT112/84 and SW780.

[0404] FISH analysis was performed by using FGFR3 Split Dual Color FISH Probe (Split signal probe set, GSP Lab., Inc.) to detect translocation of a part of the FGFR3 gene on human chromosome 4 to another chromosome, and by using FGFR3 and BAIAP2L1 FISH Probe (Fusion signal probe set, GSP Lab., Inc.) to detect integration of the FGFR3 gene on human chromosome 4 and the BAIAP2L1 gene on human chromosome 7 into the same chromosome.

[0405] As shown in Fig. 5, the results confirmed that, in FFPE samples prepared from SW780, signals of two colors were detected separately by FISH analysis with a Split signal probe (A2 of Fig. 5), and merged signal of two colors was detected by FISH analysis with a Fusion signal probe set (B2 of Fig. 5). Accordingly, the above-mentioned method showed that separation of the FGFR3 gene and fusion of the FGFR3 and BAIAP2L1 genes can be detected by the FISH method.

[Example 6]

Evaluation of various cell lines that express an FGFR3-TACC3 fusion polypeptide or an FGFR3-BAIAP2L1 fusion polypeptide

(1) Evaluation of FGFR3-dependency of various cell lines

[0406] siRNA against FGFR3 or BAIAP2L1 was added to a total of four types of cells: bladder cancer-derived human cell lines RT4 and SW780 which express an FGFR3-TACC3 fusion polypeptide or an FGFR3-BAIAP2L1 fusion polypeptide; the UM-UC-14 cell line which expresses a mutant FGFR3 polypeptide but does not express the fusion polypeptides; and the BFTC-905 cell line which express the wild-type FGFR3 polypeptide but does not express the fusion polypeptides, and effects of each type of siRNA on cell proliferation were examined.

[0407] The ON-TARGET plus siRNA Reagents (Thermo Fisher Scientific) were used for the siRNAs.

[0408] The cells plated in 96-well plates (UM-UC-14 and BFTC-905: 1.5E+03 cells/well; and SW780 and RT4: 2.5E+03 cells/well) were cultured for seven days in the presence of each siRNA or mock siRNA (used as a control) in ten-fold serial dilutions (3 steps) at a maximum concentration of 10 nM. Cell proliferation after seven days was measured by CellTiter-Glo™ Luminescent Cell Viability Assay (Promega).

[0409] As shown in Fig. 6, the result showed that the proliferation activity of cells which express a wild-type FGFR3 polypeptide but does not express the fusion polypeptides were not inhibited by siRNAs against each of FGFR3 and BAIAP2L1. On the other hand, the proliferation activity of the cell line which expresses a mutant FGFR3 polypeptide but does not express the fusion polypeptides, and the proliferation activity of cells which express an FGFR3-TACC3 fusion polypeptide were inhibited only by siRNA against FGFR3. On the other hand, proliferation of cells expressing an FGFR3-BAIAP2L1 fusion polypeptide was confirmed to be inhibited by either of the siRNAs against each of FGFR3 and BAIAP2L1.

(2) Evaluation of apoptosis induction by an FGFR inhibitor against cancer cells that express an FGFR3-BAIAP2L1 fusion polypeptide

[0410] Each of six compounds A to F (Tables 2-1 and 2-2), which are substances that suppress the kinase activity of FGFR, were added to a total of four types of cells: bladder cancer-derived human cell line SW780 which expresses an FGFR3-BAIAP2L1 fusion polypeptide; the BFTC-905 cell line which expresses the wild-type FGFR polypeptide but does not express the fusion polypeptides; the UM-UC-14 cell line which expresses the mutant FGFR3 polypeptide but does not express the fusion polypeptides; and the HT-1376 cell line which does not express FGFR3 to assess whether apoptosis was induced.

[0411] The cells plated in a PrimeSurface™ 96U plates (Sumitomo Bakelite Co. Ltd.) (UM-UC-14 and BFTC-905: 3.0E+03 cells/well; and SW780 and HT-1376: 5.0E+03 cells/well) were cultured for four days in the presence of DMSO (used as a control) or each compound in three-fold serial dilutions (4 steps) at a maximum concentration of 20 μM. Cell proliferation and caspase activity after four days was measured by CellTiter-Glo™ Luminescent Cell Viability Assay (Promega) Caspase-Glo™ 3/7 assay (Promega), respectively. The sum of caspase activity in a single well measured by Caspase-Glo™ 3/7 was divided by the relative viable cell count in a single well calculated from the CellTiter-Glo™ value to calculate the Apoptosis value. Apoptosis induction in each cell was evaluated by dividing the Apoptosis value by the Apoptosis value for each cell calculated under the DMSO-added conditions.

[0412] As shown in Fig. 7, the results confirmed that while apoptosis was not induced by the inhibitor in cells unresponsive to an FGFR inhibitor, apoptosis was induced by the FGFR inhibitor in cells responsive to an FGFR inhibitor.

(3) *In vivo* cell proliferation inhibitory activity of FGFR inhibitors against cells expressing the FGFR3-BAIAP2L1 fusion polypeptide.

[0413] Antitumor effect was assessed using cancer-bearing mice prepared by transplanting cells of the human bladder cancer cell line SW780 (ATCC) subcutaneously in the inguinal region of BALB/c nude mice (Charles River Japan, Inc.). Nude mice were quarantined for about one week before use, and subjected to subcutaneous transplantation of 5 x 10^6 SW780 cells in the inguinal region. When the tumor size reached about 200 mm^3, the mice were used in experiments. Compound A was suspended in a solution containing 10% DMSO, 10% Cremophor EL, 15% PEG400, and 15% HPCD, and orally administered to the mice at 20 mL/kg once a day. Antitumor effect was determined by comparing the tumor growth during 11 days after the first day of administration (Day 10 when the first day of administration is set at Day 0) with that of the control group.

Tumor growth inhibitory effect (TGI) = (1 - [Average tumor growth level of treated group] / [Average tumor growth level of control group]) x 100 (%)

[0414] The result is shown in Table 5.

[0415] FGFR inhibitors exhibited a markedly significant tumor growth inhibitory effect in mice bearing tumor cells expressing the FGFR3-BAIAP2L1 fusion polypeptide in a concentration-dependent manner.

[Table 5]

	ANTITUMOR EFFECT	
	DOSE (mg/kg)	TGI AFTER 11 DAYS(%)
Vehicle		-

(continued)

	ANTITUMOR EFFECT	
	DOSE (mg/kg)	TGI AFTER 11 DAYS(%)
COMPOUND A	25	47
	50	79
	100	111

[Example 7]

Examination of transforming ability and tumorigenic ability of FGFR3-BAIAP2L1 fusion polypeptides

(1) Evaluation of transforming ability of an FGFR3-BAIAP2L1 fusion polypeptide

[0416] A cDNA (SEQ ID NO: 10) encoding FGFR3 (SEQ ID NO: 6) and a cDNA (SEQ ID NO: 31) encoding FGFR3-BAIAP2L1 (SEQ ID NO: 32) were each subcloned into a lentiviral expression vector pReceiver-Lv156 (GeneCopoeia); and lentivirus for expression of each polypeptide was produced using the Lenti-Pac™ Lentiviral Packaging Systems (GeneCopoeia).

[0417] Rat fetus-derived RAT-2 cells were infected with each lentivirus, and the cells were cultured under a condition with a selection marker Puromycin to establish RAT-2 cells that stably express the FGFR3 polypeptide or the FGFR3-BAIAP2L1 fusion polypeptide. As shown in Fig. 8, morphological changes of the established cells stably expressing the FGFR3-BAIAP2L1 fusion polypeptide were observed in monolayer culture.

[0418] Untreated RAT-2 cells (parent cells), RAT-2 cells stably expressing the FGFR3 polypeptide, or RAT-2 cells stably expressing the FGFR3-BAIAP2L1 fusion polypeptide plated at 2.0 x 10^3 cells/well in a PrimeSurface™ 96U plate (Sumitomo Bakelite Co. Ltd.) were cultured for 14 days. As shown in Fig. 9, when the cells after 14 days were observed and photographed, scaffold-independent cell proliferation was found to be enhanced only in RAT-2 cells stably expressing the FGFR3-BAIAP2L1 fusion polypeptide.

[0419] From the result, the FGFR3-BAIAP2L1 fusion polypeptide was confirmed to have transforming ability in normal cells.

(2) Evaluation of the transforming ability of an FGFR3-BAIAP2L1 fusion polypeptide lacking a dimerization-promoting region

[0420] A cDNA encoding FGFR3-BAIAP2L1 ΔBAR, which lacks the BAR domain which is a region promoting dimerization of the BAIAP2L1 polypeptide (amino acid sequence: SEQ ID NO: 8 / nucleic acid sequence: SEQ ID NO: 12), was produced by a site-directed mutagenesis method using the PCR method. cDNAs encoding each of FGFR3 (same as the above), FGFR3-BAIAP2L1 (same as the above), and FGFR3-BAIAP2L1 ΔBAR were subcloned into the pCXND3 vector (KAKETSUKEN) to produce vectors for expressing each of the polypeptides.

[0421] The pCXND3 vector (vehicle) or a vector for expressing each polypeptide was introduced into human embryonic kidney 293 cells using the FuGENE™ HD Transfection Reagent (Promega). One day later, the cells were collected as cell lysates using Cell Lysis Buffer (Cell Signaling Technology). As shown in Fig. 10, when each cell lysate was analyzed by Western blotting using a Phospho-FGF Receptor (Tyr653/654) Antibody (Cell Signaling Technology) or an anti-FGFR3 antibody (Santa Cruz), FGFR phosphorylation which was enhanced on the FGFR3-BAIAP2L1 fusion polypeptide was confirmed to be attenuated in the FGFR3-BAIAP2L1 ΔBAR fusion polypeptide lacking the BAR domain which is a region promoting dimerization of the BAIAP2L1 polypeptide.

[0422] Furthermore, by a method similar to that of the aforementioned examination (1), RAT-2 cells that stably express the BAIAP2L1 polypeptide (the same as the above) or the FGFR3-BAIAP2L1 ΔBAR fusion polypeptide (the same as the above) were established using lentiviruses.

[0423] Untreated RAT-2 cells (parent cells), RAT-2 cells stably expressing the FGFR3 polypeptide, RAT-2 cells stably expressing the BAIAP2L1 polypeptide, RAT-2 cells stably expressing the FGFR3-BAIAP2L1 fusion polypeptide, or RAT-2 cells stably expressing the FGFR3-BAIAP2L1 ΔBAR fusion polypeptide were plated at 2.0 x 10^3 cells/well in a PrimeSurface™ 96U plate (Sumitomo Bakelite Co. Ltd.), and cultured for 14 days. The cell count after 14 days was determined by the CellTiter-Glo™ Luminescent Cell Viability Assay (Promega). As shown in Fig. 11, it was observed that RAT-2 cells stably expressing the BAIAP2L1 polypeptide did not have scaffold-independent cell proliferation ability, and scaffold-independent cell proliferation ability observed in RAT-2 cells stably expressing the FGFR3-BAIAP2L1 fusion polypeptide was lost in RAT-2 cells stably expressing the FGFR3-BAIAP2L1 ΔBAR fusion polypeptide.

[0424] Accordingly, the transforming ability of an FGFR3-BAIAP2L1 fusion polypeptide on normal cells was confirmed to be caused by enhanced trans-autophosphorylation of the FGFR3 polypeptide due to the dimerization-promoting domain in the BAIAP2L1 polypeptide.

(3) Evaluation of tumorigenic ability of an FGFR3-BAIAP2L1 fusion polypeptide, and tumor enlargement-suppressing activity of an FGFR inhibitor

[0425] RAT-2 cells that stably express the FGFR3 polypeptide, the BAIAP2L1 polypeptide, the FGFR3-BAIAP2L1 fusion polypeptide, or the FGFR3-BAIAP2L1 ΔBAR fusion polypeptide established in the above-mentioned experiments (1) and (2) were inoculated subcutaneously into the inguinal region of BALB/c nude mice (Charles River Laboratories Japan) at 4.8 - 5.4 x 10^6 cells, and the mice were observed for 15 days. As shown in Fig. 12, tumor enlargement was confirmed only in mice inoculated with RAT-2 cells stably expressing the FGFR3-BAIAP2L1 fusion polypeptide.

[0426] Furthermore, RAT-2 cells that stably express FGFR3-BAIAP2L1 were inoculated into nude mice at 5.04 x 10^6 cells. From seven days after planting the cells, an FGFR inhibitor compound A (same as the above) suspended in a solution containing 10% DMSO, 10% Cremophor EL, 15% PEG400, and 15% HPCD was orally administered once daily to mice at a concentration of 20 mL/kg. As shown in Fig. 13, tumor enlargement enhanced by the FGFR3-BAIAP2L1 fusion polypeptide was observed to be significantly suppressed by the FGFR inhibitor in a concentration-dependent manner.

[0427] The FGFR3-BAIAP2L1 fusion polypeptide was confirmed to have very strong tumorigenic ability, and this tumorigenic ability was suppressed by the FGFR inhibitor.

Industrial Applicability

[0428] Fusion polypeptides comprising an FGFR3 polypeptide and another polypeptide of the present invention are expressed specifically in various types of cancer cells including bladder cancer cells. The proliferation of cells expressing such fusion polypeptides is significantly inhibited by compounds having FGFR inhibitory activity. Thus, the use of a fusion polypeptide of the present invention as a biomarker for FGFR inhibitor-based cancer therapy enables to assess each patient for the applicability or mode of use of the FGFR inhibitor, and enables to avoid side effects and control the mode of therapy to produce the best therapeutic effect in the FGFR inhibitor-based therapy. Thus, this allows personalized medicine.

[0429] In addition, the use of fusion polypeptides of the present invention as a target in developing cancer therapeutic agents that target FGFR, *i.e.*, molecularly targeted therapeutic agents, enables to provide FGFR inhibitors with high level of specificity and antitumor activity to target cancer cells as well as cancer therapeutic agents comprising the inhibitors.

[0430] FGFR inhibitors obtained as described above have high specificity towards target cancer cells, and thus it becomes possible to provide cancer therapeutic agents with great antitumor activity but few side effects.

[0431] Furthermore, fusion polypeptides of the present invention have a close correlation to various types of cancers, and thus cancer susceptibility (sensitivity to cancer) of subjects, whether subjects are affected with cancer, or whether cancer has progressed in subjects can be tested by determining the presence or absence of the fusion polypeptide of the present invention or a polynucleotide encoding the fusion polypeptide in samples from subjects which include not only cancer patients but also healthy persons.

[0432] In addition, fusion polypeptides of the present invention have a close correlation to various types of cancers, and thus FGFR inhibitors with high specificity to FGFR can be provided by identifying a test compound that inhibits the proliferation of cells (such as cancer cells) expressing the fusion polypeptides of the present invention by comparing the cell proliferation level between in the presence and absence of the test compound.

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Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
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Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
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Gly Thr Ser Ser Phe Lys Glu Ser Ala Leu Arg Lys Gln Ser Leu Tyr
545                 550                 555                 560

Leu Lys Phe Asp Pro Leu Leu Arg Asp Ser Pro Gly Arg Pro Val Pro
                565                 570                 575

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            580                 585                 590

Gly Arg Pro Arg Glu Ala Lys Leu Val Glu Phe Asp Phe Leu Gly Ala
        595                 600                 605

Leu Asp Ile Pro Val Pro Gly Pro Pro Pro Gly Val Pro Ala Pro Gly
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Gly Pro Pro Leu Ser Thr Gly Pro Ile Val Asp Leu Leu Gln Tyr Ser
625                 630                 635                 640

Gln Lys Asp Leu Asp Ala Val Val Lys Ala Thr Gln Glu Glu Asn Arg
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Glu Leu Arg Ser Arg Cys Glu Glu Leu His Gly Lys Asn Leu Glu Leu
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Gly Lys Ile Met Asp Arg Phe Glu Glu Val Val Tyr Gln Ala Met Glu
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Glu Val Gln Lys Gln Lys Glu Leu Ser Lys Ala Glu Ile Gln Lys Val
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Leu Lys Glu Lys Asp Gln Leu Thr Thr Asp Leu Asn Ser Met Glu Lys
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705                 710                 715                 720

Ser Phe Ser Asp Leu Phe Lys Arg Phe Glu Lys Gln Lys Glu Val Ile
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Tyr Leu Ala Arg Ile Thr Gln Glu Gly Gln Arg Tyr Gln Ala Leu Lys
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Ala His Ala Glu Glu Lys Leu Gln Leu Ala Asn Glu Glu Ile Ala Gln
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Val Arg Ser Lys Ala Gln Ala Glu Ala Leu Ala Leu Gln Ala Ser Leu
785                 790                 795                 800

Arg Lys Glu Gln Met Arg Ile Gln Ser Leu Glu Lys Thr Val Glu Gln
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Lys Thr Lys Glu Asn Glu Glu Leu Thr Arg Ile Cys Asp Asp Leu Ile
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Ser Lys Met Glu Lys Ile
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<212> DNA
<213> Homo sapiens

<400> 10

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<210> 11

<211> 2421
<212> DNA
<213> Homo sapiens

<400> 11

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<211> 1536
<212> DNA
<213> Homo sapiens

<400> 12

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<211> 2517
<212> DNA
<213> Homo sapiens

<400> 13

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<211> 383
<212> DNA
<213> Homo sapiens

<400> 14

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gacgtaaagg cgacacagga ggagaaccgg gagctgagga gcaggtgtga ggagctccac 180

gggaagaacc tggaactggg gaagatcatg gacaggttcg aagaggttgt gtaccaggcc 240

atggaggaag ttcagaagca gaaggaactt tccaaagctg aaatccagaa agttctaaaa 300

gaaaaagacc aacttaccac agatctgaac tccatggaga agtccttctc cgacctcttc 360

aagcgttttg agaaacagaa aga 383

<210> 15
<211> 448
<212> DNA
<213> Homo sapiens

<400> 15

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atgccgcgcc ctcccagagg cccaccttca agcagctggt ggaggacctg gaccgtgtcc 180

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aaaaccttag ttcctattcc ttagacag 448

<210> 16
<211> 427
<212> DNA
<213> Homo sapiens

<400> 16

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ctgaact                                                               427
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<213> Artificial Sequence

<220>
<223> An artificially synthesized primer sequence

<400> 17
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<210> 18
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<212> DNA
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<220>
<223> An artificially synthesized primer sequence

<400> 18
ccatcgtagt aggcttttcc tg 22

<210> 19
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<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 19

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<210> 20
<211> 4
<212> PRT
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<223> Peptide linker sequence

<400> 20

Ser Gly Gly Gly
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<210> 21
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<220>
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<400> 21

Gly Gly Gly Gly Ser
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<210> 22
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<400> 22

Ser Gly Gly Gly Gly
1 5

<210> 23
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<400> 23

Gly Gly Gly Gly Gly Ser
1 5

<210> 24
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<400> 24

Ser Gly Gly Gly Gly Gly
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<210> 25
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Gly Gly Gly Gly Gly Gly Ser
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Ser Gly Gly Gly Gly Gly Gly
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<210> 27
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<400> 27

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Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
            20                  25                  30

ggg cga gcg gca gaa gtc ccg ggc cca gag ccc ggc cag cag gag cag        144
Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

ttg gtc ttc ggc agc ggg gat gct gtg gag ctg agc tgt ccc ccg ccc        192
Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

ggg ggt ggt ccc atg ggg ccc act gtc tgg gtc aag gat ggc aca ggg        240
Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

ctg gtg ccc tcg gag cgt gtc ctg gtg ggg ccc cag cgg ctg cag gtg        288
Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

ctg aat gcc tcc cac gag gac tcc ggg gcc tac agc tgc cgg cag cgg        336
Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

ctc acg cag cgc gta ctg tgc cac ttc agt gtg cgg gtg aca gac gct        384
Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

cca tcc tcg gga gat gac gaa gac ggg gag gac gag gct gag gac aca        432
Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

ggt gtg gac aca ggg gcc cct tac tgg aca cgg ccc gag cgg atg gac        480
Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

aag aag ctg ctg gcc gtg ccg gcc gcc aac acc gtc cgc ttc cgc tgc        528
Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
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cca gcc gct ggc aac ccc act ccc tcc atc tcc tgg ctg aag aac ggc        576
Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

agg gag ttc cgc ggc gag cac cgc att gga ggc atc aag ctg cgg cat        624
Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

cag cag tgg agc ctg gtc atg gaa agc gtg gtg ccc tcg gac cgc ggc        672
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Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

aac tac acc tgc gtc gtg gag aac aag ttt ggc agc atc cgg cag acg      720
Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
225                 230                 235                 240

tac acg ctg gac gtg ctg gag cgc tcc ccg cac cgg ccc atc ctg cag      768
Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255

gcg ggg ctg ccg gcc aac cag acg gcg gtg ctg ggc agc gac gtg gag      816
Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270

ttc cac tgc aag gtg tac agt gac gca cag ccc cac atc cag tgg ctc      864
Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285

aag cac gtg gag gtg aat ggc agc aag gtg ggc ccg gac ggc aca ccc      912
Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

tac gtt acc gtg ctc aag tcc tgg atc agt gag agt gtg gag gcc gac      960
Tyr Val Thr Val Leu Lys Ser Trp Ile Ser Glu Ser Val Glu Ala Asp
305                 310                 315                 320

gtg cgc ctc cgc ctg gcc aat gtg tcg gag cgg gac ggg ggc gag tac     1008
Val Arg Leu Arg Leu Ala Asn Val Ser Glu Arg Asp Gly Gly Glu Tyr
                325                 330                 335

ctc tgt cga gcc acc aat ttc ata ggc gtg gcc gag aag gcc ttt tgg     1056
Leu Cys Arg Ala Thr Asn Phe Ile Gly Val Ala Glu Lys Ala Phe Trp
            340                 345                 350

ctg agc gtt cac ggg ccc cga gca gcc gag gag gag ctg gtg gag gct     1104
Leu Ser Val His Gly Pro Arg Ala Ala Glu Glu Glu Leu Val Glu Ala
        355                 360                 365

gac gag gcg ggc agt gtg tat gca ggc atc ctc agc tac ggg gtg ggc     1152
Asp Glu Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly
    370                 375                 380

ttc ttc ctg ttc atc ctg gtg gtg gcg gct gtg acg ctc tgc cgc ctg     1200
Phe Phe Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu
385                 390                 395                 400

cgc agc ccc ccc aag aaa ggc ctg ggc tcc ccc acc gtg cac aag atc     1248
Arg Ser Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile
                405                 410                 415

tcc cgc ttc ccg ctc aag cga cag gtg tcc ctg gag tcc aac gcg tcc     1296
Ser Arg Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser
            420                 425                 430

atg agc tcc aac aca cca ctg gtg cgc atc gca agg ctg tcc tca ggg     1344
Met Ser Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly
        435                 440                 445

gag ggc ccc acg ctg gcc aat gtc tcc gag ctc gag ctg cct gcc gac     1392
Glu Gly Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp
    450                 455                 460
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ccc aaa tgg gag ctg tct cgg gcc cgg ctg acc ctg ggc aag ccc ctt        1440
Pro Lys Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu
465                 470                 475                 480

ggg gag ggc tgc ttc ggc cag gtg gtc atg gcg gag gcc atc ggc att        1488
Gly Glu Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile
                485                 490                 495

gac aag gac cgg gcc gcc aag cct gtc acc gta gcc gtg aag atg ctg        1536
Asp Lys Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu
            500                 505                 510

aaa gac gat gcc act gac aag gac ctg tcg gac ctg gtg tct gag atg        1584
Lys Asp Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met
        515                 520                 525

gag atg atg aag atg atc ggg aaa cac aaa aac atc atc aac ctg ctg        1632
Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu
    530                 535                 540

ggc gcc tgc acg cag ggc ggg ccc ctg tac gtg ctg gtg gag tac gcg        1680
Gly Ala Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala
545                 550                 555                 560

gcc aag ggt aac ctg cgg gag ttt ctg cgg gcg cgg cgg ccc ccg ggc        1728
Ala Lys Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly
                565                 570                 575

ctg gac tac tcc ttc gac acc tgc aag ccg ccc gag gag cag ctc acc        1776
Leu Asp Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr
            580                 585                 590

ttc aag gac ctg gtg tcc tgt gcc tac cag gtg gcc cgg ggc atg gag        1824
Phe Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu
        595                 600                 605

tac ttg gcc tcc cag aag tgc atc cac agg gac ctg gct gcc cgc aat        1872
Tyr Leu Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn
    610                 615                 620

gtg ctg gtg acc gag gac aac gtg atg aag atc gca gac ttc ggg ctg        1920
Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu
625                 630                 635                 640

gcc cgg gac gtg cac aac ctc gac tac tac aag aag aca acc aac ggc        1968
Ala Arg Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly
                645                 650                 655

cgg ctg ccc gtg aag tgg atg gcg cct gag gcc ttg ttt gac cga gtc        2016
Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val
            660                 665                 670

tac act cac cag agt gac gtc tgg tcc ttt ggg gtc ctg ctc tgg gag        2064
Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu
        675                 680                 685

atc ttc acg ctg ggg ggc tcc ccg tac ccc ggc atc cct gtg gag gag        2112
Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu
    690                 695                 700

ctc ttc aag ctg ctg aag gag ggc cac cgc atg gac aag ccc gcc aac        2160
Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn
705                 710                 715                 720
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tgc aca cac gac ctg tac atg atc atg cgg gag tgc tgg cat gcc gcg      2208
Cys Thr His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala
                725                 730                 735

ccc tcc cag agg ccc acc ttc aag cag ctg gtg gag gac ctg gac cgt      2256
Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg
            740                 745                 750

gtc ctt acc gtg acg tcc acc gac gta aag gcg aca cag gag gag aac      2304
Val Leu Thr Val Thr Ser Thr Asp Val Lys Ala Thr Gln Glu Glu Asn
        755                 760                 765

cgg gag ctg agg agc agg tgt gag gag ctc cac ggg aag aac ctg gaa      2352
Arg Glu Leu Arg Ser Arg Cys Glu Glu Leu His Gly Lys Asn Leu Glu
    770                 775                 780

ctg ggg aag atc atg gac agg ttc gaa gag gtt gtg tac cag gcc atg      2400
Leu Gly Lys Ile Met Asp Arg Phe Glu Glu Val Val Tyr Gln Ala Met
785                 790                 795                 800

gag gaa gtt cag aag cag aag gaa ctt tcc aaa gct gaa atc cag aaa      2448
Glu Glu Val Gln Lys Gln Lys Glu Leu Ser Lys Ala Glu Ile Gln Lys
                805                 810                 815

gtt cta aaa gaa aaa gac caa ctt acc aca gat ctg aac tcc atg gag      2496
Val Leu Lys Glu Lys Asp Gln Leu Thr Thr Asp Leu Asn Ser Met Glu
            820                 825                 830

aag tcc ttc tcc gac ctc ttc aag cgt ttt gag aaa cag aaa gag gtg      2544
Lys Ser Phe Ser Asp Leu Phe Lys Arg Phe Glu Lys Gln Lys Glu Val
        835                 840                 845

atc gag ggc tac cgc aag aac gaa gag tca ctg aag aag tgc gtg gag      2592
Ile Glu Gly Tyr Arg Lys Asn Glu Glu Ser Leu Lys Lys Cys Val Glu
    850                 855                 860

gat tac ctg gca agg atc acc cag gag ggc cag agg tac caa gcc ctg      2640
Asp Tyr Leu Ala Arg Ile Thr Gln Glu Gly Gln Arg Tyr Gln Ala Leu
865                 870                 875                 880

aag gcc cac gcg gag gag aag ctg cag ctg gca aac gag gag atc gcc      2688
Lys Ala His Ala Glu Glu Lys Leu Gln Leu Ala Asn Glu Glu Ile Ala
                885                 890                 895

cag gtc cgg agc aag gcc cag gcg gaa gcg ttg gcc ctc cag gcc agc      2736
Gln Val Arg Ser Lys Ala Gln Ala Glu Ala Leu Ala Leu Gln Ala Ser
            900                 905                 910

ctg agg aag gag cag atg cgc atc cag tcg ctg gag aag aca gtg gag      2784
Leu Arg Lys Glu Gln Met Arg Ile Gln Ser Leu Glu Lys Thr Val Glu
        915                 920                 925

cag aag act aaa gag aac gag gag ctg acc agg atc tgc gac gac ctc      2832
Gln Lys Thr Lys Glu Asn Glu Glu Leu Thr Arg Ile Cys Asp Asp Leu
    930                 935                 940

atc tcc aag atg gag aag atc tga                                      2856
Ile Ser Lys Met Glu Lys Ile
945                 950
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<210> 28

<211> 951
<212> PRT
<213> Homo sapiens

<400> 28

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1               5                   10                  15

Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
            20                  25                  30

Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
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225 230 235 240

Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
245 250 255

Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
260 265 270

Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
275 280 285

Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
290 295 300

Tyr Val Thr Val Leu Lys Ser Trp Ile Ser Glu Ser Val Glu Ala Asp
305 310 315 320

Val Arg Leu Arg Leu Ala Asn Val Ser Glu Arg Asp Gly Gly Glu Tyr
325 330 335

Leu Cys Arg Ala Thr Asn Phe Ile Gly Val Ala Glu Lys Ala Phe Trp
340 345 350

Leu Ser Val His Gly Pro Arg Ala Ala Glu Glu Glu Leu Val Glu Ala
355 360 365

Asp Glu Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly
370 375 380

Phe Phe Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu
385 390 395 400

Arg Ser Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile
405 410 415

Ser Arg Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser
420 425 430

Met Ser Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly
435 440 445

Glu Gly Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp
450 455 460

Pro Lys Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu
465 470 475 480

Gly Glu Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile
485 490 495

Asp Lys Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu
500 505 510

Lys Asp Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met
515 520 525

Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu
530 535 540

Gly Ala Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala
545 550 555 560

Ala Lys Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly
565 570 575

Leu Asp Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr
580 585 590

Phe Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu
595 600 605

Tyr Leu Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn
610 615 620

Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu
625 630 635 640

Ala Arg Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly
645 650 655

Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val
660 665 670

Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu
675 680 685

Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu
690 695 700

Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn
705 710 715 720

Cys Thr His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala
725 730 735

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Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg
            740                 745                 750

Val Leu Thr Val Thr Ser Thr Asp Val Lys Ala Thr Gln Glu Glu Asn
        755                 760                 765

Arg Glu Leu Arg Ser Arg Cys Glu Glu Leu His Gly Lys Asn Leu Glu
    770                 775                 780

Leu Gly Lys Ile Met Asp Arg Phe Glu Glu Val Val Tyr Gln Ala Met
785                 790                 795                 800

Glu Glu Val Gln Lys Gln Lys Glu Leu Ser Lys Ala Glu Ile Gln Lys
                805                 810                 815

Val Leu Lys Glu Lys Asp Gln Leu Thr Thr Asp Leu Asn Ser Met Glu
            820                 825                 830

Lys Ser Phe Ser Asp Leu Phe Lys Arg Phe Glu Lys Gln Lys Glu Val
        835                 840                 845

Ile Glu Gly Tyr Arg Lys Asn Glu Glu Ser Leu Lys Lys Cys Val Glu
    850                 855                 860

Asp Tyr Leu Ala Arg Ile Thr Gln Glu Gly Gln Arg Tyr Gln Ala Leu
865                 870                 875                 880

Lys Ala His Ala Glu Glu Lys Leu Gln Leu Ala Asn Glu Glu Ile Ala
                885                 890                 895

Gln Val Arg Ser Lys Ala Gln Ala Glu Ala Leu Ala Leu Gln Ala Ser
            900                 905                 910

Leu Arg Lys Glu Gln Met Arg Ile Gln Ser Leu Glu Lys Thr Val Glu
        915                 920                 925

Gln Lys Thr Lys Glu Asn Glu Glu Leu Thr Arg Ile Cys Asp Asp Leu
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Ile Ser Lys Met Glu Lys Ile
945                 950
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<211> 4467
<212> DNA
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<220>

