(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 2 428 508 B9**

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:
Corrected version no 1 (W1 B1)
Corrections, see
Description Paragraph(s) 81, 199, 226

(48) Corrigendum issued on:
20.04.2016 Bulletin 2016/16

(45) Date of publication and mention of the grant of the patent:
16.12.2015 Bulletin 2015/51

(21) Application number: **10772177.1**

(22) Date of filing: **06.05.2010**

(51) Int Cl.:
C07D 239/48 *(2006.01)* ***A61K 31/4965*** *(2006.01)*
A61K 31/497 *(2006.01)* ***A61K 31/505*** *(2006.01)*
A61K 31/506 *(2006.01)* ***A61P 35/00*** *(2006.01)*
C07D 241/26 *(2006.01)* ***C07D 401/12*** *(2006.01)*
C07D 401/14 *(2006.01)* ***C07D 403/12*** *(2006.01)*
C07D 405/12 *(2006.01)* ***C07D 405/14*** *(2006.01)*
C07D 409/12 *(2006.01)* ***C07D 413/12*** *(2006.01)*
C07D 417/12 *(2006.01)* ***C07D 471/08*** *(2006.01)*
C07D 491/113 *(2006.01)*

(86) International application number:
PCT/JP2010/057751

(87) International publication number:
WO 2010/128659 (11.11.2010 Gazette 2010/45)

(54) **DIAMINO HETEROCYCLIC CARBOXAMIDE COMPOUND**

HETEROZYKLISCHE DIAMINO-CARBOXAMID-VERBINDUNG

COMPOSÉ DE CARBOXAMIDE HÉTÉROCYCLIQUE DIAMINO

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR
Designated Extension States:
RS

(30) Priority: **08.05.2009 JP 2009113936**

(43) Date of publication of application:
14.03.2012 Bulletin 2012/11

(60) Divisional application:
15189570.3 / 3 009 428

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EP 2 428 508 B9

Description

TECHNICAL FIELD

[0001] The present invention relates to diamino heterocyclic carboxamide compounds useful as active ingredients in pharmaceutical compositions, particularly pharmaceutical compositions for cancer therapy.

BACKGROUND ART

[0002] Lung cancer is caused by disordered growth of tracheal, bronchial and/or alveolar cells as a result of losing their normal functions. The number of people who die of lung cancer is the largest of the total of cancer deaths (17%), and worldwide about 1.3 million people die of lung cancer each year.

[0003] Treatment for lung cancer is divided into three major categories: surgical operation (surgical therapy), anticancer agent (chemotherapy) and radioactive irradiation (radiation therapy), but the effectiveness of treatment will vary depending on the tissue type of lung cancer. For example, although a definite diagnosis of lung cancer is made by a pathologist based on his cytohistopathological diagnosis on a microscope specimen, small cell lung cancer, which constitutes about 20% of lung cancer cases, has often reached an advanced stage at the time of discovery because it generally has a high grade of malignancy and will rapidly grow and spread and will often metastasize to other organs. For this reason, chemotherapy and/or radiation therapy is often used for treatment of this cancer, but the prognosis is poor because small cell lung cancer will often recur although it is relatively sensitive to these therapies. On the other hand, in the case of non-small cell lung cancer, which constitutes the remainder of about 80%, surgical therapy is considered for use until a certain stage, but there is little opportunity to use surgical operation in the subsequent stages where chemotherapy and/or radiation therapy is mainly used for treatment.

[0004] Thus, in either type of lung cancer, chemotherapy is an important option for treatment.

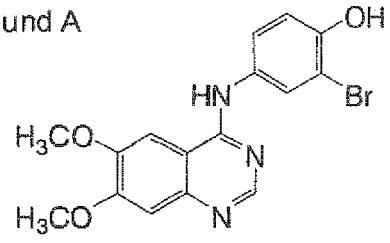
[0005] ALK (Anaplastic Lymphoma Kinase) is a receptor tyrosine kinase and is a protein having a transmembrane region in the middle part, flanked by a tyrosine kinase region on the carboxyl-terminal side and an extracellular region on the amino-terminal side. It has previously been reported that full-length ALK is expressed in several types of cancer cells of ectodermal origin (e.g., neuroblastoma, glioblastoma, breast cancer, melanoma) (Non-patent Document 1). In some cases of human malignant lymphoma, it has also been reported that the ALK gene is fused with another gene (e.g., NPM gene, CLTCL gene, TFG gene, TPM3 gene, ATIC gene, and TPM4 gene) as a result of chromosomal translocation, and thereby produces an oncogenic fusion tyrosine kinase (Science, vol. 263, p. 1281, 1994; Blood, vol. 86, p. 1954, 1995; Blood, vol. 95, p. 3204, 2000; Blood, vol. 94, p. 3265, 1999; Oncogene, vol. 20, p. 5623, 2001). Also in the case of inflammatory myofibroblastic tumor, it is known that the ALK gene is fused with another gene (e.g., CARS gene, SEC31L1 gene, and RanBP2 gene) as a result of chromosomal translocation, and thereby produces a fusion tyrosine kinase (Laboratory Investigation, a journal of technical methods and pathology, vol. 83, p. 1255, 2003; International Journal of Cancer, vol. 118, p. 1181, 2006; Medicinal Research Reviews, vol. 28, p. 372, 2008). Most of partner molecules to be fused with ALK have a complex-forming domain, and the generated fusion products per se also appear to form complexes. This complex formation would induce uncontrol of ALK tyrosine kinase activity and abnormal activation of intracellular signals, thereby causing canceration (Cellular and Molecular Life Science, vol. 61, p. 2939, 2004; Nature Reviews Cancer, vol. 8, p. 11, 2008).

[0006] Moreover, recent reports have indicated the presence of a TPM4-ALK fusion protein in esophageal cancer by proteomics analysis procedures (World Journal of Gastroenterology, vol. 12, p. 7104, 2006; Journal of Molecular Medicine, vol. 85, p. 863, 2007), Further, a fusion gene between EML4 (echinoderm microtubule associated protein like-4) and ALK was confirmed in specimens from lung cancer patients, and it was also reported that this EML4-ALK fusion gene has tumorgenicity and is a causal gene of cancer, and that inhibitors against its kinase activity suppress the growth of various cells where the EML4-ALK fusion protein is expressed (Patent Document 1 and Non-patent Document 2). These documents further show that inhibitors of the EML4-ALK fusion protein are useful as therapeutic agents for lung cancer in EML4-ALK polynucleotide-positive lung cancer patients. Further, in lung cancer, the presence of many variants of EML4-ALK has been proved (Patent Document 1; Annals of surgical oncology, vol. 17, p. 889, 2010; Molecular Cancer Research, vol. 7, p. 1466, 2009; Clinical Cancer Research, vol. 15, p. 3143, 2009; Cancer, vol. 115, p. 1723, 2009; Clinical Cancer Research, vol. 14, p. 6618, 2008; Clinical Cancer Research, vol. 14, p. 4275, 2008), and the presence of TFG-ALK (Cell, vol. 131, p. 1190, 2007) and KIF5B-ALK (Clinical Cancer Research, vol. 15, p. 3143, 2009) has been reported. Furthermore, it is known that there have been cases in which EML4-ALK is expressed in lung cancer patients as well as colon cancer patients and breast cancer patients (Molecular Cancer Research, vol. 7, p. 1466, 2009).

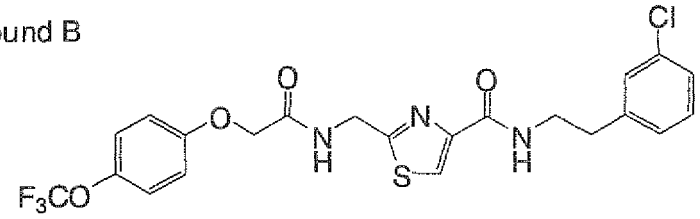
[0007] Moreover, Patent Document 1 shows the following compounds A to D (each being known as an ALK inhibitor) as examples of compounds having inhibitory activity against the EML4-ALK fusion protein, and it also discloses the actual values of their inhibitory activity against the EML4-ALK fusion protein. However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

[Formula 1]

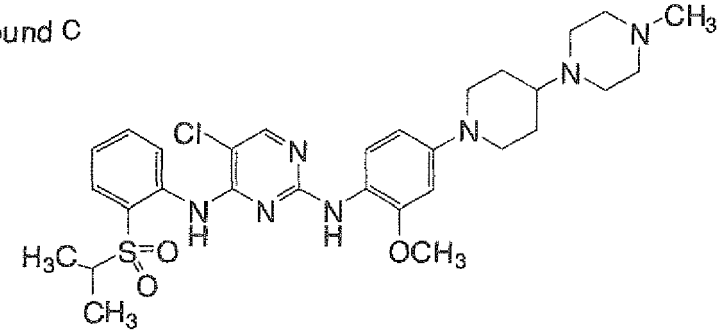
Compound A



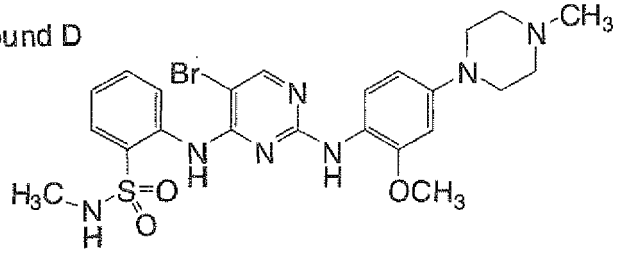
Compound B



Compound C



Compound D



Their respective chemical names are: 4-[(3'-bromo-4'-hydroxyphenyl)amino]-6,7-dimethoxyquinazoline (also called WHI-P154) for compound A; N-[2-(3-chlorophenyl)ethyl]-2-[(1[4-(trifluoromethoxy)phenoxy]acetyl}amino)methyl]-1,3-thiazole-4-carboxamide for compound B; 5-chloro-N^4-[2-(isopropylsulfonyl)phenyl]-N^2-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine (also called TAE684) for compound C; and 2-[(5-bromo-2-{[2-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}pyrimidin-4-yl)amino]-N-methylbenzenesulfonamide for compound D.

[0008] Moreover, in ALK fusion protein-expressing lymphoma cells, a compound having ALK inhibitory activity, WHI-P154 (compound A shown above), has been reported to inhibit cell growth and induce apoptosis (Non-patent Document 3). However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

[0009] Likewise, TAE684 (compound C shown above) is known as an inhibitor of a fusion protein from a fusion gene between NPM gene and ALK gene.

[0010] TAE684 structurally differs from the compounds of the present invention in that the center ring sandwiched between two -NH groups is a chloro-substituted pyrimidine ring.

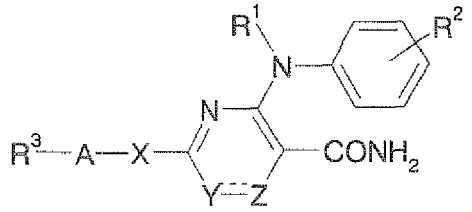
[0011] Moreover, TAE684 has been reported to inhibit the spread of anaplastic large cell lymphoma (ALCL) by its inhibitory activity against the NPM-ALK fusion protein (Non-patent Document 4). On the other hand, although it is described that compounds including TAE684 have inhibitory activity against focal adhesion kinase (FAK) and are thereby useful for preventing and/or treating non-small cell lung cancer and small cell lung cancer, there is no information about

actual therapeutic effects on these lung cancers (Patent Document 2). Furthermore, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

[0012] Further reports were issued showing that ELM4-ALK is expressed in non-small cell lung cancer cells (NCI-H2228), that TFG-ALK is expressed in non-small cell lung cancer patients, and that TAE684 inhibits the growth of non-small cell lung cancer cells (NCI-H2228) (Patent Document 1 and Non-patent Documents 5 and 6).

[0013] Further, it is reported that the compound below has Syk inhibitory activity and is useful as an active ingredient in agents for preventing or treating a disease in which Syk is involved, such as allergy, inflammation, immune disease, thrombus, and cancer (Patent Document 3).

[Formula 2]

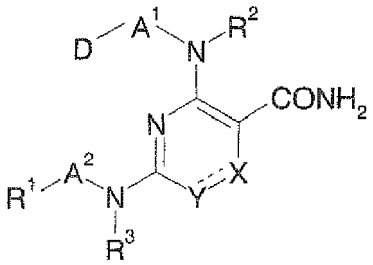


(For the symbols in the formula, refer to the publication.)

[0014] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention. Furthermore, the inhibitory activity against the kinase activity of EML4-ALK fusion protein is neither disclosed nor suggested, and there is no specific disclosure about therapeutic effects on cancer.

[0015] Further, it is reported that the compound below has inhibitory activity against protein kinase C and is useful as an active ingredient in agents for preventing or treating a disease in which protein kinase C is involved, such as diabetic complication, ischemia, inflammation, and cancer (Patent Document 4).

[Formula 3]

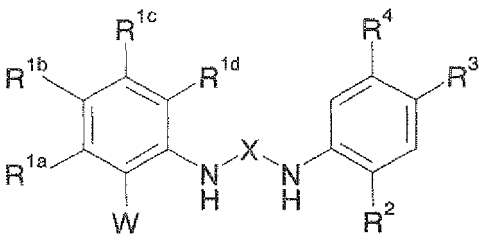


(For the symbols in the formula, refer to the publication.)

[0016] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention. Furthermore, the inhibitory activity against the kinase activity of EML4-ALK fusion protein is neither disclosed nor suggested, and there is no specific disclosure about therapeutic effects on cancer.

[0017] Further, it is reported that the compound below has inhibitory activity against the kinase activity of EML4-ALK fusion protein and mutant EGFR protein and is useful as an active ingredient in therapeutic agents for cancer including lung cancer, etc (Patent Document 5).

[Formula 4]

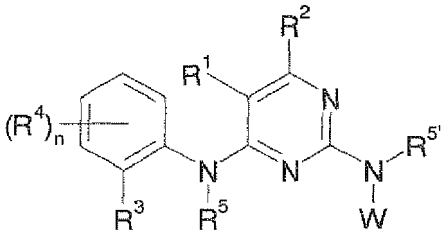


(In the formula, -X- is 1,3,5-triazine-2,4-diyl or quinazoline-2,4-diyl which may be substituted. For other symbols in the formula, refer to the publication.)

[0018] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

[0019] Further, it is reported that the compound below has inhibitory activity against various kinases including ALK and is useful for treating cell proliferative disease (Patent Document 6).

[Formula 5]

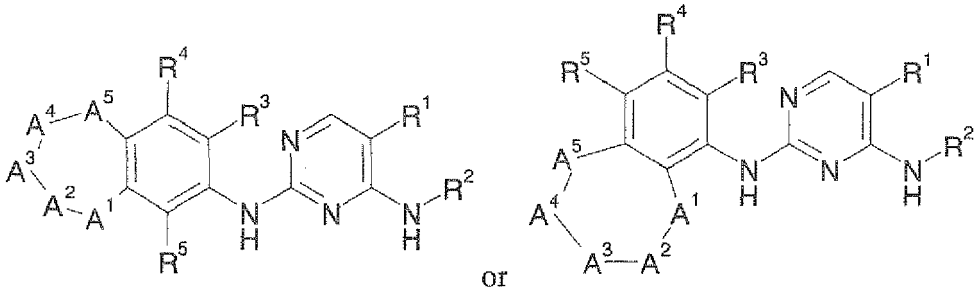


(For the symbols in the formula, refer to the publication.)

[0020] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

[0021] Further, it is reported that the compound below has inhibitory activity against ALK and/or c-Met and is useful for treating proliferative disease (Patent Document 7).

[Formula 6]

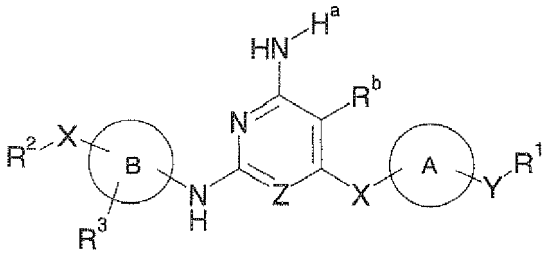


(For the symbols in the formula, refer to the publication.)

[0022] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

[0023] Further, it is reported that the compound below has inhibitory activity against various kinases including ALK and is useful for treating hyperproliferative disease and angiogenic disease (Patent Document 8).