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<400> 29

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Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1               5                   10                  15

gtg gcc ggc gcc tcc tcg gag tcc ttg ggg acg gag cag cgc gtc gtg       96
Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
            20                  25                  30

ggg cga gcg gca gaa gtc ccg ggc cca gag ccc ggc cag cag gag cag      144
Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

ttg gtc ttc ggc agc ggg gat gct gtg gag ctg agc tgt ccc ccg ccc      192
Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

ggg ggt ggt ccc atg ggg ccc act gtc tgg gtc aag gat ggc aca ggg      240
Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

ctg gtg ccc tcg gag cgt gtc ctg gtg ggg ccc cag cgg ctg cag gtg      288
Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

ctg aat gcc tcc cac gag gac tcc ggg gcc tac agc tgc cgg cag cgg      336
Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

ctc acg cag cgc gta ctg tgc cac ttc agt gtg cgg gtg aca gac gct      384
Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

cca tcc tcg gga gat gac gaa gac ggg gag gac gag gct gag gac aca      432
Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

ggt gtg gac aca ggg gcc cct tac tgg aca cgg ccc gag cgg atg gac      480
Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

aag aag ctg ctg gcc gtg ccg gcc gcc aac acc gtc cgc ttc cgc tgc      528
Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

cca gcc gct ggc aac ccc act ccc tcc atc tcc tgg ctg aag aac ggc      576
Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

agg gag ttc cgc ggc gag cac cgc att gga ggc atc aag ctg cgg cat      624
Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

cag cag tgg agc ctg gtc atg gaa agc gtg gtg ccc tcg gac cgc ggc      672
Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

aac tac acc tgc gtc gtg gag aac aag ttt ggc agc atc cgg cag acg      720
Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
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225                 230                 235                 240

tac acg ctg gac gtg ctg gag cgc tcc ccg cac cgg ccc atc ctg cag        768
Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255

gcg ggg ctg ccg gcc aac cag acg gcg gtg ctg ggc agc gac gtg gag        816
Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270

ttc cac tgc aag gtg tac agt gac gca cag ccc cac atc cag tgg ctc        864
Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285

aag cac gtg gag gtg aat ggc agc aag gtg ggc ccg gac ggc aca ccc        912
Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

tac gtt acc gtg ctc aag tcc tgg atc agt gag agt gtg gag gcc gac        960
Tyr Val Thr Val Leu Lys Ser Trp Ile Ser Glu Ser Val Glu Ala Asp
305                 310                 315                 320

gtg cgc ctc cgc ctg gcc aat gtg tcg gag cgg gac ggg ggc gag tac       1008
Val Arg Leu Arg Leu Ala Asn Val Ser Glu Arg Asp Gly Gly Glu Tyr
                325                 330                 335

ctc tgt cga gcc acc aat ttc ata ggc gtg gcc gag aag gcc ttt tgg       1056
Leu Cys Arg Ala Thr Asn Phe Ile Gly Val Ala Glu Lys Ala Phe Trp
            340                 345                 350

ctg agc gtt cac ggg ccc cga gca gcc gag gag gag ctg gtg gag gct       1104
Leu Ser Val His Gly Pro Arg Ala Ala Glu Glu Glu Leu Val Glu Ala
        355                 360                 365

gac gag gcg ggc agt gtg tat gca ggc atc ctc agc tac ggg gtg ggc       1152
Asp Glu Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly
    370                 375                 380

ttc ttc ctg ttc atc ctg gtg gtg gcg gct gtg acg ctc tgc cgc ctg       1200
Phe Phe Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu
385                 390                 395                 400

cgc agc ccc ccc aag aaa ggc ctg ggc tcc ccc acc gtg cac aag atc       1248
Arg Ser Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile
                405                 410                 415

tcc cgc ttc ccg ctc aag cga cag gtg tcc ctg gag tcc aac gcg tcc       1296
Ser Arg Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser
            420                 425                 430

atg agc tcc aac aca cca ctg gtg cgc atc gca agg ctg tcc tca ggg       1344
Met Ser Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly
        435                 440                 445

gag ggc ccc acg ctg gcc aat gtc tcc gag ctc gag ctg cct gcc gac       1392
Glu Gly Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp
    450                 455                 460

ccc aaa tgg gag ctg tct cgg gcc cgg ctg acc ctg ggc aag ccc ctt       1440
Pro Lys Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu
465                 470                 475                 480

ggg gag ggc tgc ttc ggc cag gtg gtc atg gcg gag gcc atc ggc att       1488
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Gly Glu Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile
                485                 490                 495

gac aag gac cgg gcc gcc aag cct gtc acc gta gcc gtg aag atg ctg      1536
Asp Lys Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu
            500                 505                 510

aaa gac gat gcc act gac aag gac ctg tcg gac ctg gtg tct gag atg      1584
Lys Asp Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met
        515                 520                 525

gag atg atg aag atg atc ggg aaa cac aaa aac atc atc aac ctg ctg      1632
Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu
    530                 535                 540

ggc gcc tgc acg cag ggc ggg ccc ctg tac gtg ctg gtg gag tac gcg      1680
Gly Ala Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala
545                 550                 555                 560

gcc aag ggt aac ctg cgg gag ttt ctg cgg gcg cgg cgg ccc ccg ggc      1728
Ala Lys Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly
                565                 570                 575

ctg gac tac tcc ttc gac acc tgc aag ccg ccc gag gag cag ctc acc      1776
Leu Asp Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr
            580                 585                 590

ttc aag gac ctg gtg tcc tgt gcc tac cag gtg gcc cgg ggc atg gag      1824
Phe Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu
        595                 600                 605

tac ttg gcc tcc cag aag tgc atc cac agg gac ctg gct gcc cgc aat      1872
Tyr Leu Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn
    610                 615                 620

gtg ctg gtg acc gag gac aac gtg atg aag atc gca gac ttc ggg ctg      1920
Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu
625                 630                 635                 640

gcc cgg gac gtg cac aac ctc gac tac tac aag aag aca acc aac ggc      1968
Ala Arg Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly
                645                 650                 655

cgg ctg ccc gtg aag tgg atg gcg cct gag gcc ttg ttt gac cga gtc      2016
Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val
            660                 665                 670

tac act cac cag agt gac gtc tgg tcc ttt ggg gtc ctg ctc tgg gag      2064
Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu
        675                 680                 685

atc ttc acg ctg ggg ggc tcc ccg tac ccc ggc atc cct gtg gag gag      2112
Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu
    690                 695                 700

ctc ttc aag ctg ctg aag gag ggc cac cgc atg gac aag ccc gcc aac      2160
Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn
705                 710                 715                 720

tgc aca cac gac ctg tac atg atc atg cgg gag tgc tgg cat gcc gcg      2208
Cys Thr His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala
                725                 730                 735
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ccc tcc cag agg ccc acc ttc aag cag ctg gtg gag gac ctg gac cgt      2256
Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg
            740                 745                 750

gtc ctt acc gtg acg tcc acc gac gtg agt gct ggc tct ggc ctg gtg      2304
Val Leu Thr Val Thr Ser Thr Asp Val Ser Ala Gly Ser Gly Leu Val
        755                 760                 765

cca ccc gcc tat gcc cct ccc cct gcc gtc ccc ggc cat cct gcc ccc      2352
Pro Pro Ala Tyr Ala Pro Pro Pro Ala Val Pro Gly His Pro Ala Pro
    770                 775                 780

cag agt gct gag gtg tgg ggc ggg cct tct ggc cca ggt gcc ctg gct      2400
Gln Ser Ala Glu Val Trp Gly Gly Pro Ser Gly Pro Gly Ala Leu Ala
785                 790                 795                 800

gac ctg gac tgc tca agc tct tcc cag agc cca gga agt tct gag aac      2448
Asp Leu Asp Cys Ser Ser Ser Ser Gln Ser Pro Gly Ser Ser Glu Asn
                805                 810                 815

caa atg gtg tct cca gga aaa gtg tct ggc agc cct gag caa gcc gtg      2496
Gln Met Val Ser Pro Gly Lys Val Ser Gly Ser Pro Glu Gln Ala Val
            820                 825                 830

gag gaa aac ctt agt tcc tat tcc tta gac aga aga gtg aca ccc gcc      2544
Glu Glu Asn Leu Ser Ser Tyr Ser Leu Asp Arg Arg Val Thr Pro Ala
        835                 840                 845

tct gag acc cta gaa gac cct tgc agg aca gag tcc cag cac aaa gcg      2592
Ser Glu Thr Leu Glu Asp Pro Cys Arg Thr Glu Ser Gln His Lys Ala
    850                 855                 860

gag act ccg cac gga gcc gag gaa gaa tgc aaa gcg gag act ccg cac      2640
Glu Thr Pro His Gly Ala Glu Glu Glu Cys Lys Ala Glu Thr Pro His
865                 870                 875                 880

gga gcc gag gag gaa tgc cgg cac ggt ggg gtc tgt gct ccc gca gca      2688
Gly Ala Glu Glu Glu Cys Arg His Gly Gly Val Cys Ala Pro Ala Ala
                885                 890                 895

gtg gcc act tcg cct cct ggt gca atc cct aag gaa gcc tgc gga gga      2736
Val Ala Thr Ser Pro Pro Gly Ala Ile Pro Lys Glu Ala Cys Gly Gly
            900                 905                 910

gca ccc ctg cag ggt ctg cct ggc gaa gcc ctg ggc tgc cct gcg ggt      2784
Ala Pro Leu Gln Gly Leu Pro Gly Glu Ala Leu Gly Cys Pro Ala Gly
        915                 920                 925

gtg ggc acc ccc gtg cca gca gat ggc act cag acc ctt acc tgt gca      2832
Val Gly Thr Pro Val Pro Ala Asp Gly Thr Gln Thr Leu Thr Cys Ala
    930                 935                 940

cac acc tct gct cct gag agc aca gcc cca acc aac cac ctg gtg gct      2880
His Thr Ser Ala Pro Glu Ser Thr Ala Pro Thr Asn His Leu Val Ala
945                 950                 955                 960

ggc agg gcc atg acc ctg agt cct cag gaa gaa gtg gct gca ggc caa      2928
Gly Arg Ala Met Thr Leu Ser Pro Gln Glu Glu Val Ala Ala Gly Gln
                965                 970                 975

atg gcc agc tcc tcg agg agc gga cct gta aaa cta gaa ttt gat gta      2976
Met Ala Ser Ser Ser Arg Ser Gly Pro Val Lys Leu Glu Phe Asp Val
            980                 985                 990
```

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tct gat ggc gcc acc agc aaa agg  gca ccc cca cca agg  aga ctg gga     3024
Ser Asp Gly Ala Thr Ser Lys Arg  Ala Pro Pro Pro Arg  Arg Leu Gly
        995                 1000                 1005

gag agg  tcc ggc ctc aag cct  ccc ttg agg aaa gca  gca gtg agg        3069
Glu Arg  Ser Gly Leu Lys Pro  Pro Leu Arg Lys Ala  Ala Val Arg
    1010                 1015                 1020

cag caa  aag gcc ccg cag gag  gtg gag gag gac gac  ggt agg agc        3114
Gln Gln  Lys Ala Pro Gln Glu  Val Glu Glu Asp Asp  Gly Arg Ser
    1025                 1030                 1035

gga gca  gga gag gac ccc ccc  atg cca gct tct cgg  ggc tct tac        3159
Gly Ala  Gly Glu Asp Pro Pro  Met Pro Ala Ser Arg  Gly Ser Tyr
    1040                 1045                 1050

cac ctc  gac tgg gac aaa atg  gat gac cca aac ttc  atc ccg ttc        3204
His Leu  Asp Trp Asp Lys Met  Asp Asp Pro Asn Phe  Ile Pro Phe
    1055                 1060                 1065

gga ggt  gac acc aag tct ggt  tgc agt gag gcc cag  ccc cca gaa        3249
Gly Gly  Asp Thr Lys Ser Gly  Cys Ser Glu Ala Gln  Pro Pro Glu
    1070                 1075                 1080

agc cct  gag acc agg ctg ggc  cag cca gcg gct gaa  cag ttg cat        3294
Ser Pro  Glu Thr Arg Leu Gly  Gln Pro Ala Ala Glu  Gln Leu His
    1085                 1090                 1095

gct ggg  cct gcc acg gag gag  cca ggt ccc tgt ctg  agc cag cag        3339
Ala Gly  Pro Ala Thr Glu Glu  Pro Gly Pro Cys Leu  Ser Gln Gln
    1100                 1105                 1110

ctg cat  tca gcc tca gcg gag  gac acg cct gtg gtg  cag ttg gca        3384
Leu His  Ser Ala Ser Ala Glu  Asp Thr Pro Val Val  Gln Leu Ala
    1115                 1120                 1125

gcc gag  acc cca aca gca gag  agc aag gag aga gcc  ttg aac tct        3429
Ala Glu  Thr Pro Thr Ala Glu  Ser Lys Glu Arg Ala  Leu Asn Ser
    1130                 1135                 1140

gcc agc  acc tcg ctt ccc aca  agc tgt cca ggc agt  gag cca gtg        3474
Ala Ser  Thr Ser Leu Pro Thr  Ser Cys Pro Gly Ser  Glu Pro Val
    1145                 1150                 1155

ccc acc  cat cag cag ggg cag  cct gcc ttg gag ctg  aaa gag gag        3519
Pro Thr  His Gln Gln Gly Gln  Pro Ala Leu Glu Leu  Lys Glu Glu
    1160                 1165                 1170

agc ttc  aga gac ccc gct gag  gtt cta ggc acg ggc  gcg gag gtg        3564
Ser Phe  Arg Asp Pro Ala Glu  Val Leu Gly Thr Gly  Ala Glu Val
    1175                 1180                 1185

gat tac  ctg gag cag ttt gga  act tcc tcg ttt aag  gag tcg gcc        3609
Asp Tyr  Leu Glu Gln Phe Gly  Thr Ser Ser Phe Lys  Glu Ser Ala
    1190                 1195                 1200

ttg agg  aag cag tcc tta tac  ctc aag ttc gac ccc  ctc ctg agg        3654
Leu Arg  Lys Gln Ser Leu Tyr  Leu Lys Phe Asp Pro  Leu Leu Arg
    1205                 1210                 1215

gac agt  cct ggt aga cca gtg  ccc gtg gcc acc gag  acc agc agc        3699
Asp Ser  Pro Gly Arg Pro Val  Pro Val Ala Thr Glu  Thr Ser Ser
```

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    1220                1225                1230

atg cac ggt gca aat gag act ccc tca gga cgt ccg cgg gaa gcc        3744
Met His Gly Ala Asn Glu Thr Pro Ser Gly Arg Pro Arg Glu Ala
    1235                1240                1245

aag ctt gtg gag ttc gat ttc ttg gga gca ctg gac att cct gtg        3789
Lys Leu Val Glu Phe Asp Phe Leu Gly Ala Leu Asp Ile Pro Val
    1250                1255                1260

cca ggc cca ccc cca ggt gtt ccc gcg cct ggg ggc cca ccc ctg        3834
Pro Gly Pro Pro Pro Gly Val Pro Ala Pro Gly Gly Pro Pro Leu
    1265                1270                1275

tcc acc gga cct ata gtg gac ctg ctc cag tac agc cag aag gac        3879
Ser Thr Gly Pro Ile Val Asp Leu Leu Gln Tyr Ser Gln Lys Asp
    1280                1285                1290

ctg gat gca gtg gta aag gcg aca cag gag gag aac cgg gag ctg        3924
Leu Asp Ala Val Val Lys Ala Thr Gln Glu Glu Asn Arg Glu Leu
    1295                1300                1305

agg agc agg tgt gag gag ctc cac ggg aag aac ctg gaa ctg ggg        3969
Arg Ser Arg Cys Glu Glu Leu His Gly Lys Asn Leu Glu Leu Gly
    1310                1315                1320

aag atc atg gac agg ttc gaa gag gtt gtg tac cag gcc atg gag        4014
Lys Ile Met Asp Arg Phe Glu Glu Val Val Tyr Gln Ala Met Glu
    1325                1330                1335

gaa gtt cag aag cag aag gaa ctt tcc aaa gct gaa atc cag aaa        4059
Glu Val Gln Lys Gln Lys Glu Leu Ser Lys Ala Glu Ile Gln Lys
    1340                1345                1350

gtt cta aaa gaa aaa gac caa ctt acc aca gat ctg aac tcc atg        4104
Val Leu Lys Glu Lys Asp Gln Leu Thr Thr Asp Leu Asn Ser Met
    1355                1360                1365

gag aag tcc ttc tcc gac ctc ttc aag cgt ttt gag aaa cag aaa        4149
Glu Lys Ser Phe Ser Asp Leu Phe Lys Arg Phe Glu Lys Gln Lys
    1370                1375                1380

gag gtg atc gag ggc tac cgc aag aac gaa gag tca ctg aag aag        4194
Glu Val Ile Glu Gly Tyr Arg Lys Asn Glu Glu Ser Leu Lys Lys
    1385                1390                1395

tgc gtg gag gat tac ctg gca agg atc acc cag gag ggc cag agg        4239
Cys Val Glu Asp Tyr Leu Ala Arg Ile Thr Gln Glu Gly Gln Arg
    1400                1405                1410

tac caa gcc ctg aag gcc cac gcg gag gag aag ctg cag ctg gca        4284
Tyr Gln Ala Leu Lys Ala His Ala Glu Glu Lys Leu Gln Leu Ala
    1415                1420                1425

aac gag gag atc gcc cag gtc cgg agc aag gcc cag gcg gaa gcg        4329
Asn Glu Glu Ile Ala Gln Val Arg Ser Lys Ala Gln Ala Glu Ala
    1430                1435                1440

ttg gcc ctc cag gcc agc ctg agg aag gag cag atg cgc atc cag        4374
Leu Ala Leu Gln Ala Ser Leu Arg Lys Glu Gln Met Arg Ile Gln
    1445                1450                1455

tcg ctg gag aag aca gtg gag cag aag act aaa gag aac gag gag        4419
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```
Ser Leu  Glu Lys Thr Val Glu  Gln Lys Thr Lys Glu  Asn Glu Glu
    1460                1465                1470

ctg acc  agg atc tgc gac gac  ctc atc tcc aag atg  gag aag atc        4464
Leu Thr  Arg Ile Cys Asp Asp  Leu Ile Ser Lys Met  Glu Lys Ile
    1475                1480                1485

tga                                                                   4467
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<210> 30
<211> 1488
<212> PRT
<213> Homo sapiens

<400> 30

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Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1               5                   10                  15

Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
            20                  25                  30

Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190
```

```
Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
225                 230                 235                 240

Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255

Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270

Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285

Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

Tyr Val Thr Val Leu Lys Ser Trp Ile Ser Glu Ser Val Glu Ala Asp
305                 310                 315                 320

Val Arg Leu Arg Leu Ala Asn Val Ser Glu Arg Asp Gly Gly Glu Tyr
                325                 330                 335

Leu Cys Arg Ala Thr Asn Phe Ile Gly Val Ala Glu Lys Ala Phe Trp
            340                 345                 350

Leu Ser Val His Gly Pro Arg Ala Ala Glu Glu Glu Leu Val Glu Ala
        355                 360                 365

Asp Glu Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly
    370                 375                 380

Phe Phe Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu
385                 390                 395                 400

Arg Ser Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile
                405                 410                 415

Ser Arg Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser
            420                 425                 430

Met Ser Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly
```

```
            435                 440                 445

Glu Gly Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp
    450                 455                 460

Pro Lys Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu
465                 470                 475                 480

Gly Glu Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile
                485                 490                 495

Asp Lys Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu
            500                 505                 510

Lys Asp Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met
        515                 520                 525

Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu
    530                 535                 540

Gly Ala Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala
545                 550                 555                 560

Ala Lys Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly
                565                 570                 575

Leu Asp Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr
            580                 585                 590

Phe Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu
        595                 600                 605

Tyr Leu Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn
    610                 615                 620

Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu
625                 630                 635                 640

Ala Arg Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly
                645                 650                 655

Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val
            660                 665                 670

Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu
        675                 680                 685
```

```
Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu
    690                 695                 700

Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn
705                 710                 715                 720

Cys Thr His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala
                725                 730                 735

Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg
            740                 745                 750

Val Leu Thr Val Thr Ser Thr Asp Val Ser Ala Gly Ser Gly Leu Val
        755                 760                 765

Pro Pro Ala Tyr Ala Pro Pro Pro Ala Val Pro Gly His Pro Ala Pro
    770                 775                 780

Gln Ser Ala Glu Val Trp Gly Gly Pro Ser Gly Pro Gly Ala Leu Ala
785                 790                 795                 800

Asp Leu Asp Cys Ser Ser Ser Ser Gln Ser Pro Gly Ser Ser Glu Asn
                805                 810                 815

Gln Met Val Ser Pro Gly Lys Val Ser Gly Ser Pro Glu Gln Ala Val
            820                 825                 830

Glu Glu Asn Leu Ser Ser Tyr Ser Leu Asp Arg Arg Val Thr Pro Ala
        835                 840                 845

Ser Glu Thr Leu Glu Asp Pro Cys Arg Thr Glu Ser Gln His Lys Ala
    850                 855                 860

Glu Thr Pro His Gly Ala Glu Glu Glu Cys Lys Ala Glu Thr Pro His
865                 870                 875                 880

Gly Ala Glu Glu Glu Cys Arg His Gly Gly Val Cys Ala Pro Ala Ala
                885                 890                 895

Val Ala Thr Ser Pro Pro Gly Ala Ile Pro Lys Glu Ala Cys Gly Gly
            900                 905                 910

Ala Pro Leu Gln Gly Leu Pro Gly Glu Ala Leu Gly Cys Pro Ala Gly
        915                 920                 925

Val Gly Thr Pro Val Pro Ala Asp Gly Thr Gln Thr Leu Thr Cys Ala
    930                 935                 940
```

His Thr Ser Ala Pro Glu Ser Thr Ala Pro Thr Asn His Leu Val Ala
945 950 955 960

Gly Arg Ala Met Thr Leu Ser Pro Gln Glu Glu Val Ala Ala Gly Gln
965 970 975

Met Ala Ser Ser Ser Arg Ser Gly Pro Val Lys Leu Glu Phe Asp Val
980 985 990

Ser Asp Gly Ala Thr Ser Lys Arg Ala Pro Pro Pro Arg Arg Leu Gly
995 1000 1005

Glu Arg Ser Gly Leu Lys Pro Pro Leu Arg Lys Ala Ala Val Arg
1010 1015 1020

Gln Gln Lys Ala Pro Gln Glu Val Glu Glu Asp Asp Gly Arg Ser
1025 1030 1035

Gly Ala Gly Glu Asp Pro Pro Met Pro Ala Ser Arg Gly Ser Tyr
1040 1045 1050

His Leu Asp Trp Asp Lys Met Asp Asp Pro Asn Phe Ile Pro Phe
1055 1060 1065

Gly Gly Asp Thr Lys Ser Gly Cys Ser Glu Ala Gln Pro Pro Glu
1070 1075 1080

Ser Pro Glu Thr Arg Leu Gly Gln Pro Ala Ala Glu Gln Leu His
1085 1090 1095

Ala Gly Pro Ala Thr Glu Glu Pro Gly Pro Cys Leu Ser Gln Gln
1100 1105 1110

Leu His Ser Ala Ser Ala Glu Asp Thr Pro Val Val Gln Leu Ala
1115 1120 1125

Ala Glu Thr Pro Thr Ala Glu Ser Lys Glu Arg Ala Leu Asn Ser
1130 1135 1140

Ala Ser Thr Ser Leu Pro Thr Ser Cys Pro Gly Ser Glu Pro Val
1145 1150 1155

Pro Thr His Gln Gln Gly Gln Pro Ala Leu Glu Leu Lys Glu Glu
1160 1165 1170

Ser Phe Arg Asp Pro Ala Glu Val Leu Gly Thr Gly Ala Glu Val
1175 1180 1185

```
Asp Tyr  Leu Glu Gln Phe Gly  Thr Ser Ser Phe Lys  Glu Ser Ala
    1190                 1195                 1200

Leu Arg  Lys Gln Ser Leu Tyr  Leu Lys Phe Asp Pro  Leu Leu Arg
    1205                 1210                 1215

Asp Ser  Pro Gly Arg Pro Val  Pro Val Ala Thr Glu  Thr Ser Ser
    1220                 1225                 1230

Met His  Gly Ala Asn Glu Thr  Pro Ser Gly Arg Pro  Arg Glu Ala
    1235                 1240                 1245

Lys Leu  Val Glu Phe Asp Phe  Leu Gly Ala Leu Asp  Ile Pro Val
    1250                 1255                 1260

Pro Gly  Pro Pro Pro Gly Val  Pro Ala Pro Gly Gly  Pro Pro Leu
    1265                 1270                 1275

Ser Thr  Gly Pro Ile Val Asp  Leu Leu Gln Tyr Ser  Gln Lys Asp
    1280                 1285                 1290

Leu Asp  Ala Val Val Lys Ala  Thr Gln Glu Glu Asn  Arg Glu Leu
    1295                 1300                 1305

Arg Ser  Arg Cys Glu Glu Leu  His Gly Lys Asn Leu  Glu Leu Gly
    1310                 1315                 1320

Lys Ile  Met Asp Arg Phe Glu  Glu Val Val Tyr Gln  Ala Met Glu
    1325                 1330                 1335

Glu Val  Gln Lys Gln Lys Glu  Leu Ser Lys Ala Glu  Ile Gln Lys
    1340                 1345                 1350

Val Leu  Lys Glu Lys Asp Gln  Leu Thr Thr Asp Leu  Asn Ser Met
    1355                 1360                 1365

Glu Lys  Ser Phe Ser Asp Leu  Phe Lys Arg Phe Glu  Lys Gln Lys
    1370                 1375                 1380

Glu Val  Ile Glu Gly Tyr Arg  Lys Asn Glu Glu Ser  Leu Lys Lys
    1385                 1390                 1395

Cys Val  Glu Asp Tyr Leu Ala  Arg Ile Thr Gln Glu  Gly Gln Arg
    1400                 1405                 1410

Tyr Gln  Ala Leu Lys Ala His  Ala Glu Glu Lys Leu  Gln Leu Ala
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1415 1420 1425

Asn Glu Glu Ile Ala Gln Val Arg Ser Lys Ala Gln Ala Glu Ala
1430 1435 1440

Leu Ala Leu Gln Ala Ser Leu Arg Lys Glu Gln Met Arg Ile Gln
1445 1450 1455

Ser Leu Glu Lys Thr Val Glu Gln Lys Thr Lys Glu Asn Glu Glu
1460 1465 1470

Leu Thr Arg Ile Cys Asp Asp Leu Ile Ser Lys Met Glu Lys Ile
1475 1480 1485

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<212> DNA
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<221> CDS
<222> (1)..(3765)

<400> 31

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Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1               5                   10                  15

gtg gcc ggc gcc tcc tcg gag tcc ttg ggg acg gag cag cgc gtc gtg       96
Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
            20                  25                  30

ggg cga gcg gca gaa gtc ccg ggc cca gag ccc ggc cag cag gag cag      144
Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

ttg gtc ttc ggc agc ggg gat gct gtg gag ctg agc tgt ccc ccg ccc      192
Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

ggg ggt ggt ccc atg ggg ccc act gtc tgg gtc aag gat ggc aca ggg      240
Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

ctg gtg ccc tcg gag cgt gtc ctg gtg ggg ccc cag cgg ctg cag gtg      288
Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

ctg aat gcc tcc cac gag gac tcc ggg gcc tac agc tgc cgg cag cgg      336
Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

ctc acg cag cgc gta ctg tgc cac ttc agt gtg cgg gtg aca gac gct      384
Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

cca tcc tcg gga gat gac gaa gac ggg gag gac gag gct gag gac aca      432
```

```
Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

ggt gtg gac aca ggg gcc cct tac tgg aca cgg ccc gag cgg atg gac      480
Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

aag aag ctg ctg gcc gtg ccg gcc gcc aac acc gtc cgc ttc cgc tgc      528
Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

cca gcc gct ggc aac ccc act ccc tcc atc tcc tgg ctg aag aac ggc      576
Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

agg gag ttc cgc ggc gag cac cgc att gga ggc atc aag ctg cgg cat      624
Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

cag cag tgg agc ctg gtc atg gaa agc gtg gtg ccc tcg gac cgc ggc      672
Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

aac tac acc tgc gtc gtg gag aac aag ttt ggc agc atc cgg cag acg      720
Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
225                 230                 235                 240

tac acg ctg gac gtg ctg gag cgc tcc ccg cac cgg ccc atc ctg cag      768
Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255

gcg ggg ctg ccg gcc aac cag acg gcg gtg ctg ggc agc gac gtg gag      816
Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270

ttc cac tgc aag gtg tac agt gac gca cag ccc cac atc cag tgg ctc      864
Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285

aag cac gtg gag gtg aat ggc agc aag gtg ggc ccg gac ggc aca ccc      912
Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

tac gtt acc gtg ctc aag tcc tgg atc agt gag agt gtg gag gcc gac      960
Tyr Val Thr Val Leu Lys Ser Trp Ile Ser Glu Ser Val Glu Ala Asp
305                 310                 315                 320

gtg cgc ctc cgc ctg gcc aat gtg tcg gag cgg gac ggg ggc gag tac     1008
Val Arg Leu Arg Leu Ala Asn Val Ser Glu Arg Asp Gly Gly Glu Tyr
                325                 330                 335

ctc tgt cga gcc acc aat ttc ata ggc gtg gcc gag aag gcc ttt tgg     1056
Leu Cys Arg Ala Thr Asn Phe Ile Gly Val Ala Glu Lys Ala Phe Trp
            340                 345                 350

ctg agc gtt cac ggg ccc cga gca gcc gag gag gag ctg gtg gag gct     1104
Leu Ser Val His Gly Pro Arg Ala Ala Glu Glu Glu Leu Val Glu Ala
        355                 360                 365

gac gag gcg ggc agt gtg tat gca ggc atc ctc agc tac ggg gtg ggc     1152
Asp Glu Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly
    370                 375                 380
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ttc ttc ctg ttc atc ctg gtg gtg gcg gct gtg acg ctc tgc cgc ctg      1200
Phe Phe Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu
385                 390                 395                 400

cgc agc ccc ccc aag aaa ggc ctg ggc tcc ccc acc gtg cac aag atc      1248
Arg Ser Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile
                405                 410                 415

tcc cgc ttc ccg ctc aag cga cag gtg tcc ctg gag tcc aac gcg tcc      1296
Ser Arg Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser
            420                 425                 430

atg agc tcc aac aca cca ctg gtg cgc atc gca agg ctg tcc tca ggg      1344
Met Ser Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly
        435                 440                 445

gag ggc ccc acg ctg gcc aat gtc tcc gag ctc gag ctg cct gcc gac      1392
Glu Gly Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp
    450                 455                 460

ccc aaa tgg gag ctg tct cgg gcc cgg ctg acc ctg ggc aag ccc ctt      1440
Pro Lys Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu
465                 470                 475                 480

ggg gag ggc tgc ttc ggc cag gtg gtc atg gcg gag gcc atc ggc att      1488
Gly Glu Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile
                485                 490                 495

gac aag gac cgg gcc gcc aag cct gtc acc gta gcc gtg aag atg ctg      1536
Asp Lys Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu
            500                 505                 510

aaa gac gat gcc act gac aag gac ctg tcg gac ctg gtg tct gag atg      1584
Lys Asp Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met
        515                 520                 525

gag atg atg aag atg atc ggg aaa cac aaa aac atc atc aac ctg ctg      1632
Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu
    530                 535                 540

ggc gcc tgc acg cag ggc ggg ccc ctg tac gtg ctg gtg gag tac gcg      1680
Gly Ala Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala
545                 550                 555                 560

gcc aag ggt aac ctg cgg gag ttt ctg cgg gcg cgg cgg ccc ccg ggc      1728
Ala Lys Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly
                565                 570                 575

ctg gac tac tcc ttc gac acc tgc aag ccg ccc gag gag cag ctc acc      1776
Leu Asp Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr
            580                 585                 590

ttc aag gac ctg gtg tcc tgt gcc tac cag gtg gcc cgg ggc atg gag      1824
Phe Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu
        595                 600                 605

tac ttg gcc tcc cag aag tgc atc cac agg gac ctg gct gcc cgc aat      1872
Tyr Leu Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn
    610                 615                 620

gtg ctg gtg acc gag gac aac gtg atg aag atc gca gac ttc ggg ctg      1920
Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu
625                 630                 635                 640
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gcc cgg gac gtg cac aac ctc gac tac tac aag aag aca acc aac ggc      1968
Ala Arg Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly
                645                 650                 655

cgg ctg ccc gtg aag tgg atg gcg cct gag gcc ttg ttt gac cga gtc      2016
Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val
            660                 665                 670

tac act cac cag agt gac gtc tgg tcc ttt ggg gtc ctg ctc tgg gag      2064
Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu
        675                 680                 685

atc ttc acg ctg ggg ggc tcc ccg tac ccc ggc atc cct gtg gag gag      2112
Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu
    690                 695                 700

ctc ttc aag ctg ctg aag gag ggc cac cgc atg gac aag ccc gcc aac      2160
Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn
705                 710                 715                 720

tgc aca cac gac ctg tac atg atc atg cgg gag tgc tgg cat gcc gcg      2208
Cys Thr His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala
                725                 730                 735

ccc tcc cag agg ccc acc ttc aag cag ctg gtg gag gac ctg gac cgt      2256
Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg
            740                 745                 750

gtc ctt acc gtg acg tcc acc gac aat gtt atg gaa cag ttc aat cct      2304
Val Leu Thr Val Thr Ser Thr Asp Asn Val Met Glu Gln Phe Asn Pro
        755                 760                 765

ggg ctg cga aat tta ata aac ctg ggg aaa aat tat gag aaa gct gta      2352
Gly Leu Arg Asn Leu Ile Asn Leu Gly Lys Asn Tyr Glu Lys Ala Val
    770                 775                 780

aac gct atg atc ctg gca gga aaa gcc tac tac gat gga gtg gcc aag      2400
Asn Ala Met Ile Leu Ala Gly Lys Ala Tyr Tyr Asp Gly Val Ala Lys
785                 790                 795                 800

atc ggt gag att gcc act ggg tcc ccc gtg tca act gaa ctg gga cat      2448
Ile Gly Glu Ile Ala Thr Gly Ser Pro Val Ser Thr Glu Leu Gly His
                805                 810                 815

gtc ctc ata gag att tca agt acc cac aag aaa ctc aac gag agt ctt      2496
Val Leu Ile Glu Ile Ser Ser Thr His Lys Lys Leu Asn Glu Ser Leu
            820                 825                 830

gat gaa aat ttt aaa aaa ttc cac aaa gag att atc cat gag ctg gag      2544
Asp Glu Asn Phe Lys Lys Phe His Lys Glu Ile Ile His Glu Leu Glu
        835                 840                 845

aag aag ata gaa ctt gac gtg aaa tat atg aac gca act cta aaa aga      2592
Lys Lys Ile Glu Leu Asp Val Lys Tyr Met Asn Ala Thr Leu Lys Arg
    850                 855                 860

tac caa aca gaa cac aag aat aaa tta gag tct ttg gag aaa tcc caa      2640
Tyr Gln Thr Glu His Lys Asn Lys Leu Glu Ser Leu Glu Lys Ser Gln
865                 870                 875                 880

gct gag ttg aag aag atc aga agg aaa agc caa gga agc cga aac gca      2688
Ala Glu Leu Lys Lys Ile Arg Arg Lys Ser Gln Gly Ser Arg Asn Ala
```

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                885                 890                 895

ctc aaa tat gaa cac aaa gaa att gag tat gtg gag acc gtt act tct       2736
Leu Lys Tyr Glu His Lys Glu Ile Glu Tyr Val Glu Thr Val Thr Ser
            900                 905                 910

cgt cag agt gaa atc cag aaa ttc att gca gat ggt tgc aaa gag gct       2784
Arg Gln Ser Glu Ile Gln Lys Phe Ile Ala Asp Gly Cys Lys Glu Ala
        915                 920                 925

ctg ctt gaa gag aag agg cgc ttc tgc ttt ctg gtt gat aag cac tgt       2832
Leu Leu Glu Glu Lys Arg Arg Phe Cys Phe Leu Val Asp Lys His Cys
    930                 935                 940

ggc ttt gca aac cac ata cat tat tat cac tta cag tct gca gaa cta       2880
Gly Phe Ala Asn His Ile His Tyr Tyr His Leu Gln Ser Ala Glu Leu
945                 950                 955                 960

ctg aat tcc aag ctg cct cgg tgg cag gag acc tgt gtt gat gcc atc       2928
Leu Asn Ser Lys Leu Pro Arg Trp Gln Glu Thr Cys Val Asp Ala Ile
                965                 970                 975

aaa gtg cca gag aaa atc atg aat atg atc gaa gaa ata aag acc cca       2976
Lys Val Pro Glu Lys Ile Met Asn Met Ile Glu Glu Ile Lys Thr Pro
            980                 985                 990

gcc tct acc ccc gtg tct gga act  cct cag gct tca ccc  atg atc gag     3024
Ala Ser Thr Pro Val Ser Gly Thr  Pro Gln Ala Ser Pro  Met Ile Glu
        995                 1000                 1005

aga agc  aat gtg gtt agg aaa  gat tac gac acc ctt  tct aaa tgc        3069
Arg Ser  Asn Val Val Arg Lys  Asp Tyr Asp Thr Leu  Ser Lys Cys
    1010                 1015                 1020

tca cca  aag atg ccc ccc gct  cct tca ggc aga gca  tat acc agt        3114
Ser Pro  Lys Met Pro Pro Ala  Pro Ser Gly Arg Ala  Tyr Thr Ser
    1025                 1030                 1035

ccc ttg  atc gat atg ttt aat  aac cca gcc acg gct  gcc ccg aat        3159
Pro Leu  Ile Asp Met Phe Asn  Asn Pro Ala Thr Ala  Ala Pro Asn
    1040                 1045                 1050

tca caa  agg gta aat aat tca  aca ggt act tcc gaa  gat ccc agt        3204
Ser Gln  Arg Val Asn Asn Ser  Thr Gly Thr Ser Glu  Asp Pro Ser
    1055                 1060                 1065

tta cag  cga tca gtt tcg gtt  gca acg gga ctg aac  atg atg aag        3249
Leu Gln  Arg Ser Val Ser Val  Ala Thr Gly Leu Asn  Met Met Lys
    1070                 1075                 1080

aag cag  aaa gtg aag acc atc  ttc ccg cac act gcg  ggc tcc aac        3294
Lys Gln  Lys Val Lys Thr Ile  Phe Pro His Thr Ala  Gly Ser Asn
    1085                 1090                 1095

aag acc  tta ctc agc ttt gca  cag gga gat gtc atc  acg ctg ctc        3339
Lys Thr  Leu Leu Ser Phe Ala  Gln Gly Asp Val Ile  Thr Leu Leu
    1100                 1105                 1110

atc ccc  gag gag aag gat ggc  tgg ctc tat gga gaa  cac gac gtg        3384
Ile Pro  Glu Glu Lys Asp Gly  Trp Leu Tyr Gly Glu  His Asp Val
    1115                 1120                 1125

tcc aag  gcg agg ggt tgg ttc  ccg tcg tcg tac acg  aag ttg ctg        3429
```

```
Ser Lys Ala Arg Gly Trp Phe Pro Ser Ser Tyr Thr Lys Leu Leu
    1130                1135                1140

gaa gaa aat gag aca gaa gca gtg acc gtg ccc acg cca agc ccc       3474
Glu Glu Asn Glu Thr Glu Ala Val Thr Val Pro Thr Pro Ser Pro
    1145                1150                1155

aca cca gtg aga agc atc agc acc gtg aac ttg tct gag aat agc       3519
Thr Pro Val Arg Ser Ile Ser Thr Val Asn Leu Ser Glu Asn Ser
    1160                1165                1170

agt gtt gtc atc ccc cca ccc gac tac ttg gaa tgc ttg tcc atg       3564
Ser Val Val Ile Pro Pro Pro Asp Tyr Leu Glu Cys Leu Ser Met
    1175                1180                1185

ggg gca gct gcc gac agg aga gca gat tcg gcc agg acg aca tcc       3609
Gly Ala Ala Ala Asp Arg Arg Ala Asp Ser Ala Arg Thr Thr Ser
    1190                1195                1200

acc ttt aag gcc cca gcg tcc aag ccc gag acc gcg gct cct aac       3654
Thr Phe Lys Ala Pro Ala Ser Lys Pro Glu Thr Ala Ala Pro Asn
    1205                1210                1215

gat gcc aac ggg act gca aag ccg cct ttt ctc agc gga gaa aac       3699
Asp Ala Asn Gly Thr Ala Lys Pro Pro Phe Leu Ser Gly Glu Asn
    1220                1225                1230

ccc ttt gcc act gtg aaa ctc cgc ccg act gtg acg aat gat cgc       3744
Pro Phe Ala Thr Val Lys Leu Arg Pro Thr Val Thr Asn Asp Arg
    1235                1240                1245

tcg gca ccc atc att cga tga                                       3765
Ser Ala Pro Ile Ile Arg
    1250
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<210> 32
<211> 1254
<212> PRT
<213> Homo sapiens

<400> 32

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Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1               5                   10                  15

Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
            20                  25                  30

Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80
```

```
Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
225                 230                 235                 240

Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255

Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270

Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285

Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

Tyr Val Thr Val Leu Lys Ser Trp Ile Ser Glu Ser Val Glu Ala Asp
305                 310                 315                 320

Val Arg Leu Arg Leu Ala Asn Val Ser Glu Arg Asp Gly Gly Glu Tyr
                325                 330                 335
```

```
Leu Cys Arg Ala Thr Asn Phe Ile Gly Val Ala Glu Lys Ala Phe Trp
            340                 345                 350

Leu Ser Val His Gly Pro Arg Ala Ala Glu Glu Glu Leu Val Glu Ala
        355                 360                 365

Asp Glu Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly
    370                 375                 380

Phe Phe Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu
385                 390                 395                 400

Arg Ser Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile
                405                 410                 415

Ser Arg Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser
            420                 425                 430

Met Ser Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly
        435                 440                 445

Glu Gly Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp
    450                 455                 460

Pro Lys Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu
465                 470                 475                 480

Gly Glu Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile
                485                 490                 495

Asp Lys Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu
            500                 505                 510

Lys Asp Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met
        515                 520                 525

Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu
    530                 535                 540

Gly Ala Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala
545                 550                 555                 560

Ala Lys Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly
                565                 570                 575

Leu Asp Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr
            580                 585                 590
```

```
Phe Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu
        595                 600                 605

Tyr Leu Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn
    610                 615                 620

Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu
625                 630                 635                 640

Ala Arg Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly
                645                 650                 655

Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val
            660                 665                 670

Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu
        675                 680                 685

Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu
    690                 695                 700

Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn
705                 710                 715                 720

Cys Thr His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala
                725                 730                 735

Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg
            740                 745                 750

Val Leu Thr Val Thr Ser Thr Asp Asn Val Met Glu Gln Phe Asn Pro
        755                 760                 765

Gly Leu Arg Asn Leu Ile Asn Leu Gly Lys Asn Tyr Glu Lys Ala Val
    770                 775                 780

Asn Ala Met Ile Leu Ala Gly Lys Ala Tyr Tyr Asp Gly Val Ala Lys
785                 790                 795                 800

Ile Gly Glu Ile Ala Thr Gly Ser Pro Val Ser Thr Glu Leu Gly His
                805                 810                 815

Val Leu Ile Glu Ile Ser Ser Thr His Lys Lys Leu Asn Glu Ser Leu
            820                 825                 830

Asp Glu Asn Phe Lys Lys Phe His Lys Glu Ile Ile His Glu Leu Glu
```

835 840 845

Lys Lys Ile Glu Leu Asp Val Lys Tyr Met Asn Ala Thr Leu Lys Arg
850 855 860

Tyr Gln Thr Glu His Lys Asn Lys Leu Glu Ser Leu Glu Lys Ser Gln
865 870 875 880

Ala Glu Leu Lys Lys Ile Arg Arg Lys Ser Gln Gly Ser Arg Asn Ala
885 890 895

Leu Lys Tyr Glu His Lys Glu Ile Glu Tyr Val Glu Thr Val Thr Ser
900 905 910

Arg Gln Ser Glu Ile Gln Lys Phe Ile Ala Asp Gly Cys Lys Glu Ala
915 920 925

Leu Leu Glu Glu Lys Arg Arg Phe Cys Phe Leu Val Asp Lys His Cys
930 935 940

Gly Phe Ala Asn His Ile His Tyr Tyr His Leu Gln Ser Ala Glu Leu
945 950 955 960

Leu Asn Ser Lys Leu Pro Arg Trp Gln Glu Thr Cys Val Asp Ala Ile
965 970 975

Lys Val Pro Glu Lys Ile Met Asn Met Ile Glu Glu Ile Lys Thr Pro
980 985 990

Ala Ser Thr Pro Val Ser Gly Thr Pro Gln Ala Ser Pro Met Ile Glu
995 1000 1005

Arg Ser Asn Val Val Arg Lys Asp Tyr Asp Thr Leu Ser Lys Cys
1010 1015 1020

Ser Pro Lys Met Pro Pro Ala Pro Ser Gly Arg Ala Tyr Thr Ser
1025 1030 1035

Pro Leu Ile Asp Met Phe Asn Asn Pro Ala Thr Ala Ala Pro Asn
1040 1045 1050

Ser Gln Arg Val Asn Asn Ser Thr Gly Thr Ser Glu Asp Pro Ser
1055 1060 1065

Leu Gln Arg Ser Val Ser Val Ala Thr Gly Leu Asn Met Met Lys
1070 1075 1080

```
Lys Gln Lys Val Lys Thr Ile Phe Pro His Thr Ala Gly Ser Asn
    1085                1090                1095

Lys Thr Leu Leu Ser Phe Ala Gln Gly Asp Val Ile Thr Leu Leu
    1100                1105                1110

Ile Pro Glu Glu Lys Asp Gly Trp Leu Tyr Gly Glu His Asp Val
    1115                1120                1125

Ser Lys Ala Arg Gly Trp Phe Pro Ser Ser Tyr Thr Lys Leu Leu
    1130                1135                1140

Glu Glu Asn Glu Thr Glu Ala Val Thr Val Pro Thr Pro Ser Pro
    1145                1150                1155

Thr Pro Val Arg Ser Ile Ser Thr Val Asn Leu Ser Glu Asn Ser
    1160                1165                1170

Ser Val Val Ile Pro Pro Pro Asp Tyr Leu Glu Cys Leu Ser Met
    1175                1180                1185

Gly Ala Ala Ala Asp Arg Arg Ala Asp Ser Ala Arg Thr Thr Ser
    1190                1195                1200

Thr Phe Lys Ala Pro Ala Ser Lys Pro Glu Thr Ala Ala Pro Asn
    1205                1210                1215

Asp Ala Asn Gly Thr Ala Lys Pro Pro Phe Leu Ser Gly Glu Asn
    1220                1225                1230

Pro Phe Ala Thr Val Lys Leu Arg Pro Thr Val Thr Asn Asp Arg
    1235                1240                1245

Ser Ala Pro Ile Ile Arg
    1250
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<210> 33
<211> 2850
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(2850)

<400> 33

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atg ggc gcc cct gcc tgc gcc ctc gcg ctc tgc gtg gcc gtg gcc atc          48
Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1               5                   10                  15
```

```
gtg gcc ggc gcc tcc tcg gag tcc ttg ggg acg gag cag cgc gtc gtg        96
Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
            20                  25                  30

ggg cga gcg gca gaa gtc ccg ggc cca gag ccc ggc cag cag gag cag       144
Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

ttg gtc ttc ggc agc ggg gat gct gtg gag ctg agc tgt ccc ccg ccc       192
Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

ggg ggt ggt ccc atg ggg ccc act gtc tgg gtc aag gat ggc aca ggg       240
Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

ctg gtg ccc tcg gag cgt gtc ctg gtg ggg ccc cag cgg ctg cag gtg       288
Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

ctg aat gcc tcc cac gag gac tcc ggg gcc tac agc tgc cgg cag cgg       336
Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

ctc acg cag cgc gta ctg tgc cac ttc agt gtg cgg gtg aca gac gct       384
Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

cca tcc tcg gga gat gac gaa gac ggg gag gac gag gct gag gac aca       432
Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

ggt gtg gac aca ggg gcc cct tac tgg aca cgg ccc gag cgg atg gac       480
Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

aag aag ctg ctg gcc gtg ccg gcc gcc aac acc gtc cgc ttc cgc tgc       528
Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

cca gcc gct ggc aac ccc act ccc tcc atc tcc tgg ctg aag aac ggc       576
Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

agg gag ttc cgc ggc gag cac cgc att gga ggc atc aag ctg cgg cat       624
Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

cag cag tgg agc ctg gtc atg gaa agc gtg gtg ccc tcg gac cgc ggc       672
Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

aac tac acc tgc gtc gtg gag aac aag ttt ggc agc atc cgg cag acg       720
Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
225                 230                 235                 240

tac acg ctg gac gtg ctg gag cgc tcc ccg cac cgg ccc atc ctg cag       768
Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255

gcg ggg ctg ccg gcc aac cag acg gcg gtg ctg ggc agc gac gtg gag       816
Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270
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ttc cac tgc aag gtg tac agt gac gca cag ccc cac atc cag tgg ctc       864
Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285

aag cac gtg gag gtg aat ggc agc aag gtg ggc ccg gac ggc aca ccc       912
Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

tac gtt acc gtg ctc aag acg gcg ggc gct aac acc acc gac aag gag       960
Tyr Val Thr Val Leu Lys Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu
305                 310                 315                 320

cta gag gtt ctc tcc ttg cac aac gtc acc ttt gag gac gcc ggg gag      1008
Leu Glu Val Leu Ser Leu His Asn Val Thr Phe Glu Asp Ala Gly Glu
                325                 330                 335

tac acc tgc ctg gcg ggc aat tct att ggg ttt tct cat cac tct gcg      1056
Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala
            340                 345                 350

tgg ctg gtg gtg ctg cca gcc gag gag gag ctg gtg gag gct gac gag      1104
Trp Leu Val Val Leu Pro Ala Glu Glu Glu Leu Val Glu Ala Asp Glu
        355                 360                 365

gcg ggc agt gtg tat gca ggc atc ctc agc tac ggg gtg ggc ttc ttc      1152
Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly Phe Phe
    370                 375                 380

ctg ttc atc ctg gtg gtg gcg gct gtg acg ctc tgc cgc ctg cgc agc      1200
Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu Arg Ser
385                 390                 395                 400

ccc ccc aag aaa ggc ctg ggc tcc ccc acc gtg cac aag atc tcc cgc      1248
Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile Ser Arg
                405                 410                 415

ttc ccg ctc aag cga cag gtg tcc ctg gag tcc aac gcg tcc atg agc      1296
Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser Met Ser
            420                 425                 430

tcc aac aca cca ctg gtg cgc atc gca agg ctg tcc tca ggg gag ggc      1344
Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly
        435                 440                 445

ccc acg ctg gcc aat gtc tcc gag ctc gag ctg cct gcc gac ccc aaa      1392
Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys
    450                 455                 460

tgg gag ctg tct cgg gcc cgg ctg acc ctg ggc aag ccc ctt ggg gag      1440
Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu
465                 470                 475                 480

ggc tgc ttc ggc cag gtg gtc atg gcg gag gcc atc ggc att gac aag      1488
Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys
                485                 490                 495

gac cgg gcc gcc aag cct gtc acc gta gcc gtg aag atg ctg aaa gac      1536
Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu Lys Asp
            500                 505                 510

gat gcc act gac aag gac ctg tcg gac ctg gtg tct gag atg gag atg      1584
Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met
```

```
        515                 520                 525

atg aag atg atc ggg aaa cac aaa aac atc atc aac ctg ctg ggc gcc      1632
Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala
    530                 535                 540

tgc acg cag ggc ggg ccc ctg tac gtg ctg gtg gag tac gcg gcc aag      1680
Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys
545                 550                 555                 560

ggt aac ctg cgg gag ttt ctg cgg gcg cgg cgg ccc ccg ggc ctg gac      1728
Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp
                565                 570                 575

tac tcc ttc gac acc tgc aag ccg ccc gag gag cag ctc acc ttc aag      1776
Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys
            580                 585                 590

gac ctg gtg tcc tgt gcc tac cag gtg gcc cgg ggc atg gag tac ttg      1824
Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu
        595                 600                 605

gcc tcc cag aag tgc atc cac agg gac ctg gct gcc cgc aat gtg ctg      1872
Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu
    610                 615                 620

gtg acc gag gac aac gtg atg aag atc gca gac ttc ggg ctg gcc cgg      1920
Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg
625                 630                 635                 640

gac gtg cac aac ctc gac tac tac aag aag aca acc aac ggc cgg ctg      1968
Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu
                645                 650                 655

ccc gtg aag tgg atg gcg cct gag gcc ttg ttt gac cga gtc tac act      2016
Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr
            660                 665                 670

cac cag agt gac gtc tgg tcc ttt ggg gtc ctg ctc tgg gag atc ttc      2064
His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe
        675                 680                 685

acg ctg ggg ggc tcc ccg tac ccc ggc atc cct gtg gag gag ctc ttc      2112
Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe
    690                 695                 700

aag ctg ctg aag gag ggc cac cgc atg gac aag ccc gcc aac tgc aca      2160
Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr
705                 710                 715                 720

cac gac ctg tac atg atc atg cgg gag tgc tgg cat gcc gcg ccc tcc      2208
His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser
                725                 730                 735

cag agg ccc acc ttc aag cag ctg gtg gag gac ctg gac cgt gtc ctt      2256
Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu
            740                 745                 750

acc gtg acg tcc acc gac gta aag gcg aca cag gag gag aac cgg gag      2304
Thr Val Thr Ser Thr Asp Val Lys Ala Thr Gln Glu Glu Asn Arg Glu
        755                 760                 765

ctg agg agc agg tgt gag gag ctc cac ggg aag aac ctg gaa ctg ggg      2352
```

```
Leu Arg Ser Arg Cys Glu Glu Leu His Gly Lys Asn Leu Glu Leu Gly
    770                 775                 780

aag atc atg gac agg ttc gaa gag gtt gtg tac cag gcc atg gag gaa      2400
Lys Ile Met Asp Arg Phe Glu Glu Val Val Tyr Gln Ala Met Glu Glu
785                 790                 795                 800

gtt cag aag cag aag gaa ctt tcc aaa gct gaa atc cag aaa gtt cta      2448
Val Gln Lys Gln Lys Glu Leu Ser Lys Ala Glu Ile Gln Lys Val Leu
                805                 810                 815

aaa gaa aaa gac caa ctt acc aca gat ctg aac tcc atg gag aag tcc      2496
Lys Glu Lys Asp Gln Leu Thr Thr Asp Leu Asn Ser Met Glu Lys Ser
            820                 825                 830

ttc tcc gac ctc ttc aag cgt ttt gag aaa cag aaa gag gtg atc gag      2544
Phe Ser Asp Leu Phe Lys Arg Phe Glu Lys Gln Lys Glu Val Ile Glu
        835                 840                 845

ggc tac cgc aag aac gaa gag tca ctg aag aag tgc gtg gag gat tac      2592
Gly Tyr Arg Lys Asn Glu Glu Ser Leu Lys Lys Cys Val Glu Asp Tyr
    850                 855                 860

ctg gca agg atc acc cag gag ggc cag agg tac caa gcc ctg aag gcc      2640
Leu Ala Arg Ile Thr Gln Glu Gly Gln Arg Tyr Gln Ala Leu Lys Ala
865                 870                 875                 880

cac gcg gag gag aag ctg cag ctg gca aac gag gag atc gcc cag gtc      2688
His Ala Glu Glu Lys Leu Gln Leu Ala Asn Glu Glu Ile Ala Gln Val
                885                 890                 895

cgg agc aag gcc cag gcg gaa gcg ttg gcc ctc cag gcc agc ctg agg      2736
Arg Ser Lys Ala Gln Ala Glu Ala Leu Ala Leu Gln Ala Ser Leu Arg
            900                 905                 910

aag gag cag atg cgc atc cag tcg ctg gag aag aca gtg gag cag aag      2784
Lys Glu Gln Met Arg Ile Gln Ser Leu Glu Lys Thr Val Glu Gln Lys
        915                 920                 925

act aaa gag aac gag gag ctg acc agg atc tgc gac gac ctc atc tcc      2832
Thr Lys Glu Asn Glu Glu Leu Thr Arg Ile Cys Asp Asp Leu Ile Ser
    930                 935                 940

aag atg gag aag atc tga                                              2850
Lys Met Glu Lys Ile
945
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<210> 34
<211> 949
<212> PRT
<213> Homo sapiens

<400> 34

```
Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1               5                   10                  15

Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
            20                  25                  30
```

```
Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
225                 230                 235                 240

Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255

Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270

Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285
```

```
Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

Tyr Val Thr Val Leu Lys Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu
305                 310                 315                 320

Leu Glu Val Leu Ser Leu His Asn Val Thr Phe Glu Asp Ala Gly Glu
                325                 330                 335

Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala
            340                 345                 350

Trp Leu Val Val Leu Pro Ala Glu Glu Glu Leu Val Glu Ala Asp Glu
        355                 360                 365

Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly Phe Phe
    370                 375                 380

Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu Arg Ser
385                 390                 395                 400

Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile Ser Arg
                405                 410                 415

Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser Met Ser
            420                 425                 430

Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly
        435                 440                 445

Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys
    450                 455                 460

Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu
465                 470                 475                 480

Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys
                485                 490                 495

Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu Lys Asp
            500                 505                 510

Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met
        515                 520                 525

Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala
    530                 535                 540
```

```
Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys
545                 550                 555                 560

Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp
                565                 570                 575

Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys
            580                 585                 590

Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu
        595                 600                 605

Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu
    610                 615                 620

Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg
625                 630                 635                 640

Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu
                645                 650                 655

Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr
            660                 665                 670

His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe
        675                 680                 685

Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe
    690                 695                 700

Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr
705                 710                 715                 720

His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser
                725                 730                 735

Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu
            740                 745                 750

Thr Val Thr Ser Thr Asp Val Lys Ala Thr Gln Glu Glu Asn Arg Glu
        755                 760                 765

Leu Arg Ser Arg Cys Glu Glu Leu His Gly Lys Asn Leu Glu Leu Gly
    770                 775                 780

Lys Ile Met Asp Arg Phe Glu Glu Val Val Tyr Gln Ala Met Glu Glu
```

785 790 795 800

Val Gln Lys Gln Lys Glu Leu Ser Lys Ala Glu Ile Gln Lys Val Leu
805 810 815

Lys Glu Lys Asp Gln Leu Thr Thr Asp Leu Asn Ser Met Glu Lys Ser
820 825 830

Phe Ser Asp Leu Phe Lys Arg Phe Glu Lys Gln Lys Glu Val Ile Glu
835 840 845

Gly Tyr Arg Lys Asn Glu Glu Ser Leu Lys Lys Cys Val Glu Asp Tyr
850 855 860

Leu Ala Arg Ile Thr Gln Glu Gly Gln Arg Tyr Gln Ala Leu Lys Ala
865 870 875 880

His Ala Glu Glu Lys Leu Gln Leu Ala Asn Glu Glu Ile Ala Gln Val
885 890 895

Arg Ser Lys Ala Gln Ala Glu Ala Leu Ala Leu Gln Ala Ser Leu Arg
900 905 910

Lys Glu Gln Met Arg Ile Gln Ser Leu Glu Lys Thr Val Glu Gln Lys
915 920 925

Thr Lys Glu Asn Glu Glu Leu Thr Arg Ile Cys Asp Asp Leu Ile Ser
930 935 940

Lys Met Glu Lys Ile
945

<210> 35
<211> 4461
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<220>
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<222> (1)..(4461)

<400> 35

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Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1               5                   10                  15

gtg gcc ggc gcc tcc tcg gag tcc ttg ggg acg gag cag cgc gtc gtg        96
Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
            20                  25                  30

ggg cga gcg gca gaa gtc ccg ggc cca gag ccc ggc cag cag gag cag       144
```

```
Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

ttg gtc ttc ggc agc ggg gat gct gtg gag ctg agc tgt ccc ccg ccc      192
Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

ggg ggt ggt ccc atg ggg ccc act gtc tgg gtc aag gat ggc aca ggg      240
Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

ctg gtg ccc tcg gag cgt gtc ctg gtg ggg ccc cag cgg ctg cag gtg      288
Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

ctg aat gcc tcc cac gag gac tcc ggg gcc tac agc tgc cgg cag cgg      336
Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

ctc acg cag cgc gta ctg tgc cac ttc agt gtg cgg gtg aca gac gct      384
Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

cca tcc tcg gga gat gac gaa gac ggg gag gac gag gct gag gac aca      432
Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

ggt gtg gac aca ggg gcc cct tac tgg aca cgg ccc gag cgg atg gac      480
Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

aag aag ctg ctg gcc gtg ccg gcc gcc aac acc gtc cgc ttc cgc tgc      528
Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

cca gcc gct ggc aac ccc act ccc tcc atc tcc tgg ctg aag aac ggc      576
Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

agg gag ttc cgc ggc gag cac cgc att gga ggc atc aag ctg cgg cat      624
Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

cag cag tgg agc ctg gtc atg gaa agc gtg gtg ccc tcg gac cgc ggc      672
Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

aac tac acc tgc gtc gtg gag aac aag ttt ggc agc atc cgg cag acg      720
Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
225                 230                 235                 240

tac acg ctg gac gtg ctg gag cgc tcc ccg cac cgg ccc atc ctg cag      768
Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255

gcg ggg ctg ccg gcc aac cag acg gcg gtg ctg ggc agc gac gtg gag      816
Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270

ttc cac tgc aag gtg tac agt gac gca cag ccc cac atc cag tgg ctc      864
Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285
```

```
aag cac gtg gag gtg aat ggc agc aag gtg ggc ccg gac ggc aca ccc      912
Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

tac gtt acc gtg ctc aag acg gcg ggc gct aac acc acc gac aag gag      960
Tyr Val Thr Val Leu Lys Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu
305                 310                 315                 320

cta gag gtt ctc tcc ttg cac aac gtc acc ttt gag gac gcc ggg gag     1008
Leu Glu Val Leu Ser Leu His Asn Val Thr Phe Glu Asp Ala Gly Glu
                325                 330                 335

tac acc tgc ctg gcg ggc aat tct att ggg ttt tct cat cac tct gcg     1056
Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala
            340                 345                 350

tgg ctg gtg gtg ctg cca gcc gag gag gag ctg gtg gag gct gac gag     1104
Trp Leu Val Val Leu Pro Ala Glu Glu Glu Leu Val Glu Ala Asp Glu
        355                 360                 365

gcg ggc agt gtg tat gca ggc atc ctc agc tac ggg gtg ggc ttc ttc     1152
Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly Phe Phe
    370                 375                 380

ctg ttc atc ctg gtg gtg gcg gct gtg acg ctc tgc cgc ctg cgc agc     1200
Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu Arg Ser
385                 390                 395                 400

ccc ccc aag aaa ggc ctg ggc tcc ccc acc gtg cac aag atc tcc cgc     1248
Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile Ser Arg
                405                 410                 415

ttc ccg ctc aag cga cag gtg tcc ctg gag tcc aac gcg tcc atg agc     1296
Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser Met Ser
            420                 425                 430

tcc aac aca cca ctg gtg cgc atc gca agg ctg tcc tca ggg gag ggc     1344
Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly
        435                 440                 445

ccc acg ctg gcc aat gtc tcc gag ctc gag ctg cct gcc gac ccc aaa     1392
Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys
    450                 455                 460

tgg gag ctg tct cgg gcc cgg ctg acc ctg ggc aag ccc ctt ggg gag     1440
Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu
465                 470                 475                 480

ggc tgc ttc ggc cag gtg gtc atg gcg gag gcc atc ggc att gac aag     1488
Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys
                485                 490                 495

gac cgg gcc gcc aag cct gtc acc gta gcc gtg aag atg ctg aaa gac     1536
Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu Lys Asp
            500                 505                 510

gat gcc act gac aag gac ctg tcg gac ctg gtg tct gag atg gag atg     1584
Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met
        515                 520                 525

atg aag atg atc ggg aaa cac aaa aac atc atc aac ctg ctg ggc gcc     1632
Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala
    530                 535                 540
```

tgc acg cag ggc ggg ccc ctg tac gtg ctg gtg gag tac gcg gcc aag 1680
Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys
545 550 555 560

ggt aac ctg cgg gag ttt ctg cgg gcg cgg cgg ccc ccg ggc ctg gac 1728
Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp
565 570 575

tac tcc ttc gac acc tgc aag ccg ccc gag gag cag ctc acc ttc aag 1776
Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys
580 585 590

gac ctg gtg tcc tgt gcc tac cag gtg gcc cgg ggc atg gag tac ttg 1824
Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu
595 600 605

gcc tcc cag aag tgc atc cac agg gac ctg gct gcc cgc aat gtg ctg 1872
Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu
610 615 620

gtg acc gag gac aac gtg atg aag atc gca gac ttc ggg ctg gcc cgg 1920
Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg
625 630 635 640

gac gtg cac aac ctc gac tac tac aag aag aca acc aac ggc cgg ctg 1968
Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu
645 650 655

ccc gtg aag tgg atg gcg cct gag gcc ttg ttt gac cga gtc tac act 2016
Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr
660 665 670

cac cag agt gac gtc tgg tcc ttt ggg gtc ctg ctc tgg gag atc ttc 2064
His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe
675 680 685

acg ctg ggg ggc tcc ccg tac ccc ggc atc cct gtg gag gag ctc ttc 2112
Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe
690 695 700

aag ctg ctg aag gag ggc cac cgc atg gac aag ccc gcc aac tgc aca 2160
Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr
705 710 715 720

cac gac ctg tac atg atc atg cgg gag tgc tgg cat gcc gcg ccc tcc 2208
His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser
725 730 735

cag agg ccc acc ttc aag cag ctg gtg gag gac ctg gac cgt gtc ctt 2256
Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu
740 745 750

acc gtg acg tcc acc gac gtg agt gct ggc tct ggc ctg gtg cca ccc 2304
Thr Val Thr Ser Thr Asp Val Ser Ala Gly Ser Gly Leu Val Pro Pro
755 760 765

gcc tat gcc cct ccc cct gcc gtc ccc ggc cat cct gcc ccc cag agt 2352
Ala Tyr Ala Pro Pro Pro Ala Val Pro Gly His Pro Ala Pro Gln Ser
770 775 780

gct gag gtg tgg ggc ggg cct tct ggc cca ggt gcc ctg gct gac ctg 2400
Ala Glu Val Trp Gly Gly Pro Ser Gly Pro Gly Ala Leu Ala Asp Leu

```
785                 790                 795                 800

gac tgc tca agc tct tcc cag agc cca gga agt tct gag aac caa atg       2448
Asp Cys Ser Ser Ser Ser Gln Ser Pro Gly Ser Ser Glu Asn Gln Met
                805                 810                 815

gtg tct cca gga aaa gtg tct ggc agc cct gag caa gcc gtg gag gaa       2496
Val Ser Pro Gly Lys Val Ser Gly Ser Pro Glu Gln Ala Val Glu Glu
            820                 825                 830

aac ctt agt tcc tat tcc tta gac aga aga gtg aca ccc gcc tct gag       2544
Asn Leu Ser Ser Tyr Ser Leu Asp Arg Arg Val Thr Pro Ala Ser Glu
        835                 840                 845

acc cta gaa gac cct tgc agg aca gag tcc cag cac aaa gcg gag act       2592
Thr Leu Glu Asp Pro Cys Arg Thr Glu Ser Gln His Lys Ala Glu Thr
    850                 855                 860

ccg cac gga gcc gag gaa gaa tgc aaa gcg gag act ccg cac gga gcc       2640
Pro His Gly Ala Glu Glu Glu Cys Lys Ala Glu Thr Pro His Gly Ala
865                 870                 875                 880

gag gag gaa tgc cgg cac ggt ggg gtc tgt gct ccc gca gca gtg gcc       2688
Glu Glu Glu Cys Arg His Gly Gly Val Cys Ala Pro Ala Ala Val Ala
                885                 890                 895

act tcg cct cct ggt gca atc cct aag gaa gcc tgc gga gga gca ccc       2736
Thr Ser Pro Pro Gly Ala Ile Pro Lys Glu Ala Cys Gly Gly Ala Pro
            900                 905                 910

ctg cag ggt ctg cct ggc gaa gcc ctg ggc tgc cct gcg ggt gtg ggc       2784
Leu Gln Gly Leu Pro Gly Glu Ala Leu Gly Cys Pro Ala Gly Val Gly
        915                 920                 925

acc ccc gtg cca gca gat ggc act cag acc ctt acc tgt gca cac acc       2832
Thr Pro Val Pro Ala Asp Gly Thr Gln Thr Leu Thr Cys Ala His Thr
    930                 935                 940

tct gct cct gag agc aca gcc cca acc aac cac ctg gtg gct ggc agg       2880
Ser Ala Pro Glu Ser Thr Ala Pro Thr Asn His Leu Val Ala Gly Arg
945                 950                 955                 960

gcc atg acc ctg agt cct cag gaa gaa gtg gct gca ggc caa atg gcc       2928
Ala Met Thr Leu Ser Pro Gln Glu Glu Val Ala Ala Gly Gln Met Ala
                965                 970                 975

agc tcc tcg agg agc gga cct gta aaa cta gaa ttt gat gta tct gat       2976
Ser Ser Ser Arg Ser Gly Pro Val Lys Leu Glu Phe Asp Val Ser Asp
            980                 985                 990

ggc gcc acc agc aaa agg gca ccc  cca cca agg aga ctg  gga gag agg     3024
Gly Ala Thr Ser Lys Arg Ala Pro  Pro Pro Arg Arg Leu  Gly Glu Arg
        995                 1000                 1005

tcc ggc  ctc aag cct ccc ttg  agg aaa gca gca gtg  agg cag caa        3069
Ser Gly  Leu Lys Pro Pro Leu  Arg Lys Ala Ala Val  Arg Gln Gln
    1010                 1015                 1020

aag gcc  ccg cag gag gtg gag  gag gac gac ggt agg  agc gga gca        3114
Lys Ala  Pro Gln Glu Val Glu  Glu Asp Asp Gly Arg  Ser Gly Ala
    1025                 1030                 1035

gga gag  gac ccc ccc atg cca  gct tct cgg ggc tct  tac cac ctc        3159
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```
Gly Glu  Asp Pro Pro Met Pro  Ala Ser Arg Gly Ser  Tyr His Leu
    1040                 1045                 1050

gac tgg  gac aaa atg gat gac  cca aac ttc atc ccg  ttc gga ggt       3204
Asp Trp  Asp Lys Met Asp Asp  Pro Asn Phe Ile Pro  Phe Gly Gly
    1055                 1060                 1065

gac acc  aag tct ggt tgc agt  gag gcc cag ccc cca  gaa agc cct       3249
Asp Thr  Lys Ser Gly Cys Ser  Glu Ala Gln Pro Pro  Glu Ser Pro
    1070                 1075                 1080

gag acc  agg ctg ggc cag cca  gcg gct gaa cag ttg  cat gct ggg       3294
Glu Thr  Arg Leu Gly Gln Pro  Ala Ala Glu Gln Leu  His Ala Gly
    1085                 1090                 1095

cct gcc  acg gag gag cca ggt  ccc tgt ctg agc cag  cag ctg cat       3339
Pro Ala  Thr Glu Glu Pro Gly  Pro Cys Leu Ser Gln  Gln Leu His
    1100                 1105                 1110

tca gcc  tca gcg gag gac acg  cct gtg gtg cag ttg  gca gcc gag       3384
Ser Ala  Ser Ala Glu Asp Thr  Pro Val Val Gln Leu  Ala Ala Glu
    1115                 1120                 1125

acc cca  aca gca gag agc aag  gag aga gcc ttg aac  tct gcc agc       3429
Thr Pro  Thr Ala Glu Ser Lys  Glu Arg Ala Leu Asn  Ser Ala Ser
    1130                 1135                 1140

acc tcg  ctt ccc aca agc tgt  cca ggc agt gag cca  gtg ccc acc       3474
Thr Ser  Leu Pro Thr Ser Cys  Pro Gly Ser Glu Pro  Val Pro Thr
    1145                 1150                 1155

cat cag  cag ggg cag cct gcc  ttg gag ctg aaa gag  gag agc ttc       3519
His Gln  Gln Gly Gln Pro Ala  Leu Glu Leu Lys Glu  Glu Ser Phe
    1160                 1165                 1170

aga gac  ccc gct gag gtt cta  ggc acg ggc gcg gag  gtg gat tac       3564
Arg Asp  Pro Ala Glu Val Leu  Gly Thr Gly Ala Glu  Val Asp Tyr
    1175                 1180                 1185

ctg gag  cag ttt gga act tcc  tcg ttt aag gag tcg  gcc ttg agg       3609
Leu Glu  Gln Phe Gly Thr Ser  Ser Phe Lys Glu Ser  Ala Leu Arg
    1190                 1195                 1200

aag cag  tcc tta tac ctc aag  ttc gac ccc ctc ctg  agg gac agt       3654
Lys Gln  Ser Leu Tyr Leu Lys  Phe Asp Pro Leu Leu  Arg Asp Ser
    1205                 1210                 1215

cct ggt  aga cca gtg ccc gtg  gcc acc gag acc agc  agc atg cac       3699
Pro Gly  Arg Pro Val Pro Val  Ala Thr Glu Thr Ser  Ser Met His
    1220                 1225                 1230

ggt gca  aat gag act ccc tca  gga cgt ccg cgg gaa  gcc aag ctt       3744
Gly Ala  Asn Glu Thr Pro Ser  Gly Arg Pro Arg Glu  Ala Lys Leu
    1235                 1240                 1245

gtg gag  ttc gat ttc ttg gga  gca ctg gac att cct  gtg cca ggc       3789
Val Glu  Phe Asp Phe Leu Gly  Ala Leu Asp Ile Pro  Val Pro Gly
    1250                 1255                 1260

cca ccc  cca ggt gtt ccc gcg  cct ggg ggc cca ccc  ctg tcc acc       3834
Pro Pro  Pro Gly Val Pro Ala  Pro Gly Gly Pro Pro  Leu Ser Thr
    1265                 1270                 1275
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gga cct ata gtg gac ctg ctc cag tac agc cag aag gac ctg gat       3879
Gly Pro Ile Val Asp Leu Leu Gln Tyr Ser Gln Lys Asp Leu Asp
    1280                1285                1290

gca gtg gta aag gcg aca cag gag gag aac cgg gag ctg agg agc       3924
Ala Val Val Lys Ala Thr Gln Glu Glu Asn Arg Glu Leu Arg Ser
    1295                1300                1305

agg tgt gag gag ctc cac ggg aag aac ctg gaa ctg ggg aag atc       3969
Arg Cys Glu Glu Leu His Gly Lys Asn Leu Glu Leu Gly Lys Ile
    1310                1315                1320

atg gac agg ttc gaa gag gtt gtg tac cag gcc atg gag gaa gtt       4014
Met Asp Arg Phe Glu Glu Val Val Tyr Gln Ala Met Glu Glu Val
    1325                1330                1335

cag aag cag aag gaa ctt tcc aaa gct gaa atc cag aaa gtt cta       4059
Gln Lys Gln Lys Glu Leu Ser Lys Ala Glu Ile Gln Lys Val Leu
    1340                1345                1350

aaa gaa aaa gac caa ctt acc aca gat ctg aac tcc atg gag aag       4104
Lys Glu Lys Asp Gln Leu Thr Thr Asp Leu Asn Ser Met Glu Lys
    1355                1360                1365

tcc ttc tcc gac ctc ttc aag cgt ttt gag aaa cag aaa gag gtg       4149
Ser Phe Ser Asp Leu Phe Lys Arg Phe Glu Lys Gln Lys Glu Val
    1370                1375                1380

atc gag ggc tac cgc aag aac gaa gag tca ctg aag aag tgc gtg       4194
Ile Glu Gly Tyr Arg Lys Asn Glu Glu Ser Leu Lys Lys Cys Val
    1385                1390                1395

gag gat tac ctg gca agg atc acc cag gag ggc cag agg tac caa       4239
Glu Asp Tyr Leu Ala Arg Ile Thr Gln Glu Gly Gln Arg Tyr Gln
    1400                1405                1410

gcc ctg aag gcc cac gcg gag gag aag ctg cag ctg gca aac gag       4284
Ala Leu Lys Ala His Ala Glu Glu Lys Leu Gln Leu Ala Asn Glu
    1415                1420                1425

gag atc gcc cag gtc cgg agc aag gcc cag gcg gaa gcg ttg gcc       4329
Glu Ile Ala Gln Val Arg Ser Lys Ala Gln Ala Glu Ala Leu Ala
    1430                1435                1440

ctc cag gcc agc ctg agg aag gag cag atg cgc atc cag tcg ctg       4374
Leu Gln Ala Ser Leu Arg Lys Glu Gln Met Arg Ile Gln Ser Leu
    1445                1450                1455

gag aag aca gtg gag cag aag act aaa gag aac gag gag ctg acc       4419
Glu Lys Thr Val Glu Gln Lys Thr Lys Glu Asn Glu Glu Leu Thr
    1460                1465                1470

agg atc tgc gac gac ctc atc tcc aag atg gag aag atc tga           4461
Arg Ile Cys Asp Asp Leu Ile Ser Lys Met Glu Lys Ile
    1475                1480                1485
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<210> 36
<211> 1486
<212> PRT
<213> Homo sapiens

<400> 36

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Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1               5                   10                  15

Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
            20                  25                  30

Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
225                 230                 235                 240

Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255
```