[Formula 7]

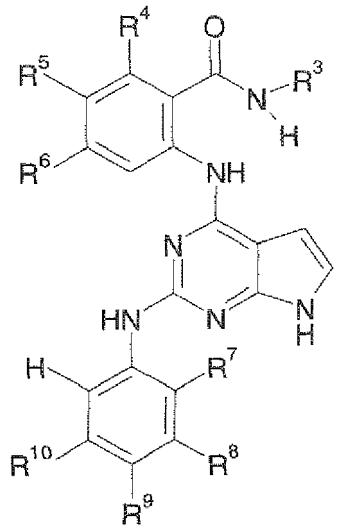


(For the symbols in the formula, refer to the publication.)

[0024] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

[0025] Further, it is reported that the compound below has inhibitory activity against various kinases including IGF-1R and ALK and is useful for treating cancer (Patent Document 9).

[Formula 8]

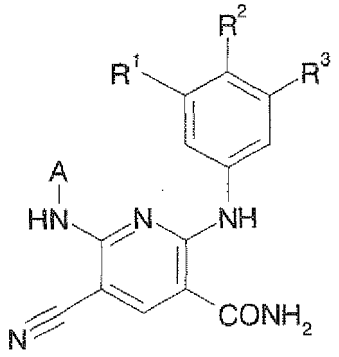


(For the symbols in the formula, refer to the publication.)

[0026] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

[0027] Further, it is reported that the compound below has Syk inhibitory activity and is useful for treating allergy, autoimmune disease, cancer, and abnormal myeloid cell growth (Patent Document 10).

[Formula 9]

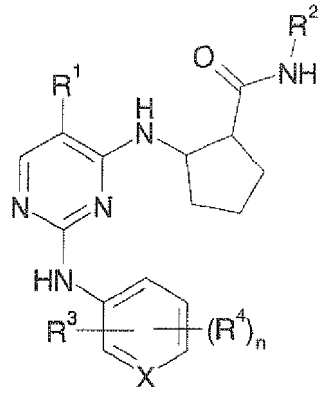


(For the symbols in the formula, refer to the publication.)

[0028] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention. Furthermore, the inhibitory activity against the kinase activity of EML4-ALK fusion protein is neither disclosed nor suggested, and there is no specific disclosure about therapeutic effects on cancer.

[0029] Further, it is reported that the compound below has inhibitory activity against Aurora-B kinase and is useful for treating cancer, infectious disease, inflammation, and autoimmune disease (Patent Document 11).

[Formula 10]

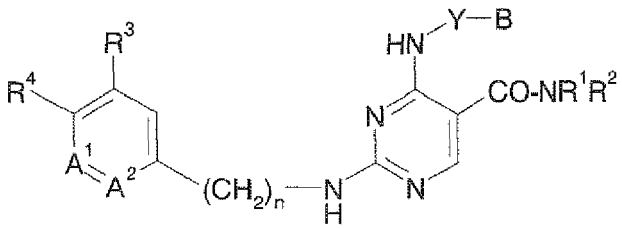


(For the symbols in the formula, refer to the publication.)

[0030] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention. Furthermore, the inhibitory activity against the kinase activity of EML4-ALK fusion protein is neither disclosed nor suggested.

[0031] Further, it is reported that the compound below has STAT6 activation inhibitory activity and Th2 cell differentiation inhibitory activity and is useful for treating respiratory disease, asthma, and chronic obstructive pulmonary disease (Patent Document 12).

[Formula 11]

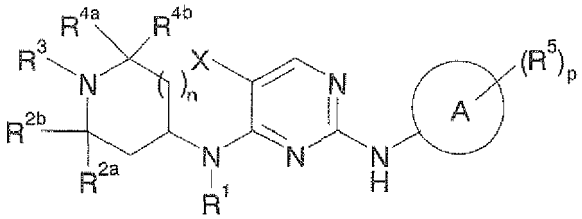


(For the symbols in the formula, refer to the publication.)

[0032] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention. Furthermore, the inhibitory activity against the kinase activity of EML4-ALK fusion protein is neither disclosed nor suggested, and there is no specific disclosure about therapeutic effects on cancer.

[0033] Further, it is reported that the compound below has PKC inhibitory activity and is useful for treating allergy, inflammation, diabetes, cancer and the like (Patent Document 13).

[Formula 12]

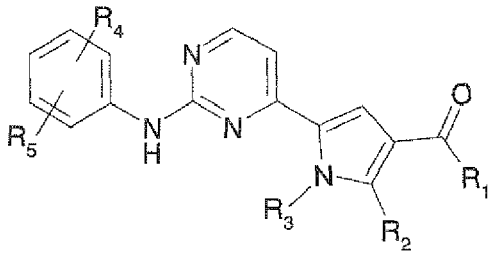


(For the symbols in the formula, refer to the publication.)

[0034] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention. Furthermore, the inhibitory activity against the kinase activity of EML4-ALK fusion protein is neither disclosed nor suggested, and there is no specific disclosure about therapeutic effects on cancer.

[0035] Further, it is reported that the compound below has inhibitory activity against PLK-1 and PLK-3 and is useful for treating cancer, cell proliferative disease, virus infection disease, autoimmune disease, and neurodegenerative disease (Patent Document 14).

[Formula 13]

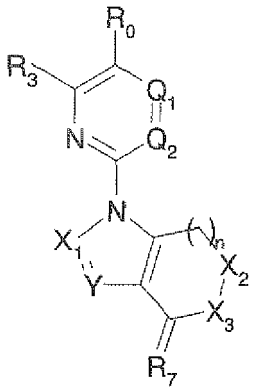


(For the symbols in the formula, refer to the publication.)

[0036] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention. Furthermore, the inhibitory activity against the kinase activity of EML4-ALK fusion protein is neither disclosed nor suggested.

[0037] Further, it is reported that the compound below has HSP-90 inhibitory activity and is useful for treating cell proliferative disease, cancer, inflammation, arthritis, and angiogenic disease (Patent Document 15).

[Formula 14]

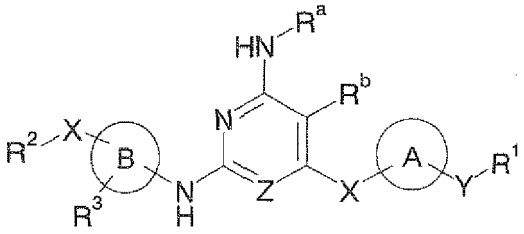


(For the symbols in the formula, refer to the publication.)

[0038] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention. Furthermore, the inhibitory activity against the kinase activity of EML4-ALK fusion protein is neither disclosed nor suggested.

[0039] Further, it is reported that the compound below has ALK, c-Met and Mps1 kinase inhibitory activity and is useful for treating hyperproliferative disease, cancer, and angiogenic disease (Patent Document 16).

[Formula 15]

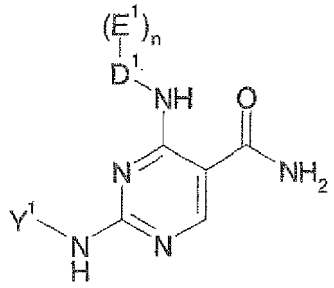


(For the symbols in the formula, refer to the publication.)

[0040] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

[0041] Further, it is reported that the compound below has inhibitory activity against Syk and Jak and is useful for treating heart disease, inflammation, autoimmune disease, and cell proliferative disease (Patent Document 17).

[Formula 16]

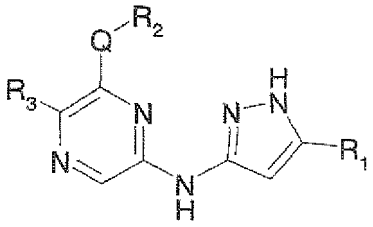


(For the symbols in the formula, refer to the publication.)

[0042] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention. Furthermore, the inhibitory activity against the kinase activity of EML4-ALK fusion protein is neither disclosed nor suggested.

[0043] Further, it is reported that the compound below has IKK inhibitory activity and is useful for treating inflammation, immunopathy, cancer, neurodegenerative disease, age-related disease, heart disease, and dysbolism (Patent Document 18).

[Formula 17]

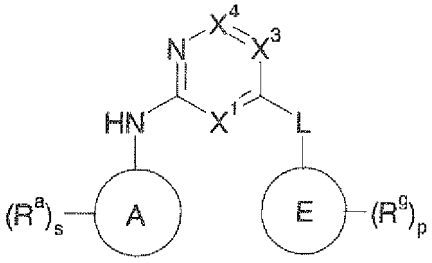


(For the symbols in the formula, refer to the publication.)

[0044] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention. Furthermore, the inhibitory activity against the kinase activity of EML4-ALK fusion protein is neither disclosed nor suggested.

[0045] Further, it is reported that the compound below has inhibitory activity against various kinases including ALK and is useful for treating cell proliferative disease and cancer (Patent Document 19).

[Formula 18]

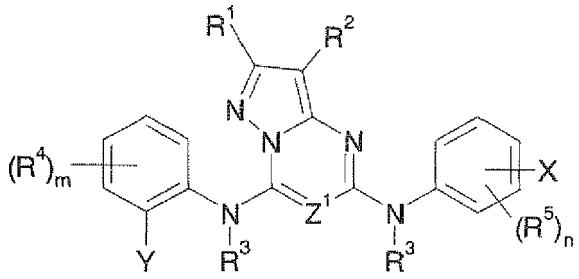


(For the symbols in the formula, refer to the publication.)

[0046] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

[0047] Further, it is reported that the compound below has ALK, ROS, IGF-1R and InsR kinase inhibitory activity and is useful for treating cell proliferative disease (Patent Document 20).

[Formula 19]



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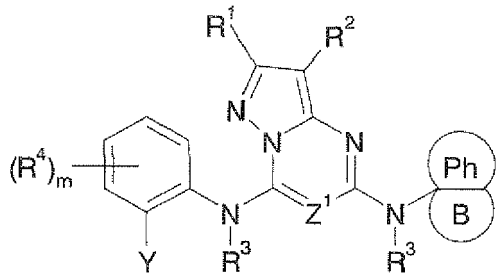
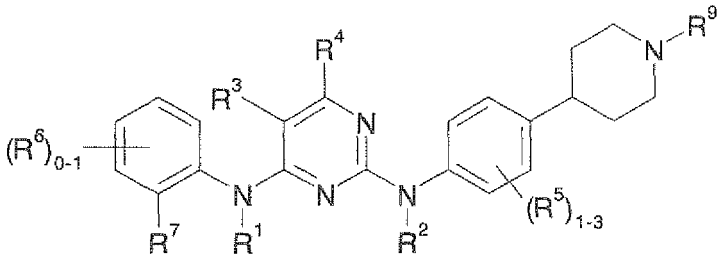


(For the symbols in the formula, refer to the publication.)

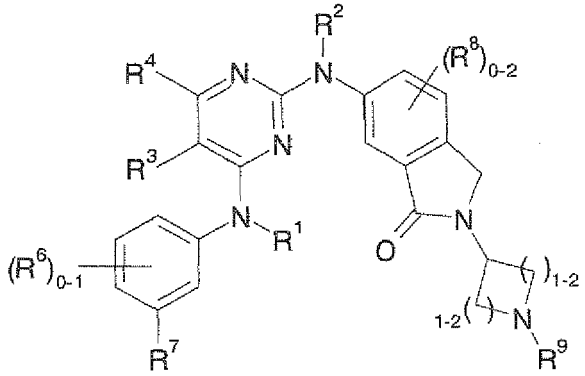
[0048] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

[0049] Further, it is reported that the compound below has ALK, ROS, IGF-1R and InsR kinase inhibitory activity and is useful for treating cell proliferative disease (Patent Document 21).

[Formula 20]



or



(For the symbols in the formula, refer to the publication.)

[0050] However, there is no specific disclosure about the diamino heterocyclic carboxamide compounds according to the present invention.

CITATION LIST

PATENT DOCUMENTS

[0051]

Patent Document 1: European Patent Publication No. EP 1914240
Patent Document 2: International Publication No. WO 2004/080980
Patent Document 3: International Publication No. WO 00/75113
Patent Document 4: International Publication No. WO 00/76980
Patent Document 5: International Publication No. WO 2009/008371
Patent Document 6: International Publication No. WO 2008/073687
Patent Document 7: International Publication No. WO 2008/051547
Patent Document 8: International Publication No. WO 2009/032703
Patent Document 9: International Publication No. WO 2009/020990
Patent Document 10: Japanese Patent Publication No. 2008-13499
Patent Document 11: International Publication No. WO 2008/077885
Patent Document 12: International Publication No. WO 2004/002964
Patent Document 13: International Publication No. WO 2009/012421
Patent Document 14: International Publication No. WO 2009/040399
Patent Document 15: International Publication No. WO 2008/024974
Patent Document 16: International Publication No. WO 2009/032694
Patent Document 17: International Publication No. WO 2009/136995
Patent Document 18: International Publication No. WO 2009/089042
Patent Document 19: International Publication No. WO 2009/143389

Patent Document 20: International Publication No. WO 2009/126514
Patent Document 21: International Publication No. WO 2009/126515

NON-PATENT DOCUMENTS

[0052]

Non-patent Document 1: International Journal of Cancer, vol. 100, p. 49, 2002
Non-patent Document 2: Nature, vol. 448, no. 2, p. 561, 2007
Non-patent Document 3: Laboratory Investigation, vol. 85, p. 1544, 2005
Non-patent Document 4: Proceedings of the National Academy of Science, vol. 104, no. 1, p. 270, 2007
Non-patent Document 5: Cell, vol. 131, p. 1190, 2007
Non-patent Document 6: Proceedings of the National Academy of Science, vol. 104, no. 50, p. 19936, 2007

SUMMARY OF INVENTION

TECHNICAL PROBLEMS

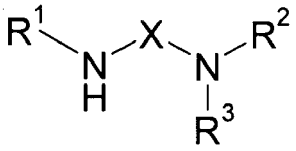
[0053] The present invention provides a compound which is useful as an active ingredient in pharmaceutical compositions, particularly pharmaceutical compositions for cancer therapy, and which can be used more safely as an active ingredient in pharmaceutical compositions.

SOLUTION TO PROBLEMS

[0054] As a result of extensive and intensive studies on compounds useful as active ingredients in pharmaceutical compositions for cancer therapy, the inventors of the present invention have found that the diamino heterocyclic carboxamide compound of the present invention has excellent inhibitory activity against the kinase activity of EML4-ALK fusion proteins, and is useful as an active ingredient in pharmaceutical compositions for cancer therapy. This finding led to the completion of the present invention.

[0055] Namely, the present invention relates to a compound of formula (I) or a salt thereof, as well as a pharmaceutical composition comprising a compound of formula (I) or a salt thereof and an excipient.

[Formula 21]

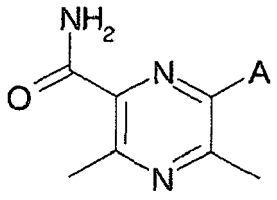


(I)

(wherein the symbols are as defined below:

[0056] -X-: a group of formula (II)

[Formula 22]



(II)

[0057] A: chloro, ethyl or isopropyl;

R^1:

(1) phenyl in which the carbon at the 4-position is substituted with -W-Y-Z and the carbon at the 3-position may be substituted with a group selected from the group consisting of halogen, R^{00} and -O-R^{00};
-W-: a bond, piperidine-1,4-diyl, or piperazine-1,4-diyl;
-Y-: a bond;
Z: a non-aromatic heterocyclic ring which may be substituted with one or more R^{00};

R^2:

(i) cycloalkyl which may be substituted with one or more groups selected from the group consisting of -N(C_{1-6} linear or branched alkyl)$_2$, C_{1-6} linear or branched alkyl, -COO- C_{1-6} linear or branched alkyl, -OH, -COOH, -CONH-R^{ZB} and morpholinyl, or

(ii) a non-aromatic heterocyclic ring which may be substituted with one or more groups selected from the group consisting of C_{1-6} linear or branched alkyl, -CO- C_{1-6} linear or branched alkyl, oxo, -CO-R^{ZB} and benzyl;

R^{ZB}: phenyl which may be substituted with a group selected from the group consisting of halogen and -O-linear or branched C_{1-6} alkyl;

R^3: -H.

[0058] Unless otherwise specified, when symbols used in one chemical formula are also used in another chemical formula, the same symbols have the same meanings.

[0059] The present invention also relates to an inhibitor against the kinase activity of EML4-ALK fusion protein, which comprises a compound of formula (I) or a salt thereof.

[0060] Moreover, the present invention also relates to a pharmaceutical composition for cancer therapy, which comprises a compound of formula (I) or a salt thereof. It is to be noted that the pharmaceutical composition includes a therapeutic agent for cancer, which comprises a compound of formula (I) or a salt thereof.