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Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270

Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285

Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

Tyr Val Thr Val Leu Lys Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu
305                 310                 315                 320

Leu Glu Val Leu Ser Leu His Asn Val Thr Phe Glu Asp Ala Gly Glu
                325                 330                 335

Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala
            340                 345                 350

Trp Leu Val Val Leu Pro Ala Glu Glu Glu Leu Val Glu Ala Asp Glu
        355                 360                 365

Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly Phe Phe
    370                 375                 380

Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu Arg Ser
385                 390                 395                 400

Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile Ser Arg
                405                 410                 415

Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser Met Ser
            420                 425                 430

Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly
        435                 440                 445

Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys
    450                 455                 460

Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu
465                 470                 475                 480

Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys
                485                 490                 495

Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu Lys Asp
```

500 505 510

Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met
515 520 525

Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala
530 535 540

Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys
545 550 555 560

Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp
565 570 575

Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys
580 585 590

Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu
595 600 605

Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu
610 615 620

Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg
625 630 635 640

Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu
645 650 655

Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr
660 665 670

His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe
675 680 685

Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe
690 695 700

Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr
705 710 715 720

His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser
725 730 735

Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu
740 745 750

Thr Val Thr Ser Thr Asp Val Ser Ala Gly Ser Gly Leu Val Pro Pro
755 760 765

Ala Tyr Ala Pro Pro Pro Ala Val Pro Gly His Pro Ala Pro Gln Ser
770 775 780

Ala Glu Val Trp Gly Gly Pro Ser Gly Pro Gly Ala Leu Ala Asp Leu
785 790 795 800

Asp Cys Ser Ser Ser Ser Gln Ser Pro Gly Ser Ser Glu Asn Gln Met
805 810 815

Val Ser Pro Gly Lys Val Ser Gly Ser Pro Glu Gln Ala Val Glu Glu
820 825 830

Asn Leu Ser Ser Tyr Ser Leu Asp Arg Arg Val Thr Pro Ala Ser Glu
835 840 845

Thr Leu Glu Asp Pro Cys Arg Thr Glu Ser Gln His Lys Ala Glu Thr
850 855 860

Pro His Gly Ala Glu Glu Glu Cys Lys Ala Glu Thr Pro His Gly Ala
865 870 875 880

Glu Glu Glu Cys Arg His Gly Gly Val Cys Ala Pro Ala Ala Val Ala
885 890 895

Thr Ser Pro Pro Gly Ala Ile Pro Lys Glu Ala Cys Gly Gly Ala Pro
900 905 910

Leu Gln Gly Leu Pro Gly Glu Ala Leu Gly Cys Pro Ala Gly Val Gly
915 920 925

Thr Pro Val Pro Ala Asp Gly Thr Gln Thr Leu Thr Cys Ala His Thr
930 935 940

Ser Ala Pro Glu Ser Thr Ala Pro Thr Asn His Leu Val Ala Gly Arg
945 950 955 960

Ala Met Thr Leu Ser Pro Gln Glu Glu Val Ala Ala Gly Gln Met Ala
965 970 975

Ser Ser Ser Arg Ser Gly Pro Val Lys Leu Glu Phe Asp Val Ser Asp
980 985 990

Gly Ala Thr Ser Lys Arg Ala Pro Pro Pro Arg Arg Leu Gly Glu Arg
995 1000 1005

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Ser Gly  Leu Lys Pro Pro Leu  Arg Lys Ala Ala Val  Arg Gln Gln
    1010                 1015                 1020

Lys Ala  Pro Gln Glu Val Glu  Glu Asp Asp Gly Arg  Ser Gly Ala
    1025                 1030                 1035

Gly Glu  Asp Pro Pro Met Pro  Ala Ser Arg Gly Ser  Tyr His Leu
    1040                 1045                 1050

Asp Trp  Asp Lys Met Asp Asp  Pro Asn Phe Ile Pro  Phe Gly Gly
    1055                 1060                 1065

Asp Thr  Lys Ser Gly Cys Ser  Glu Ala Gln Pro Pro  Glu Ser Pro
    1070                 1075                 1080

Glu Thr  Arg Leu Gly Gln Pro  Ala Ala Glu Gln Leu  His Ala Gly
    1085                 1090                 1095

Pro Ala  Thr Glu Glu Pro Gly  Pro Cys Leu Ser Gln  Gln Leu His
    1100                 1105                 1110

Ser Ala  Ser Ala Glu Asp Thr  Pro Val Val Gln Leu  Ala Ala Glu
    1115                 1120                 1125

Thr Pro  Thr Ala Glu Ser Lys  Glu Arg Ala Leu Asn  Ser Ala Ser
    1130                 1135                 1140

Thr Ser  Leu Pro Thr Ser Cys  Pro Gly Ser Glu Pro  Val Pro Thr
    1145                 1150                 1155

His Gln  Gln Gly Gln Pro Ala  Leu Glu Leu Lys Glu  Glu Ser Phe
    1160                 1165                 1170

Arg Asp  Pro Ala Glu Val Leu  Gly Thr Gly Ala Glu  Val Asp Tyr
    1175                 1180                 1185

Leu Glu  Gln Phe Gly Thr Ser  Ser Phe Lys Glu Ser  Ala Leu Arg
    1190                 1195                 1200

Lys Gln  Ser Leu Tyr Leu Lys  Phe Asp Pro Leu Leu  Arg Asp Ser
    1205                 1210                 1215

Pro Gly  Arg Pro Val Pro Val  Ala Thr Glu Thr Ser  Ser Met His
    1220                 1225                 1230

Gly Ala  Asn Glu Thr Pro Ser  Gly Arg Pro Arg Glu  Ala Lys Leu
    1235                 1240                 1245
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Val Glu Phe Asp Phe Leu Gly Ala Leu Asp Ile Pro Val Pro Gly
1250 1255 1260

Pro Pro Pro Gly Val Pro Ala Pro Gly Gly Pro Pro Leu Ser Thr
1265 1270 1275

Gly Pro Ile Val Asp Leu Leu Gln Tyr Ser Gln Lys Asp Leu Asp
1280 1285 1290

Ala Val Val Lys Ala Thr Gln Glu Glu Asn Arg Glu Leu Arg Ser
1295 1300 1305

Arg Cys Glu Glu Leu His Gly Lys Asn Leu Glu Leu Gly Lys Ile
1310 1315 1320

Met Asp Arg Phe Glu Glu Val Val Tyr Gln Ala Met Glu Glu Val
1325 1330 1335

Gln Lys Gln Lys Glu Leu Ser Lys Ala Glu Ile Gln Lys Val Leu
1340 1345 1350

Lys Glu Lys Asp Gln Leu Thr Thr Asp Leu Asn Ser Met Glu Lys
1355 1360 1365

Ser Phe Ser Asp Leu Phe Lys Arg Phe Glu Lys Gln Lys Glu Val
1370 1375 1380

Ile Glu Gly Tyr Arg Lys Asn Glu Glu Ser Leu Lys Lys Cys Val
1385 1390 1395

Glu Asp Tyr Leu Ala Arg Ile Thr Gln Glu Gly Gln Arg Tyr Gln
1400 1405 1410

Ala Leu Lys Ala His Ala Glu Glu Lys Leu Gln Leu Ala Asn Glu
1415 1420 1425

Glu Ile Ala Gln Val Arg Ser Lys Ala Gln Ala Glu Ala Leu Ala
1430 1435 1440

Leu Gln Ala Ser Leu Arg Lys Glu Gln Met Arg Ile Gln Ser Leu
1445 1450 1455

Glu Lys Thr Val Glu Gln Lys Thr Lys Glu Asn Glu Glu Leu Thr
1460 1465 1470

Arg Ile Cys Asp Asp Leu Ile Ser Lys Met Glu Lys Ile

1475 1480 1485

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<211> 3759
<212> DNA
<213> Homo sapiens

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<222> (1)..(3759)

<400> 37

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atg ggc gcc cct gcc tgc gcc ctc gcg ctc tgc gtg gcc gtg gcc atc        48
Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1               5                   10                  15

gtg gcc ggc gcc tcc tcg gag tcc ttg ggg acg gag cag cgc gtc gtg        96
Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
            20                  25                  30

ggg cga gcg gca gaa gtc ccg ggc cca gag ccc ggc cag cag gag cag       144
Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

ttg gtc ttc ggc agc ggg gat gct gtg gag ctg agc tgt ccc ccg ccc       192
Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

ggg ggt ggt ccc atg ggg ccc act gtc tgg gtc aag gat ggc aca ggg       240
Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

ctg gtg ccc tcg gag cgt gtc ctg gtg ggg ccc cag cgg ctg cag gtg       288
Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

ctg aat gcc tcc cac gag gac tcc ggg gcc tac agc tgc cgg cag cgg       336
Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

ctc acg cag cgc gta ctg tgc cac ttc agt gtg cgg gtg aca gac gct       384
Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

cca tcc tcg gga gat gac gaa gac ggg gag gac gag gct gag gac aca       432
Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

ggt gtg gac aca ggg gcc cct tac tgg aca cgg ccc gag cgg atg gac       480
Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

aag aag ctg ctg gcc gtg ccg gcc gcc aac acc gtc cgc ttc cgc tgc       528
Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

cca gcc gct ggc aac ccc act ccc tcc atc tcc tgg ctg aag aac ggc       576
Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

agg gag ttc cgc ggc gag cac cgc att gga ggc atc aag ctg cgg cat       624
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Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

cag cag tgg agc ctg gtc atg gaa agc gtg gtg ccc tcg gac cgc ggc      672
Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

aac tac acc tgc gtc gtg gag aac aag ttt ggc agc atc cgg cag acg      720
Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
225                 230                 235                 240

tac acg ctg gac gtg ctg gag cgc tcc ccg cac cgg ccc atc ctg cag      768
Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255

gcg ggg ctg ccg gcc aac cag acg gcg gtg ctg ggc agc gac gtg gag      816
Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270

ttc cac tgc aag gtg tac agt gac gca cag ccc cac atc cag tgg ctc      864
Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285

aag cac gtg gag gtg aat ggc agc aag gtg ggc ccg gac ggc aca ccc      912
Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

tac gtt acc gtg ctc aag acg gcg ggc gct aac acc acc gac aag gag      960
Tyr Val Thr Val Leu Lys Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu
305                 310                 315                 320

cta gag gtt ctc tcc ttg cac aac gtc acc ttt gag gac gcc ggg gag     1008
Leu Glu Val Leu Ser Leu His Asn Val Thr Phe Glu Asp Ala Gly Glu
                325                 330                 335

tac acc tgc ctg gcg ggc aat tct att ggg ttt tct cat cac tct gcg     1056
Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala
            340                 345                 350

tgg ctg gtg gtg ctg cca gcc gag gag gag ctg gtg gag gct gac gag     1104
Trp Leu Val Val Leu Pro Ala Glu Glu Glu Leu Val Glu Ala Asp Glu
        355                 360                 365

gcg ggc agt gtg tat gca ggc atc ctc agc tac ggg gtg ggc ttc ttc     1152
Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly Phe Phe
    370                 375                 380

ctg ttc atc ctg gtg gtg gcg gct gtg acg ctc tgc cgc ctg cgc agc     1200
Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu Arg Ser
385                 390                 395                 400

ccc ccc aag aaa ggc ctg ggc tcc ccc acc gtg cac aag atc tcc cgc     1248
Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile Ser Arg
                405                 410                 415

ttc ccg ctc aag cga cag gtg tcc ctg gag tcc aac gcg tcc atg agc     1296
Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser Met Ser
            420                 425                 430

tcc aac aca cca ctg gtg cgc atc gca agg ctg tcc tca ggg gag ggc     1344
Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly
        435                 440                 445
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ccc acg ctg gcc aat gtc tcc gag ctc gag ctg cct gcc gac ccc aaa       1392
Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys
    450                 455                 460

tgg gag ctg tct cgg gcc cgg ctg acc ctg ggc aag ccc ctt ggg gag       1440
Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu
465                 470                 475                 480

ggc tgc ttc ggc cag gtg gtc atg gcg gag gcc atc ggc att gac aag       1488
Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys
                485                 490                 495

gac cgg gcc gcc aag cct gtc acc gta gcc gtg aag atg ctg aaa gac       1536
Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu Lys Asp
            500                 505                 510

gat gcc act gac aag gac ctg tcg gac ctg gtg tct gag atg gag atg       1584
Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met
        515                 520                 525

atg aag atg atc ggg aaa cac aaa aac atc atc aac ctg ctg ggc gcc       1632
Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala
    530                 535                 540

tgc acg cag ggc ggg ccc ctg tac gtg ctg gtg gag tac gcg gcc aag       1680
Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys
545                 550                 555                 560

ggt aac ctg cgg gag ttt ctg cgg gcg cgg cgg ccc ccg ggc ctg gac       1728
Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp
                565                 570                 575

tac tcc ttc gac acc tgc aag ccg ccc gag gag cag ctc acc ttc aag       1776
Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys
            580                 585                 590

gac ctg gtg tcc tgt gcc tac cag gtg gcc cgg ggc atg gag tac ttg       1824
Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu
        595                 600                 605

gcc tcc cag aag tgc atc cac agg gac ctg gct gcc cgc aat gtg ctg       1872
Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu
    610                 615                 620

gtg acc gag gac aac gtg atg aag atc gca gac ttc ggg ctg gcc cgg       1920
Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg
625                 630                 635                 640

gac gtg cac aac ctc gac tac tac aag aag aca acc aac ggc cgg ctg       1968
Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu
                645                 650                 655

ccc gtg aag tgg atg gcg cct gag gcc ttg ttt gac cga gtc tac act       2016
Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr
            660                 665                 670

cac cag agt gac gtc tgg tcc ttt ggg gtc ctg ctc tgg gag atc ttc       2064
His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe
        675                 680                 685

acg ctg ggg ggc tcc ccg tac ccc ggc atc cct gtg gag gag ctc ttc       2112
Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe
    690                 695                 700
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aag ctg ctg aag gag ggc cac cgc atg gac aag ccc gcc aac tgc aca      2160
Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr
705                 710                 715                 720

cac gac ctg tac atg atc atg cgg gag tgc tgg cat gcc gcg ccc tcc      2208
His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser
                725                 730                 735

cag agg ccc acc ttc aag cag ctg gtg gag gac ctg gac cgt gtc ctt      2256
Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu
            740                 745                 750

acc gtg acg tcc acc gac aat gtt atg gaa cag ttc aat cct ggg ctg      2304
Thr Val Thr Ser Thr Asp Asn Val Met Glu Gln Phe Asn Pro Gly Leu
        755                 760                 765

cga aat tta ata aac ctg ggg aaa aat tat gag aaa gct gta aac gct      2352
Arg Asn Leu Ile Asn Leu Gly Lys Asn Tyr Glu Lys Ala Val Asn Ala
    770                 775                 780

atg atc ctg gca gga aaa gcc tac tac gat gga gtg gcc aag atc ggt      2400
Met Ile Leu Ala Gly Lys Ala Tyr Tyr Asp Gly Val Ala Lys Ile Gly
785                 790                 795                 800

gag att gcc act ggg tcc ccc gtg tca act gaa ctg gga cat gtc ctc      2448
Glu Ile Ala Thr Gly Ser Pro Val Ser Thr Glu Leu Gly His Val Leu
                805                 810                 815

ata gag att tca agt acc cac aag aaa ctc aac gag agt ctt gat gaa      2496
Ile Glu Ile Ser Ser Thr His Lys Lys Leu Asn Glu Ser Leu Asp Glu
            820                 825                 830

aat ttt aaa aaa ttc cac aaa gag att atc cat gag ctg gag aag aag      2544
Asn Phe Lys Lys Phe His Lys Glu Ile Ile His Glu Leu Glu Lys Lys
        835                 840                 845

ata gaa ctt gac gtg aaa tat atg aac gca act cta aaa aga tac caa      2592
Ile Glu Leu Asp Val Lys Tyr Met Asn Ala Thr Leu Lys Arg Tyr Gln
    850                 855                 860

aca gaa cac aag aat aaa tta gag tct ttg gag aaa tcc caa gct gag      2640
Thr Glu His Lys Asn Lys Leu Glu Ser Leu Glu Lys Ser Gln Ala Glu
865                 870                 875                 880

ttg aag aag atc aga agg aaa agc caa gga agc cga aac gca ctc aaa      2688
Leu Lys Lys Ile Arg Arg Lys Ser Gln Gly Ser Arg Asn Ala Leu Lys
                885                 890                 895

tat gaa cac aaa gaa att gag tat gtg gag acc gtt act tct cgt cag      2736
Tyr Glu His Lys Glu Ile Glu Tyr Val Glu Thr Val Thr Ser Arg Gln
            900                 905                 910

agt gaa atc cag aaa ttc att gca gat ggt tgc aaa gag gct ctg ctt      2784
Ser Glu Ile Gln Lys Phe Ile Ala Asp Gly Cys Lys Glu Ala Leu Leu
        915                 920                 925

gaa gag aag agg cgc ttc tgc ttt ctg gtt gat aag cac tgt ggc ttt      2832
Glu Glu Lys Arg Arg Phe Cys Phe Leu Val Asp Lys His Cys Gly Phe
    930                 935                 940

gca aac cac ata cat tat tat cac tta cag tct gca gaa cta ctg aat      2880
Ala Asn His Ile His Tyr Tyr His Leu Gln Ser Ala Glu Leu Leu Asn
```

```
945                 950                 955                 960

tcc aag ctg cct cgg tgg cag gag acc tgt gtt gat gcc atc aaa gtg      2928
Ser Lys Leu Pro Arg Trp Gln Glu Thr Cys Val Asp Ala Ile Lys Val
                965                 970                 975

cca gag aaa atc atg aat atg atc gaa gaa ata aag acc cca gcc tct      2976
Pro Glu Lys Ile Met Asn Met Ile Glu Glu Ile Lys Thr Pro Ala Ser
            980                 985                 990

acc ccc gtg tct gga act cct cag  gct tca ccc atg atc  gag aga agc    3024
Thr Pro Val Ser Gly Thr Pro Gln  Ala Ser Pro Met Ile  Glu Arg Ser
        995                 1000                1005

aat gtg  gtt agg aaa gat tac  gac acc ctt tct aaa  tgc tca cca      3069
Asn Val  Val Arg Lys Asp Tyr  Asp Thr Leu Ser Lys  Cys Ser Pro
    1010                 1015                 1020

aag atg  ccc ccc gct cct tca  ggc aga gca tat acc  agt ccc ttg      3114
Lys Met  Pro Pro Ala Pro Ser  Gly Arg Ala Tyr Thr  Ser Pro Leu
    1025                 1030                 1035

atc gat  atg ttt aat aac cca  gcc acg gct gcc ccg  aat tca caa      3159
Ile Asp  Met Phe Asn Asn Pro  Ala Thr Ala Ala Pro  Asn Ser Gln
    1040                 1045                 1050

agg gta  aat aat tca aca ggt  act tcc gaa gat ccc  agt tta cag      3204
Arg Val  Asn Asn Ser Thr Gly  Thr Ser Glu Asp Pro  Ser Leu Gln