[0061] Moreover, the present invention also relates to a pharmaceutical composition comprising a compound of formula (1) or a salt thereof and a pharmaceutical excipient; a pharmaceutical composition for use in a method for preventing and treating cancer, lung cancer, non-small lung cancer, small cell lung cancer, EML4-ALK fusion polynucleotide-positive cancer, EML4-ALK fusion polynucleotide-positive lung cancer, or EML4-ALK fusion polynucleotide-positive non-small lung cancer, comprising a compound of formula (I) or a salt thereof , a compound of formula (1) or a salt thereof for use in a method as an inhibitor against the kinase activity of EML4-ALK fusion protein; a compound of formula (I) or a salt thereof for use in a method for the prevention and treatment of cancer .

ADVANTAGEOUS EFFECT OF INVENTION

[0062] The compound of formula (I) or a salt thereof has inhibitory activity against the kinase activity of EML4-ALK fusion protein, as well as growth inhibitory activity against EML4-ALK fusion protein-dependent cells, and can be used as an active ingredient in pharmaceutical compositions for preventing and/or treating cancer, such as lung cancer in one embodiment, non-small cell lung cancer or small cell lung cancer in another embodiment, ALK fusion polynucleotide-positive cancer in yet another embodiment, ALK fusion polynucleotide-positive lung cancer in yet another embodiment, ALK fusion polynucleotide-positive non-small cell lung cancer in yet another embodiment, ALK fusion protein-positive cancer in yet another embodiment, ALK fusion protein-positive lung cancer in yet another embodiment, ALK fusion protein-positive non-small cell lung cancer in yet another embodiment, EML4-ALK fusion polynucleotide-positive cancer in yet another embodiment, EML4-ALK fusion polynucleotide-positive lung cancer in yet another embodiment, EML4-ALK fusion polynucleotide-positive non-small cell lung cancer in yet another embodiment, EML4-ALK fusion protein-positive cancer in yet another embodiment, EML4-ALK fusion protein-positive lung cancer in yet another embodiment, or EML4-ALK fusion protein-positive non-small cell lung cancer in yet another embodiment.

DESCRIPTION OF EMBODIMENTS

[0063] The present invention will now be described in more detail below.

[0064] As used herein, the term "halogen" means F, Cl, Br or I.

[0065] The term "lower alkyl" refers to linear or branched alkyl containing 1 to 6 carbon atoms (hereinafter abbreviated as "C_{1-6}"). Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl,

and the like. Another embodiment is C_{1-4} alkyl, and yet another embodiment is methyl, ethyl or isopropyl.

[0066] The term "lower alkenyl" refers to a monovalent group of a C_{2-6} linear or branched hydrocarbon chain having at least one double bond. Examples include vinyl, propenyl, isopropenyl, butenyl, pentenyl, 1-methylvinyl, 1-methyl-2-propenyl, 1,3-butadienyl, 1,3-pentadienyl, etc. Another embodiment is isopropenyl.

[0067] The term "cycloalkyl" refers to an optionally bridged C_{3-10} saturated cyclic hydrocarbon group, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, adamantyl, etc. Other examples include those partially unsaturated, such as cyclopentenyl, cyclohexenyl, cyclooctadienyl, bicyclo[3.1.1]heptenyl, etc.

[0068] The term "cyclic amino" refers to a monovalent group of a 3- to 8-membered monocyclic non-aromatic cyclic amine which has at least one nitrogen atom and may further have the same or different one or more heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein at least one nitrogen atom has a binding hand. Specific examples include aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, azepanyl, azocanyl, piperazinyl, homopiperazinyl, morpholinyl, oxazepanyl, thiomorpholinyl, thiazepanyl, and the like. Alternatively, another embodiment is a monovalent group of a 5- or 6-membered monocyclic non-aromatic cyclic amine. Yet another embodiment is pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl. It should be noted that such a ring may be bridged, as exemplified by 2,5-diazabicyclo[2.2.1]heptyl, 9-azabicyclo[3.3.1]nonyl and the like, or may have an unsaturated bond in part of the ring, as exemplified by dihydropyrrolyl, dihydropyridyl, tetrahydropyridyl, tetrahydropyrazyl, or the like.

[0069] The term "non-aromatic heterocyclic ring" refers to a monovalent group of a 3- to 10-membered monocyclic non-aromatic heterocyclic ring which has 1 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Examples include aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, azepanyl, diazepanyl, azocanyl, piperazinyl, homopiperazinyl, morpholinyl, oxazepanyl, thiomorpholinyl, thiazepanyl, tetrahydropyranyl, tetrahydrofuryl, dioxanyl, dioxolanyl, tetrahydrothienyl, tetrahydrothiopyranyl, and the like. Another embodiment is a monovalent group of a 5- or 6-membered monocyclic non-aromatic heterocyclic ring. It should be noted that such a ring may be bridged, as exemplified by 2,5-diazabicyclo[2.2.1]heptyl, 9-azabicyclo[3.3.1]nonyl or the like, or may have an unsaturated bond in part of the ring, as exemplified by dihydropyrrolyl, dihydropyridyl, tetrahydropyridyl, tetrahydropyrazyl or the like.

[0070] The term "aromatic heterocyclic ring" refers to a monovalent group of a 5- to 10-membered monocyclic aromatic heterocyclic ring which has 1 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Examples include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, thienyl, furyl, 1,2,4-oxadiazolyl and the like. Another embodiment is pyridyl, imidazolyl, or pyrazolyl. Yet another embodiment is pyridyl.

[0071] The term "ALK fusion polynucleotide" refers to a fusion polynucleotide in which the ALK gene is fused with another gene and thereby expresses an oncogenic fusion tyrosine kinase. Examples include EML4-ALK fusion polynucleotide, TFG-ALK fusion polynucleotide, KIF5-ALK fusion polynucleotide, NPM-ALK fusion polynucleotide, CLTCL-ALK fusion polynucleotide, TPM3-ALK fusion polynucleotide, TPM4-ALK fusion polynucleotide, ATIC-ALK fusion polynucleotide, CARS-ALK fusion polynucleotide, SEC31L1-ALK fusion polynucleotide, RanBP2-ALK fusion polynucleotide and the like.

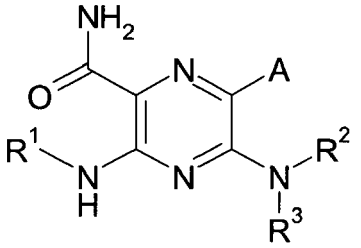
[0072] The term "ALK fusion protein" refers to a fusion tyrosine kinase produced by expression of ALK fusion polynucleotide.

[0073] The term "EML4-ALK fusion polynucleotide" refers to a fusion polynucleotide in which the ALK gene is fused with the EML4 gene and thereby expresses an oncogenic ALK fusion protein, including variants thereof, such as EML4-ALK fusion polynucleotide v1 (polynucleotide of SEQ ID NO: 1 of Patent Document 1), EML4-ALK fusion polynucleotide v2 (polynucleotide of SEQ ID NO: 6 of Patent Document 1) and EML4-ALK fusion polynucleotide v3 (polynucleotide of SEQ ID NO: 129 of Patent Document 1), as well as various variants (Annals of surgical oncology, vol. 17, p. 889, 2010, Molecular Cancer Research, vol. 7, p. 1466, 2009, Clinical Cancer Research, vo. 15, p. 3143, 2009, Cancer, vol. 115, p. 1723, 2009, Clinical Cancer Research, vol. 14, p. 6618, 2008, Clinical Cancer Research, vol. 14, p. 4275, 2008, etc.).

[0074] The term "EML4-ALK fusion protein" refers to a fusion tyrosine kinase created by expression of EML4-ALK fusion polynucleotide.

A compound of formula (I) or a salt thereof wherein -X- in formula (I) represents a group of formula (II) means a compound of formula (V) or a salt thereof.

[Formula 24]



(V)

[0075] The phrase "may be substituted" is intended to mean "unsubstituted" or "having 1 to 5 substituents." When substituted with a plurality of groups, these groups may be the same or different from each other.

[0076] The phrase "is (are) substituted" or "substituted" is intended to mean "having 1 to 5 substituents." When substituted with a plurality of groups, these groups may be the same or different from each other.

[0077] The phrase "lower alkyl which may be substituted with one or more halogens" refers to, for example, lower alkyl which may be substituted with the same or different 1 to 7 halogens. Another embodiment is lower alkyl which may be substituted with 1 to 5 halogens. Yet another embodiment is lower alkyl which may be substituted with 1 to 3 halogens.

[0078] The phrase "lower alkenyl which may be substituted with one or more halogens" refers to, for example, lower alkenyl which may be substituted with 1 to 3 halogens.

[0079] Some embodiments of the compounds of formula (I) or a salt thereof are given below.

(1) Compounds of formula (I) or a salt thereof, wherein

(1-4) -X- is a group of formula (II), and A is chloro, ethyl or isopropyl,
(1-5) -X- is a group of formula (II), and A is chloro,
(1-6) -X- is a group of formula (II), and A is ethyl or isopropyl,
(1-7) -X- is a group of formula (II), and A is ethyl, or
(1-8) -X- is a group of formula (II), and A is isopropyl.

(2) Compounds of formula (I) or a salt thereof, wherein

(2-2) R^1 is phenyl in which the carbon at the 4-position is substituted with -W-Y-Z and the carbon at the 3-position may be substituted with a group selected from the group consisting of halogen, R^{00}, and -O- R^{00}, R^{00} is lower alkyl which may be substituted with one or more halogens, -Y- is a bond, and Z is a non-aromatic heterocyclic ring which may be substituted with one or more R^{00},
(2-3) R^1 is phenyl in which the carbon at the 4-position is substituted with a group selected from the group consisting of 4-(4-methylpiperazin-1-yl)piperidin-1-yl, 4-(1-methylpiperidin-4-yl)piperazin-1-yl, 4-methylpiperazin-1-yl and 4-isopropylpiperazin-1-yl and the carbon at the 3-position may be substituted with a group selected from the group consisting of fluoro, methyl, trifluoromethyl and methoxy,
(2-4) R^1 is phenyl in which the carbon at the 4-position is substituted with 4-(4-methylpiperazin-1-yl)piperidin-1-yl and the carbon at the 3-position may be substituted with a group selected from the group consisting of methyl, trifluoromethyl and methoxy,
(2-5) R^1 is phenyl in which the carbon at the 4-position is substituted with 4-methylpiperazin-1-yl and the carbon at the 3-position may be substituted with a group selected from the group consisting of fluoro and methoxy,
(2-6) R^1 is 4-{4-(4-methylpiperazin-1-yl)piperidin-1-yl}phenyl,
(2-7) R^1 is 3-methyl-4-{4-(4-methylpiperazin-1-yl)piperidin-1-yl}phenyl,
(2-8) R^1 is 4-{4-(4-methylpiperazin-1-yl)piperidin-1-yl}-3-(trifluoromethyl)phenyl,
(2-9) R^1 is 3-methoxy-4-{4-(4-methylpiperazin-1-yl)piperidin-1-yl}phenyl,
(2-10) R^1 is 4-(4-methylpiperazin-l-yl)phenyl,
(2-11) R^1 is 3-fluoro-4-(4-methylpiperazin-1-yl)phenyl,
(2-12) R^1 is 3-methoxy-4-(4-methylpiperazin-1-yl)phenyl,
(2-13) R^1 is 3-methyl-4-{4-(1-methylpiperidin-4-yl)piperazin-1-yl}phenyl, or
(2-14) R^1 is 4-(4-isopropylpiperazin-1-yl)-3-methylphenyl.

(3) Compounds of formula (I) or a salt thereof, wherein

(3-1) R^2 is

(i) cycloalkyl which may be substituted with one or more groups selected from the group consisting of -N(lower alkyl)$_2$, lower alkyl, -COO-lower alkyl, -OH, -COOH, -CONH-R^{ZB}, and morpholinyl, or
(ii) a non-aromatic heterocyclic ring which may be substituted with one or more groups selected from the group consisting of lower alkyl, -CO-lower alkyl, oxo, -CO-R^{ZB}, and benzyl,

(3-2) R^2 is cycloalkyl which may be substituted with one or more groups selected from the group consisting of -N(lower alkyl)$_2$, lower alkyl, -COO-lower alkyl, -OH, -COOH, -CONH-R^{ZB}, and morpholinyl,
(3-3) R^2 is a non-aromatic heterocyclic ring which may be substituted with one or more groups selected from the group consisting of lower alkyl, -CO-lower alkyl, oxo, -CO-R^{ZB}, and benzyl,
(3-4) R^2 is

(i) cyclohexyl which may be substituted with one or more groups selected from the group consisting of -N(lower alkyl)$_2$, lower alkyl, -COO-lower alkyl, -OH, -COOH, -CONH-R^{ZB}, and morpholinyl,
(ii) piperidinyl which may be substituted with one or more groups selected from the group consisting of lower alkyl, -CO-lower alkyl, oxo, -CO-R^{ZB}, and benzyl, or
(iii) tetrahydropyranyl,

(3-5) R^2 is cyclohexyl which may be substituted with one or more groups selected from the group consisting of -N(lower alkyl)$_2$, lower alkyl, -COO-lower alkyl, -OH, - COOH, -CONH-R^{ZB}, and morpholinyl,
(3-6) R^2 is piperidinyl which may be substituted with one or more groups selected from the group consisting of lower alkyl, -CO-lower alkyl, oxo, -CO-R^{ZB}, and benzyl,
(3-7) R^2 is tetrahydropyranyl,
(3-8) R^2 is 4-hydroxycyclohexyl, 4-hydroxy-4-methylcyclohexyl, or tetrahydropyran-4-yl,
(3-9) R^2 is 4-hydroxycyclohexyl,
(3-10) R^2 is 4-hydroxy-4-methylcyclohexyl, or
(3-11) R^2 is tetrahydropyran-4-yl.

(4) Compounds of formula (I) or a salt thereof, wherein R^3 is -H.
(5) Compounds, in which any combination of two or more of (1) to (4) shown above is applied. Examples of embodiments of the combination include:

(5-1) Compounds or a salt thereof, in which (1) and (4) shown above are applied,
(5-2) Compounds or a salt thereof, in which (1), (2), and (4) shown above are applied,
(5-3) Compounds or a salt thereof, in which (1), (2), (3), and (4) shown above are applied,
(5-6) Compounds or a salt thereof, in which (1-4), (2-2), (3-1), and (4) shown above are applied,
(5-7) Compounds or a salt thereof, in which (1-4), (2-3), (3-1), and (4) shown above are applied,
(5-8) Compounds or a salt thereof, in which (1-4), (2-3), (3-8), and (4) shown above are applied, and
(5-9) Compounds or a salt thereof, in which any consistent combination of two or more selected from the group consisting of (1-5), (1-7), (1-8), (2-6), (2-7), (2-8), (2-9), (2-10), (2-11), (2-12), (2-13), (2-14), (3-9), (3-10), (3-11) and (4) shown above is applied.

Other embodiments of the compound of formula (I) or a salt thereof are given below.
(6) Compounds of formula (I) or a salt thereof, wherein

(6-2) -X- is a group of formula (II), and A is ethyl or isopropyl,
(6-3) -X- is a group of formula (II), and A is ethyl, or
(6-4) -X- is a group of formula (II), and A is isopropyl.

(7) Compounds of formula (I) or a salt thereof, wherein

(7-2) R^1 is phenyl in which the carbon at the 4-position is substituted with -W-Y-Z and, as another substituent, the carbon at the carbon at the 3-position may be substituted with R^{00} or -O- R^{00}, -W- is piperidine-1,4-diyl (attached via the nitrogen atom to phenyl to which - W- is attached) or a bond, -Y- is a bond, and -Z is piperazin-1-yl in which the nitrogen atom at the 4-position may be substituted with lower alkyl,
(7-3) R^1 is phenyl in which the carbon at the 4-position is substituted with 4-(4-methylpiperazin-1-yl)piperidin-1-yl and, as another substituent, the carbon at the 3-position may be substituted with methyl, trifluoromethyl, methoxy, or ethoxy,
(7-4) R^1 is 3-methyl-4-{4-(4-methylpiperazin-1-yl)piperidin-1-yl}phenyl,

(7-5) R^1 is 4-{4-(4-methylpiperazin-1-yl)piperidin-1-yl}-3-(trifluoromethyl)phenyl,
(7-6) R^1 is 3-methoxy-4-{4-(4-methylpiperazin-1-yl)piperidin-1-yl}phenyl,
(7-7) R^1 is 3-ethoxy-4-{4-(4-methylpiperazin-1-yl)piperidin-1-yl}phenyl,
(7-8) R^1 is 4-{4-(4-methylpiperazin-1-yl)piperidin-1-yl}phenyl,
(7-9) R^1 is phenyl in which the carbon at the 4-position is substituted with 4-methylpiperazin-1-yl or 4-isopropylpiperazin-1-yl and, as another substituent, the carbon at the 3-position may be substituted with methyl, trifluoromethyl, or methoxy,
(7-10) R^1 is 3-methyl-4-(4-methylpiperazin-1-yl)phenyl,
(7-11) R^1 is 4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl,
(7-12) R^1 is 3-methoxy-4-(4-methylpiperazin-1-yl)phenyl,
(7-13) R^1 is 4-(4-methylpiperazin-1-yl)phenyl,
(7-14) R^1 is 4-(4-isopropylpiperazin-1-yl)-3-methylphenyl,
(7-15) R^1 is phenyl in which the carbon at the 3-position is substituted with $-SO_2-R^{00}$,
(7-16) R^1 is 3-(methylsulfonyl)phenyl,
(7-21) R^1 is 2-methoxy-4-{4-(4-methylpiperazin-1-yl)piperidin-1-yl}phenyl,
(7-23) R^1 is 4-morpholin-4-ylphenyl,
(7-24) R^1 is 4-(1-methylpiperidin-4-yl)phenyl,
(7-25) R^1 is 4-{4-(cyclopropylmethyl)piperazin-1-yl}-3-(trifluoromethyl)phenyl, or
(7-26) R^1 is 4-{3-(dimethylamino)pyrrolidin-1-yl}-3-(trifluoromethyl)phenyl.

(8) Compounds of formula (I) or a salt thereof, wherein

(8-1) R^2 is cycloalkyl substituted with -OH and lower alkyl,
(8-2) R^2 is cyclohexyl substituted with -OH and lower alkyl,
(8-3) R^2 is cyclohexyl in which the carbon at the 4-position is substituted with -OH and lower alkyl,
(8-4) R^2 is cyclohexyl in which the carbon at the 4-position is substituted with -OH and methyl,
(8-5) R^2 is cycloalkyl substituted with -OH,
(8-6) R^2 is cyclohexyl substituted with -OH,
(8-7) R^2 is 4-hydroxycyclohexyl,
(8-8) R^2 is a non-aromatic heterocyclic ring which may be substituted with lower alkyl,
(8-9) R^2 is tetrahydropyranyl which may be substituted with lower alkyl, or piperidinyl which may be substituted with lower alkyl,
(8-10) R^2 is tetrahydropyran-4-yl,
(8-11) R^2 is piperidin-4-yl in which the nitrogen atom at the 1-position may be substituted with lower alkyl,
(8-12) R^2 is 1-methylpiperidin-4-yl, or
(8-13) R^2 is piperidin-4-yl.

(9) Compounds of formula (I) or a salt thereof, wherein R^3 is -H.
(10) Compounds of (6-3) shown above or a salt thereof.
(11) Compounds of (7-4), (7-5), (7-6), (7-7), (7-8), (7-10), (7-13), or (7-14) shown above or a salt thereof.
(12) Compounds of (8-4), (8-7), (8-10), or (8-13) shown above or a salt thereof.
(13) Compounds, in which

(13-1) any combination of two or more of (6) to (9) shown above is applied, or a salt thereof, or
(13-2) any combination of two or more of (9) to (12) shown above is applied, or a salt thereof.

[0080] Examples of specific compounds falling within the present invention include the following compounds.

6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
5-[(trans-4-hydroxycyclohexyl)amino]-6-isopropyl-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-3-(trifluoromethyl)phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,

5-[(trans-4-hydroxycyclohexyl)amino]-6-isopropyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-3-(trifluoromethyl)phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(cis-4-hydroxy-4-methylcyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(4-isopropylpiperazin-1-yl)-3-methylphenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxy-4-methylcyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-chloro-5-[(trans-4-hydroxycyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-ethyl-3-({3-methoxy-4-[4-(4-methylpiperazin-2-yl)piperidin-1-yl]phenyl}amido)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-isopropyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-ethyl-3-{[3-fluoro-4-(4-methylpiperazin-1-yl)phenyl]amino}-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-isopropyl-3-[3-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide.
6-isopropyl-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide, or
6-ethyl-3-({3-methyl-4-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide, or a salt thereof.

[0081] Examples of specific compounds falling within the present invention include those selected from Compound groups P and Q shown below.

Compound group P:

a group consisting of 6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide.
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-3-(trifluoromethyl)phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[3-methyl-4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(cis-4-hydxoxy-4-methylcyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(4-isopropylpiperazin-1-yl)-3-methylphenyl]amino}pyrazine-2-carboxamide,
3-({3-ethoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxy-4-methylcyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-ethyl-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(piperidin-4-ylamino)pyrazine-2-carboxamide,
6-ethyl-3-{[4-(4-methylpiperazin-2-yl)phenyl]amino}-5-{tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-ethyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide, and
6-ethyl-3-({3-methoxy-4-[4-(4-methylpiperazin-1-yl)pipendin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide, as well as salts of these compounds.

Compound group Q:

a group consisting of 6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxy-4-methylcyclohexyl)amino]-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-[(1-methyl-1H-indazol-6-yl)amino]pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({3-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
5-[(trans-4-hydroxycyclohexyl)amino]-6-isopropyl-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[3-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[3-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-[(4-morpholin-4-ylphenyl)amino]pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(1-methylpiperidin-4-yl)phenyl]amino}pyrazine-2-carboxamide,
5-[(trans-4-hydroxycyclohexyl)amino]-6-isopropyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-3-(trifluoromethyl)phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(cis-4-hydroxy-4-methylcyclohexyl)amino]-3-{[3-methyl-4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide,
3-({4-[4-(cyclopropylmethyl)piperazin-1-yl]-3-(trifluoromethyl)phenyl}amino)-6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]pyrazine-2-carboxamide,
3-({4-[3-(dimethylamino)pyrrolidin-1-y1]-3-(trifluoromethyl)phenyl}amino)-6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]pyrazine-2-carboxamide,
6-ethyl-5-[(cis-4-ethyl-4-hydroxycyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-ethyl-4-hydroxycyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(cis-4-hydroxy-4-isopropylcyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxy-4-isopropylcyclohexyl)amino]-3-({3-methyl-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide, and
6-ethyl-3-(3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-[(1-methylpiperidin-4-yl)amino]pyrazine-2-carboxamide, as well as salts of these compounds.

[0082] The compounds of formula (I) may have tautomers and/or geometrical isomers (including cis-trans isomers of compounds having a saturated ring group such as a cycloalkyl group), depending on the type of their substituents. Even when the compounds of formula (I) appear herein only in one isomer form, the present invention encompasses the other isomers, and also encompasses separated isomers or mixtures thereof.

[0083] Further, since some compounds of formula (I) have an asymmetric carbon atom or axial asymmetry, optical isomers based on this asymmetry may also exist. The present invention also encompasses separated optical isomers of the compounds of formula (I) or mixtures thereof.

[0084] Likewise, salts of the compounds of formula (I) are pharmaceutically acceptable salts of the compounds of formula (I). The compounds of formula (I) may form acid or base addition salts, depending on the type of their substituents. Specific examples include acid addition salts with inorganic acids (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, and the like) or with organic acids (e.g., formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, mandelic acid, tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, aspartic acid, glutamic acid, and the like), salts with inorganic bases (e.g., sodium, potassium, magnesium, calcium, aluminum, and the like) or with organic bases (e.g., methylamine, ethylamine, ethanolamine, lysine, ornithine, and the like), salts with various amino acids and amino acid derivatives (e.g., acetylleucine, and the like), as

well as ammonium salt, etc.

[0085] Moreover, the present invention also encompasses the compounds of formula (I) and salts thereof in the form of various hydrates, solvates, and crystalline polymorphic substances. The present invention also encompasses the compounds labeled with various radioactive or non-radioactive isotopes.

[0086] The compounds of formula (I) and pharmaceutically acceptable salts thereof can be prepared by applying various known synthesis methods on the basis of characteristics derived from their skeletal structure or the type of their substituents. In some cases, depending on the type of functional group, it is technically effective to replace such a functional group with an appropriate protecting group (a group which can be easily converted into the original functional group) at the starting material stage or at the intermediate stage. Examples of such a protecting group include those described in Greene and Wuts, "Greene's Protective Groups in Organic Synthesis (fourth edition, 2007)" and so on, which may be selected and used as appropriate, depending on reaction conditions. In such a method, after introduction of the protecting group and subsequent reaction, the protecting group may be removed if necessary to obtain a desired compound.

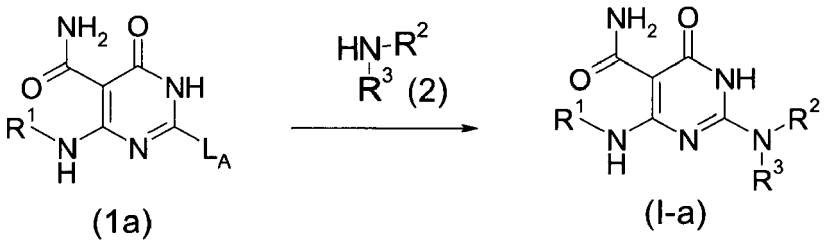
[0087] Likewise, a prodrug of the compound of formula (I) can be prepared by introducing a specific group at the starting material stage or at the intermediate stage, as in the case of the above protecting group, or by subjecting the obtained compound of formula (I) to further reaction. The reaction may be accomplished by applying conventional esterification, amidation, dehydration or other techniques known to those skilled in the art.

[0088] Explanation will be given below of typical processes for preparing the compounds of formula (I). Each process may also be accomplished by reference to the documents cited in this explanation. It should be noted that the processes of the present invention are not limited to the examples illustrated below.

(Preparation Process 1) (not part of the invention)

[0089]

[Formula 26]



(In the formula, $-L_A$ represents a leaving group, and examples include lower alkylsulfanyl.)

[0090] This process is intended to prepare the compound of the present invention (I-a) by reacting compound (1a) with compound (2).

[0091] In this reaction, compounds (1a) and (2) are used in equal amounts or one of them is used in an excessive amount. A mixture of these compounds is stirred in a solvent inert to the reaction or in the absence of a solvent under cooling to reflux conditions, preferably at 0°C to 200°C, generally for 0.1 hours to 5 days. The reaction may be performed using a microwave reaction system, because it is advantageous for smooth reaction in some cases. A solvent used for this purpose is not particularly limited, as long as it is inert to the reaction, and examples include aromatic hydrocarbons (e.g., benzene, toluene, xylene), ethers (e.g., diethyl ether, tetrahydrofuran (THF), dioxane, dimethoxyethane), halogenated hydrocarbons (e.g., 1,2-dichloroethane, chloroform), alcohols (e.g., methanol, ethanol, 2-propanol), 1-methyl-2-pyrrolidinone (NMP), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), 1,3-dimethyl-2-imidazolidinone (DMI), dimethyl sulfoxide (DMSO), acetonitrile, and mixtures thereof. The reaction may be performed in the presence of an organic base (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, or the like) or an inorganic base (e.g., potassium carbonate, sodium carbonate, potassium hydroxide, or the like), because it is advantageous for smooth reaction in some cases.

[0092] When the reaction is performed in the presence of such a base as shown above, depending on the properties or the like of starting compounds, the desired reaction is impossible or difficult to proceed, for example, due to decomposition or the like of the starting compounds. In this case, the reaction may be performed in the presence of a mineral acid (e.g., hydrochloric acid, hydrobromic acid, and the like), an organic acid (e.g., acetic acid, propionic acid, and the like) or a sulfonic acid (e.g., methanesulfonic acid, p-toluenesulfonic acid, and the like), because it is advantageous for smooth reaction in some cases. Further, when $-L_A$ is lower alkylsulfanyl, the S atom may be oxidized with various oxidizing agents such as Oxone®, m-chloroperbenzoic acid (mCPBA) and peracetic acid to convert the lower alkylsulfanyl

into lower alkylsulfinyl or lower alkylsulfonyl and then the lower alkylsulfinyl or lower alkylsulfonyl may be reacted with compound (2), because it is advantageous for smooth reaction in some cases.

[Documents]

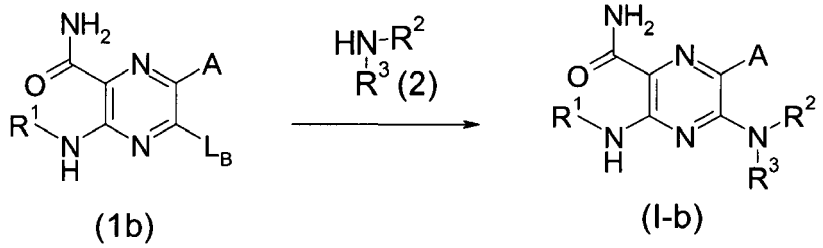
[0093] S. R. Sandler and W. Karo, "Organic Functional Group Preparations," second edition, vol. 1, Academic Press Inc., 1991

[0094] The Chemical Society of Japan, "Fifth Series of Experimental Chemistry," vol. 14 (2005) (MARUZEN Co., Ltd., Japan)

(Preparation Process 2)

[0095]

[Formula 27]



(1b) (I-b)

(In the formula, $-L_B$ represents a leaving group, and examples include a halogen (e.g., F, Cl), a sulfonyloxy group (e.g., methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy), lower alkylsulfanyl, and lower alkylsulfonyl.)

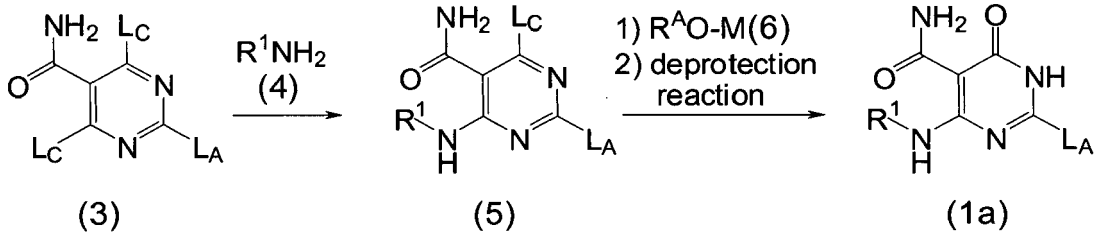
[0096] This process is intended to prepare the compound of the present invention (I-b) by reacting compound (1b) with compound (2).

[0097] In this reaction, the procedure of Preparation Process 1 may be applied.

(Starting Material Synthesis 1) (not part of the invention)

[0098]

[Formula 28]



(3) (5) (1a)

(In the formula, $-L_C$ represents a leaving group, and examples include a halogen (e.g., F, Cl) and a sulfonyloxy group (e.g., methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy); R^A represents acyl, benzyl, lower alkyl, or -H; and M represents an alkali metal.)

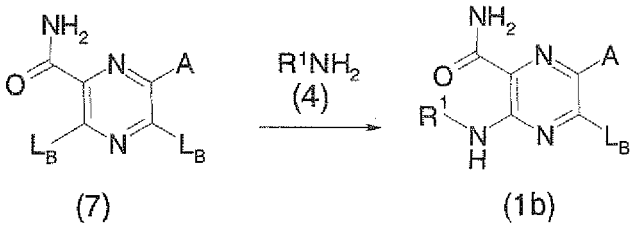
[0099] This process is intended to prepare compound (1a) by reacting compound (5), which is obtained by reacting compound (3) with compound (4), with compound (6) and thereafter subjecting to deprotection reaction to remove R^A.

[0100] In the reaction which gives compound (5), the procedure of Preparation Process 1 may be applied. In the reaction which gives compound (1a), the procedure of Preparation Process 1 may be applied and the reaction may be performed using compound (6) or a reagent which produces compound (6) in the system, and thereafter deprotection reaction may be conducted under reaction conditions which are selected as appropriate from, for example, reaction conditions described in Greene and Wuts, "Greene's Protective Groups in Organic Synthesis (fourth edition, 2007)." Examples of compound (6) include sodium acetate and sodium methoxide. It is to be noted that compound (1a) can also be prepared by performing the reaction using a hydrogen peroxide solution in place of compound (6) and thereafter performing acid treatment with hydrochloric acid or the like.

(Starting Material Synthesis 2)

[0101]

[Formula 29]



[0102] This process is intended to prepare compound (1b) by reacting compound (7) with compound (4).

[0103] In this reaction, the procedure of Preparation Process 1 may be applied.

[0104] The compound of formula (I) is isolated and purified as a free compound or as a pharmaceutically acceptable salt, hydrate, solvate or crystalline polymorphic substance thereof. A pharmaceutically acceptable salt of the compound of formula (I) may also be prepared by being subjected to conventional salt-forming reaction.

[0105] Isolation and purification may be accomplished by applying conventional chemical operations such as extraction, fractional crystallization, various types of fractionation chromatography, etc.