    1055                 1060                 1065

cga tca  gtt tcg gtt gca acg  gga ctg aac atg atg  aag aag cag      3249
Arg Ser  Val Ser Val Ala Thr  Gly Leu Asn Met Met  Lys Lys Gln
    1070                 1075                 1080

aaa gtg  aag acc atc ttc ccg  cac act gcg ggc tcc  aac aag acc      3294
Lys Val  Lys Thr Ile Phe Pro  His Thr Ala Gly Ser  Asn Lys Thr
    1085                 1090                 1095

tta ctc  agc ttt gca cag gga  gat gtc atc acg ctg  ctc atc ccc      3339
Leu Leu  Ser Phe Ala Gln Gly  Asp Val Ile Thr Leu  Leu Ile Pro
    1100                 1105                 1110

gag gag  aag gat ggc tgg ctc  tat gga gaa cac gac  gtg tcc aag      3384
Glu Glu  Lys Asp Gly Trp Leu  Tyr Gly Glu His Asp  Val Ser Lys
    1115                 1120                 1125

gcg agg  ggt tgg ttc ccg tcg  tcg tac acg aag ttg  ctg gaa gaa      3429
Ala Arg  Gly Trp Phe Pro Ser  Ser Tyr Thr Lys Leu  Leu Glu Glu
    1130                 1135                 1140

aat gag  aca gaa gca gtg acc  gtg ccc acg cca agc  ccc aca cca      3474
Asn Glu  Thr Glu Ala Val Thr  Val Pro Thr Pro Ser  Pro Thr Pro
    1145                 1150                 1155

gtg aga  agc atc agc acc gtg  aac ttg tct gag aat  agc agt gtt      3519
Val Arg  Ser Ile Ser Thr Val  Asn Leu Ser Glu Asn  Ser Ser Val
    1160                 1165                 1170

gtc atc  ccc cca ccc gac tac  ttg gaa tgc ttg tcc  atg ggg gca      3564
Val Ile  Pro Pro Pro Asp Tyr  Leu Glu Cys Leu Ser  Met Gly Ala
    1175                 1180                 1185

gct gcc  gac agg aga gca gat  tcg gcc agg acg aca  tcc acc ttt      3609
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Ala Ala  Asp Arg Arg Ala Asp  Ser Ala Arg Thr Thr  Ser Thr Phe
    1190                 1195                 1200

aag gcc  cca gcg tcc aag ccc  gag acc gcg gct cct  aac gat gcc        3654
Lys Ala  Pro Ala Ser Lys Pro  Glu Thr Ala Ala Pro  Asn Asp Ala
    1205                 1210                 1215

aac ggg  act gca aag ccg cct  ttt ctc agc gga gaa  aac ccc ttt        3699
Asn Gly  Thr Ala Lys Pro Pro  Phe Leu Ser Gly Glu  Asn Pro Phe
    1220                 1225                 1230

gcc act  gtg aaa ctc cgc ccg  act gtg acg aat gat  cgc tcg gca        3744
Ala Thr  Val Lys Leu Arg Pro  Thr Val Thr Asn Asp  Arg Ser Ala
    1235                 1240                 1245

ccc atc  att cga tga                                                  3759
Pro Ile  Ile Arg
    1250
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            20                  25                  30

Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
        35                  40                  45

Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
    50                  55                  60

Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140
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Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
    210                 215                 220

Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
225                 230                 235                 240

Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255

Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270

Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285

Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

Tyr Val Thr Val Leu Lys Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu
305                 310                 315                 320

Leu Glu Val Leu Ser Leu His Asn Val Thr Phe Glu Asp Ala Gly Glu
                325                 330                 335

Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala
            340                 345                 350

Trp Leu Val Val Leu Pro Ala Glu Glu Glu Leu Val Glu Ala Asp Glu
        355                 360                 365

Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly Phe Phe
    370                 375                 380

Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu Arg Ser
385                 390                 395                 400
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Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile Ser Arg
                405                 410                 415

Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser Met Ser
            420                 425                 430

Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly
        435                 440                 445

Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys
    450                 455                 460

Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu
465                 470                 475                 480

Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys
                485                 490                 495

Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu Lys Asp
            500                 505                 510

Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met
        515                 520                 525

Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala
    530                 535                 540

Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys
545                 550                 555                 560

Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp
                565                 570                 575

Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys
            580                 585                 590

Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu
        595                 600                 605

Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu
    610                 615                 620

Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg
625                 630                 635                 640

Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu
                645                 650                 655
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Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr
            660                 665                 670

His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe
        675                 680                 685

Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe
    690                 695                 700

Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr
705                 710                 715                 720

His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser
                725                 730                 735

Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu
            740                 745                 750

Thr Val Thr Ser Thr Asp Asn Val Met Glu Gln Phe Asn Pro Gly Leu
        755                 760                 765

Arg Asn Leu Ile Asn Leu Gly Lys Asn Tyr Glu Lys Ala Val Asn Ala
    770                 775                 780

Met Ile Leu Ala Gly Lys Ala Tyr Tyr Asp Gly Val Ala Lys Ile Gly
785                 790                 795                 800

Glu Ile Ala Thr Gly Ser Pro Val Ser Thr Glu Leu Gly His Val Leu
                805                 810                 815

Ile Glu Ile Ser Ser Thr His Lys Lys Leu Asn Glu Ser Leu Asp Glu
            820                 825                 830

Asn Phe Lys Lys Phe His Lys Glu Ile Ile His Glu Leu Glu Lys Lys
        835                 840                 845

Ile Glu Leu Asp Val Lys Tyr Met Asn Ala Thr Leu Lys Arg Tyr Gln
    850                 855                 860

Thr Glu His Lys Asn Lys Leu Glu Ser Leu Glu Lys Ser Gln Ala Glu
865                 870                 875                 880

Leu Lys Lys Ile Arg Arg Lys Ser Gln Gly Ser Arg Asn Ala Leu Lys
                885                 890                 895

Tyr Glu His Lys Glu Ile Glu Tyr Val Glu Thr Val Thr Ser Arg Gln
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            900                 905                 910

Ser Glu Ile Gln Lys Phe Ile Ala Asp Gly Cys Lys Glu Ala Leu Leu
        915                 920                 925

Glu Glu Lys Arg Arg Phe Cys Phe Leu Val Asp Lys His Cys Gly Phe
    930                 935                 940

Ala Asn His Ile His Tyr Tyr His Leu Gln Ser Ala Glu Leu Leu Asn
945                 950                 955                 960

Ser Lys Leu Pro Arg Trp Gln Glu Thr Cys Val Asp Ala Ile Lys Val
                965                 970                 975

Pro Glu Lys Ile Met Asn Met Ile Glu Glu Ile Lys Thr Pro Ala Ser
            980                 985                 990

Thr Pro Val Ser Gly Thr Pro Gln  Ala Ser Pro Met Ile  Glu Arg Ser
        995                 1000                 1005

Asn Val  Val Arg Lys Asp Tyr  Asp Thr Leu Ser Lys  Cys Ser Pro
    1010                 1015                 1020

Lys Met  Pro Pro Ala Pro Ser  Gly Arg Ala Tyr Thr  Ser Pro Leu
    1025                 1030                 1035

Ile Asp  Met Phe Asn Asn Pro  Ala Thr Ala Ala Pro  Asn Ser Gln
    1040                 1045                 1050

Arg Val  Asn Asn Ser Thr Gly  Thr Ser Glu Asp Pro  Ser Leu Gln
    1055                 1060                 1065

Arg Ser  Val Ser Val Ala Thr  Gly Leu Asn Met Met  Lys Lys Gln
    1070                 1075                 1080

Lys Val  Lys Thr Ile Phe Pro  His Thr Ala Gly Ser  Asn Lys Thr
    1085                 1090                 1095

Leu Leu  Ser Phe Ala Gln Gly  Asp Val Ile Thr Leu  Leu Ile Pro
    1100                 1105                 1110

Glu Glu  Lys Asp Gly Trp Leu  Tyr Gly Glu His Asp  Val Ser Lys
    1115                 1120                 1125

Ala Arg  Gly Trp Phe Pro Ser  Ser Tyr Thr Lys Leu  Leu Glu Glu
    1130                 1135                 1140
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Asn Glu  Thr Glu Ala Val Thr  Val Pro Thr Pro Ser  Pro Thr Pro
    1145                 1150                 1155

Val Arg  Ser Ile Ser Thr Val  Asn Leu Ser Glu Asn  Ser Ser Val
    1160                 1165                 1170

Val Ile  Pro Pro Pro Asp Tyr  Leu Glu Cys Leu Ser  Met Gly Ala
    1175                 1180                 1185

Ala Ala  Asp Arg Arg Ala Asp  Ser Ala Arg Thr Thr  Ser Thr Phe
    1190                 1195                 1200

Lys Ala  Pro Ala Ser Lys Pro  Glu Thr Ala Ala Pro  Asn Asp Ala
    1205                 1210                 1215

Asn Gly  Thr Ala Lys Pro Pro  Phe Leu Ser Gly Glu  Asn Pro Phe
    1220                 1225                 1230

Ala Thr  Val Lys Leu Arg Pro  Thr Val Thr Asn Asp  Arg Ser Ala
    1235                 1240                 1245

Pro Ile  Ile Arg
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<400> 39

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Glu Gly Pro Trp Leu Glu Glu Glu Glu Glu Ala Tyr Gly Trp Met Asp
1               5                   10                  15

Phe
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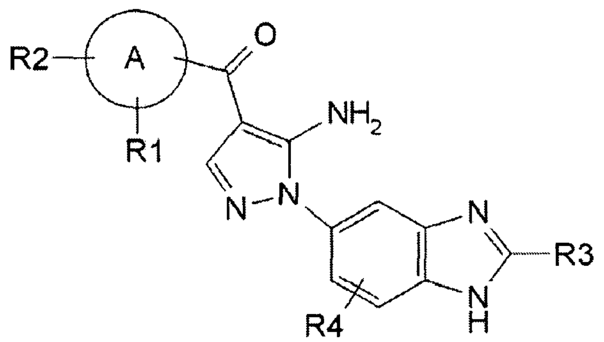
Claims

1. A compound having FGFR inhibitory activity or a pharmaceutically acceptable salt thereof for use in a method of treating or preventing cancer in a patient who has been identified to express a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide or to carry a polynucleotide encoding the fusion polypeptide, wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7,
wherein the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8, and
wherein the compound or a pharmaceutically acceptable salt thereof is capable of inhibiting a growth of a cancer cell expressing the fusion polypeptide or having a nucleotide encoding the fusion polypeptide.

2. The compound or a pharmaceutically acceptable salt thereof for use in a method of treating or preventing cancer in a patient according to claim 1, wherein the cancer is bladder cancer, brain tumor, head and neck squamous cell carcinoma, lung cancer, lung adenocarcinoma, lung squamous cell carcinoma, skin melanoma, esophageal cancer, gastric cancer, or liver cancer, in particular bladder cancer.

3. The compound or a pharmaceutically acceptable salt thereof for use in a method of treating or preventing cancer in a patient according to claim 1 or 2, wherein the compound having FGFR inhibitory activity or a pharmaceutically acceptable salt thereof is any one of the compounds or a pharmaceutically acceptable salt thereof represented by:

[Compound 1]



(I)

wherein R_1, R_2, R_3, and R_4 each independently represents the group listed below:

R_1 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

R_2 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$; or

R_1 and R_2, together with an atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein the heterocyclyl or heteroaryl is optionally substituted by halogen;

R_3 represents hydrogen, C_{1-5} alkyl, C_{6-10} aryl C_{1-6} alkyl, or C_{1-4} haloalkyl;

R_4 represents hydrogen, halogen, C_{1-3} alkyl, C_{1-4} haloalkyl, hydroxy, cyano, nitro, C_{1-4} alkoxy, $-(CH_2)_nZ_1$, $-NR_6R_7$, $-OR_5$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $NR_{17}SO_2R_{18}$, COOH, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

A represents a 5- to 10-membered heteroaryl ring or C_{6-10} aryl ring;

R_5 represents C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{1-3} alkoxy C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{6-10} aryl, C_{6-10} aryl C_{1-3} alkyl, or 3- to 10-membered heterocyclyl C_{1-3} alkyl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, or C_{1-6} trihydroxy alkyl which is optionally substituted by one or more groups independently selected from group Q;

R_6 and R_7, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl C_{1-3} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, or cyano(C_{1-3} alkyl); or alternatively R_6 and R_7, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

n represents 1 to 3;

R_8 and R_9, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, or halogen; or alternatively R_8 and R_9, together with a carbon atom linked thereto, form a cycloaliphatic ring;

Z_1 represents hydrogen, $NR_{10}R_{11}$, -OH, or 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{10} and R_{11}, which can be the same or different, each represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, cyano(C_{1-3} alkyl), or C_{1-3} alkylsulfonyl C_{1-4} alkyl; or alternatively R_{10} and R_{11}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{12} and R_{13}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, 3- to 10-membered cycloaliphatic ring, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; or alternatively R_{12} and R_{13}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{14} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{15} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{16} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{17} represents hydrogen or C_{1-4} alkyl;

R_{18} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{19} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{20} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{21}, represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{22} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{23} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{24} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{25} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{26} and R_{27}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively R_{26} and R_{27}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{28} and R_{29}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively R_{28} and R_{29}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{30} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{31} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-

membered heterocyclyl;

R_{32} represents C_{1-4} alkyl or C_{6-10} aryl;

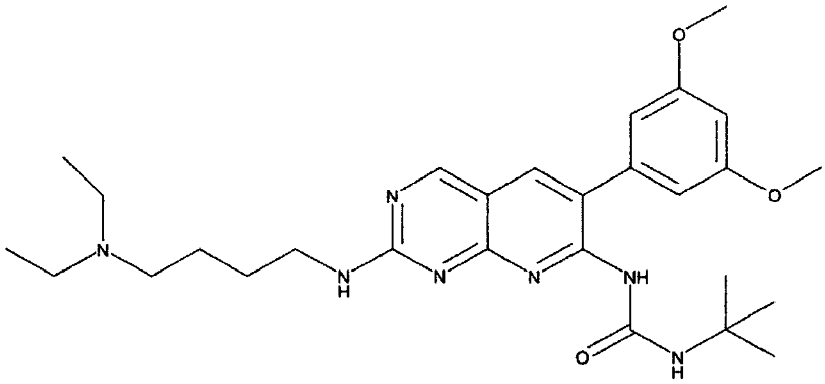
<group P>

halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, 3- to 10-membered heterocyclylamino, $-SO_2R_{16}$, -CN, $-NO_2$, and 3- to 10-membered heterocyclyl;

<group Q>

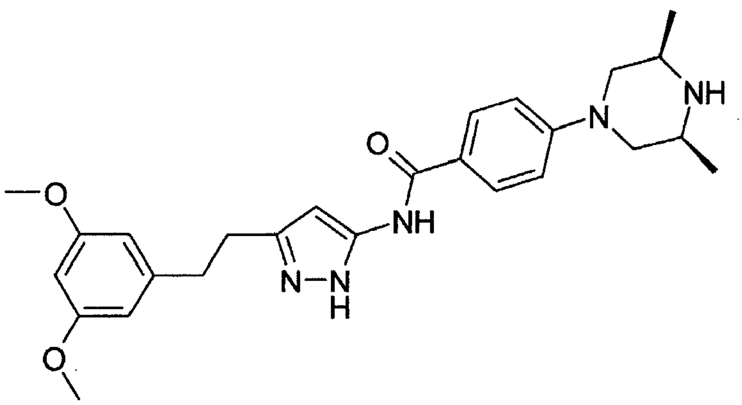
halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl amine, - SO_2R_{16}, -CN, $-NO_2$, C_{3-7} cycloalkyl, $-COR_{19}$, and 3- to 10-membered heterocyclyl which is optionally substituted by C_{1-4} alkyl;

[Compound 2]



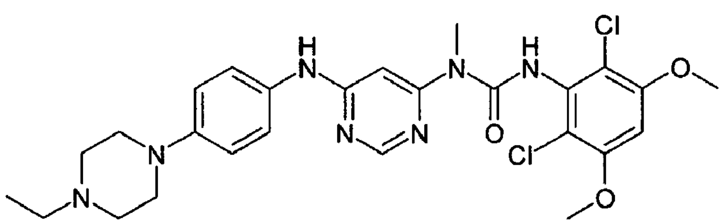
,

[Compound 3]

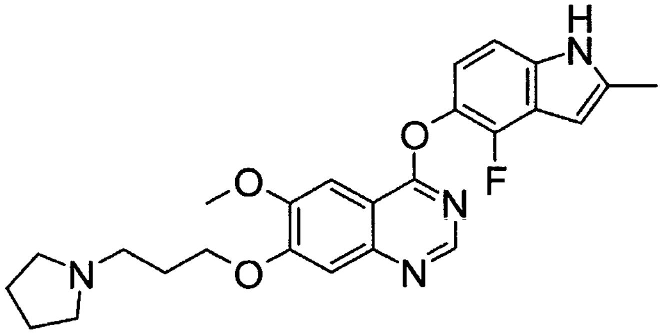


,

[Compound 4]

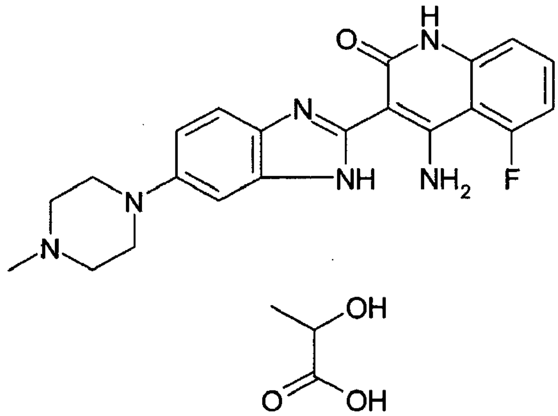


[Compound 5]



, or

[Compound 6]

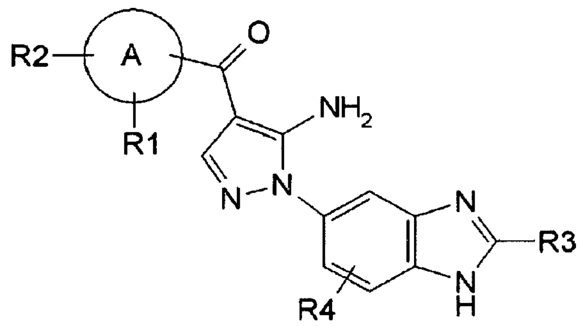


4. A method for selecting a patient, in particular a patient having bladder cancer, brain tumor, head and neck squamous cell carcinoma, lung cancer, lung adenocarcinoma, lung squamous cell carcinoma, skin melanoma, esophageal cancer, gastric cancer, or liver cancer, to which an anticancer agent comprising a compound having FGFR inhibitory activity or a pharmaceutically acceptable salt thereof is applicable, which comprises the steps of:

(a) determining the presence or absence of a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide or a polynucleotide encoding a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide in a sample isolated from a subject,
wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7, and
wherein the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8; and
(b) selecting a patient confirmed to have the fusion polypeptide or the polynucleotide as a patient to which the anticancer agent is applicable,
wherein the compound or a pharmaceutically acceptable salt thereof is capable of inhibiting a growth of a cancer cell expressing the fusion polypeptide or having a nucleotide encoding the fusion polypeptide.

5. The method of claim 4, wherein the compound having FGFR inhibitory activity or a pharmaceutically acceptable salt thereof is any one of the compounds or a pharmaceutically acceptable salt thereof represented by:

[Compound 1]



(I)

wherein R_1, R_2, R_3, and R_4 each independently represents the group listed below:

R_1 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

R_2 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$; or

R_1 and R_2, together with an atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein the heterocyclyl or heteroaryl is optionally substituted by halogen;

R_3 represents hydrogen, C_{1-5} alkyl, C_{6-10} aryl C_{1-6} alkyl, or C_{1-4} haloalkyl;

R_4 represents hydrogen, halogen, C_{1-3} alkyl, C_{1-4} haloalkyl, hydroxy, cyano, nitro, C_{1-4} alkoxy, $-(CH_2)_nZ_1$, $-NR_6R_7$, $-OR_5$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $NR_{17}SO_2R_{18}$, COOH, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

A represents a 5- to 10-membered heteroaryl ring or C_{6-10} aryl ring;

R_5 represents C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{1-3} alkoxy C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{6-10} aryl, C_{6-10} aryl C_{1-3} alkyl, or 3- to 10-membered heterocyclyl C_{1-3} alkyl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, or C_{1-6} trihydroxy alkyl which is optionally substituted by one or more groups independently selected from group Q;

R_6 and R_7, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl C_{1-3} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, or cyano(C_{1-3} alkyl); or alternatively R_6 and R_7, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

n represents 1 to 3;

R_8 and R_9, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, or halogen; or alternatively R_8 and R_9, together with a carbon atom linked thereto, form a cycloaliphatic ring;

Z_1 represents hydrogen, $NR_{10}R_{11}$, -OH, or 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{10} and R_{11}, which can be the same or different, each represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, cyano(C_{1-3} alkyl), or C_{1-3} alkylsulfonyl C_{1-4} alkyl; or alternatively R_{10} and R_{11}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{12} and R_{13}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, 3- to 10-membered cycloaliphatic ring, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; or alternatively R_{12} and R_{13}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{14} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{15} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{16} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{17} represents hydrogen or C_{1-4} alkyl;

R_{18} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{19} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{20} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{21} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{22} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{23} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{24} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{25} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{26} and R_{27}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively R_{26} and R_{27}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{28} and R_{29}, which can be the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively R_{28} and R_{29}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{30} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{31} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{32} represents C_{1-4} alkyl or C_{6-10} aryl;

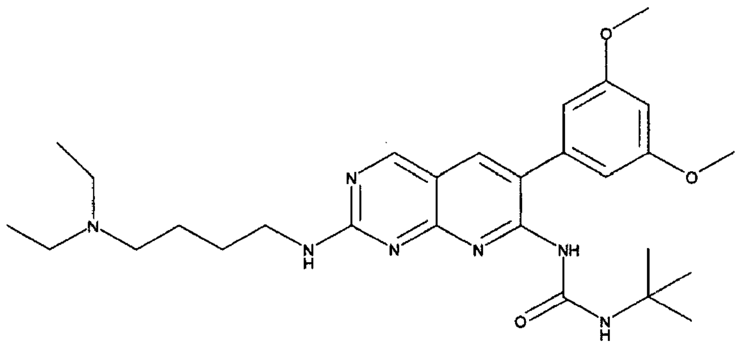
<group P>

halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, 3- to 10-membered heterocyclylamino, $-SO_2R_{16}$, -CN, $-NO_2$, and 3- to 10-membered heterocyclyl;

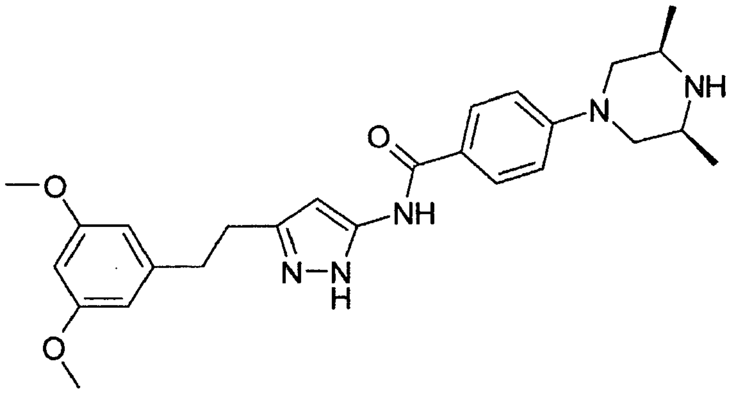
<group Q>

halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl amine, $-SO_2R_{16}$, -CN, $-NO_2$, C_{3-7} cycloalkyl, $-COR_{19}$, and 3- to 10-membered heterocyclyl which is optionally substituted by C_{1-4} alkyl.

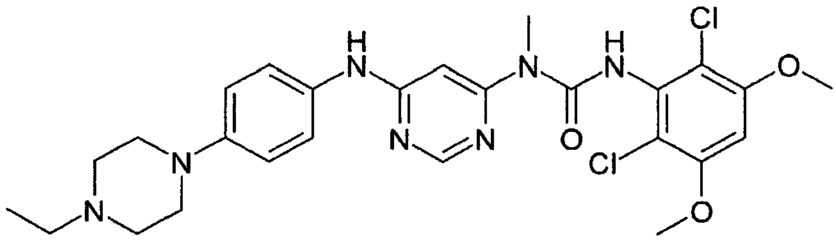
[Compound 2]



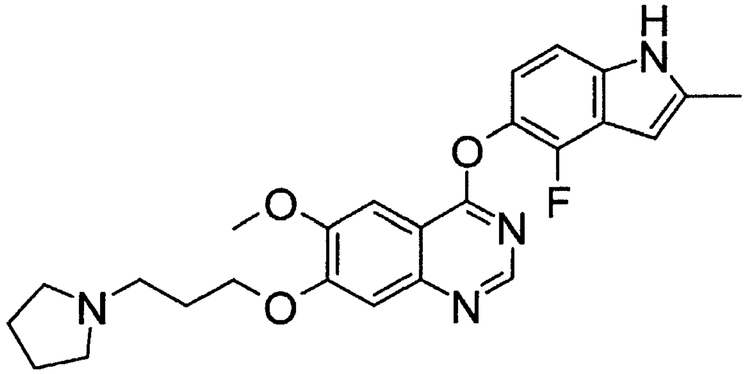
[Compound 3]



[Compound 4]

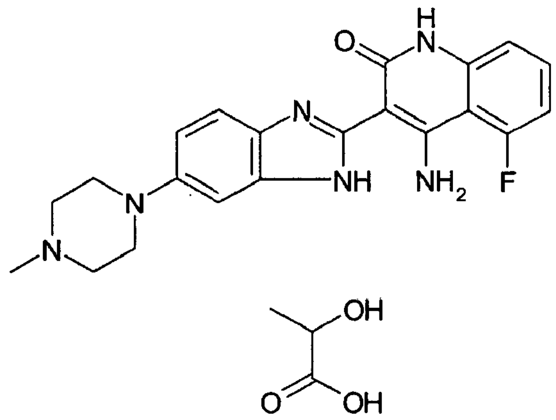


[Compound 5]



, or

[Compound 6]



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6. A method for testing cancer susceptibility of a subject, whether a subject is affected with cancer, or whether cancer has progressed in a subject, in particular wherein the cancer is bladder cancer, brain tumor, head and neck squamous cell carcinoma, lung cancer, lung adenocarcinoma, lung squamous cell carcinoma, skin melanoma, esophageal cancer, gastric cancer, or liver cancer, by determining the presence or absence of a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide or determining the presence or absence of a polynucleotide encoding a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide in a sample isolated from the subject,
wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7,
wherein the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8; and
wherein the method is based on the criterion that a subject is more likely to develop cancer, is affected with cancer, or has progressed cancer when the fusion polypeptide or polynucleotide encoding the fusion polypeptide is detected.

7. A fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide:

wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7, and
the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8, in particular wherein the fusion polypeptide is derived from bladder cancer or lung cancer, more particularly wherein the fusion polypeptide consists of the amino acid sequence of SEQ ID NO: 32 or 38.

8. A polynucleotide encoding the fusion polypeptide of claim 7, in particular wherein the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 16, more particularly wherein the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 31 or 37, or a vector comprising said polynucleotide.

9. A recombinant cell comprising the vector of claim 8.

10. A method for detecting

(a) a fusion polypeptide that comprises an FGFR3 polypeptide and a BAIAP2L1 polypeptide, which comprises the step of detecting the fusion polypeptide in a sample isolated from a subject by using an antibody or antigen-binding fragment thereof that binds to the fusion polypeptide of claim 7, or
(b) a polynucleotide encoding a fusion polypeptide that comprises an FGFR3 polypeptide and a BAIAP2L1 polypeptide, which comprises the step of detecting a polynucleotide encoding the fusion polypeptide in a sample isolated from a subject by using a pair of oligonucleotide primers consisting of sense and antisense primers each hybridizing to a polynucleotide encoding the fusion polypeptide of claim 7 for detecting or amplifying the polynucleotide.

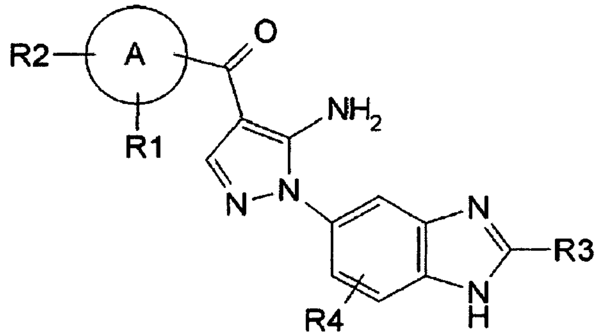
Patentansprüche

1. Verbindung mit FGFR-inhibitorischer Aktivität oder ein pharmazeutisch verträgliches Salz davon zur Verwendung in einem Verfahren des Behandelns oder Verhinderns von Krebs in einem Patienten, der identifiziert wurde, ein Fusionspolypeptid, umfassend ein FGFR3-Polypeptid und ein BAIAP2L1-Polypeptid, zu exprimieren oder ein Polynukleotid, kodierend das Fusionspolypeptid, zu tragen,
wobei das FGFR3-Polypeptid das gesamte oder ein Teil eines Wildtyp-Polypeptids ist, bestehend aus der Aminosäuresequenz von SEQ ID NR: 6 oder 7,
wobei das BAIAP2L1-Polypeptid das gesamte oder ein Teil eines Wildtyp-Polypeptids ist, bestehend aus der Aminosäuresequenz von SEQ ID NR: 8, und
wobei die Verbindung oder ein pharmazeutisch verträgliches Salz davon in der Lage ist, ein Wachstum einer Krebszelle zu inhibieren, die das Fusionspolypeptid exprimiert oder ein Nukleotid, kodierend das Fusionspolypeptid, hat.

2. Verbindung oder ein pharmazeutisch verträgliches Salz davon zur Verwendung in einem Verfahren des Behandelns oder Verhinderns von Krebs in einem Patienten gemäß Anspruch 1, wobei der Krebs Blasenkrebs, Hirntumor, Plattenepithelkarzinom des Kopf-/Halsbereiches ("head and neck squamous cell 11 carcinoma"), Lungenkrebs, Lungenadenokarzinom, Plattenepithelkarzinom der Lunge ("lung squamous cell carcinoma"), Hautmelanom, Ösophaguskrebs, Magenkrebs oder Leberkrebs, insbesondere Blasenkrebs, ist.

3. Verbindung oder ein pharmazeutisch verträgliches Salz davon zur Verwendung in einem Verfahren des Behandelns oder Verhinderns von Krebs in einem Patienten gemäß Anspruch 1 oder 2, wobei die Verbindung mit FGFR-inhibitorischer Aktivität oder ein pharmazeutisch verträgliches Salz davon eine beliebige der Verbindungen oder eines pharmazeutisch verträglichen Salzes davon ist, dargestellt durch:

[Verbindung 1]



(I)

wobei R_1, R_2, R_3 und R_4 jeweils unabhängig die Gruppe darstellen, die nachstehend aufgelistet ist:

R_1 stellt dar Wasserstoff, Hydroxy, Halogen, Cyano, Nitro, C_{1-4}-Haloalkyl, C_{1-6}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{3-7}-Cycloalkyl, C_{6-10}-Aryl-C_{1-4}-Alkyl, -OR_5, -NR_6R_7, -$(CR_8R_9)_nZ_1$, -$C(O)NR_{12}R_{13}$, -SR_{14}, -SOR_{15}, -SO_2R_{16}, -$NR_{17}SO_2R_{18}$, COOH, C_{6-10}-Aryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe Q, -COR_{19}, -$COOR_{20}$, -$OC(O)R_{21}$, -$NR_{22}C(O)R_{23}$, -$NR_{24}C(S)R_{25}$, -$C(S)NR_{26}R_{27}$, -$SO_2NR_{28}R_{29}$, -OSO_2R_{30}, -SO_3R_{31} oder -$Si(R_{32})_3$;

R_2 stellt dar Wasserstoff, Hydroxy, Halogen, Cyano, Nitro, C_{1-4}-Haloalkyl, C_{1-6}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{3-7}-Cycloalkyl, C_{6-10}-Aryl C_{1-4}-Alkyl, -OR_5, -NR_6R_7, -$(CR_8R_9)_nZ_1$, -$C(O)NR_{12}R_{13}$, -SR_{14}, -SOR_{15}, -SO_2R_{16}, -$NR_{17}SO_2R_{18}$, COOH, C_{6-10}-Aryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe Q, -COR_{19}, -$COOR_{20}$, -$OC(O)R_{21}$, -$NR_{22}C(O)R_{23}$, -$NR_{24}C(S)R_{25}$, -$C(S)NR_{26}R_{27}$, -$SO_2NR_{28}R_{29}$, -OSO_2R_{30}, -SO_3R_{31} oder -$Si(R_{32})_3$; oder
R_1 und R_2 zusammen mit einem Atom, das daran gebunden ist, bilden 3-bis 10-gliedriges Heterocyclyl oder 5-

bis 10-gliedriges Heteroaryl, wobei das Heterocyclyl oder Heteroaryl optional durch Halogen substituiert ist;
R_3 stellt Wasserstoff, C_{1-5}-Alkyl, C_{6-10}-Aryl, C_{1-6}-Alkyl oder C_{1-4}-Haloalkyl dar;
R_4 stellt Wasserstoff, Halogen, C_{1-3}-Alkyl, C_{1-4}-Haloalkyl, Hydroxy, Cyano, Nitro, C_{1-4}-Alkoxy, $-(CH_2)_nZ_1$, $-NR_6R_7$, $-OR_5$, $-C(O)NR_{12}R_{13}$. $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $NR_{17}SO_2R_{18}$, COOH, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22C}(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$ oder $-Si(R_{32})_3$ dar;
A stellt einen 5- bis 10-gliedrigen Heteroarylring oder einen C_{6-10}-Arylring dar;
R_5 stellt C_{1-5}-Alkyl, C_{3-7}-Cycloalkyl, C_{3-7}-Cycloalkyl-C_{1-3}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxy-C_{1-4}-Alkyl, C_{1-3}-Alkoxy-C_{1-4}-Alkoxy-C_{1-4}-Alkyl, C_{1-4}-Aminoalkyl, C_{1-4}-Alkylamino-C_{1-4}-Alkyl, Di(C_{1-4}-Alkyl)amino-C_{1-4}-Alkyl, C_{6-10}-Aryl, C_{6-10}-Aryl-C_{1-3}-Alkyl oder 3- bis 10-gliedriges Heterocyclyl-C_{1-3}-Alkyl, 3- bis 10-gliedriges Heterocyclyl, 5- bis 10-gliedriges Heteroaryl, 5- bis 10-gliedriges Heteroaryl-C_{1-3}-Alkyl, C_{1-6}-Monohydroxyalkyl, C_{1-6}-Dihydroxyalkyl oder C_{1-6}-Trihydroxyalkyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q, dar;
R_6 und R_7, die die gleichen oder verschieden sein können, stellen jeweils Wasserstoff, C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxy-C_{1-4}-Alkyl, C_{6-10}-Aryl-C_{1-3}-Alkyl, 3- bis 10-gliedriges Heterocyclyl-C_{1-3}-Alkyl, 5- bis 10-gliedriges Heteroaryl-C_{1-3}-Alkyl, C_{1-6}-Monohydroxyalkyl, C_{1-6}-Dihydroxyalkyl, C_{1-6}-Trihydroxyalkyl, 3- bis 10-gliedriges Heterocyclyl, C_{1-4}-Aminoalkyl, C_{1-4}-Alkylamino-C_{1-4}-Alkyl, Di(C_{1-4}-Alkyl)amino-C_{1-4}-Alkyl oder Cyano(C_{1-3}-Alkyl) dar; oder R_6 und R_7 bilden alternativ dazu zusammen mit einem Stickstoffatom, das daran gebunden ist, 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl;
n stellt 1 bis 3 dar;
R_8 und R_9, die die gleichen oder verschieden sein können, stellen jeweils Wasserstoff, C_{1-4}-Alkyl oder Halogen dar; oder R_8 und R_9 bilden alternativ dazu zusammen mit einem Kohlenstoffatom, das daran gebunden ist, einen cylcoaliphatischen Ring;
Z_1 stellt Wasserstoff, $NR_{10}R_{11}$, -OH oder 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl dar, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q;
R_{10} und R_{11}, die die gleichen oder verschieden sein können, stellen jeweils C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxy-C_{1-4}-Alkyl, Cyano(C_{1-3}-Alkyl) oder C_{1-3}-Alkylsulfonyl-C_{1-4}-Alkyl dar; oder R_{10} und R_{11} bilden alternativ dazu zusammen mit einem Stickstoffatom, das daran gebunden ist, 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl;
R_{12} und R_{13}, die die gleichen oder verschieden sein können, stellen jeweils Wasserstoff, C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxy-C_{1-4}-Alkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl, 3- bis 10-gliedriges Heterocyclyl, C_{6-10}-Aryl-C_{1-4}-Alkyl, 3- bis 10-gliedriges Heterocyclyl-C_{1-3}-Alkyl, 5- bis 10-gliedriges Heteroaryl-C_{1-3}-Alkyl, Cyano(C_{1-3}-Alkyl), C_{1-3}-Alkylsulfonyl-C_{1-4}-Alkyl, einen 3- bis 10-gliedrigen cycloaliphatischen Ring, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar; oder R_{12} und R_{13} bilden alternativ dazu zusammen mit einem Stickstoffatom, das daran gebunden ist, 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q;
R_{14} stellt C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, oder 5- bis 10-gliedriges Heteroaryl oder 3-bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q, dar;
R_{15} stellt C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, oder 5- bis 10-gliedriges Heteroaryl oder 3-bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q, dar;
R_{16} stellt C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, oder 5- bis 10-gliedriges Heteroaryl oder 3-bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q, dar;
R_{17} stellt Wasserstoff oder C_{1-4}-Alkyl dar;
R_{18} stellt C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, oder 5- bis 10-gliedriges Heteroaryl oder 3-bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q, dar;
R_{19} stellt Wasserstoff, C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl oder 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe Q, dar;
R_{20} stellt C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{21} stellt C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{22} stellt Wasserstoff, C_{1-4}-Alkyl oder C_{1-4}-Haloalkyl dar;

R_{23} stellt Wasserstoff, C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{24} stellt Wasserstoff, C_{1-4}-Alkyl oder C_{1-4}-Haloalkyl dar;

R_{25} stellt C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{26} und R_{27}, die die gleichen oder verschieden sein können, stellen jeweils Wasserstoff, C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxyl-C_{1-4}-Alkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl, 3- bis 10-gliedriges Heterocyclyl, C_{6-10}-Aryl-C_{1-4}-Alkyl, 3- bis 10-gliedriges Heterocyclyl-C_{1-3}-Alkyl, 5- bis 10-gliedriges Heteroaryl-C_{1-3}-Alkyl, Cyano(C_{1-3}-Alkyl), C_{1-3}-Alkylsulfonyl-C_{1-4}-Alkyl oder einen 3- bis 10-gliedrigen cycloaliphatischen Ring dar; oder R_{26} und R_{27} bilden alternativ dazu zusammen mit einem Stickstoffatom, das daran gebunden ist, 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl;

R_{28} und R_{29}, die die gleichen oder verschieden sein können, stellen jeweils Wasserstoff, C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxyl-C_{1-4}-Alkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl, 3- bis 10-gliedriges Heterocyclyl, C_{6-10}-Aryl-C_{1-4}-Alkyl, 3- bis 10-gliedriges Heterocyclyl-C_{1-3}-Alkyl, 5- bis 10-gliedriges Heteroaryl-C_{1-3}-Alkyl, Cyano(C_{1-3}-Alkyl), C_{1-3}-Alkylsulfonyl, C_{1-4}-Alkyl oder einen 3- bis 10-gliedrigen cycloaliphatischen Ring dar; oder R_{28} und R_{29} bilden alternativ dazu zusammen mit einem Stickstoffatom, das daran gebunden ist, 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl;

R_{30} stellt C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{31} stellt C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{32} stellt C_{1-4}-Alkyl oder C_{6-10}-Aryl dar;

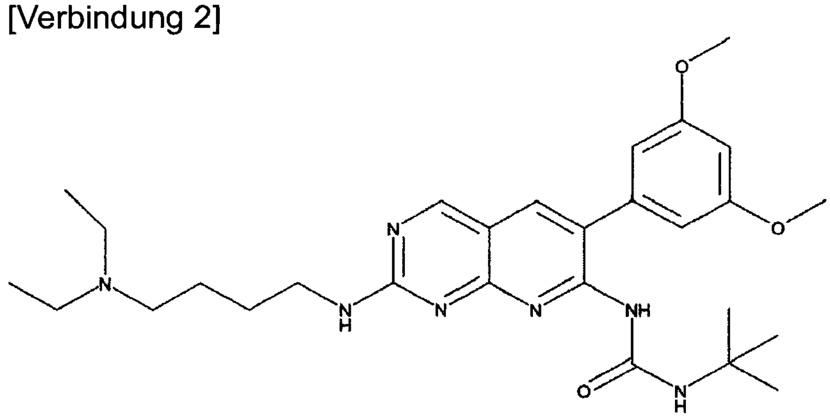
<Gruppe P>

Halogen, C_{1-4}-Alkyl, C_{1-4}-Hatoalkyl, -OH, C_{1-3}-Alkoxy, C_{1-3}-Haloalkoxy, 3- bis 10-gliedriges Heterocyclylamino, $-SO_2R_{16}$, -CN, $-NO_2$ und 3- bis 10-gliedriges Heterocyclyl;

<Gruppe Q>

Halogen, C_{1-4}-Alkyl, C_{1-4}-Haloalkyl, -OH, C_{1-3}-Alkoxy, C_{1-6}-Monohydroxyalkyl, C_{1-6}-Dihydroxyalkyl, C_{1-6}-Trihydroxyalkyl, 3- bis 10-gliedriges Heterocyclylamin, $-SO_2R_{16}$, -CN, $-NO_2$, C_{3-7}-Cycloalkyl, $-COR_{19}$ und 3- bis 10-gliedriges Heterocyclyl, das optional durch C_{1-4}-Alkyl substituiert ist;

[Verbindung 2]



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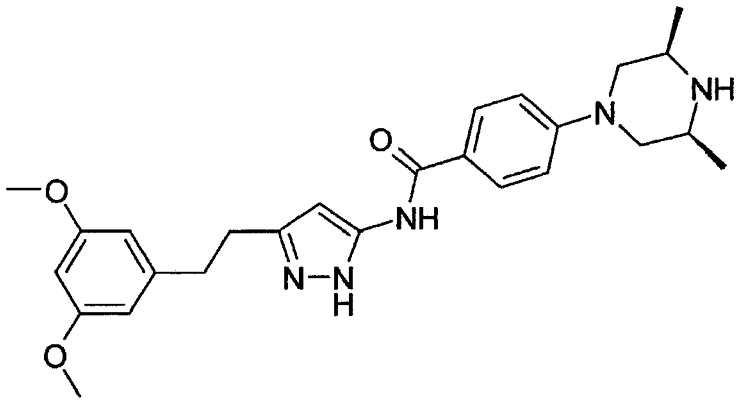
[Verbindung 3]



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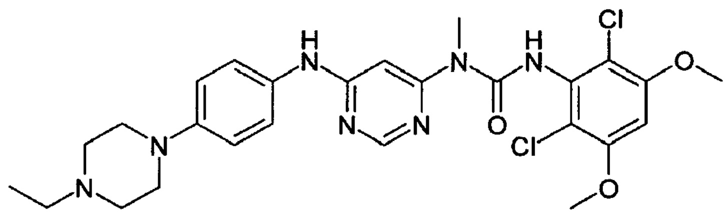
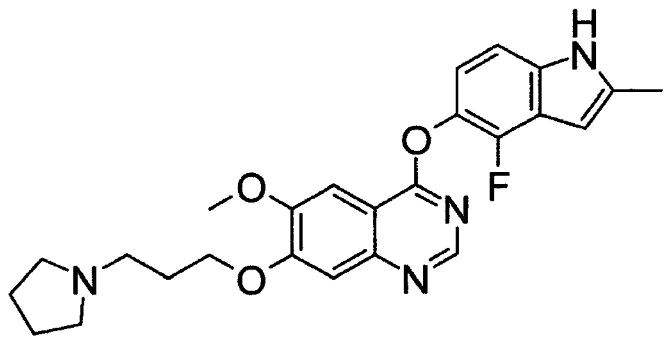
[Verbindung 4]



[Verbindung 5]



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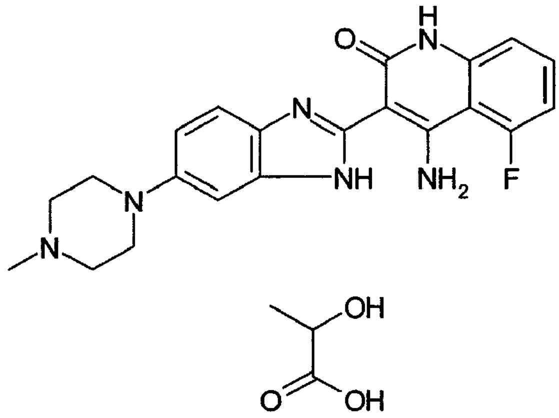
oder

[Verbindung 6]



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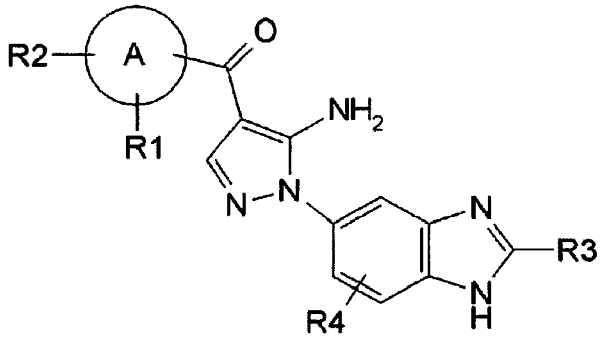
4. Verfahren zum Auswählen eines Patienten, insbesondere eines Patienten, der Blasenkrebs, Hirntumor, Plattenepithelkarzinom des Kopf-/Halsbereiches, Lungenkrebs, Lungenadenokarzinom, Plattenepithelkarzinom der Lunge, Hautmelanom, Ösophaguskrebs, Magenkrebs oder Leberkrebs hat, an den ein Antikrebsmittel, umfassend eine Verbindung mit FGFR-inhibitorischer Aktivität oder ein pharmazeutisch verträgliches Salz davon anwendbar ist, das die Schritte von umfasst:

(a) Bestimmen der Anwesenheit oder Abwesenheit eines Fusionspolypeptids, umfassend ein FGFR3-Polypeptid und ein BAIAP2L1-Polypeptid oder ein Polynukleotid, kodierend ein Fusionspolypeptid, umfassend ein FGFR3-Polypeptid und ein BAIAP2L1-Polypeptid, in einer Probe, die von einem Subjekt isoliert ist, wobei das FGFR3-Polypeptid das gesamte oder ein Teil eines Wildtyp-Polypeptids ist, bestehend aus der Aminosäuresequenz von SEQ ID NR: 6 oder 7, und wobei das BAIAP2L1-Polypeptid das gesamte oder ein Teil eines Wildtyp-Polypeptids ist, bestehend aus der Aminosäuresequenz von SEQ ID NR: 8, und
(b) Auswählen eines Patienten, von dem bestätigt wurde, dass er das Fusionspolypeptid oder das Polynukleotid hat, als einen Patient, an den das Antikrebsmittel anwendbar ist,
wobei die Verbindung oder ein pharmazeutisch verträgliches Salz davon in der Lage ist, ein Wachstum einer Krebszelle zu inhibieren, die das Fusionspolypeptid exprimiert oder ein Nukleotid hat, das das Fusionspolypeptid kodiert.

5. Verfahren von Anspruch 4, wobei die Verbindung mit FGFR-inhibitorischer Aktivität oder ein pharmazeutisch verträgliches Salz davon eine beliebige der Verbindungen oder eines pharmazeutisch verträglichen Salzes davon ist, dargestellt durch:

[Verbindung 1]



(I)

wobei R_1, R_2, R_3 und R_4 jeweils unabhängig die Gruppe darstellen, die nachstehend aufgelistet ist:

R_1 stellt dar Wasserstoff, Hydroxy, Halogen, Cyano, Nitro, C_{1-4}-Haloalkyl, C_{1-6}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl,

C_{3-7}-Cycloalkyl, C_{6-10}-Aryl-C_{1-4}-Alkyl, -OR_5, -NR_6R_7, -$(CR_8R_9)_nZ_1$, -C(O)$NR_{12}R_{13}$, -SR_{14}, -SOR_{15}, -SO_2R_{16}, -$NR_{17}SO_2R_{18}$, COOH, C_{6-10}-Aryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe Q, -COR_{19}, -$COOR_{20}$, -OC(O)R_{21}, -NR_{22}C(O)R_{23}, -NR_{24}C(S)R_{25}, -C(S)$NR_{26}R_{27}$, -$SO_2NR_{28}R_{29}$, -OSO_2R_{30}, -SO_3R_{31} oder -Si$(R_{32})_3$;

R_2 stellt dar Wasserstoff, Hydroxy, Halogen, Cyano, Nitro, C_{1-4}-Haloalkyl, C_{1-6}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{3-7}-Cycloalkyl, C_{6-10}-Aryl C_{1-4}-Alkyl, -OR_5, -NR_6R_7, -$(CR_8R_9)_nZ_1$, -C(O)$NR_{12}R_{13}$, -SR_{14}, -SOR_{15}, -SO_2R_{16}, -$NR_{17}SO_2R_{18}$, COOH, C_{6-10}-Aryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe Q, -COR_{19}, -$COOR_{20}$, -OC(O)R_{21}, -NR_{22}C(O)R_{23}, -NR_{24}C(S)R_{25}, -C(S)$NR_{26}R_{27}$, -$SO_2NR_{28}R_{29}$, -OSO_2R_3, -SO_3R_{31} oder -Si$(R_{32})_3$; oder

R_1 und R_2 zusammen mit einem Atom, das daran gebunden ist, bilden 3-bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl, wobei das Heterocyclyl oder Heteroaryl optional durch Halogen substituiert ist;

R_3 stellt Wasserstoff, C_{1-5}-Alkyl, C_{6-10}-Aryl, C_{1-6}-Alkyl oder C_{1-4}-Haloalkyl dar;

R_4 stellt Wasserstoff, Halogen, C_{1-3}-Alkyl, C_{1-4}-Haloalkyl, Hydroxy, Cyano, Nitro, C_{1-4}-Alkoxy, -$(CH_2)_nZ_1$, -NR_6R_7, -OR_5, -C(O)$NR_{12}R_{13}$, -SR_{14}, -SOR_{15}, -SO_2R_{16}, $NR_{17}SO_2R_{18}$, COOH, -COR_{19}, -$COOR_{20}$, -OC(O)R_{21}, -NR_{22}C(O)R_{23}, -NR_{24}C(S)R_{25}, -C(S)$NR_{26}R_{27}$, -$SO_2NR_{28}R_{29}$, -OSO_2R_{30}, -SO_3R_{31} oder -Si$(R_{32})_3$ dar;