[0106] Various isomers can be prepared by selecting appropriate starting compounds or can be separated on the basis of differences in the physical and chemical properties of isomers. For example, optical isomers can be derived into optically pure isomers by conventional optical resolution techniques (e.g., fractional crystallization resulting in a diastereomer salt with an optically active base or acid, chromatography on a chiral column or the like, and the like). They can also be prepared from appropriate optically active starting compounds.

[0107] The compounds of formula (I) were confirmed for their pharmacological activity in the following tests. Unless otherwise specified, the test examples shown below may be accomplished by a method described in EP 1914240 or any publicly-known method and, when using commercially available reagents, kits, or the like, may be accomplished in accordance with the instructions attached to these commercially available products. It is to be noted that the term "EML4-ALK fusion protein v1" refers to a polypeptide of the amino acid sequence represented by SEQ ID NO: 2 of Patent Document 1, and the term "EML4-ALK fusion protein v3" refers to a polypeptide of the amino acid sequence represented by SEQ ID NO: 130 of Patent Document 1.

Test Example 1: Evaluation of inhibitory activity against the kinase activity of EML4-ALK fusion protein

[0108] A recombinant retrovirus was created from expression plasmid FLAG-EML4-ALKv1/pMX-iresCD8 in which cDNA for EML4-ALK fusion protein v1 was integrated, and injected into mouse lymphoid cell line BA/F3 cells. Using a magnetic bead reagent for cell separation and a purification column (anti-CD8 monoclonal antibody immobilized on magnetic beads and a MiniMACS purification column; both are products of Miltenyi Biotec Inc.), cell surface CD8-expressing cells were purified to establish EML4-ALK fusion protein v1-expressing BA/F3 cells. From the cells, EML4-ALK fusion protein v1 was purified and subjected to kinase activity evaluation. EML4-ALK fusion protein v1 was investigated for its phosphorylation activity toward a peptide substrate by using a kinase activity detection kit (HTRF KinEASE-TK; Cisbio Inc.). Test compounds were each added to a reaction solution containing the enzyme protein to give 8 final concentrations from 1000 nM to 0.3 nM, followed by addition of ATP and reaction for 1 hour. The ATP concentration used was 100 μM. Another reaction solution was prepared to contain the enzyme protein but no test compound (in which the solvent DMSO alone was added at 0.4% in place of the test compound), followed by reaction in the same manner with or without ATP addition. In the absence of the test compound, the phosphorylation count without ATP addition and with ATP addition was assumed to be 100% inhibition and 0% inhibition, respectively. The concentration causing 50% inhibition (IC_{50}) was calculated for each test compound by the logistic regression method.

[0109] As a result, some compounds of the present invention were found to have inhibitory activity against the kinase activity of EML4-ALK fusion protein v1. Table 1 shows the IC_{50} values obtained for some compounds of the present invention. Ex denotes Example No. In the table below, Compound X denotes a racemic form of the compound of Example 174 shown in International Publication No. WO 2009/136995 (rac-2-{[(1R,2S)-2-aminocyclohexyl]amino}-4-{[4'-(morpholin-4-yl)biphenyl-4-yl]amino}pyrimidine-5-carboxamide), and Compound Y denotes the compound of Examples 26-22 shown in International Publication No. WO 00/76980 (S-{[2-(dimethylamino)ethyl]amino}-6-ethyl-3-[(3-methylphenyl)amino]pyrazine-2-carboxamide).

[Table 1] (# not part of the invention)

Ex	IC_{50}(nM)	Ex	IC_{50}(nM)	Ex	IC_{50}(nM)
86#	17	383#	0.23	534	1.0
110#	0.99	387	0.26	538	2.3
284#	8.9	388	0.17	544	1.9
325	5.3	391	0.22	545	11
328#	76	392	0.21	546	7.8
340	0.37	399#	0.94	547	1.5
341	2.8	406#	0.34	549	2.1
343	2.1	426	0.49	550	11
347#	1.7	459	0.26	553	1.4
354	0.77	466	0.93	554	4.5
355	0.33	490	3.1	558	2.2
357	17	491	2.8	Compound X	220
370	0.65	493	2.6	Compound Y	>1000
377	0.24	494	4.1		
378	0.26	512	1.5		

Test Example 2: Evaluation of growth inhibitory activity against EML4-ALK fusion protein-dependent cells

[0110] EML4-ALK fusion protein v1-expressing BA/F3 cells can grow in the absence of IL-3. In other words, they are cells that EML4-ALK fusion protein v1-dependently grow.

[0111] In a 96-well plate (Iwaki), BA/F3 cells expressing EML4-ALK fusion protein v1 were seeded at 500 cells per well in RPMI1640 medium (Invitrogen) containing 10% fetal bovine serum, followed by addition of a test compound (final concentration: 10 μM to 0.1 nM). As a negative control, DMSO used as a solvent of the test compound was added. Then, the cells were cultured under 5% CO_2 at 37°C for 2 days. A cell counting reagent (AlmarBlue; Biosource) was added, and the cells were cultured for 150 minutes, followed by measurement of fluorescence intensity with a luminometer (Safire; Tecan) in accordance with instructions attached to the reagent. Assuming that the value measured for the medium alone and the value measured for the negative control were 100% inhibition and 0% inhibition, respectively, the inhibition rate was calculated for each compound to thereby determine the concentration causing 50% inhibition (IC_{50} value) by the logistic regression method.

[0112] As a result, some compounds of the present invention showed growth inhibitory activity against BA/F3 cells expressing EML4-ALK fusion protein v1. Table 2 shows the IC_{50} values obtained for some compounds of the present invention. Ex denotes Example No. In the table below, Compound X and Compound Y respectively denote the compounds described in Test Example 1.

[Table 2] (# not part of the invention)

Ex	IC_{50}(nM)	Ex	IC_{50}(nM)	Ex	IC_{50}(nM)
86#	68	383#	5.9	534	24
110#	64	387	10	538	7.7
284#	85	388	4.1	544	27
325	20	391	6.5	545	25
328#	76	392	6.3	546	23
340	9.5	399#	11	547	5.7
341	11	406#	9.8	549	14

(continued)

Ex	IC_{50}(nM)	Ex	IC_{50}(nM)	Ex	IC_{50}(nM)
343	11	426	11	550	39
347#	17	459	8.1	553	4.7
354	8.6	466	9.3	554	14
355	9.2	490	18	558	16
357	60	491	16	Compound X	821
370	4.9	493	19	Compound Y	>1000
377	6.9	494	42		
378	6.1	512	19		

[0113] From the results of Test Examples 1 and 2 shown above, it was confirmed that the compounds of the present invention had inhibitory activity against the kinase activity of EML4-ALK fusion protein v1 and growth inhibitory activity against EML4-ALK fusion protein v1-expressing BA/F3 cells. On the other hand, Compounds X and Y described in Test Example 1 were confirmed to have extremely weak inhibitory activity against the kinase activity of EML4-ALK fusion protein v1 and growth inhibitory activity against EML4-ALK fusion protein v1-expressing BA/F3 cells, compared with the compounds of the present invention.

Test Example 3: Antitumor test (*in vivo*) on EML4-ALK fusion protein-dependent cells

[0114] Expression plasmid EML4-ALKv1/pMXS in which cDNA for EML4-ALK fusion protein v1 was integrated was trasfected into 3T3 fibroblast cells by the phosphate calcium method to thereby establish EML4-ALK fusion protein v1 expressing 3T3 cells. 3×10^6 cells of EML4-ALK fusion protein v1 expressing 3T3 cells suspended in PBS were inoculated subcutaneously by injection to the back of 5 weeks old male Balb/c nude mice (Charles River Japan, Inc.). After 7 days of the inoculation, the administration of test compound was initiated. The test was conducted in the solvent group and the compound group, 4 animals per group. The test compound was suspended in a solvent composed of 0.5% methylcellulose and administered orally at a dose of 10 mg/kg. Administrations were performed once a day for 5 days, and body weight and tumor size were measured every other day. Tumor volume was calculated using the following formula.

$$[\text{Tumor volume } (\text{mm}^3)] = [\text{Tumor major axis } (\text{mm})] \times [\text{tumor minor axis } (\text{mm})]^2 \times 0.5$$

[0115] Assuming that the tumor volume of the solvent group on the day of starting and the day of finishing administration of the test compound was 100% inhibition and 0% inhibition, respectively, the inhibition rate of the test compound was calculated. When regression of tumor volume is induced from the day of starting administration, the tumor volume on the day of starting administration and the state in which the tumor disappeared were assumed to be 0% regression and 100% regression, respectively, and the rate of regression of the test compound was calculated.

[0116] As a result, it was confirmed that among the compounds of the present invention, there were compounds that inhibited growth of tumor of EML4-ALK fusion protein v1 expressing 3T3 cells and compounds that induced regression of tumor of EML4-ALK fusion protein v1 expressing 3T3 cells. Table 3 shows the inhibition rate of some compounds of the present invention. It is to be noted that in the table below, the numerical values specified with "(regression)" each indicate a rate of regression. Ex denotes Example No.

[Table 3]

Ex	(%)
370	81
378	92
392	28 (regression)
426	81
466	54 (regression)

(continued)

Ex	(%)
546	79
549	67 (regression)
553	63
558	37 (regression)

[0117] Thus, when orally administered, the compounds of the present invention inhibited tumor growth in mice inoculated with EML4-ALK fusion protein v1 expressing 3T3 cells or induced regression of tumor, thereby confirming that the compounds of the present invention had oral activity.

Test Example 4: Antitumor test (*in vivo*) on EML4-ALK fusion protein-dependent cells

[0118] The antitumor effects on EML4-ALK fusion protein-dependent cells can also be confirmed by use of human non-small cell lung cancers cell line NCI-H2228 cells (cells derived from EML4-ALK fusion polynucleotide-positive lung cancer patients (EML4-ALK fusion protein v3-dependent cells)) in place of the EML4-ALK fusion protein v1 expressing 3T3 cells of Test Example 3, as shown below.

[0119] 3×10^6 cells of NCI-H2228 cells suspended in 50% Matrigel (Invitrogen) were inoculated subcutaneously by injection to the back of 5 weeks old male NOD/SCID mice (Charles River Japan, Inc.). After 3 weeks of the inoculation, the administration of test compounds was initiated. The test was conducted in the solvent group and test compound groups, 6 animals per group. The test compounds were each dissolved in a solvent composed of 10% 1-methyl-2-pyrrolidinone (SIGMA-ALDRICH Inc.)/90% polyethylene glycol 300 (Fluka Inc.) and administered orally at a dose of 1 mg/kg. Administrations were performed once a day for 14 days, and body weight and tumor size were measured every other day. Tumor volume was calculated using the following formula.

$$[\text{Tumor volume } (\text{mm}^3)] = [\text{Tumor major axis } (\text{mm})] \times [\text{tumor minor axis } (\text{mm})]^2 \times 0.5$$

[0120] Assuming that the tumor volume of the solvent group on the day of starting and the day of finishing administration was 100% inhibition and 0% inhibition, respectively, the inhibition rate was calculated for each compound.

[0121] As a result, it was confirmed that among the compounds of the present invention, there were compounds that inhibited growth of tumor of NCI-H2228 cells. For example, the compound of Example 549 inhibited growth of tumor of NCI-H2228 cells by 69%.

[0122] Thus, when orally administered, the compounds of the present invention inhibited tumor growth in mice inoculated with human non-small cell lung cancer cell line NCI-H2228 cells, thereby confirming that the compounds of the present invention had oral activity.

[0123] On the other hand, when Compounds X and Y described in Test Example 1 were administered, no significant growth inhibition against NCI-H2228 cells (tumor) was shown, compared with the solvent group. The significance test was conducted by Student's t-test.

[0124] In view of the foregoing, in Test Examples 1 and 2, the compounds of the present invention were confirmed to have inhibitory activity against the kinase activity of EML4-ALK fusion protein, as well as growth inhibitory activity against EML4-ALK fusion protein-dependent cells. Further, in Test Examples 3 and 4, the compounds of the present invention were also confirmed to have an antitumor effect on EML4-ALK fusion protein-dependent cells (tumor) based on the above actions. These indicate that the compounds of the present invention are useful as active ingredients in pharmaceutical compositions for preventing and/or treating cancer, such as lung cancer in one embodiment, non-small cell lung cancer or small cell lung cancer in another embodiment, ALK fusion polynucleotide-positive cancer in yet another embodiment, ALK fusion polynucleotide-positive lung cancer in yet another embodiment, ALK fusion polynucleotide-positive non-small cell lung cancer in yet another embodiment, ALK fusion protein-positive cancer in yet another embodiment, ALK fusion protein-positive lung cancer in yet another embodiment, ALK fusion protein-positive non-small cell lung cancer in yet another embodiment, EML4-ALK fusion polynucleotide-positive cancer in yet another embodiment, EML4-ALK fusion polynucleotide-positive lung cancer in yet another embodiment, EML4-ALK fusion polynucleotide-positive non-small cell lung cancer in yet another embodiment, EML4-ALK fusion protein-positive cancer in yet another embodiment, EML4-ALK fusion protein-positive lung cancer in yet another embodiment, or EML4-ALK fusion protein-positive

non-small cell lung cancer in yet another embodiment.

[0125] So far, as to the ALK gene, the presence of various types of active point mutation and overexpression associated with gene amplification have been confirmed in cells derived from neuroblastoma patients (Nature, vol. 455, p. 971, 2008; Cancer Research, vol. 68, p. 3389, 2008). Further, it is known that a compound having inhibitory activity against the kinase activity of ALK protein shows an antitumor effect on cells derived from mutant ALK polynucleotide-positive cancer patients and cells derived from cancer patients with overexpression of ALK polynucleotide (Cancer Research, vol. 68, p. 3389, 2008). These indicate that the compounds of the present invention are useful as active ingredients in pharmaceutical compositions for preventing and/or treating neuroblastoma, such as mutant ALK polynucleotide-positive cancer in one embodiment, cancer with overexpression of ALK polynucleotide in another embodiment, mutant ALK polynucleotide-positive neuroblastoma in yet another embodiment, or neuroblastoma with overexpression of ALK polynucleotide in yet another embodiment.

[0126] The compounds of formula (I) were also confirmed for their pharmacological activity in the following tests. Unless otherwise specified, the test examples shown below may be accomplished in a known manner and, when using commercially available reagents and/or kits, may be accomplished in accordance with the instructions attached to these commercially available products.

Test Example 5: Evaluation of inhibitory activity against the kinase activity of RET protein

[0127] A partial protein of only a kinase domain of RET protein was purchased from Carna Biosciences Inc., Japan. The phosphorylation activity toward a peptide substrate was investigated using an EZ reader (Caliper). Test compounds were each mixed with a protein solution to give 8 final concentrations from 100 nM to 0.03 nM, followed by addition of a mixed liquid of ATP and substrate peptide (Caliper) and reaction for 30 minutes. The ATP concentration used was 100 μM. A reaction liquid which contained protein but no test compound (in which the solvent DMSO alone was added at 0.8% in place of the test compound) was prepared, followed by reaction in the same manner with or without ATP addition. In the absence of the test compound, the phosphorylation peptide peak without ATP addition and with ATP addition was assumed to be 100% inhibition and 0% inhibition, respectively. The test compound concentration causing 50% inhibition (IC_{50} value) was calculated by the logistic regression method.

[0128] As a result, some compounds of the present invention showed inhibitory activity against the kinase activity of RET protein. Table 4 shows the IC_{50} values obtained for some compounds of the present invention. Ex denotes Example No.

[Table 4]

Ex	IC_{50}(nM)	Ex	IC_{50}(nM)	Ex	IC_{50}(nM)
565	1.1	571	1.1	577	3.4
566	0.95	572	1.3	578	1.5
567	1.7	573	1.0	579	1.1
568	1.5	574	1.0	580	3.6
569	1.0	575	1.3	581	2.9
570	2.3	576	1.3	582	1.1

[0129] RET (Rearranged during transfection) is a receptor tyrosine kinase and is a protein having a transmembrane region in the middle part, flanked by a tyrosine kinase region on the carboxyl-terminal side and an extracellular region on the amino-terminal side.