A stellt einen 5- bis 10-gliedrigen Heteroarylring oder einen C_{6-10}-Arylring dar;

R_5 stellt C_{1-5}-Alkyl, C_{3-7}-Cycloalkyl, C_{3-7}-Cycloalkyl-C_{1-3}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxy-C_{1-4}-Alkyl, C_{1-3}-Alkoxy-C_{1-4}-Alkoxy-C_{1-4}-Alkyl, C_{1-4}-Aminoalkyl, C_{1-4}-Alkylamino-C_{1-4}-Alkyl, Di(C_{1-4}-Alkyl)amino-C_{1-4}-Alkyl, C_{6-10}-Aryl, C_{6-10}-Aryl-C_{1-3}-Alkyl oder 3- bis 10-gliedriges Heterocyclyl-C_{1-3}-Alkyl, 3- bis 10-gliedriges Heterocyclyl, 5- bis 10-gliedriges Heteroaryl, 5- bis 10-gliedriges Heteroaryl-C_{1-3}-Alkyl, C_{1-6}-Monohydroxyalkyl, C_{1-6}-Dihydroxyalkyl oder C_{1-6}-Trihydroxyalkyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q, dar;

R_6 und R_7, die die gleichen oder verschieden sein können, stellen jeweils Wasserstoff, C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxy-C_{1-4}-Alkyl, C_{6-10}-Aryl-C_{1-3}-Alkyl, 3- bis 10-gliedriges Heterocyclyl-C_{1-3}-Alkyl, 5- bis 10-gliedriges Heteroaryl-C_{1-3}-Alkyl, C_{1-6}-Monohydroxyalkyl, C_{1-6}-Dihydroxyalkyl, C_{1-6}-Trihydroxyalkyl, 3- bis 10-gliedriges Heterocyclyl, C_{1-4}-Aminoalkyl, C_{1-4}-Alkylamino-C_{1-4}-Alkyl, Di(C_{1-4}-Alkyl)amino-C_{1-4}-Alkyl oder Cyano(C_{1-3}-Alkyl) dar; oder R_6 und R_7 bilden alternativ dazu zusammen mit einem Stickstoffatom, das daran gebunden ist, 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl;

n stellt 1 bis 3 dar;

R_8 und R_9, die die gleichen oder verschieden sein können, stellen jeweils Wasserstoff, C_{1-4}-Alkyl oder Halogen dar; oder R_8 und R_9 bilden alternativ dazu zusammen mit einem Kohlenstoffatom, das daran gebunden ist, einen cylcoaliphatischen Ring;

Z_1 stellt Wasserstoff, $NR_{10}R_{11}$, -OH oder 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q, dar;

R_{10} und R_{11}, die die gleichen oder verschieden sein können, stellen jeweils C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxy-C_{1-4}-Alkyl, Cyano(C_{1-3}-Alkyl) oder C_{1-3}-Alkylsulfonyl-C_{1-4}-Alkyl dar; oder R_{10} und R_{11} bilden alternativ dazu zusammen mit einem Stickstoffatom, das daran gebunden ist, 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl;

R_{12} und R_{13}, die die gleichen oder verschieden sein können, stellen jeweils Wasserstoff, C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxy-C_{1-4}-Alkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl, 3- bis 10-gliedriges Heterocyclyl, C_{6-10}-Aryl-C_{1-4}-Alkyl, 3- bis 10-gliedriges Heterocyclyl-C_{1-3}-Alkyl, 5- bis 10-gliedriges Heteroaryl-C_{1-3}-Alkyl, Cyano(C_{1-3}-Alkyl), C_{1-3}-Alkylsulfonyl-C_{1-4}-Alkyl, einen 3- bis 10-gliedrigen cycloaliphatischen Ring, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar; oder R_{12} und R_{13} bilden alternativ dazu zusammen mit einem Stickstoffatom, das daran gebunden ist, 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q;

R_{14} stellt C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, oder 5- bis 10-gliedriges Heteroaryl oder 3-bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q, dar;

R_{15} stellt C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, oder 5- bis 10-gliedriges Heteroaryl oder 3-bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q, dar;

R_{16} stellt C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, das optional durch eine oder mehrere

Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, oder 5- bis 10-gliedriges Heteroaryl oder 3-bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q, dar;

R_{17} stellt Wasserstoff oder C_{1-4}-Alkyl dar;

R_{18} stellt C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe P, oder 5- bis 10-gliedriges Heteroaryl oder 3-bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus Gruppe Q, dar;

R_{19} stellt Wasserstoff, C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl oder 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl, das optional durch eine oder mehrere Gruppen substituiert ist, unabhängig ausgewählt aus der Gruppe Q, dar;

R_{20} stellt C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{21} stellt C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{22} stellt Wasserstoff, C_{1-4}-Alkyl oder C_{1-4}-Haloalkyl dar;

R_{23} stellt Wasserstoff, C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{24} stellt Wasserstoff, C_{1-4}-Alkyl oder C_{1-4}-Haloalkyl dar;

R_{25} stellt C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{26} und R_{27}, die die gleichen oder verschieden sein können, stellen jeweils Wasserstoff, C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxyl-C_{1-4}-Alkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl, 3- bis 10-gliedriges Heterocyclyl, C_{6-10}-Aryl-C_{1-4}-Alkyl, 3- bis 10-gliedriges Heterocyclyl-C_{1-3}-Alkyl, 5- bis 10-gliedriges Heteroaryl-C_{1-3}-Alkyl, Cyano(C_{1-3}-Alkyl), C_{1-3}-Alkylsulfonyl-C_{1-4}-Alkyl oder einen 3- bis 10-gliedrigen cycloaliphatischen Ring dar; oder R_{26} und R_{27} bilden alternativ dazu zusammen mit einem Stickstoffatom, das daran gebunden ist, 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl;

R_{28} und R_{29}, die die gleichen oder verschieden sein können, stellen jeweils Wasserstoff, C_{1-4}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{1-4}-Haloalkyl, C_{1-3}-Alkoxyl-C_{1-4}-Alkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl, 3- bis 10-gliedriges Heterocyclyl, C_{6-10}-Aryl-C_{1-4}-Alkyl, 3- bis 10-gliedriges Heterocyclyl-C_{1-3}-Alkyl, 5- bis 10-gliedriges Heteroaryl-C_{1-3}-Alkyl, Cyano(C_{1-3}-Alkyl), C_{1-3}-Alkylsulfonyl-C_{1-4}Alkyl oder einen 3- bis 10-gliedrigen cycloaliphatischen Ring dar; oder R_{28} und R_{29} bilden alternativ dazu zusammen mit einem Stickstoffatom, das daran gebunden ist, 3- bis 10-gliedriges Heterocyclyl oder 5- bis 10-gliedriges Heteroaryl;

R_{30} stellt C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{31} stellt C_{1-4}-Alkyl, C_{3-7}-Cycloalkyl, C_{1-4}-Haloalkyl, C_{6-10}-Aryl, 5- bis 10-gliedriges Heteroaryl oder 3- bis 10-gliedriges Heterocyclyl dar;

R_{32} stellt C_{1-4}-Alkyl oder C_{6-10}-Aryl dar;

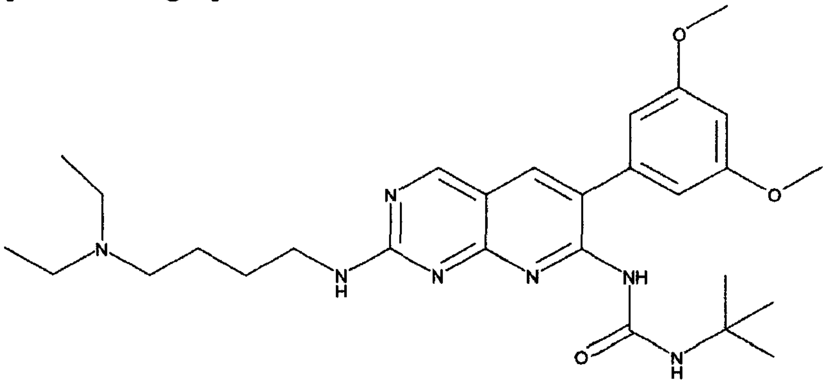
<Gruppe P>

Halogen, C_{1-4}-Alkyl, C_{1-4}-Haloalkyl, -OH, C_{1-3}-Alkoxy, C_{1-3}-Haloalkoxy, 3- bis 10-gliedriges Heterocyclylamino, $-SO_2R_{16}$, -CN, $-NO_2$ und 3- bis 10-gliedriges Heterocyclyl;

<Gruppe Q>

Halogen, C_{1-4}-Alkyl, C_{1-4}-Haloalkyl, -OH, C_{1-3}-Alkoxy, C_{1-6}-Monohydroxyalkyl, C_{1-6}-Dihydroxyalkyl, C_{1-6}-Trihydroxyalkyl, 3- bis 10-gliedriges Heterocyclylamin, $-SO_2R_{16}$, -CN, $-NO_2$, C_{3-7}-Cycloalkyl, $-COR_{19}$ und 3- bis 10-gliedriges Heterocyclyl, das optional durch C_{1-4}-Alkyl substituiert ist;

[Verbindung 2]



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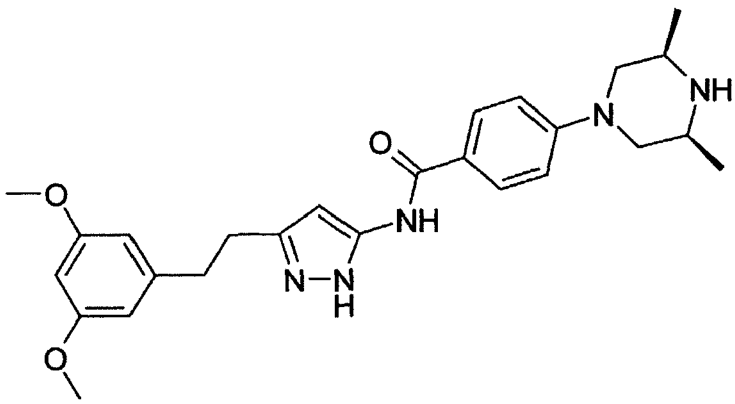
[Verbindung 3]



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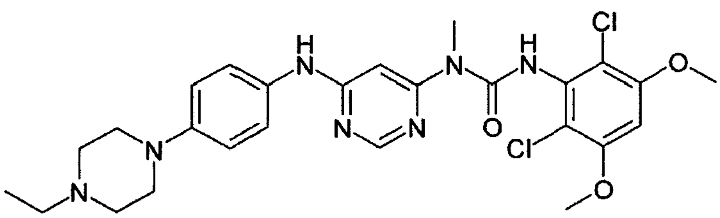
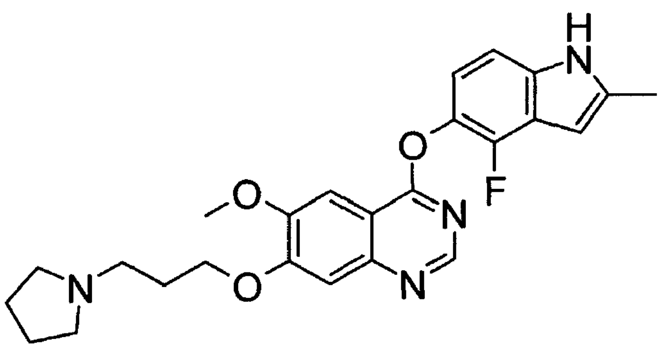
[Verbindung 4]



[Verbindung 5]



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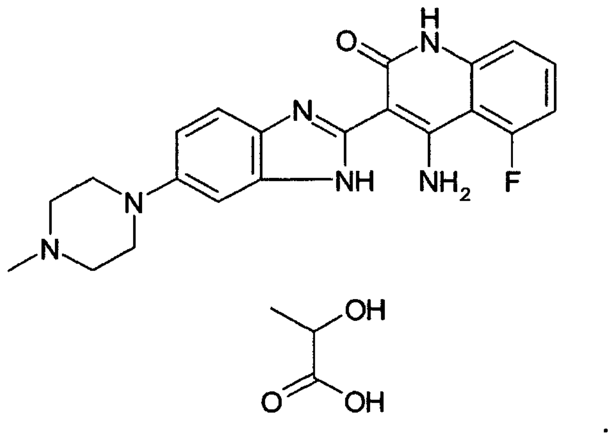
oder

[Verbindung 6]



6. Verfahren zum Testen der Empfindlichkeit eines Subjekts gegenüber Krebs, ob ein Subjekt von Krebs betroffen ist oder ob der Krebs in einem Subjekt fortgeschritten ist, insbesondere ob der Krebs Blasenkrebs, Hirntumor, Plattenepithelkarzinom des Kopf-/Halsbereiches, Lungenkrebs, Lungenadenokarzinom, Plattenepithelkarzinom der Lunge, Hautmelanom, Ösophaguskrebs, Magenkrebs oder Leberkrebs ist, durch Bestimmen der Anwesenheit oder Abwesenheit eines Fusionspolypeptids, umfassend ein FGFR3-Polypeptid und ein BAIAP2L1-Polypeptid, oder Bestimmen der Anwesenheit oder Abwesenheit eines Polynukleotids, kodierend ein Fusionspolypeptid, umfassend ein FGFR3-Polypeptid und ein BAIAP2L1-Polypeptid, in einer Probe, die von dem Subjekt isoliert ist,
wobei das FGFR3-Polypeptid das gesamte oder ein Teil eines Wildtyp-Polypeptids ist, bestehend aus der Aminosäuresequenz von SEQ ID NR: 6 oder 7,
wobei das BAIAP2L1-Polypeptid das gesamte oder ein Teil eines Wildtyp-Polypeptids ist, bestehend aus der Aminosäuresequenz von SEQ ID NR: 8, und
wobei das Verfahren auf dem Kriterium basiert, dass ein Subjekt wahrscheinlicher Krebs entwickeln wird, von Krebs betroffen ist oder fortgeschrittenen Krebs hat, wenn das Fusionspolypeptid oder Polynukleotid, das das Fusionspolypeptid kodiert, nachgewiesen wird.

7. Fusionspolypeptid, umfassend ein FGFR3-Polypeptid und ein BAIAP2L1-Polypeptid:

   wobei das FGFR3-Polypeptid das gesamte oder ein Teil eines Wildtyp-Polypeptids ist, bestehend aus der Aminosäuresequenz von SEQ ID NR: 6 oder 7, und
   das BAIAP2L1-Polypeptid das gesamte oder ein Teil eines Wildtyp-Polypeptids ist, bestehend aus der Aminosäuresequenz von SEQ ID NR: 8, insbesondere wobei das Fusionspolypeptid von Blasenkrebs oder Lungenkrebs stammt, spezifischer wobei das Fusionspolypeptid aus der Aminosäuresequenz von SEQ ID NR: 32 oder 38 besteht.

8. Polynukleotid, kodierend das Fusionspolypeptid von Anspruch 7, insbesondere wobei das Polynukleotid die Nukleotidsequenz von SEQ ID NR: 16 umfasst, spezifischer wobei das Polynukleotid die Nukleotidsequenz von SEQ ID NR: 31 oder 37 umfasst, oder ein Vektor, umfassend das Polynukleotid.

9. Rekombinante Zelle, umfassend den Vektor von Anspruch 8.

10. Verfahren zum Nachweis

   (a) eines Fusionspolypeptids, das ein FGFR3-Polypeptid und ein BAIAP2L1-Polypeptid umfasst, das den Schritt des Nachweisens des Fusionspolypeptids in einer Probe, die von einem Subjekt isoliert ist, unter Verwendung eines Antikörpers oder Antigenbindenden Fragments davon, der oder das an das Fusionspolypeptid von Anspruch 7 bindet, umfasst, oder
   (b) eines Polynukleotids, kodierend ein Fusionspolypeptid, das ein FGFR3-Polypeptid und ein BAIAP2L1-Polypeptid umfasst, das den Schritt des Nachweisens eines Polynukleotids, kodierend das Fusionspolypeptid, in

einer Probe, die von einem Subjekt isoliert ist, unter Verwendung eines Paars an Oligonukleotidprimern, bestehend aus Sinn- und Antisinn-Primern, die jeweils an ein Polynukleotid, kodierend das Fusionspolypeptid von Anspruch 7, hybridisieren, zum Nachweis oder Amplifizieren des Polynukleotids umfasst.

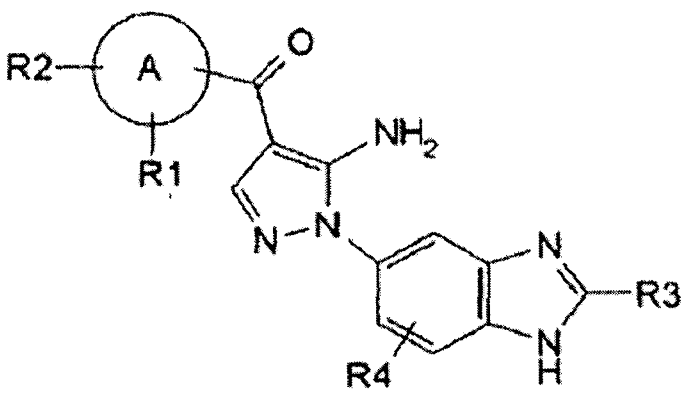
Revendications

1. Composé doté d'une activité inhibitrice du FGFR ou l'un de ses sels pharmaceutiquement acceptables pour une utilisation dans un procédé de traitement ou de prévention du cancer chez un patient qui a été identifié comme exprimant un polypeptide de fusion comprenant un polypeptide FGFR3 et un polypeptides BAIAP2L1 ou portant un polynucléotide codant pour le polypeptide de fusion,
le polypeptide FGFR3 consistant en la totalité ou une partie d'un polypeptide de type sauvage constitué de la séquence d'acides aminés de la SEQ ID NO : 6 ou 7,
le polypeptide BAIAP2L1 consistant en la totalité ou une partie d'un polypeptide de type sauvage constitué de la séquence d'acides aminés de la SEQ ID NO : 8, et
où le composé ou l'un de ses sels pharmaceutiquement acceptables est capable d'inhiber la croissance d'une cellule cancéreuse exprimant le polypeptide de fusion ou comportant un nucléotide codant pour le polypeptide de fusion.

2. Composé ou l'un de ses sels pharmaceutiquement acceptables pour une utilisation dans un procédé de traitement ou de prévention du cancer chez un patient selon la revendication 1, où le cancer est un cancer de la vessie, une tumeur cérébrale, un carcinome à cellules squameuses de la tête et du cou, un cancer du poumon, un adénocarcinome du poumon, un carcinome à cellules squameuses du poumon, un mélanome cutané, un cancer oesophagien, un cancer gastrique, ou un cancer du foie, en particulier un cancer de la vessie.

3. Composé ou l'un de ses sels pharmaceutiquement acceptables pour une utilisation dans un procédé de traitement ou de prévention du cancer chez un patient selon la revendication 1 ou 2, où le composé doté d'une activité inhibitrice du FGFR ou l'un de ses sels pharmaceutiquement acceptables est l'un quelconque des composés ou l'un de leurs sels pharmaceutiquement acceptables représentés par :

[Composé 1]



(1)

dans lequel R_1, R_2, R_3, et R_4 représentent chacun indépendamment le groupe énuméré ci-dessous :

R_1 représente un atome d'hydrogène, un groupe hydroxy, halogéno, cyano, nitro, halogénoalkyle en C_1 à C_4, alkyle en C_1 à C_6, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, cycloalkyle en C_3 à C_7, aryle en C_6 à C_{10}-alkyle en C_1 à C_4, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, ou $-Si(R_{32})_3$;
R_2 représente un atome d'hydrogène, un groupe hydroxy, halogéno, cyano, nitro, halogénoalkyle en C_1 à C_4, alkyle en C_1 à C_6, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, cycloalkyle en C_3 à C_7, aryle en C_6 à C_{10}-alkyle en C_1 à C_4, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$,

COOH, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, ou $-Si(R_{32})_3$; ou

R_1 et R_2, conjointement avec un atome qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal, où le groupe hétéro-cyclyle ou hétéroaryle est éventuellement substitué par un atome d'halogène ;

R_3 représente un atome d'hydrogène, un groupe alkyle en C_1 à C_5, aryle en C_6 à C_{10}-alkyle en C_1 à C_6, ou halogénoalkyle en C_1 à C_4 ;

R_4 représente un atome d'hydrogène, d'halogène, un groupe alkyle en C_1 à C_3, halogénoalkyle en C_1 à C_4, hydroxy, cyano, nitro, alkoxy en C_1 à C_4, $-(CH_2)_nZ_1$, $-NR_6R_7$, $-OR_5$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, -C (S) $NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, ou $-Si(R_{32})_3$;

A représente un noyau hétéroaryle penta- à décagonal ou un noyau aryle en C_6 à C_{10} ;

R_5 représente un groupe alkyle en C_1 à C_5, cycloalkyle en C_3 à C_7, cycloalkyle en C_3 à C_7-alkyle en C_1 à C_3, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkoxy en C_1 à C_4-alkyle en C_1 à C_4, aminoalkyle en C_1 à C_4, alkyle en C_1 à C_4-amino-alkyle en C_1 à C_4, di (alkyle en C_1 à C_4)amino-alkyle en C_1 à C_4, aryle en C_6 à C_{10}, aryle en C_6 à C_{10}-alkyle en C_1 à C_3, ou hétérocyclyle tri- à décagonal-alkyle en C_1 à C_3, hétérocyclyle tri- à décagonal, hétéroaryle penta- à décagonal, hétéroaryle penta- à décagonal-alkyle en C_1 à C_3, monohydroxy-alkyle en C_1 à C_6, dihydroxy-alkyle en C_1 à C_6, ou trihydroxy-alkyle en C_1 à C_6 qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_6 et R_7, qui peuvent être identiques ou différents, représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkyle en C_1 à C_4, aryle en C_6 à C_{10}-alkyle en C_1 à C_3, hétérocyclyle tri- à décagonal-alkyle en C_1 à C_3, hétéroaryle penta- à décagonal-alkyle en C_1 à C_3, monohydroxy-alkyle en C_1 à C_6, dihydroxy-alkyle en C_1 à C_6, trihydroxy-alkyle en C_1 à C_6, hétérocyclyle tri- à décagonal, aminoalkyle en C_1 à C_4, alkyle en C_1 à C_4-amino-alkyle en C_1 à C_4, di (alkyle en C_1 à C_4) amino-alkyle en C_1 à C_4, ou cyano (alkyle en C_1 à C_3) ; ou en variante, R_6 et R_7, conjointement avec un atome d'azote qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal ;

n représente 1 à 3 ;

R_8 et R_9, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle en C_1 à C_4, ou halogéno ; ou en variante, R_8 et R_9, conjointement avec un atome de carbone qui leur est lié, forment un noyau cycloaliphatique ;

Z_1 représente un atome d'hydrogène, un groupe $NR_{10}R_{11}$, -OH, ou hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{10} et R_{11}, qui peuvent être identiques ou différents, représentent chacun un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkyle en C_1 à C_4, cyano(alkyle en C_1 à C_3), ou alkyle en C_1 à C_3-sulfonyl-alkyle en C_1 à C_4 ; ou en variante, R_{10} et R_{11}, conjointement avec un atome d'azote qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal ;

R_{12} et R_{13}, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkyle en C_1 à C_4, aryle en C_6 à C_{10}, hétéroaryle penta- à décagonal, hétérocyclyle tri- à décagonal, aryle en C_6 à C_{10}-alkyle en C_1 à C_4, hétérocyclyle tri- à décagonal-alkyle en C_1 à C_3, hétéroaryle penta- à décagonal-alkyle en C_1 à C_3, cyano(alkyle en C_1 à C_3), alkyle en C_1 à C_3-sulfonyl-alkyle en C_1 à C_4, un noyau aliphatique tri- à décagonal, hétéroaryle penta- à décagonal, ou hétérocyclyle tri- à décagonal ; ou en variante, R_{12} et R_{13}, conjointement avec un atome d'azote qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{14} représente un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{15} représente un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1

à C_4, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{16} représente un groupe alkyle en C_1 à C_9, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{17} représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ;

R_{18} représente un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{19} représente un atome d'hydrogène, un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{20} représente un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{21} représente un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{22} représente un atome d'hydrogène, un groupe alkyle en C_1 à C_4, ou halogénoalkyle en C_1 à C_4 ;

R_{23} représente un atome d'hydrogène, un groupe alkyle en C_1 à C_9, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{24} représente un atome d'hydrogène, un groupe alkyle en C_1 à C_4, ou halogénoalkyle en C_1 à C_9 ;

R_{25} représente un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_9, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{26} et R_{27}, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkyle en C_1 à C_9, aryle en C_6 à C_{10}, hétéroaryle penta- à décagonal, hétérocyclyle tri- à décagonal, aryle en C_6 à C_{10}-alkyle en C_1 à C_4, hétérocyclyle tri- à décagonal-alkyle en C_1 à C_3, hétéroaryle penta- à décagonal-alkyle en C_1 à C_3, cyano(alkyle en C_1 à C_3), alkyle en C_1 à C_3-sulfonyl-alkyle en C_1 à C_4, ou un noyau aliphatique tri- à décagonal ; ou en variante, R_{26} et R_{27}, conjointement avec un atome d'azote qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal ;

R_{28} et R_{29}, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_9, alkoxy en C_1 à C_3-alkyle en C_1 à C_4, aryle en C_6 à C_{10}, hétéroaryle penta- à décagonal, hétérocyclyle tri- à décagonal, aryle en C_6 à C_{10}-alkyle en C_1 à C_4, hétérocyclyle tri- à décagonal-alkyle en C_1 à C_3, hétéroaryle penta- à décagonal-alkyle en C_1 à C_3, cyano(alkyle en C_1 à C_3), alkyle en C_1 à C_3-sulfonyl-alkyle en C_1 à C_4, ou un noyau aliphatique tri- à décagonal ; ou en variante, R_{28} et R_{29}, conjointement avec un atome d'azote qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal ;

R_{30} représente un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{31} représente un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{32} représente un groupe alkyle en C_1 à C_4, ou aryle en C_6 à C_{10} ;

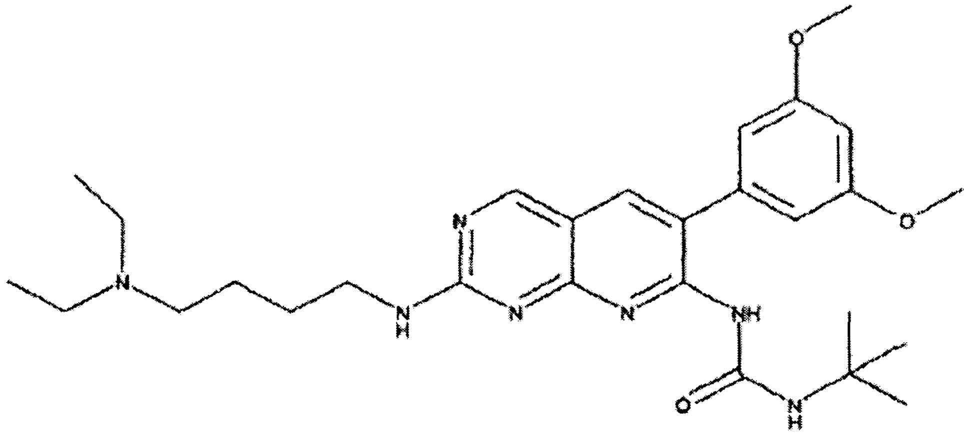
<groupe P>

un atome d'halogène, les groupes alkyle en C_1 à C_4, halogénoalkyle en C_1 à C_4, -OH, alkoxy en C_1 à C_3, halogéno-alkoxy en C_1 à C_3, hétérocyclyle tri- à décagonal-amino, - SO_2R_{16}, -CN, $-NO_2$, et hétérocyclyle tri- à décagonal ;

<groupe Q>

un atome d'halogène, les groupes alkyle en C_1 à C_4 halogénoalkyle en C_1 à C_4, -OH, alkoxy en C_1 à C_3, mono-hydroxy-alkyle en C_1 à C_6, dihydroxy-alkyle en C_1 à C_6 trihydroxy-alkyle en C_1 à C_6, hétérocyclyle tri-décagonal-amine, $-SO_2R_{16}$, -CN, $-NO_2$, cycloalkyle en C_3 à C_7 $-COR_{19}$, et hétérocyclyle tri- à décagonal qui est éventuellement substitué par un groupe alkyle en C_1 à C_4 ;

[Composé 2]



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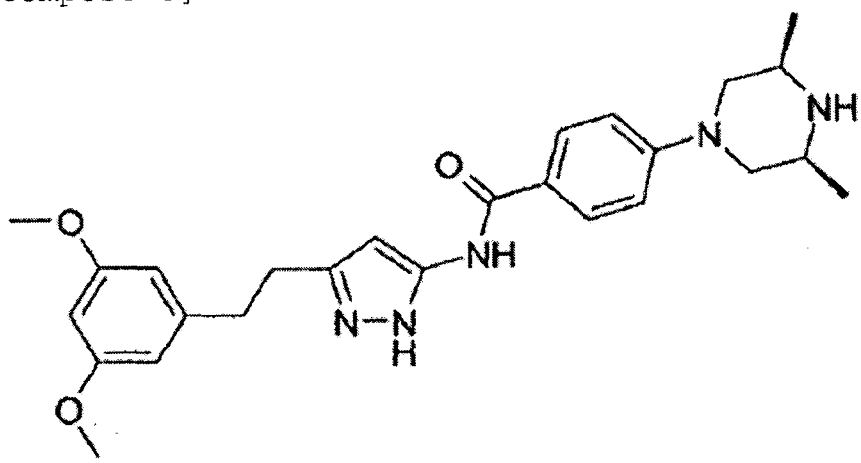
[Composé 3]



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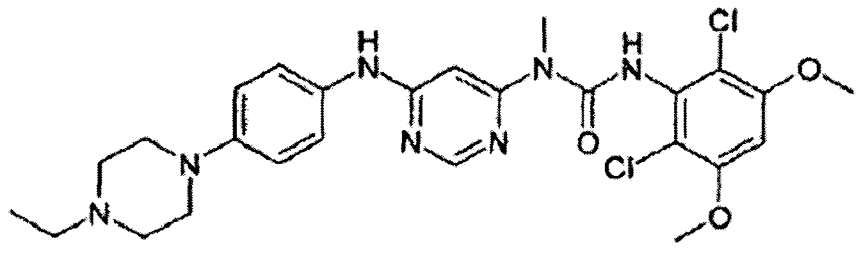
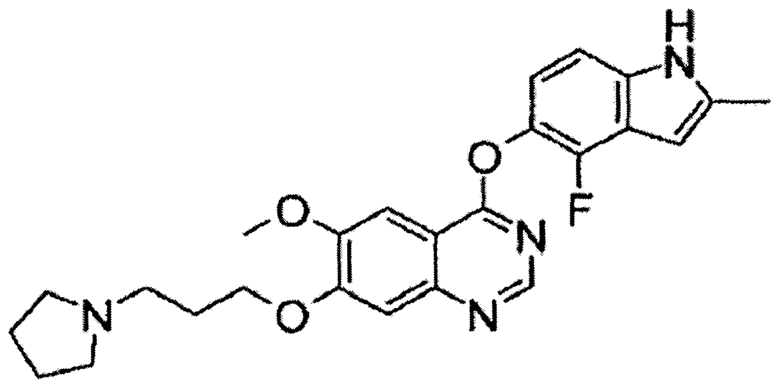
[Composé 4]



[Composé 5]



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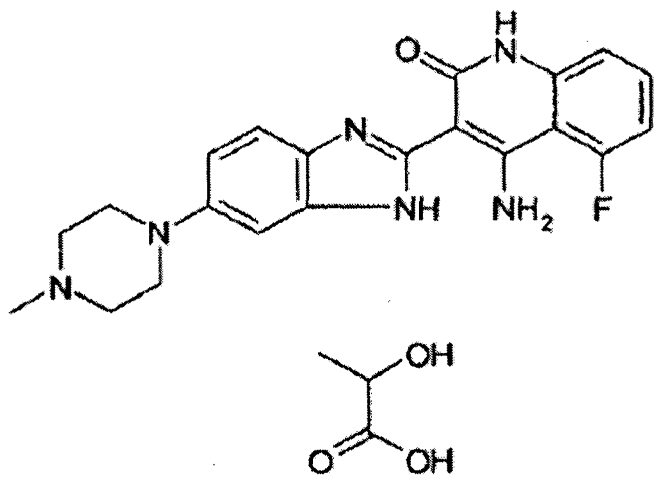
ou

[Composé 6]



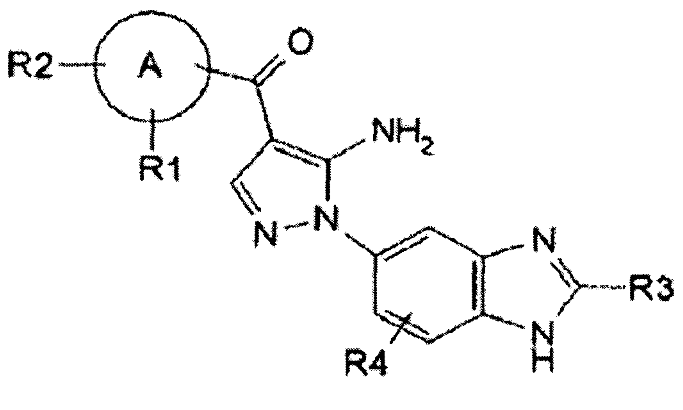
4. Procédé de sélection d'un patient, en particulier d'un patient souffrant d'un cancer de la vessie, d'une tumeur cérébrale, d'un carcinome à cellules squameuses de la tête et du cou, d'un cancer du poumon, d'un adénocarcinome du poumon, d'un carcinome à cellules squameuses du poumon, d'un mélanome cutané, d'un cancer oesophagien, d'un cancer gastrique, ou d'un cancer du foie, auquel un agent anticancéreux comprenant un composé doté d'une activité inhibitrice du FGFR ou l'un de ses sels pharmaceutiquement acceptables est applicable, qui comprend les étapes suivantes :

(a) la détermination de la présence ou de l'absence d'un polypeptide de fusion comprenant un polypeptide FGFR3 et un polypeptide BAIAP2L1 ou d'un polynucléotide codant pour un polypeptide de fusion comprenant un polypeptide FGFR3 et un polypeptide BAIAP2L1 dans un échantillon isolé d'un sujet,
le polypeptide FGFR3 consistant en la totalité ou une partie d'un polypeptide de type sauvage constitué de la séquence d'acides aminés de la SEQ ID NO : 6 ou 7, et
le polypeptide BAIAP2L1 consistant en la totalité ou une partie d'un polypeptide de type sauvage constitué de la séquence d'acides aminés de la SEQ ID NO : 8 ; et
(b) la sélection d'un patient confirmé comme ayant le polypeptide de fusion ou le polynucléotide en tant que patient auquel l'agent anticancéreux est applicable,
dans lequel le composé ou l'un de ses sels pharmaceutiquement acceptable est capable d'inhiber la croissance d'une cellule cancéreuse exprimant le polypeptide de fusion ou comportant un nucléotide codant pour le polypeptide de fusion.

5. Procédé selon la revendication 4, dans lequel le composé doté d'une activité inhibitrice du FGFR ou l'un de ses

sels pharmaceutiquement acceptables est l'un quelconque des composés ou l'un de leurs sels pharmaceutiquement acceptables représentés par :

[Composé 1]



(I)

dans lequel R_1, R_2, R_3, et R_4 représentent chacun indépendamment le groupe énuméré ci-dessous :

R_1 représente un atome d'hydrogène, un groupe hydroxy, halogéno, cyano, nitro, halogénoalkyle en C_1 à C_4, alkyle en C_1 à C_6, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, cycloalkyle en C_3 à C_7, aryle en C_6 à C_{10}-alkyle en C_1 à C_4, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-MR_{17}SO_2R_{18}$, COOH, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, ou $-Si(R_{32})_3$;

R_2 représente un atome d'hydrogène, un groupe hydroxy, halogéno, cyano, nitro, halogénoalkyle en C_1 à C_4, alkyle en C_1 à C_6, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, cycloalkyle en C_3 à C_7, aryle en C_6 à C_{10}-alkyle en C_1 à C_4, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, ou $-Si(R_{32})_3$; ou

R_1 et R_2, conjointement avec un atome qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal, où le groupe hétéro-cyclyle ou hétéroaryle est éventuellement substitué par un atome d'halogène ;

R_3 représente un atome d'hydrogène, un groupe alkyle en C_1 à C_5, aryle en C_6 à C_{10}-alkyle en C_1 à C_6, ou halogénoalkyle en C_1 à C_4 ;

R_4 représente un atome d'hydrogène, d'halogène, un groupe alkyle en C_1 à C_3, halogénoalkyle en C_1 à C_4, hydroxy, cyano, nitro, alkoxy en C_1 à C_4, $-(CH_2)_nZ_1$, $-NR_6R_7$, $-OR_5$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, ou $-Si(R_{32})_3$;

A représente un noyau hétéroaryle penta- à décagonal ou un noyau aryle en C_6 à C_{10} ;

R_5 représente un groupe alkyle en C_1 à C_5, cycloalkyle en C_3 à C_7, cycloalkyle en C_3 à C_7-alkyle en C_1 à C_3, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkyle en C_1 à C_9, alkoxy en C_1 à C_3-alkoxy en C_1 à C_4-alkyle en C_1 à C_4, aminoalkyle en C_1 à C_4, alkyle en C_1 à C_4-amino-alkyle en C_1 à C_4, di (alkyle en C_1 à C_4)amino-alkyle en C_1 à C_4, aryle en C_6 à C_{10}, aryle en C_6 à C_{10}-alkyle en C_1 à C_3, ou hétérocyclyle tri- à décagonal-alkyle en C_1 à C_3, hétérocyclyle tri- à décagonal, hétéroaryle penta- à décagonal, hétéroaryle penta- à décagonal-alkyle en C_1 à C_3, monohydroxy-alkyle en C_1 à C_6, dihydroxy-alkyle en C_1 à C_6, ou trihydroxy-alkyle en C_1 à C_6 qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_6 et R_7, qui peuvent être identiques ou différents, représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkyle en C_1 à C_4, aryle en C_6 à C_{10}-alkyle en C_1 à C_3, hétérocyclyle tri- à décagonal-alkyle en C_1 à C_3, hétéroaryle penta- à décagonal-alkyle en C_1 à C_3, monohydroxy-alkyle en C_1 à C_6, dihydroxy-alkyle en C_1 à C_6, ou trihydroxy-alkyle en C_1 à C_6, hétérocyclyle tri- à décagonal, aminoalkyle en C_1 à C_4, alkyle en C_1 à C_4-amino-alkyle en C_1 à C_4, di (alkyle en C_1 à C_4) amino-alkyle en C_1 à C_4, ou cyano (alkyle en C_1 à C_3) ; ou en variante, R_6 et R_7, conjointement avec un atome d'azote qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal ;

n représente 1 à 3 ;

R_8 et R_9, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle en C_1 à C_4, ou halogéno ; ou en variante, R_8 et R_9, conjointement avec un atome de carbone qui leur est lié, forment un noyau cycloaliphatique ;

Z_1 représente un atome d'hydrogène, $NR_{10}R_{11}$, -OH, ou un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta-à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{10} et R_{11}, qui peuvent être identiques ou différents, représentent chacun un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkyle en C_1 à C_4, cyano (alkyle en C_1 à C_3) , ou alkyle en C_1 à C_3-sulfonyl-alkyle en C_1 à C_4 ; ou en variante, R_{10} et R_{11}, conjointement avec un atome d'azote qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal ;

R_{12} et R_{13}, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkyle en C_1 à C_4, aryle en C_6 à C_{10}, hétéroaryle penta- à décagonal, hétérocyclyle tri- à décagonal, aryle en C_6 à C_{10}-alkyle en C_1 à C_4, hétérocyclyle tri- à décagonal-alkyle en C_1 à C_3, hétéroaryle penta- à décagonal-alkyle en C_1 à C_3, cyano(alkyle en C_1 à C_3), alkyle en C_1 à C_3-sulfonyl-alkyle en C_1 à C_4, un noyau aliphatique tri- à décagonal, hétéroaryle penta- à décagonal, ou hétérocyclyle tri- à décagonal ; ou en variante, R_{12} et R_{13}, conjointement avec un atome d'azote qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{14} représente un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_9, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{15} représente un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{16} représente un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{17} représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ;

R_{18} représente un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10} qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe P, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{19} représente un atome d'hydrogène, un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal qui est éventuellement substitué par un ou plusieurs groupes choisis indépendamment dans le groupe Q ;

R_{20} représente un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{21} représente un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{22} représente un atome d'hydrogène, un groupe alkyle en C_1 à C_4, ou halogénoalkyle en C_1 à C_4 ;

R_{23} représente un atome d'hydrogène, un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{24} représente un atome d'hydrogène, un groupe alkyle en C_1 à C_4, ou halogénoalkyle en C_1 à C_9 ;

R_{25} représente un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{26} et R_{27}, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkyle en C_1 à C_4, aryle en C_6 à C_{10}, hétéroaryle penta- à décagonal, hétérocyclyle tri- à décagonal, aryle en C_6 à C_{10}-alkyle en C_1 à C_4, hétérocyclyle tri- à décagonal-alkyle en C_1 à C_3, hétéroaryle penta- à décagonal-alkyle en C_1 à C_3, cyano(alkyle en C_1 à C_3), alkyle en C_1 à C_3-sulfonyl-alkyle en C_1 à C_4, ou un noyau aliphatique tri- à décagonal ; ou en variante, R_{26} et R_{27}, conjointement avec un atome d'azote qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal ;

R_{28} et R_{29}, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle en C_1 à C_4, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, halogénoalkyle en C_1 à C_4, alkoxy en C_1 à C_3-alkyle en C_1 à C_4, aryle en C_6 à C_{10}, hétéroaryle penta- à décagonal, hétérocyclyle tri- à décagonal, aryle en C_6 à C_{10}-alkyle en C_1 à C_4, hétérocyclyle tri- à décagonal-alkyle en C_1 à C_3, hétéroaryle penta- à décagonal-alkyle en C_1 à C_3, cyano (alkyle en C_1 à C_3), alkyle en C_1 à C_3-sulfonyl-alkyle en C_1 à C_4, ou un noyau aliphatique tri- à décagonal ; ou en variante, R_{28} et R_{29}, conjointement avec un atome d'azote qui leur est lié, forment un groupe hétérocyclyle tri- à décagonal ou hétéroaryle penta- à décagonal ;

R_{30} représente un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_4, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{31} représente un groupe alkyle en C_1 à C_4, cycloalkyle en C_3 à C_7, halogénoalkyle en C_1 à C_9, aryle en C_6 à C_{10}, ou hétéroaryle penta- à décagonal ou hétérocyclyle tri- à décagonal ;

R_{32} représente un groupe alkyle en C_1 à C_4, ou aryle en C_6 à C_{10} ;

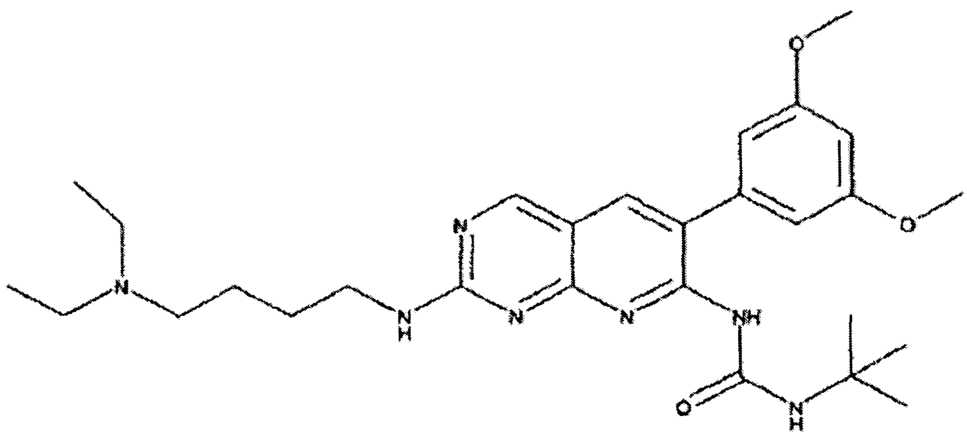
<groupe P>

un atome d'halogène, les groupes alkyle en C_1 à C_4, halogénoalkyle en C_1 à C_4, -OH, alkoxy en C_1 à C_3, halogéno-alkoxy en C_1 à C_3, hétérocyclyle tri- à décagonal-amino, - SO_2R_{16}, -CN, $-NO_2$, et hétérocyclyle tri- à décagonal ;

<groupe Q>

un atome d'halogène, les groupes alkyle en C_1 à C_4, halogénoalkyle en C_1 à C_4, -OH, alkoxy en C_1 à C_3, monohydroxy-alkyle en C_1 à C_6, dihydroxy-alkyle en C_1 à C_6, trihydroxy-alkyle en C_1 à C_6, hétérocyclyle tri- à décagonal-amine, $-SO_2R_{16}$, -CN, $-NO_2$, cycloalkyle en C_3 à C_7, $-COR_{19}$, et hétérocyclyle tri- à décagonal qui est éventuellement substitué par un groupe alkyle en C_1 à C_4 ;

[Composé 2]



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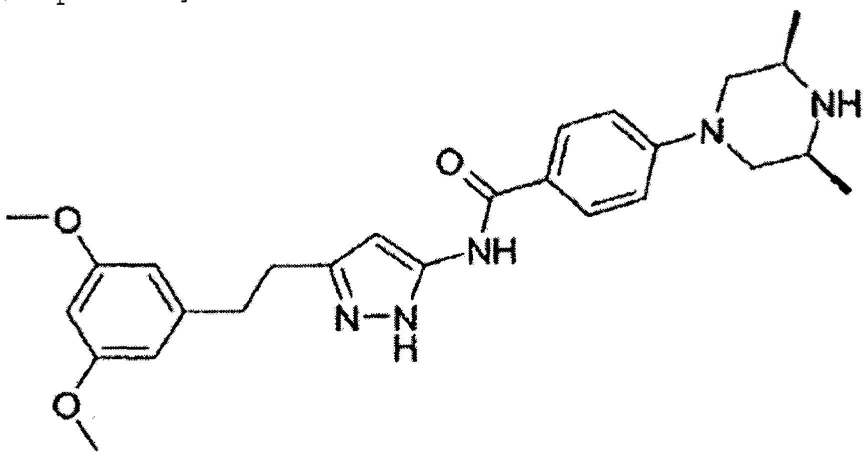
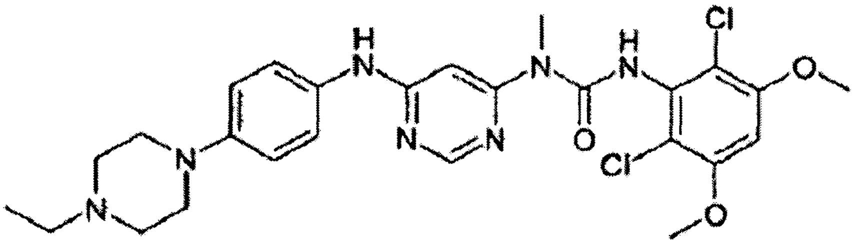
[Composé 3]

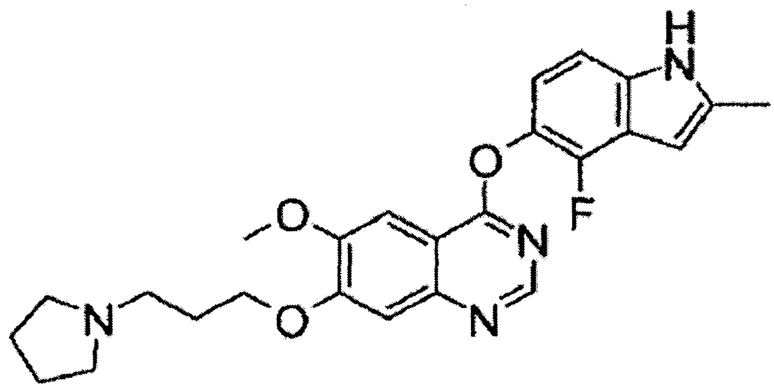


,

[Composé 4]



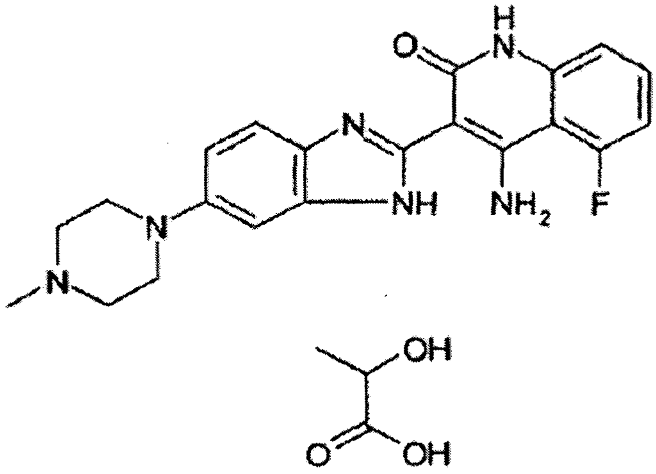
[Composé 5]



,

ou

[Composé 6]



6. Procédé d'analyse de la sensibilité à un cancer d'un sujet, qu'un sujet soit affecté par un cancer, ou que le cancer ait progressé chez un sujet, en particulier dans lequel le cancer est un cancer de la vessie, une tumeur cérébrale, un carcinome à cellules squameuses de la tête et du cou, un cancer du poumon, un adénocarcinome du poumon, un carcinome à cellules squameuses du poumon, un mélanome cutané, un cancer oesophagien, un cancer gastrique, ou un cancer du foie, par détermination de la présence ou de l'absence d'un polypeptide de fusion comprenant un polypeptide FGFR3 et un polypeptide BAIAP2L1 ou détermination de la présence ou de l'absence d'un polynucléotide codant pour un polypeptide de fusion comprenant un polypeptide FGFR3 et un polypeptide BAIAP2L1 dans un échantillon isolé du sujet,
le polypeptide FGFR3 consistant en la totalité ou une partie d'un polypeptide de type sauvage constitué de la séquence d'acides aminés de la SEQ ID NO : 6 ou 7,
le polypeptide BAIAP2L1 consistant en la totalité ou une partie d'un polypeptide de type sauvage constitué de la séquence d'acides aminés de la SEQ ID NO : 8 ; et
le procédé étant basé sur le critère qu'un sujet est plus susceptible de développer un cancer, est affecté par un cancer, ou souffre d'un cancer qui a progressé lorsque le polypeptide de fusion ou le polynucléotide codant pour le polypeptide de fusion est détecté.

7. Polypeptide de fusion comprenant un polypeptide FGFR3 et un polypeptide BAIAP2L1 ;
le polypeptide FGFR3 consistant en la totalité ou une partie d'un polypeptide de type sauvage constitué de la séquence d'acides aminés de la SEQ ID NO : 6 ou 7, et
le polypeptide BAIAP2L1 consistant en la totalité ou une partie d'un polypeptide de type sauvage constitué de la séquence d'acides aminés de la SEQ ID NO : 8, en particulier le polypeptide de fusion étant dérivé d'un cancer de la vessie ou d'un cancer du poumon, plus particulièrement le polypeptide de fusion étant constitué de la séquence d'acides aminés de la SEQ ID NO : 32 ou 38.

8. Polynucléotide codant pour le polypeptide de fusion selon la revendication 7, en particulier le polynucléotide comprenant la séquence nucléotidique de la SEQ ID NO : 16, plus particulièrement le polynucléotide comprenant la séquence nucléotidique de la SEQ ID NO : 31 ou 37, ou un vecteur comprenant ledit polynucléotide.

9. Cellule recombinante comprenant le vecteur selon la revendication 8.

10. Procédé de détection :

(a) d'un polypeptide de fusion qui comprend un polypeptide FGFR3 et un polypeptide BAIAP2L1, qui comprend l'étape de détection du polypeptide de fusion dans un échantillon isolé d'un sujet en utilisant un anticorps ou l'un de ses fragments de liaison d'antigène qui se lie au polypeptide de fusion selon la revendication 7, ou
(b) d'un polynucléotide codant pour un polypeptide de fusion qui comprend un polypeptide FGFR3 et un polypeptide BAIAP2L1, qui comprend l'étape de détection d'un polynucléotide codant pour le polypeptide de fusion dans un échantillon isolé d'un sujet en utilisant une paire d'amorces oligonucléotidiques constituées d'amorces sens et antisens s'hybridant chacune à un polynucléotide codant pour le polypeptide de fusion selon la reven-

dication 7 pour la détection ou l'amplification du polynucléotide.

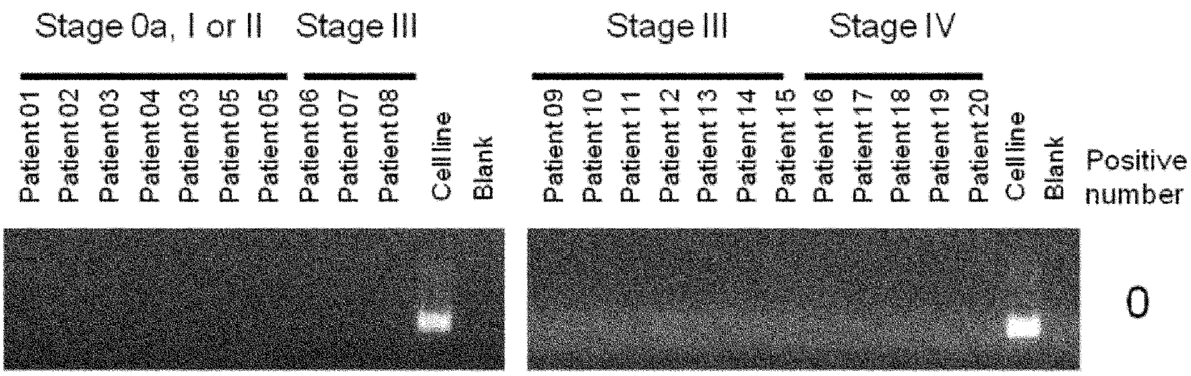

Stage 0a, I or II
Stage III
Stage III
Stage IV
Patient 01
Patient 02
Patient 03
Patient 04
Patient 03
Patient 05
Patient 05
Patient 06
Patient 07
Patient 08
Cell line
Blank
Patient 09
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Patient 15
Patient 16
Patient 17
Patient 18
Patient 19
Patient 20
Cell line
Blank
Positive number
0

FIG. 1

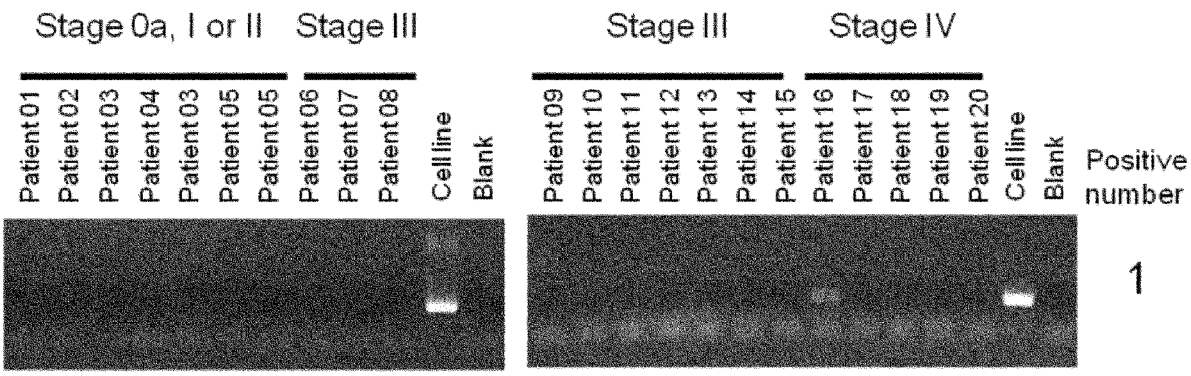

Stage 0a, I or II
Stage III
Stage III
Stage IV
Patient 01
Patient 02
Patient 03
Patient 04
Patient 03
Patient 05
Patient 05
Patient 06
Patient 07
Patient 08
Cell line
Blank
Patient 09
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Patient 15
Patient 16
Patient 17
Patient 18
Patient 19
Patient 20
Cell line
Blank
Positive number
1

FIG. 2

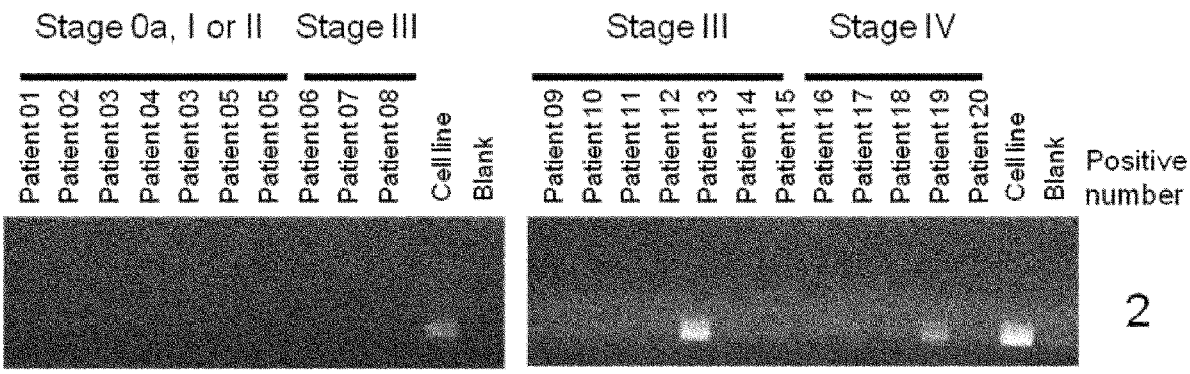
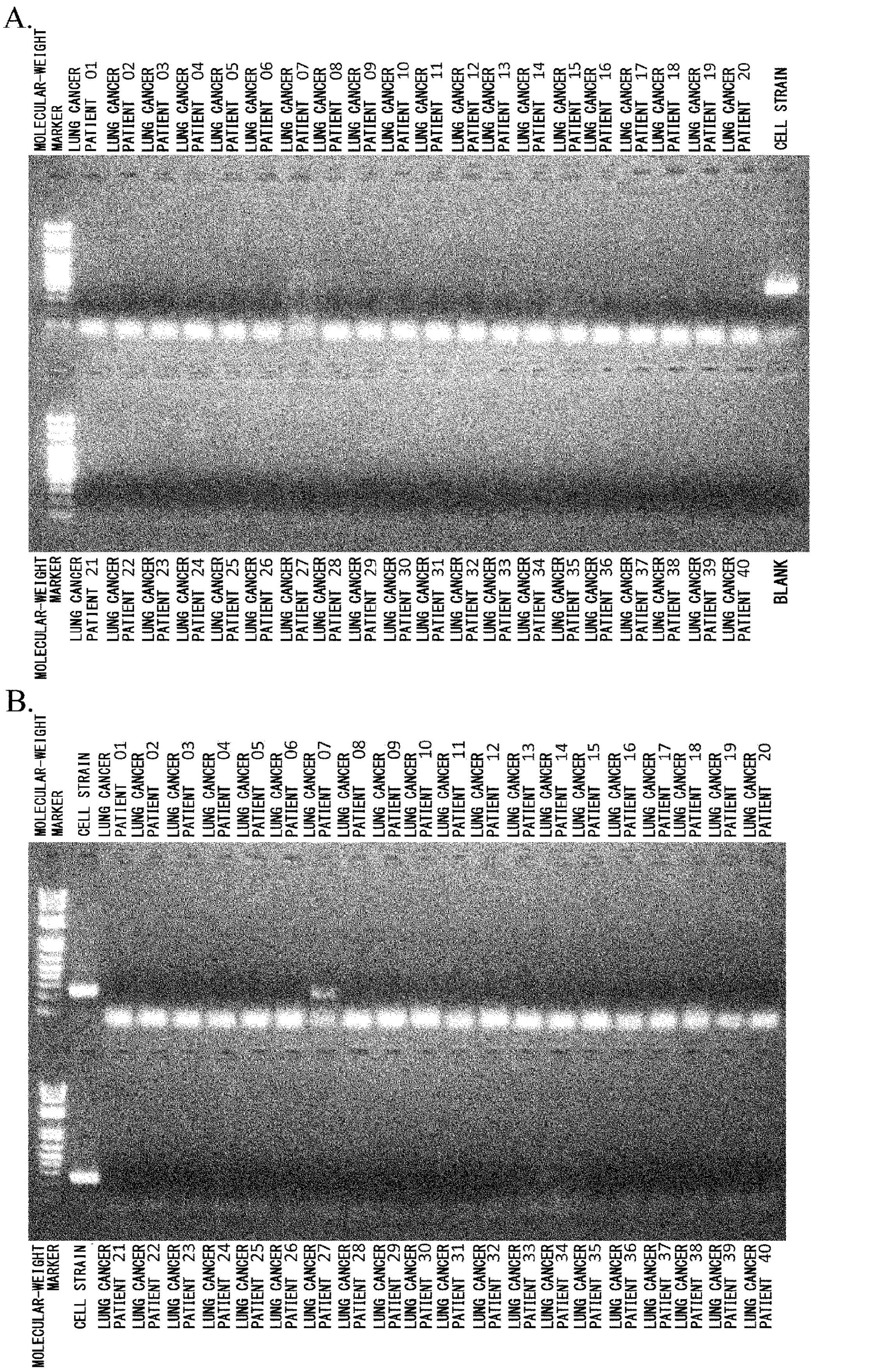

Stage 0a, I or II
Stage III
Patient 01
Patient 02
Patient 03
Patient 04
Patient 03
Patient 05
Patient 05
Patient 06
Patient 07
Patient 08
Cell line
Blank
Stage III
Stage IV
Patient 09
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Patient 15
Patient 16
Patient 17
Patient 18
Patient 19
Patient 20
Cell line
Blank
Positive number
2

FIG. 3


A.
MOLECULAR-WEIGHT MARKER
LUNG CANCER PATIENT 01
LUNG CANCER PATIENT 02
LUNG CANCER PATIENT 03
LUNG CANCER PATIENT 04
LUNG CANCER PATIENT 05
LUNG CANCER PATIENT 06
LUNG CANCER PATIENT 07
LUNG CANCER PATIENT 08
LUNG CANCER PATIENT 09
LUNG CANCER PATIENT 10
LUNG CANCER PATIENT 11
LUNG CANCER PATIENT 12
LUNG CANCER PATIENT 13
LUNG CANCER PATIENT 14
LUNG CANCER PATIENT 15
LUNG CANCER PATIENT 16
LUNG CANCER PATIENT 17
LUNG CANCER PATIENT 18
LUNG CANCER PATIENT 19
LUNG CANCER PATIENT 20
CELL STRAIN
MOLECULAR-WEIGHT MARKER
LUNG CANCER PATIENT 21
LUNG CANCER PATIENT 22
LUNG CANCER PATIENT 23
LUNG CANCER PATIENT 24
LUNG CANCER PATIENT 25
LUNG CANCER PATIENT 26
LUNG CANCER PATIENT 27
LUNG CANCER PATIENT 28
LUNG CANCER PATIENT 29
LUNG CANCER PATIENT 30
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LUNG CANCER PATIENT 35
LUNG CANCER PATIENT 36
LUNG CANCER PATIENT 37
LUNG CANCER PATIENT 38
LUNG CANCER PATIENT 39
LUNG CANCER PATIENT 40
BLANK
B.
MOLECULAR-WEIGHT MARKER
CELL STRAIN
LUNG CANCER PATIENT 01
LUNG CANCER PATIENT 02
LUNG CANCER PATIENT 03
LUNG CANCER PATIENT 04
LUNG CANCER PATIENT 05
LUNG CANCER PATIENT 06
LUNG CANCER PATIENT 07
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LUNG CANCER PATIENT 14
LUNG CANCER PATIENT 15
LUNG CANCER PATIENT 16
LUNG CANCER PATIENT 17
LUNG CANCER PATIENT 18
LUNG CANCER PATIENT 19
LUNG CANCER PATIENT 20
MOLECULAR-WEIGHT MARKER
CELL STRAIN
LUNG CANCER PATIENT 21
LUNG CANCER PATIENT 22
LUNG CANCER PATIENT 23
LUNG CANCER PATIENT 24
LUNG CANCER PATIENT 25
LUNG CANCER PATIENT 26
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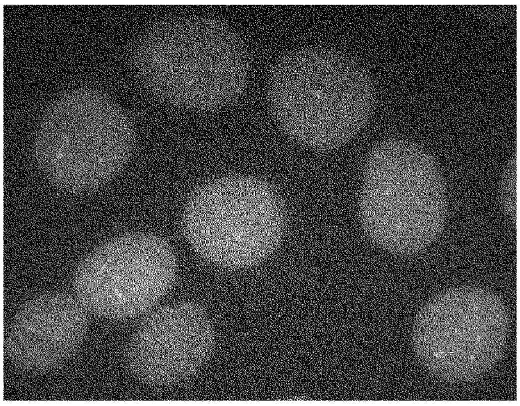
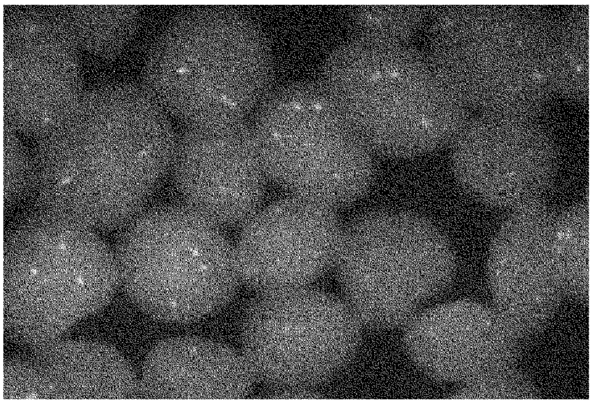
LUNG CANCER PATIENT 34
LUNG CANCER PATIENT 35
LUNG CANCER PATIENT 36
LUNG CANCER PATIENT 37
LUNG CANCER PATIENT 38
LUNG CANCER PATIENT 39
LUNG CANCER PATIENT 40

FIG. 4

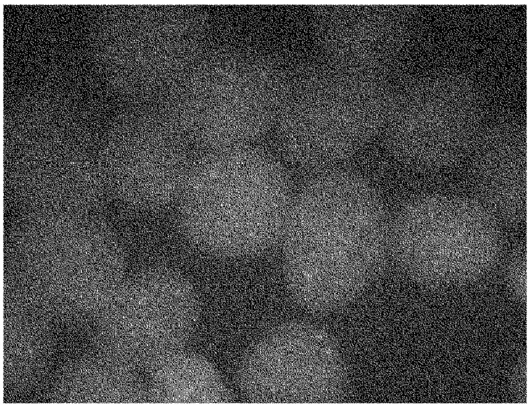
A 1.



A 2.



B 1.



B 2.

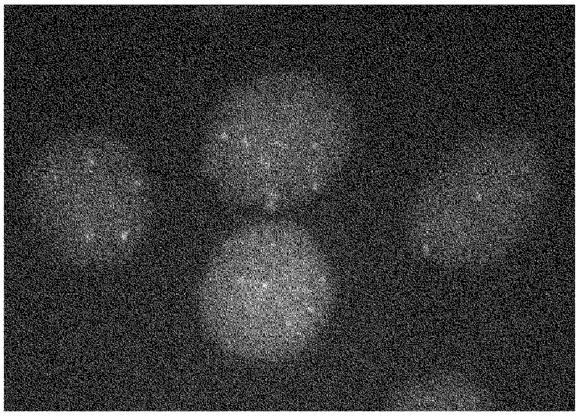


FIG. 5

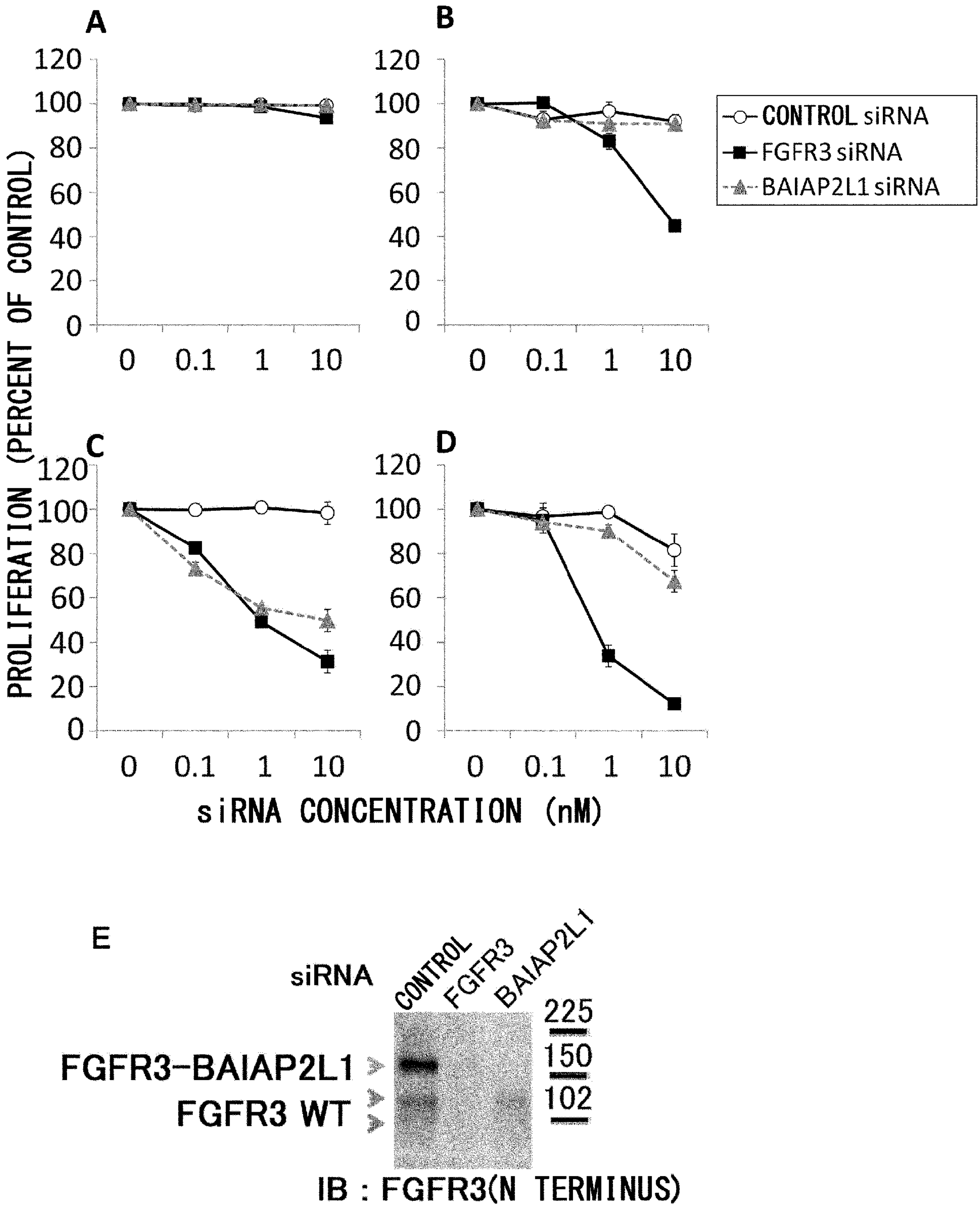

A
B
C
D
120
100
80
60
40
20
0
0
0.1
1
10
PROLIFERATION (PERCENT OF CONTROL)
siRNA CONCENTRATION (nM)
CONTROL siRNA
FGFR3 siRNA
BAIAP2L1 siRNA
E
siRNA
CONTROL
FGFR3
BAIAP2L1
FGFR3-BAIAP2L1
FGFR3 WT
225
150
102
IB : FGFR3(N TERMINUS)

FIG. 6

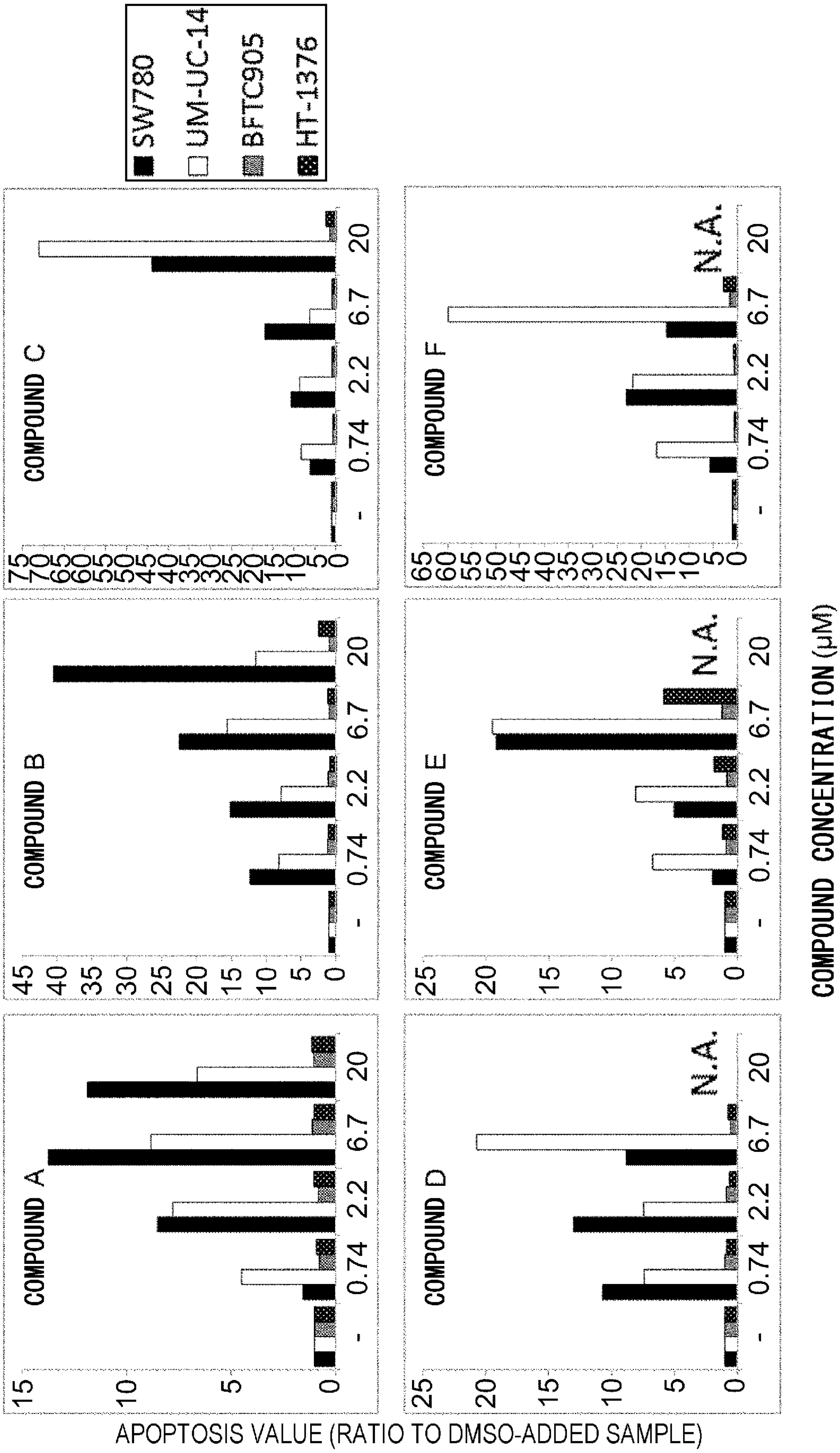
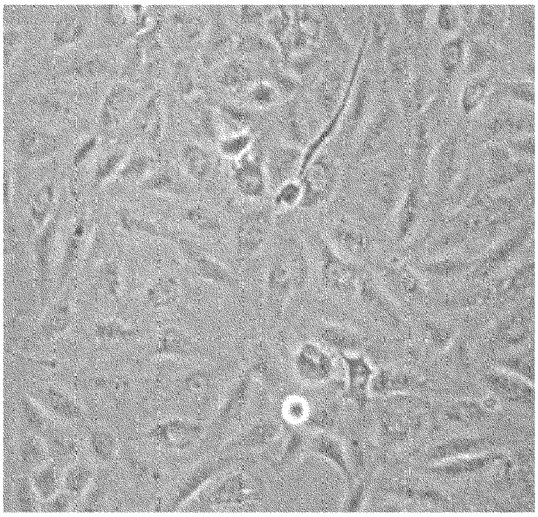

SW780
UM-UC-14
BFTC905
HT-1376
COMPOUND A
COMPOUND B
COMPOUND C
COMPOUND D
COMPOUND E
COMPOUND F
N.A.
- 0.74 2.2 6.7 20
APOPTOSIS VALUE (RATIO TO DMSO-ADDED SAMPLE)
COMPOUND CONCENTRATION (μM)

FIG. 7

MONOLAYER CULTURE

WILD-TYPE FGFR3



FGFR3-BAIAP2L1

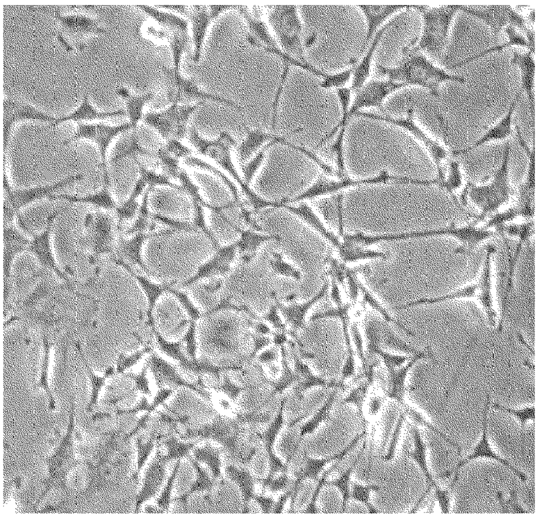


FIG. 8

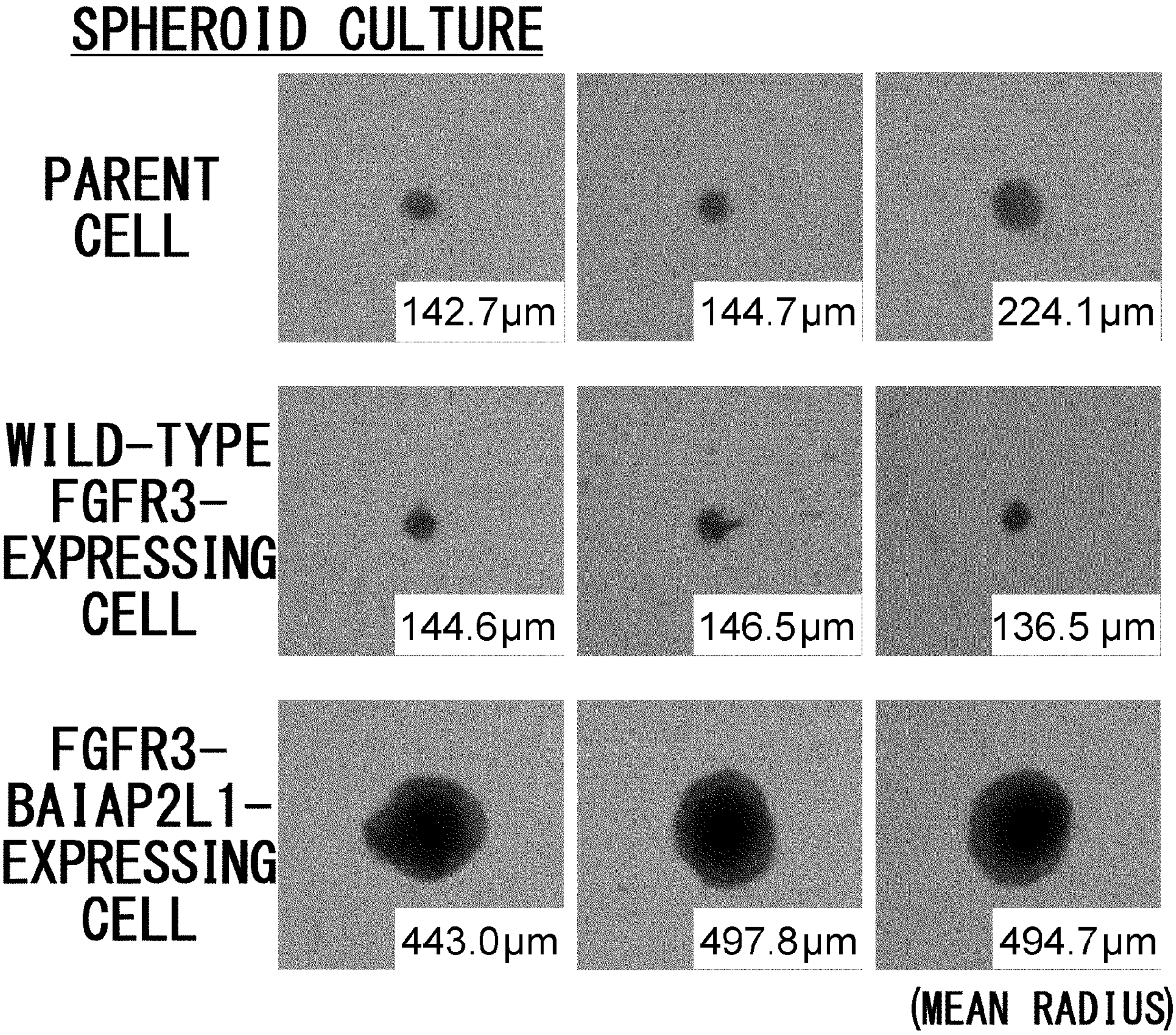

SPHEROID CULTURE
PARENT CELL
142.7μm
144.7μm
224.1μm
WILD-TYPE FGFR3-EXPRESSING CELL
144.6μm
146.5μm
136.5 μm
FGFR3-BAIAP2L1-EXPRESSING CELL
443.0μm
497.8μm
494.7μm
(MEAN RADIUS)

FIG. 9

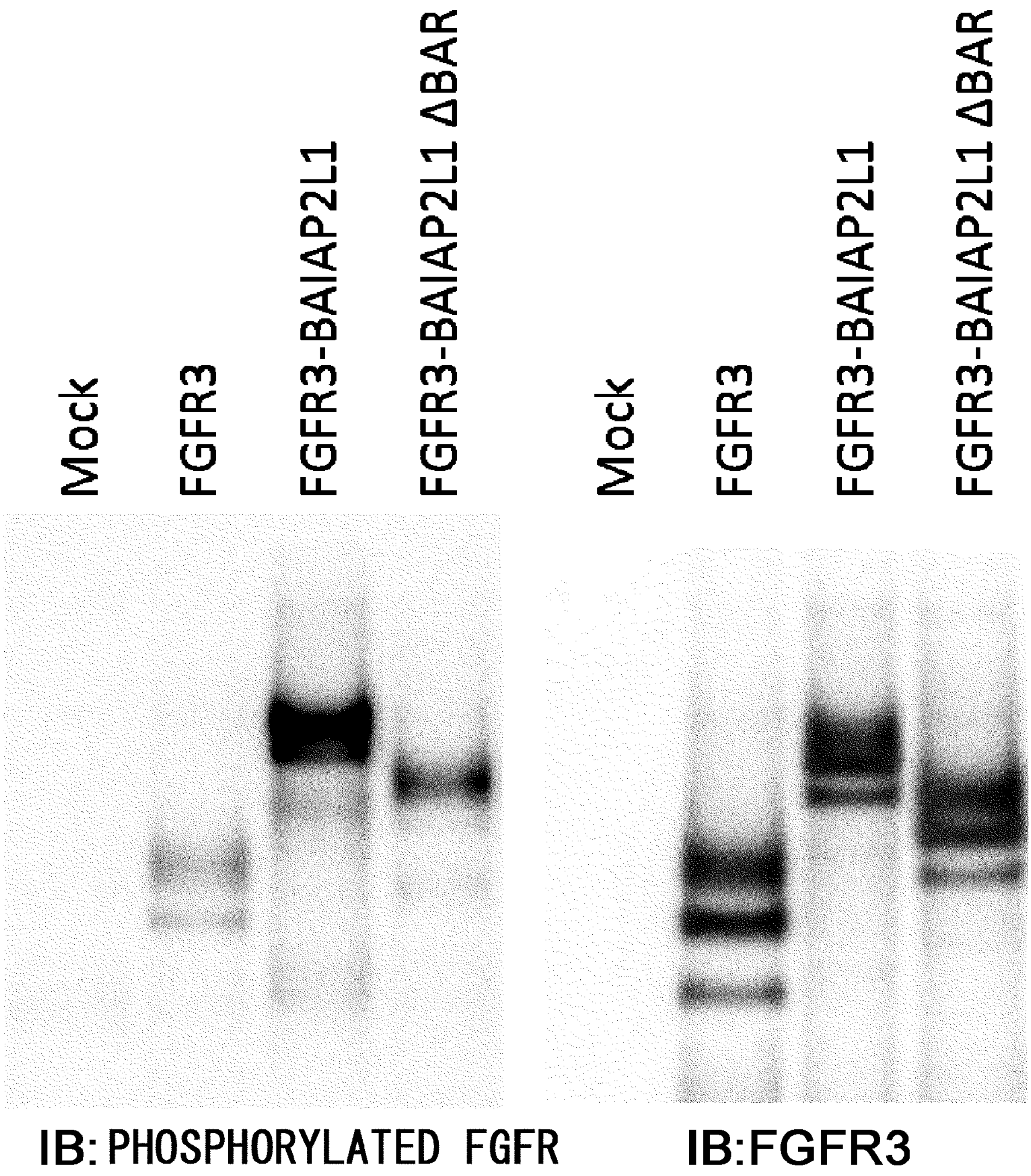

Mock
FGFR3
FGFR3-BAIAP2L1
FGFR3-BAIAP2L1 ΔBAR
Mock
FGFR3
FGFR3-BAIAP2L1
FGFR3-BAIAP2L1 ΔBAR
IB: PHOSPHORYLATED FGFR
IB:FGFR3

FIG. 10

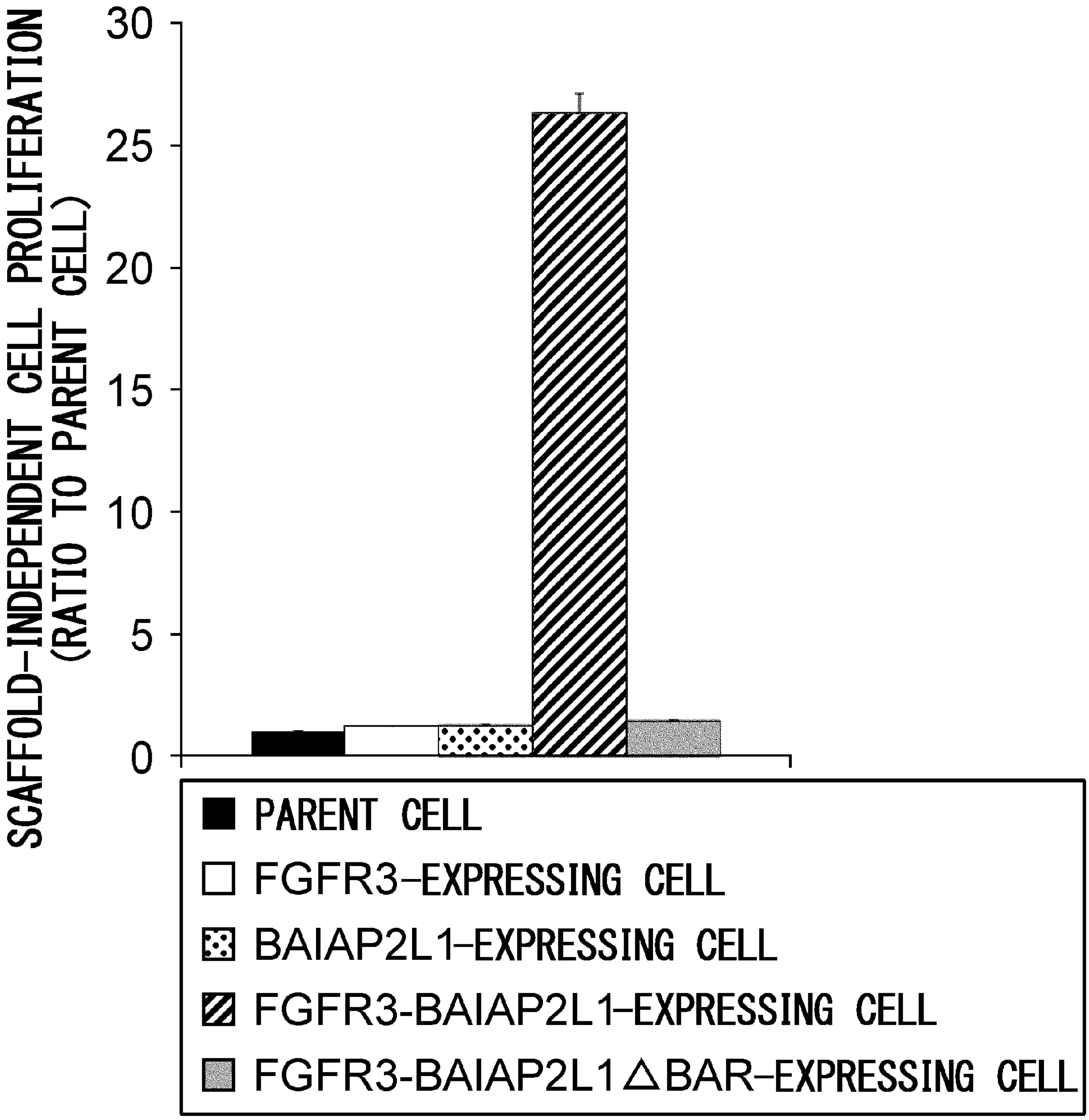

SCAFFOLD-INDEPENDENT CELL PROLIFERATION (RATIO TO PARENT CELL)
30
25
20
15
10
5
0
PARENT CELL
FGFR3-EXPRESSING CELL
BAIAP2L1-EXPRESSING CELL
FGFR3-BAIAP2L1-EXPRESSING CELL
FGFR3-BAIAP2L1△BAR-EXPRESSING CELL

FIG. 11

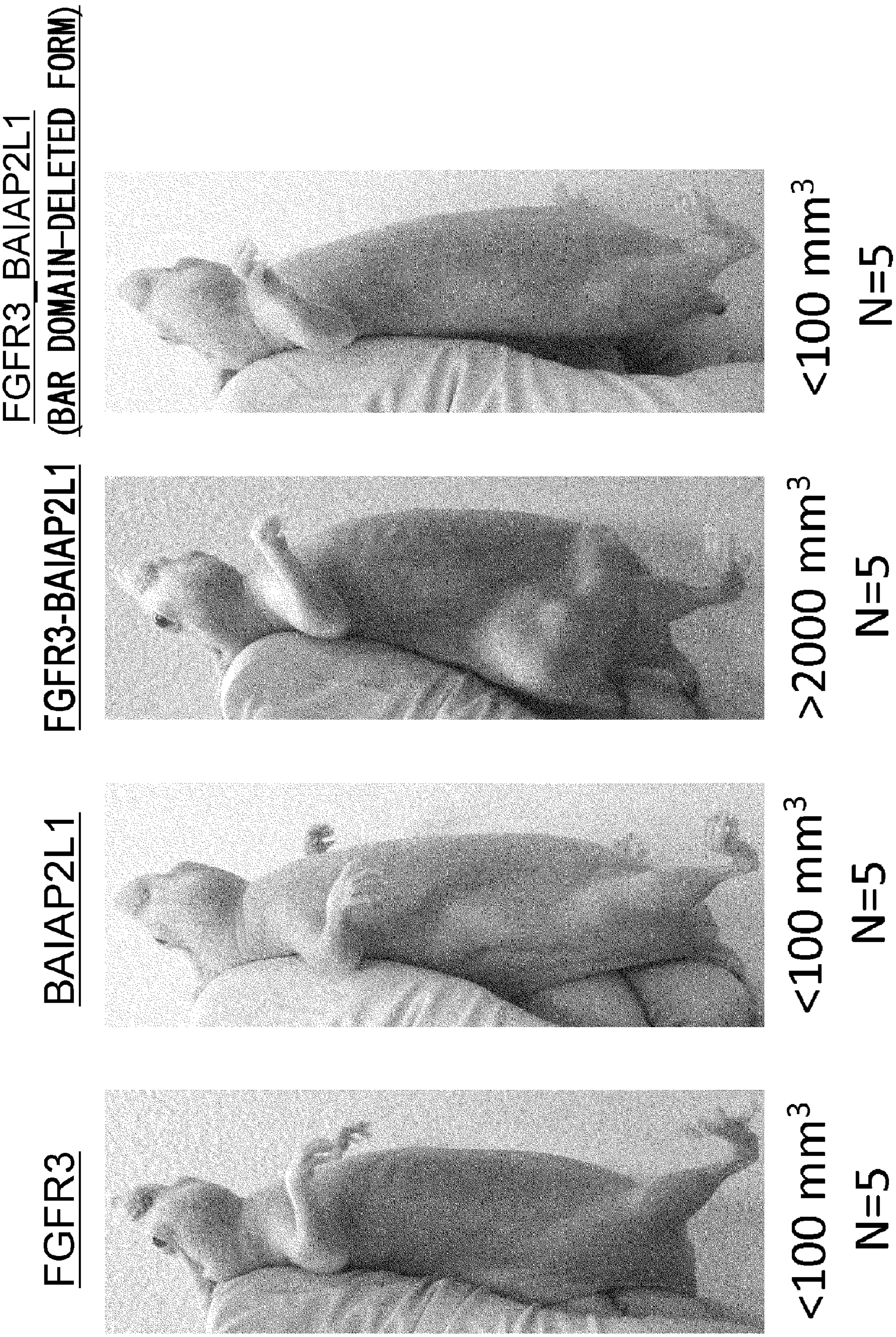

FGFR3
<100 mm³
N=5
BAIAP2L1
<100 mm³
N=5
FGFR3-BAIAP2L1
>2000 mm³
N=5
FGFR3_BAIAP2L1
(BAR DOMAIN-DELETED FORM)
<100 mm³
N=5

FIG. 12

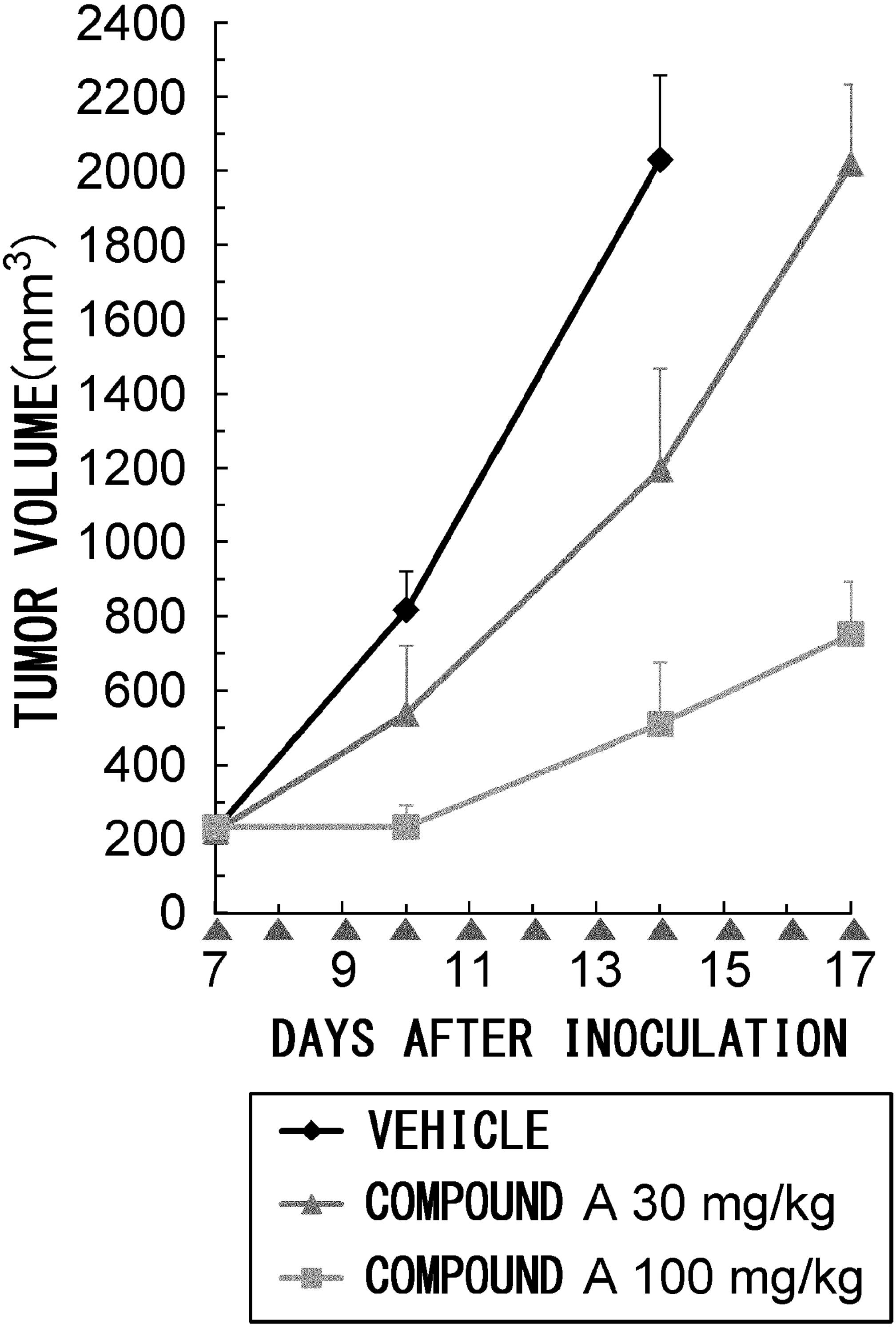

2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
TUMOR VOLUME(mm3)
7
9
11
13
15
17
DAYS AFTER INOCULATION
VEHICLE
COMPOUND A 30 mg/kg
COMPOUND A 100 mg/kg

FIG. 13

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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