[0130] From the results of Test Example 5, it was confirmed that the compounds of the present invention had inhibitory activity against the kinase activity of RET protein. So far, as to the RET gene, active point mutation has been confirmed in cells or cancer tissue specimens derived from non-small cell lung cancers, small cell lung cancer, thyroid cancer, adrenal pheochromocytoma, colon cancer, and pancreatic cancer, and fusion with H4, H4L, PRKAR1A, NCOA4, GOLGA5, HTIF1, TIF1G, TKTN1, RFG9, ELKS, PCM1, RFP, and HOOK3 genes has been confirmed in cells or cancer tissue specimens derived from thyroid cancer, ovarian cancer, and mesothelioma (point mutation in non-small cell lung cancer: Nature Genetics, 2007, 39, 347-351; point mutation in small cell lung cancer: Japanese Journal of Cancer Research, 1995, 86, 1127-1130; fusion and point mutation in thyroid cancer: Endocrine Reviews, 2006, 27, 535-560; point mutation in adrenal tumor: Journal of Clinical Endocrinology and Metabolism, 1996, 81, 2041-2046; point mutation in colon cancer: Science, 2006, 314, 268-274; point mutation in pancreatic cancer: Cancer Research, 2005, 65, 11536-11544; fusion in ovarian cancer: International Journal of Surgical Pathology, 2009, 17, 107-110; fusion in mes-

othelioma: Cancer letters, 2008, 265, 55-66). Further, it is known that a compound having inhibitory activity against the kinase activity of RET protein shows an antitumor effect on cells derived from mutant RET polynucleotide-positive cancer patients and cells derived from fusion RET polynucleotide-positive cancer patients (Endocrine Reviews, 2006, 27, 535-560). These indicate that the compounds of the present invention are useful as active ingredients in pharmaceutical compositions for preventing and/or treating thyroid cancer, such as adrenal pheochromocytoma in one embodiment, colon cancer in another embodiment, pancreatic cancer in yet another embodiment, ovarian cancer in yet another embodiment, mesothelioma in yet another embodiment, mutant RET polynucleotide-positive cancer in yet another embodiment, mutant RET polynucleotide-positive lung cancer in yet another embodiment, mutant RET polynucleotide-positive non-small cell lung cancer in yet another embodiment, mutant RET polynucleotide-positive small cell lung cancer in yet another embodiment, mutant RET polynucleotide-positive thyroid cancer in yet another embodiment, mutant RET polynucleotide-positive adrenal pheochromocytoma in yet another embodiment, mutant RET polynucleotide-positive colon cancer in yet another embodiment, mutant RET polynucleotide-positive pancreatic cancer in yet another embodiment, RET fusion polynucleotide-positive cancer in yet another embodiment, RET fusion polynucleotide-positive thyroid cancer in yet another embodiment, RET fusion polynucleotide-positive ovarian cancer in yet another embodiment, or RET fusion polynucleotide-positive mesothelioma in yet another embodiment.

Test Example 6: Evaluation of inhibitory activity against the kinase activity of ROS protein

[0131] A partial protein of only a kinase domain of ROS protein was purchased from Carna Biosciences Inc., Japan, and tests were conducted as in Test Example 5, except that the ATP concentration in the mixed solution of ATP and substrate peptide (Caliper) was 50 uM.

[0132] As a result, some compounds of the present invention showed inhibitory activity against the kinase activity of ROS protein. Table 5 shows the IC_{50} values obtained for some compounds of the present invention. Ex denotes Example No.

[Table 5]

Ex	IC_{50}(nM)	Ex	IC_{50}(nM)	Ex	IC_{50}(nM)
565	0.40	571	0.86	577	1.9
566	0.86	572	0.37	578	0.51
567	0.23	573	0.78	579	0.58
568	1.0	574	1.3	580	0.29
569	0.65	575	1.6	581	0.41
570	0.51	576	1.9	582	1.2

[0133] ROS (v-Ros avian UR2 sarcoma virus oncogene homolog 1) is a receptor tyrosine kinase and is a protein having a transmembrane region in the middle part, flanked by a tyrosine kinase region on the carboxyl-terminal side and an extracellular region on the amino-terminal side.

[0134] From the results of Test Example 6, it was confirmed that the compounds of the present invention had inhibitory activity against the kinase activity of ROS protein. So far, as to the ROS gene, fusion with the FIG gene, the SLC34A2 gene, and the CD74 gene has been confirmed in cells or cancer tissue specimens derived from non-small cell lung cancers and glioblastoma (Biochimica et Biophysica Acta (BBA) Reviews on Cancer, 2009, 1795, 37-52). Further, since it is known that siRNA which inhibits molecule expression of cell lines derived from SLC34A2-ROS fusion polynucleotide-positive cancer patients shows an antitumor effect on the cell lines (Cell, 2007, 131, 1190-1203), it can be expected that a compound having inhibitory activity against the kinase activity of ROS protein shows an antitumor effect on ROS fusion polynucleotide-positive cancer. These indicate that the compounds of the present invention are useful as active ingredients in pharmaceutical compositions for preventing and/or treating glioblastoma, such as ROS fusion polynucleotide-positive cancer in one embodiment, ROS fusion polynucleotide-positive lung cancer in another embodiment, ROS fusion polynucleotide-positive non-small cell lung cancer in yet another embodiment, or ROS fusion polynucleotide-positive glioblastoma in yet another embodiment.

Test Example 7: Evaluation of inhibitory activity against the kinase activity of FLT3 protein

[0135] A partial protein of only a kinase domain of FLT3 protein was purchased from Carna Biosciences Inc., Japan, and tests were conducted as in Test Example 5.

[0136] As a result, some compounds of the present invention showed inhibitory activity against the kinase activity of FLT3 protein. Table 6 shows the IC_{50} values obtained for some compounds of the present invention. Ex denotes Example No.

[Table 6]

Ex	IC_{50}(nM)	Ex	IC_{50}(nM)	Ex	IC_{50}(nM)
565	0.44	571	0.39	577	0.41
566	0.51	572	0.34	578	0.56
567	0.46	573	0.37	579	0.36
568	0.50	574	0.36	580	0.4.9
569	0.35	575	0.72	581	0.52
570	0.66	576	0.51	582	0.37

[0137] FLT3 (Fms- like tyrosine kinase 3) is a receptor tyrosine kinase and is a protein having a transmembrane region in the middle part, flanked by a tyrosine kinase region on the carboxyl-terminal side and an extracellular region on the amino-terminal side.

[0138] From the results of Test Example 7, it was confirmed that the compounds of the present invention had inhibitory activity against the kinase activity of FLT3 protein. So far, as to the FLT3 gene, active point mutation and internal tandem duplication mutation in the juxtamembrane region (FLT3-ITD) have been confirmed in cells derived from acute myelocytic leukemia patients, and fusion with the SPTBN1 gene has been confirmed in cells derived from atypical chronic myelocytic leukemia patients (active point mutation and internal tandem duplication in the juxtamembrane region in acute myelocytic leukemia: Current Pharmaceutical Design, 2005, 11, 3449-3457; fusion in atypical chronic myelocytic leukemia: Experimental Hematology, 2007, 35, 1723-1727). Further, it is known that a compound having inhibitory activity against the kinase activity of FLT3 protein shows an antitumor effect on cells derived from mutant FLT3 polynucleotide-positive cancer patients and cells derived from SPTBN1-FLT3 fusion polynucleotide-positive cancer patients (Current Pharmaceutical Design, 2005, 11, 3449-3457; Experimental Hematology, 2007, 35, 1723-1727). These indicate that the compounds of the present invention are useful as active ingredients in pharmaceutical compositions for preventing and/or treating acute myelocytic leukemia, such as atypical chronic myelocytic leukemia patients in one embodiment, mutant FLT3 polynucleotide-positive cancer in another embodiment, mutant FLT3 polynucleotide-positive acute myelocytic leukemia in yet another embodiment, FLT3 fusion polynucleotide-positive cancer in yet another embodiment, or FLT3 fusion polynucleotide-positive atypical chronic myelocytic leukemia in yet another embodiment.

Test Example 8: Kinase inhibition profiling

[0139] The inhibition rates against 78 types of tyrosine kinases (ABL, ARG, BTK, BMX, ITK, TEC, TXK, FRK, BLK, LCK, HCK, LYN, FGR, FYN, SRC, YES, BRK, SRM, CSK, CTK, FER, FES, ACK, TNK1, HER4, EGFR, HER2, JAK1, TYK2, JAK2, JAK3, ROS, ALK, LTK, IRR, INSR, IGF1R, DDR1, DDR2, MUSK, TRKA, TRKB, TRKC, TYRO3, AXL, MER, MET, RON, RET, FGFR4, FGFR1, FGFR2, FGFR3, FLT4, KDR, FLT1, FLT3, FMS, KIT, PDGFRa, PDGFRb, TIE2, EphA1, EphA2, EphA8, EphA7, EphA6, EphA4, EphA3, EphA5, EphB4, EphB3, EphB1 EphB2, FAK, PYK2, SYK, ZAP70) were calculated for each test compound at 5 nM. Activity measurement was made by Carna Biosciences Inc., Japan, and the data were analyzed as follows: assuming that the average signal of control wells containing all reaction components was 0% inhibition and the average signal in the absence of the enzyme was 100% inhibition, the inhibition rate was calculated for each test substance from the average signal of two test wells.

[0140] As a result, at a concentration of 5 nM, some compounds of the present invention showed 50% or more inhibitory activity against 7 types of kinases including ALK, RET, ROS and FLT3 and, hence, appear to be highly selective for specific kinases and to have fewer fears about safety, which fears are induced by inhibition of non-target kinases responsible for side effects.

[0141] A pharmaceutical composition which comprises one or more compounds of formula (I) or pharmaceutically acceptable salts thereof as an active ingredient can be prepared in a conventional manner by using a pharmaceutical excipient, a pharmaceutical carrier or other additives commonly used in the art.

[0142] Any mode of administration may be used, either oral administration in the dosage form of tablets, pills, capsules, granules, powders, solutions or the like, or parenteral administration in the dosage form of injections (e.g., intraarticular, intravenous, intramuscular, and the like), suppositories, eye drops, eye ointments, percutaneous solutions, ointments, percutaneous patches, transmucosal solutions, transmucosal patches, inhalants or the like.

[0143] Solid compositions used for oral administration include tablets, powders, granules, and the like. In these solid compositions, one or more active ingredients are mixed with at least one inert excipient, for example, lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, and/or magnesium aluminometasilicate, or the like. The compositions may also comprise inert additives, for example, lubricants (e.g., magnesium stearate and the like), disintegrating agents (e.g., carboxymethyl starch sodium and the like), stabilizers, and/or solubilizers, as in the usual cases. Tablets or pills may be coated with sugar coating or a gastric or enteric film, if necessary.

[0144] Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, or the like, and comprise commonly-used inert diluents such as purified water or ethanol. These liquid compositions may comprise, in addition to inert diluents, auxiliaries (e.g., solubilizers, wetting agents, suspending agents, and the like), sweeteners, flavors, aromatics, and/or antiseptics.

[0145] Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions or emulsions. Examples of aqueous solvents include injectable distilled water or physiological saline. Examples of non-aqueous solvents include propylene glycol, polyethylene glycol or vegetable oils (e.g., olive oil and the like), as well as alcohols (e.g., ethanol and the like) or Polysorbate 80 (pharmacopoeia name), and the like. These compositions may further comprise isotonizing agents, antiseptics, wetting agents, emulsifiers, dispersants, stabilizers or solubilizers. They are sterilized, for example, by filtration through a bacteria-retaining filter, by incorporation with disinfectants or by irradiation. Alternatively, they may be formulated into a sterile solid composition and reconstituted for use by being dissolved or suspended in sterile water or a sterile injectable solvent before use.

[0146] Formulations for external use include ointments, plasters, creams, jellies, cataplasms, sprays, lotions, eye drops, eye ointments, and the like. They comprise commonly-used ointment bases, lotion bases, aqueous or non-aqueous solutions, suspensions, emulsions or the like. Examples of ointment or lotion bases include polyethylene glycol, propylene glycol, white petrolatum, white beeswax, polyoxyethylene hydrogenated castor oil, glycerine monostearate, stearyl alcohol, cetyl alcohol, Lauromacrogol, sorbitan sesquioleate, and the like.

[0147] Transmucosal formulations such as inhalants or transnasal formulations are used in solid, liquid or semi-solid form and can be prepared in a conventionally known manner. For example, such formulations may be supplemented as appropriate with known excipients and further with pH adjustors, antiseptics, surfactants, lubricants, stabilizers, thickeners and so on. For their administration, an appropriate device for inhalation or insufflation may be used. For example, using a known device (e.g., a metered-dose inhalation device and the like) or a nebulizer, the compound(s) may be administered alone or as a powder of a formulated mixture or as a solution or suspension in combination with a pharmaceutically acceptable carrier. Dry powder inhalators or the like may be for single or multiple administration use, and dry powders or powder-containing capsules may be used in such devices. Alternatively, they may be in the form of pressurized aerosol sprays or the like which use an appropriate propellant, for example, a preferred gas such as chlorofluoroalkane, hydrofluoroalkane, carbon dioxide, or the like.

[0148] In general, for oral administration, the daily dosage is desirably about 0.001 to 100 mg/kg, preferably 0.005 to 30 mg/kg, and more preferably 0.01 to 10 mg/kg body weight, given as a single dose or in 2 to 4 divided doses. For intravenous administration, the daily dosage is desirably about 0.0001 to 10 mg/kg body weight, given in one or several doses per day. Likewise, for transmucosal formulations, the daily dosage is about 0.001 to 100 mg/kg body weight, given in one or several doses per day. The dosage may be determined as appropriate for each case in consideration of symptom, age, sex and so on.

[0149] The compounds of formula (I) can be used in combination with various therapeutic or prophylactic agents for diseases against which the compounds of formula (I) would be effective. In general, when an antitumor agent is administered alone during chemotherapy for tumor, particularly malignant tumor, the antitumor agent has a limit in its effect in terms of side effects and the like, and thus often fails to produce a sufficient antitumor effect. For this reason, in clinical cases, multidrug therapy is used in which two or more drugs with different mechanisms of action are combined. By combining antitumor agents with different mechanisms of action, this combination therapy aims to reduce side effects and/or enhance the desired antitumor effect, for example, 1) to reduce the number of non-sensitive cell population, 2) to prevent or delay the development of drug resistance, 3) to disperse toxicity by combination of drugs with different toxicity levels, and the like. In such combination therapy, drugs may be administered simultaneously or separately in succession or at desired time intervals. Formulations for simultaneous administration may be in either mixed or separate form.

[0150] Drugs which can be combined include chemotherapeutics (e.g., alkylating agent, antimetabolite, and the like), immunotherapeutic agents, hormonal therapeutic agents, and cell growth factor inhibitors, more specifically drugs such as cisplatin, carboplatin, paclitaxel, docetaxel, gemcitabine, irinotecan, vinorelbine, bevacizumab, pemetrexed and the like.

EXAMPLES

[0151] How to prepare the compounds of formula (1) will be further explained in more detail by way of the following

examples. It should be noted that the present invention is not limited to the compounds shown in the following examples. In addition, how to prepare the starting compounds is shown in preparation examples. Processes for preparing the compounds of formula (I) are not limited only to those actually shown in the following examples, and the compounds of formula (I) may also be prepared by any combination of these processes or by any process obvious to those skilled in the art.

[0152] In the examples, preparation examples and tables shown below, the following abbreviations are used as needed. Rex: Preparation Example No., Ex: Example No., Structure: chemical structural formula, Data: physical and chemical data (FAB+: FAB-MS[M+H]$^+$, ESI+: ESI-MS[M+H]$^+$, APCI/ESI+: APCI/ESI-MS[M+H]$^+$ (APCI/ESI means simultaneous measurement of APCI and ESI), FAB-: FAB-MS[M-H]$^-$, ESI-: ESI-MS[M-H]$^-$, APCI-: APCI-MS[M-H]$^-$, ^{1}H-NMR ($CDCl_3$): δ (ppm) of ^{1}H-NMR peaks in chloroform-d, ^{1}H-NMR(CD3OD): δ (ppm) of ^{1}H-NMR peaks in methanol-d, ^{1}H-NMR(CDCl3+CD3OD): δ (ppm) of ^{1}H-NMR peaks in a mixed solution of chloroform-d and methanol-d, ^{1}H-NMR(DMSO-d_6): δ (ppm) of ^{1}H-NMR peaks in DMSO-d_6, XRD: diffraction angle 2θ(°) of main peak in powder X ray diffraction measurement, HCl: which means that the intended product was obtained as hydrochloride, 2HCl: which means that the intended product was obtained as a dihydrochloride, TsOH: which means that the intended product was obtained as a p-toluene sulfonic acid salt, HFM: which means that the intended product was obtained as a hemifumaric acid salt, FM: which means that the intended product was obtained as a fumaric acid salt, Me: methyl, Et: ethyl, nPr: normalpropyl, iPr: isopropyl, cPr: cyclopropyl, cHex: cyclohexyl, Ph: phenyl, Bn: benzyl, Boc: tert-butyloxycarbonyl, Ac: acetyl. Syn: preparation process (indicating that the intended compound was prepared from corresponding starting materials as in the indicated Preparation Example or Example). In the tables shown in Preparation Examples or Examples, there are cis-trans isomers and their configurations are undecided, but as to compounds that show a single configuration of one of cis and trans, no indication of configuration is made in their chemical structural formulas and, instead, the symbol "*" is given to their preparation example Nos. or example Nos. Compounds that are give the same number following the symbol "*" indicate that one of the compounds is a cis form and the other is a trans form.

[0153] The measurement of powder X ray diffraction was performed using RINT-TTR II under the following conditions; tube: Cu, tube current: 300 mA, tube voltage: 50 kV, sampling width: 0.020°, scan rate: 4°/min, wavelength: 1.54056 Å, range of diffraction angle measured (2θ): 2.5 to 40°. It is to be noted that the powder X ray diffraction should not strictly be understood, because, due to the nature of powder X ray diffraction data, crystal lattice space and overall pattern are important in determination of crystal identity, and the relative intensity may vary in some degree depending on the direction of crystal growth, particle size, and measurement conditions.

Preparation Example 4

[0154] A mixture of 4-methyl-3-nitrobenzoic acid (1.97 g) and thionyl chloride (6 mL) was heated under reflux for 18 hours. The reaction liquid was concentrated under reduced pressure, followed by an azeotropic process with toluene to give a red-brown oil. To a mixture of the red-brown oil and THF (25 mL), diethylamine (2.6 mL) was added under ice cooling and stirred at room temperature for 5 hours. The reaction liquid was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give N,N-diethyl-4-methyl-3-nitrobenzamide (2.61 g) as a brown oil.

Preparation Example 41

[0155] To a mixture of 2-methoxy-4-nitrobenzenesulfonylchloride (600 mg) and THF (5 mL), a mixture of piperidine (406 mg) and THF (1 mL) was added and stirred at room temperature for 12 hours. After addition of 10 % hydrochloric acid, the reaction liquid was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give 1-[(2-methoxy-4-nitrophenyl)sulfonyl]piperidine (714 mg) as a yellow solid.

Preparation Example 48

[0156] A mixture of 2-fluoro-5-nitrobenzoic acid (600 mg) and thionyl chloride (2 mL) was heated under reflux for 15 hours. The reaction liquid was concentrated under reduced pressure, followed by an azeotropic process with toluene to give a yellow crystal. To a mixture of the yellow crystal and THF (11 mL), triethylamine (0.47 mL) and isopropylamine (0.29 mL) were added under ice cooling and stirred at room temperature for 5 hours. The reaction liquid was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give a yellow crystal. To a mixture of the yellow crystal (723 mg) and methanol (8 mL) and water (3 mL), ammonium chloride (2.05 g) and zinc powder (2.09 g) were added, and the mixture was heated under reflux for 3 hours. After filtration of the

reaction suspension through celite, the filtrate was concentrated under reduced pressure. The residue was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent; chloroform:methanol) to give 5-amino-2-fluoro-N-isopropylbenzamide (527 mg) as a light brown crystal.

Preparation Example 160

[0157] To a mixture of 3,5-dichloro-6-ethylpyrazine-2-carboxamide (1.0 g) and DMF (15 mL), thionyl chloride (1 mL) was added at room temperature and stirred for 20 minutes. The reaction liquid was poured into ice-cold water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent; ethyl acetate:n.-hexane) to give 3,5-dichloro-6-ethylpyrazine-2-carbonitrile (608 mg) as a slightly yellow oil.

Preparation Example 194

[0158] To a solution of a mixture of methyl 5-chloro-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxylate (Preparation Example 193) (20 mg) and THF (2 mL), O-methylhydroxylamine hydrochloride (14 mg) was added. To the reaction liquid, lithium hexamethyldisilazide (0.39 mL, 1M THF solution) was added under ice cooling and stirred for 20 minutes. The reaction liquid was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate, and then the organic layer was washed with saturated aqueous sodium chloride. After drying over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to give 5-chloro-N-methoxy-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide (21 mg) as a yellow powder.

Preparation Example 240

[0159] To a mixture of 1-(2-iodo-4-nitrophenyl)-4-methylpiperazine (Preparation Example 241) (406 mg), toluene (3 mL) and water (3 mL), sodium carbonate (496 mg), phenylboronic acid (157 mg) and tetrakis(triphenylphosphine)palladium (68 mg) were added in an argon atmosphere and stirred overnight at 110°C. The reaction liquid was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent; chloroform/methanol) to give 1-methyl-4-(5-nitrobiphenyl-2-yl)piperazine (348 mg) as a yellow brown oil.

Preparation Example 244

[0160] To a mixture of N-[2-(4-methylpiperazin-1-yl)-5-nitrophenyl]acetamide (433 mg) and DMF (5 mL), 63% sodium hydride in oil (66 mg) was added under ice cooling and stirred at room temperature for 1 hour. The reaction liquid was ice cooled again, and methyl iodide (0.11 mL) was added and stirred at room temperature for 4 hours. The reaction liquid was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent; chloroform:methanol) to give N-methyl-N-[2-(4-methylpiperazin-1-yl)-5-nitrophenyl]acetamide (200 mg) as an orange solid.

Preparation Example 246

[0161] To a mixture of tert-butyl (4-oxocyclohexyl)carbamate (3.04 g) and THF (100 mL), ethyllithium (0.5 M benzene-cyclohexane solution) (56.8 mL) was added at -78°C and stirred over 4 hours until it reached -50°C. After addition of water (150 mL), the reaction liquid was heated to room temperature and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and then dried over sodium sulfate, and the solvent was distilled off. The resulting residue was purified by silica gel column chromatography (eluent; chloroform:methanol = 30:1) and further purified (eluent; n-hexane:ethyl acetate = 2:1 to 1:1) to give tert-butyl (4-ethyl-4-hydroxycyclohexyl)carbamate (Preparation Example 246) (0.202 g), which was a low-polarity product, as a white solid and tert-butyl (4-ethyl-4-hydroxycyclohexyl)carbamate (Preparation Example 248), which was a high-polarity product, as a colorless syrup.

Preparation Example 247

[0162] To a mixture of tert-butyl (4-ethyl-4-hydroxycyclohexyl)carbamate (Preparation Example 246) (0.202 g) and dioxane (2 mL), 26% hydrogen chloride-dioxane (1.1 mL) was added under ice cooling and stirred at room temperature for 12 hours. The solvent was distilled off to give 4-amino-1-ethylcyclohexanol hydrochloride (0.140 g) as a white viscous solid.

Preparation Example 249

[0163] To a mixture of tert-butyl (4-ethyl-4-hydroxycyclohexyl)carbamate (Preparation Example 248) (0.256 g) and dioxane (2 mL), 26% hydrogen chloride-dioxane (1.4 mL) was added under ice cooling and stirred at room temperature for 17 hours. The precipitated solid was collected by filtration to give 4-amino-1-ethylcyclohexanol hydrochloride (0.152 g) as a white solid.

Preparation Example 250

[0164] To a mixture of tert-butyl (4-oxocyclohexyl)carbamate (3.04 g) and THF (100 mL), isopropyllithium (0.7 M pentane solution) (40.3 mL) was added at -78°C and stirred over 4 hours until it reached -50°C. After addition of water (150 mL), the reaction liquid was heated to room temperature and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and then dried over sodium sulfate, and the solvent was distilled off. The resulting residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 3:1) and further purified (eluent; chloroform:methanol = 30:1) to give tert-butyl (4-isopropyl-4-hydroxycyclohexyl)carbamate (Preparation Example 250) (0.854 g), which was a low-polarity product, as a white solid and tert-butyl (4-isopropyl-4-hydroxycyclohexyl)carbamate (Preparation Example 252) (0.179 g), which was a high-polarity product, as a yellow oil.

Preparation Example 251

[0165] To a mixture of tert-butyl (4-isopropyl-4-hydroxycyclohexyl)carbamate (Preparation Example 250) (0.392 g) and dioxane (3 mL), 26% hydrogen chloride-dioxane (2.0 mL) was added under ice cooling and stirred at room temperature for 18 hours. The precipitated solid was collected by filtration to give 4-amino-1-isopropylcyclohexanol hydrochloride (0.190 g) as a white solid.

Preparation Example 253

[0166] To a mixture of tert-butyl (4-isopropyl-4-hydroxycyclohexyl)carbamate (Preparation Example 252) (0.179 g) and dioxane (1.5 mL), 26% hydrogen chloride-dioxane (0.9 mL) was added under ice cooling and stirred at room temperature for 18 hours. The precipitated solid was collected by filtration to give 4-amino-1-isopropylcyclohexanol hydrochloride (0.086 g) as a white solid.

Preparation Example 287

[0167] To a mixture of propane-2-thiol (3.30 mL), potassium carbonate (6.60 g) and DMF (40 mL), 1-fluoro-4-methyl-2-nitrobenzene (4.85 g) was added and stirred at room temperature for 5 hours. After addition of water, the reaction liquid was extracted with ethyl acetate, and the extract was washed with water and saturated aqueous sodium chloride. After drying over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to give 1-(isopropylsulfanyl)-4-methyl-2-nitrobenzene (6.60 g) as a yellow oil.

Preparation Example 291

[0168] To a mixture of 1-(isopropylsulfanyl)-4-methyl-2-nitrobenzene (Preparation Example 287) (6.60 g) and chloroform (150 mL), m-chloroperbenzoic acid (18.0 g) was added and stirred at 50°C for 12 hours. After the reaction liquid was cooled, saturated aqueous sodium hydrogen carbonate and 5% aqueous sodium sulfite were added, and the reaction liquid was extracted with chloroform. After the organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to give 2-(isopropylsulfonyl)-4-methyl-1-nitrobenzene (7.41 g) as a yellow solid.

Preparation Example 292

[0169] To a mixture of 2-(isopropylsulfonyl)-4-methyl-1-nitrobenzene (Preparation Example 291) (7.41 g) and acetic

acid (70 mL), iron powder (5.43 g) was added and stirred at 80°C for 3 hours. Thereafter, insoluble materials in the reaction liquid were removed, and the solvent was distilled off under reduced pressure. After addition of ethyl acetate (150 mL) and removal of insoluble materials, the residue was washed with water and saturated aqueous sodium chloride. After drying over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was washed with ethyl acetate-diisopropyl ether to give 2-(isopropylsulfonyl)-4-methylaniline (3.86 g) as a light yellow solid.

Preparation Example 298

[0170] To a mixture of 55% sodium hydride in oil (733 mg) and DMF (20 mL), a mixture of 3-(methylsulfonyl)aniline (1.44 g) and THF (20 mL) were added under ice cooling and stirred for 30 minutes under ice cooling. After dropwise addition of a mixture of 4,6-dichloro-2-(methylsulfanyl)pyrimidine-5-carboxamide (2.0 g) and DMF (30 mL) over 15 minutes, the reaction liquid was further stirred under ice cooling for 15 minutes. After addition of 10% aqueous citric acid (300 mL) and extraction with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was concentrated, and the precipitated solid was collected by filtration and dried to give 4-chloro-2-(methylsulfanyl)-6-{[3-(methylsulfonyl)phenyl]amino}pyrimidine-5-carboxamide (1.95 g) as a light yellow solid.

Preparation Example 299

[0171] To a mixture of 4-chloro-2-(methylsulfanyl)-6-{[3-(methylsulfonyl)phenyl]amino}pyrimidine-5-carboxamide (Preparation Example 298) (1.95 g) and DMSO (30 mL), potassium carbonate (1.81 g) and 30% hydrogen peroxide solution (2.65 mL) were added and stirred at 50°C for 1.5 hours. The reaction liquid was ice-cooled, and 1M hydrochloric acid (25 mL) and thereafter water (150 mL) were added and stirred for 30 minutes. The precipitated solid was collected by filtration and washed with water to give 2-(methylsulfanyl)-4-{[3-(methylsulfonyl)phenyl]amino}-6-oxo-1,6-dihydropyrimidine-5-carboxamide (1.40 g) as a light yellow solid.

Preparation Example 304

[0172] To a mixture of 4-chloro-6-[(6-methylpyridin-3-yl)amino]-2-(methylsulfanyl)pyrimidine-5-carboxamide (Preparation Example 303) (51 mg) and methanol (1 mL), sodium methoxide (11 mg) was added under ice cooling and stirred overnight at room temperature. Water was added to the reaction liquid, and the solid was collected by filtration to give 4-methoxy-6-[(6-methylpyridin-3-yl)amino]-2-(methylsulfanyl)pyrimidine-5-carboxamide (41 mg).

Preparation Example 311

[0173] To a mixture of 4-{[3-(methylcarbamoyl)phenyl]amino}-2-(methylsulfanyl)-6-oxo-1,6-dihydropyrimidine-5-carboxamide (Preparation Example 306) (500 mg), dichloromethane (40 mL) and methanol (40 mL), a mixture of Oxone® (922 mg) and water (10 mL) was added and stirred at room temperature for 18 hours. To the reaction liquid, chloroform and water were added, and the precipitated solid was collected by filtration and washed with water to give 4-{[3-(methylcarbamoyl)phenyl]amino}-2-(methylsulfinyl)-6-oxo-1,6-dihydropyrimidine-5-carboxamide (234 mg) as a light yellow solid.

Preparation Example 339

[0174] To a mixture of 4-methoxy-6-[(6-methoxy-pyridin-3-yl)amino]-2-(methylsulfanyl)pyrimidine-5-carboxamide (Preparation Example 337) (0.35 g) and water (2.2 mL), concentrated hydrochloric acid (2.2 mL) was added and stirred at 80°C for 1.5 hours. After the reaction liquid was cooled, 1M aqueous sodium hydroxide was added so that the reaction liquid became almost neutral, and then the resulting solid was collected by filtration to give 4-[(6-methoxy-pyridin-3-yl)amino]-2-(methylsulfanyl)-6-oxo-1,6-dihydropyrimidine-5-carboxamide (0.34 g).

Preparation Example 342

[0175] To a mixture of 4,6-dichloro-2-(methylsulfanyl)pyrimidine-5-carboxylic acid (1.50 g) and dichloromethane (15 mL), oxalyl chloride (1.20 mL) and DMF (0.015 mL) were added under ice cooling and stirred 30 minutes under ice cooling and 2 hours at room temperature. The solvent was distilled off under reduced pressure, followed by an azeotropic process with toluene. The resulting residue was dissolved in THF, followed by dropwise addition of 40% aqueous methylamine at -10°C. After the dropwise addition was completed, the reaction liquid was concentrated, and water was added. The resulting solid was collected by filtration and washed with water to give a white solid. The solid was dissolved

in ethyl acetate, washed with saturated aqueous sodium chloride, and then dried over anhydrous magnesium sulfate. The solvent was distilled off. To a mixture of the resulting residue and dioxane (20 mL), 3-(methylsulfonyl)aniline hydrochloride (432 mg) and N,N-diisopropylethylamine (0.73 mL) were added and stirred at 100°C for 4 hours. After cooling, the reaction liquid was diluted with ethyl acetate and washed with saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol = 100:0 to 30:1) to give 4-chloro-N-methyl-2-(methylsulfanyl)-6-{[3-(methylsulfonyl)phenyl]amino}pyrimidine-5-carboxamide (445 mg) as a white solid.

Preparation Example 346

[0176] To a mixture of 4-chloro-2-(methylsulfanyl)-6-(quinolin-3-ylamino)pyrimidine-5-carboxamide (Preparation Example 344) (0.68 g) and sodium acetate (0.80 g), DMF (7 mL) was added and stirred at 100°C for 6 hours. After the reaction liquid was returned to room temperature, water was added, and the resulting solid was collected by filtration to give 5-carbamoyl-2-(methylsulfanyl)-6-(quinolin-3-ylamino)pyrimidin-4-yl acetate (0.71 g).

Preparation Example 349

[0177] To 5-carbamoyl-2-(methylsulfanyl)-6-(quinolin-3-ylamino)pyrimidin-4-yl acetate (Preparation Example 346) (0.71 g), ethanol (14 mL) and THF (14 mL) were added, and 1M aqueous sodium hydroxide (6 mL) was added and stirred at room temperature for 1 hour. Then, 1M hydrochloric acid (6 mL) was added, and the precipitated solid was collected by filtration and dried to give 2-(methylsulfanyl)-6-oxo-4-(quinolin-3-ylamino)-1,6-dihydropyrimidine-5-carboxamide (0.63 g).

Preparation Example 353

[0178] A mixture of 3,5-dichloro-6-ethylpyrazine-2-carboxamide (600 mg), 3-(methylsulfonyl)aniline (467 mg), N,N-diisopropylethylamine (0.48 mL) and dioxane (18 mL) was stirred in a sealed tube at 170°C for 17 hours. After cooling, the mixture was partitioned using ethyl acetate and water, and the organic layer was washed with saturated aqueous sodium chloride and then dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was washed with chloroform, and the solid was collected by filtration and dried to give 5-chloro-6-ethyl--3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (412 mg) as a yellow solid.

Preparation Example 364

[0179] To a mixture of 4-chloro-6-[(5-methylpyridin-3-yl)amino]-2-(methylsulfanyl)pyrimidine-5-carboxamide (Preparation Example 359) (194 mg) and DMF (5 mL), sodium acetate (257 mg) was added and stirred at 100°C for 5 hours. After the reaction liquid was cooled, ethyl acetate and water were added, and the precipitated powder was collected by filtration and dried to give a light yellow solid. To a mixture of the solid, ethanol (5 mL), methanol (20 mL) and THF (5 mL), 1M aqueous sodium hydroxide (3 mL) was added and stirred at room temperature for 1 hour, at 60° C for 1 hour, and at 80° C for 1 hour. After the reaction liquid was cooled, 1M hydrochloric acid (3 mL) was added, and the reaction liquid was extracted with chloroform-isopropanol. Silica gel was added to the organic layer, and the solvent was distilled off, followed by purification by silica gel column chromatography (eluent; chloroform:methanol = 100:0 to 20:1) to give a crude product. This crude product was washed with a small amount of methanol to give 4-[(5-methylpyridin-3-yl)amino]-2-(methylsulfanyl)-6-oxo-1,6-dihydropyrimidine-5-carboxamide (27 mg) as a yellow solid.

Preparation Example 397

[0180] To a mixture of 5-chloro-6-ethyl-3-{[4-(methylsulfanyl)phenyl]amino}pyrazine-2-carboxamide (Preparation Example 394) (92 mg) and acetic acid (2.5 mL), sodium tungstate dihydrate (29 mg) and 30% hydrogen peroxide solution (0.15 mL) were added and stirred at room temperature for 30 minutes. After water and ethyl acetate were added to the reaction liquid, 1M aqueous sodium hydroxide was added and stirred for 30 minutes, and the reaction liquid was partitioned. After drying over anhydrous sodium sulfate, the organic layer was filtered and concentrated. The resulting residue was washed with ethyl acetate to give 5-chloro-6-ethyl-3-{[4-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (103 mg).

Preparation Example 398

[0181] To a mixture of 3,5-dichloro-6-(1-hydroxy-1-methylethyl)pyrazine-2-carboxamide (2.64 g) and pyridine (30 mL),

mesyl chloride (2.45 mL) was added under ice cooling. After stirring at room temperature for 5 hours, pyridine was distilled off under reduced pressure, and the resulting residue was partitioned using ethyl acetate and water. The resulting organic layer was washed with 10% aqueous citric acid, saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was distilled off to give a light brown syrup. To the light brown syrup, ethanol (60 mL) and THF (30 mL) were added, and then 10% palladium on carbon (0.7 g) was added and stirred at room temperature for 14 hours under 3 atmospheric pressure of hydrogen. After filtration through celite, the filtrate was distilled off under reduced pressure, and the residue was diluted with ethyl acetate and then washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. After the solvent was distilled off, the residue was purified by silica gel column chromatography (eluent; chloroform:methanol = 100:0 to 40:1). The resulting crude product was washed with diisopropyl ether to give 3,5-di-chloro-6-isopropylpyrazine-2-carboxamide (632 mg) as a white solid.

Preparation Example 399

[0182] To a mixture of tert-butyl (1-methyl-4-oxocyclohexyl)carbamate (4.00 g) and methanol (50 mL), ammonium formate (10.2 g) and water (5 mL) were added and stirred for 1 hour until they were completely dissolved. Then, 10% palladium on carbon (2.0 g) was added and stirred at room temperature for 65 hours. After insoluble materials were separated by filtration through celite, the solvent was distilled off, and chloroform was added to the resulting residue, followed by drying over anhydrous magnesium sulfate. The solvent was distilled off to give tert-butyl (4-amino-1-methylcyclohexyl)carbamate (3.73 g) as a colorless syrup.

Preparation Example 400

[0183] To a mixture of tert-butyl (4-amino-1-methylcyclohexyl)carbamate (Preparation Example 399) (3.73 g) and ethanol (30 mL), 4M hydrogen chloride in ethyl acetate (30 mL) was added under ice cooling and stirred at room temperature for 20 hours. The precipitated solid was collected by filtration and washed with ethyl acetate to give 1-methylcyclohexane-1,4-diamino dihydrochloride (2.10 g) as a white solid.

Preparation Example 412

[0184] To a mixture of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (3.16 g), 4-bromo-3-methoxy-1-nitrobenzene (2.63 g) and DMF (31.6 mL), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), dichloromethane adduct (0.50 g) and potassium carbonate (4.24 g) were added and stirred at 80° C for 4 hours. After this mixture was concentrated under reduced pressure, water and ethyl acetate were added, and insoluble materials were filtered through celite. The organic layer was washed with saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 1:0 to 2:1) to give tert-butyl 4-(2-methoxy-4-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (2.21 g) as a yellow solid.

Preparation Example 413

[0185] To a mixture of tert-butyl 4-(2-methoxy-4-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (Preparation Example 412) (2.21 g), ethanol (40 mL) and THF (20 mL), 10% palladium on carbon (1.0 g) was added and stirred at room temperature for 3 hours under a hydrogen atmosphere at normal pressure. After filtration through celite, the filtrate was distilled off under reduced pressure to give tert-butyl 4-(4-amino-2-methoxy-phenyl)piperidine-1-carboxylate (1.97 g) as a gray solid.

Preparation Example 417

[0186] A mixture of 5-chloro-6-(1-hydroxy-1-methylethyl)-3-{[4-(4-methylpyrazin1-yl)phenyl]amino}pyrazine-2-carboxamide (Preparation Example 416) (430 mg) and acetic acid (10 mL) was stirred at 120°C for 5 hours. After the reaction liquid was cooled, the solvent was distilled off, and water and saturated aqueous sodium hydrogen carbonate were added to neutralize. After extraction with ethyl acetate, the extract was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was washed with diisopropyl ether to give 5-chloro-6-isopropenyl-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide (265 mg) as an orange solid.

Preparation Example 430

[0187] To a mixture of 7-nitro-2H-1,4-benzoxazine-3(4H)-one (2.0 g), benzyltriethylammonium chloride (470 mg), potassium carbonate (4.27 g) and acetonitrile (60 mL), 1-bromo-2-chloroethane (1.28 mL) was added and stirred at 75°C for 3 hours. After the reaction liquid was cooled, saturated aqueous sodium hydrogen carbonate was added, and the reaction liquid was extracted with ethyl acetate and the extract was washed with saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform) to give 4-(2-chloroethyl)-7-nitro-2H-1,4-benzoxazine-3(4H)-one (1.92 g) as a yellow powder.

Preparation Example 432

[0188] To a mixture of 4-(2-chloroethyl)-7-nitro-2H-1,4-benzoxazine-3(4H)-one (Preparation Example 430) (1.08 g), potassium carbonate (0.87 g) and acetonitrile (10.8 mL), 1-methylpiperazine (1.39 mL) was added and stirred at 80°C for 48 hours. After the reaction liquid was cooled, saturated aqueous sodium hydrogen carbonate was added, and the reaction liquid was extracted with ethyl acetate and the extract was washed with saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol = 100:0 to 20:1) to give 4-[2-(4-methylpiperazin-1-yl)ethyl]-7-nitro-2H-1,4-benzoxazine-3(4H)-one (690 mg) as a yellow liquid.

Preparation Example 440

[0189] A mixture of 3,5-dichloro-6-(1-hydroxy-1-methylethyl)pyrazine-2-carboxamide (1.10 g), 4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-3-(trifluoromethyl)aniline (Preparation Example 436) (1.58 g), N,N-diisopropylethylamine (0.80 mL) and dioxane (31 mL) was stirred at 100°C for 135 hours. After cooling, water was added, followed by extraction with ethyl acetate. Further, insoluble materials were separated by filtration, and the insoluble materials were dissolved in methanol and thereafter mixed with the organic layer. The solvent was distilled off under reduced pressure, followed by drying to give a brown solid. A mixture of the brown solid and acetic acid (30 mL) was stirred at 120°C for 5 hours. After the solvent was distilled off, saturated aqueous sodium hydrogen carbonate was added, and the precipitated solid was collected by filtration and washed with water. The resulting solid was purified by basic silica gel column chromatography (eluent: chloroform) to give 5-chloro-6-isopropenyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-3-(trifluoromethyl)phenyl}amino)pyrazine-2-carboxamide (0.99 g) as a yellow solid.

Preparation Example 444

[0190] After a mixture of palladium acetate (188 mg), 1,1'-binaphthalene-2,2'-diylbis(diphenylphosphine) (781 mg), cesium carbonate (4.09 g) and THF (20 mL) was stirred for 30 minutes, a mixture of 1-bromo-3-methoxy-5-nitrobenzene (1.94 g), 1-methylpiperazine (2.76 mL) and THF (20 mL) was added and heated under reflux for 14 hours. After cooling, the reaction liquid was diluted with ethyl acetate, and insoluble materials were separated by filtration. After extraction with 2M hydrochloric acid from the filtrate, the resulting aqueous layer was basified with 50% aqueous potassium hydroxide and then extracted with chloroform. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol = 100:0 to 20:1) to give 1-(3-methoxy-5-nitrophenyl)-4-methylpiperazine (1.01 g) as an orange syrup.

Preparation Example 454

[0191] To a mixture of tert-butyl 4-(4-amino-2-methoxy-phenyl)piperidine-1-carboxylate (Preparation Example 413) (4.25 g) and THF (100 mL), sodium hydrogen carbonate (1.28 g) and water (30 mL) were added, followed by dropwise addition of benzyl chloroformate (1.98 mL) under ice cooling and stirring overnight. After addition of water and extraction with ethyl acetate, the extract was washed with saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 2:1) to give tert-butyl 4-(4-{[(benzyloxy)carbonyl]amino}-2-methoxyphenyl)piperidine-1-carboxylate (4.92 g) as a colorless amorphous.

Preparation Example 455

[0192] A mixture of tert-butyl 4-(4-{[(benzyloxy)carbonyl]amino}-2-methoxyphenyl)piperidine-1-carboxylate (Preparation Example 454) (4.92 g), trifluoroacetic acid (10 mL) and 1,2-dichloroethane (50 mL) was stirred at room temperature

for 1 hour. The reaction solvent was concentrated under reduced pressure, and after addition of saturated aqueous sodium hydrogen carbonate, the residue was extracted with chloroform. After drying over anhydrous magnesium sulfate, the solvent was distilled off, and the residue was solidified by addition of diethyl ether to give benzyl (3-methoxy-4-piperidin-4-ylphenyl)carbamate (3.24 g) as a white solid.

Preparation Example 464

[0193] To a mixture of benzyl (3-methoxy-4-piperidin-4-ylphenyl)carbamate (Preparation Example 455) (1.52 g) and 1,2-dichloroethane (70 mL), formalin (3.62 mL) and sodium triacetoxyborohydride (1.42 g) were added and stirred overnight at room temperature. After addition of water and saturated aqueous sodium hydrogen carbonate, the reaction liquid was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by silica gel column chromatography (eluent; chloroform:methanol saturated aqueous ammonia = 100:0:0 to 10:1:0.1) to give benzyl [3-methoxy-4-(1-methylpiperidin-4-yl)phenyl]carbamate (1.26 g) as a white solid.

Preparation Example 467

[0194] To a mixture of 7-amino-4-[3-(4-methylpiperazin-1-yl)propyl]-2H-1,4-benzoxazine-3(4H)-one (Preparation Example 435) (300 mg) and THF (9 mL), gradual dropwise addition of borane-tetrahydrofuran complex (3.0 mL, 1M THF solution) was conducted under ice cooling under an argon atmosphere. After the dropwise addition was completed, the mixture was stirred at room temperature for 1 hour and further stirred at 70°C for 3 hours. After methanol (10 mL) was gradually added to the reaction liquid under ice cooling, 1M hydrochloric acid (5 mL) and thereafter 1M aqueous sodium hydroxide (10 mL) were added and stirred at room temperature for 1 hour. After dilution with water, the reaction liquid was extracted with ethyl acetate. After the solvent was distilled off, the residue was purified by silica gel column chromatography (eluent; chloroform :methanol = 100:0 to 20:1) to give 4-[3-(4-methylpiperazin-1-yl)propyl]-3,4-dihydro-2H-1,4-benzoxazine-7-amine (120 mg).

Preparation Example 468

[0195] To a mixture of benzyl [3-methoxy-4-(1-methylpiperidin-4-yl)phenyl]carbamate (Preparation Example 464) (1.26 g), ethanol (20 mL) and THF (10 mL), 5% palladium on carbon (0.38 g) was added and stirred overnight at room temperature under a hydrogen atmosphere at normal pressure. After filtration through celite, the filtrate was distilled off under reduced pressure to give 3-methoxy-4-(1-methylpiperidin-4-yl)aniline (0.80 g) as a light pink solid.

Preparation Example 472

[0196] To a mixture of 2-[methyl(3-nitrophenyl)amino]ethanol (780 mg) and dichloromethane (20 mL), triethylamine (0.66 mL) and mesyl chloride (0.37 mL) were added sequentially under ice cooling and stirred for 3 hours. Water was added to the reaction liquid, and the organic layer was separated and washed with saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was distilled off to give 2-[methyl(3-nitrophenyl)amino]ethyl methanesulfonate (1.0 g) as a yellow solid.

Preparation Example 473

[0197] A mixture of 2-[methyl(3-nitrophenyl)amino]ethyl methanesulfonate (Preparation Example 472) (1.0 g), 1-methylpiperazine (1.61 mL) and NMP (5 mL) was reacted at 130°C for 30 minutes using a microwave reaction system. The reaction liquid was diluted with water, extracted with a mixed solvent of chloroform and methanol (10:1), and then washed with saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol:saturated aqueous ammonia = 10:1:0.1) to give N-methyl-N-[2-(4-methylpiperazin-1-yl)ethyl]-3-nitroaniline (890 mg) as a yellow oil.

Preparation Example 502

[0198] To a mixture of 8-(2-methoxy-5-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (Preparation Example 495) (795 mg) and dioxane (16 mL), 4M hydrochloric acid (6.8 mL) was added and stirred overnight at 80°C. The reaction liquid was concentrated under reduced pressure, and saturated aqueous sodium hydrogen carbonate was added to the concentrate. The concentrate was extracted with chloroform and then washed with saturated aqueous sodium chloride. After drying over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was

purified by silica gel column chromatography (eluent; ethyl acetate:n-hexane) to give 1-(2-methoxy-5-nitrophenyl)piperidin-4-one (296 mg).

Preparation Example 503

[0199] To a mixture of 1-(2-methoxy-5-nitrophenyl)piperidin-4-one (Preparation Example 502) (296 mg), 1-methylpiperazine (0.20 mL) and 1,2-dichloroethane (11 mL), sodium triacetoxyborohydride (385 mg) was added and stirred overnight at room temperature. After addition of water and saturated aqueous sodium hydrogen carbonate, the reaction liquid was extracted with chloroform, and the organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform:methanol =100:0 to 10:1) to give 1-[1-(2-methoxy-5-nitrophenyl)piperidin-4-yl]-4-methylpiperazine (0.40 g) as a brown oil.

Preparation Example 516

[0200] To a mixture of 1-fluoro-2-methyl-4-nitrobenzene (3.0 g), potassium carbonate (5.35 g) and DMF (30 mL), 1,4-dioxa-8-azaspiro[4.5]decane (4.15 g) was added and stirred at 80°C for 20 hours. After cooling, the reaction liquid was diluted with ethyl acetate and washed with water and saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol =100:0 to 100:1) to give 8-(2-methyl-4-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (5.13 g) as a yellow solid.

Preparation Example 545

[0201] To a mixture of 5-chloro-6-(2-hydroxypropan-2-yl)-3-{[3-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide (Preparation Example 544) (300 mg) and trifluoroacetic acid (3 mL), triethylsilane (0.55 mL) was added under ice cooling and stirred under ice cooling for 10 minutes and at room temperature for 22 hours. After the reaction liquid was concentrated, the residue was diluted with chloroform and washed with saturated aqueous sodium hydrogen carbonate. After drying over anhydrous magnesium sulfate, the solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol:saturated aqueous ammonia=100:0:0 to 20:1:0.1) to give a crude product. The crude product was washed with diisopropyl ether to give 5-chloro-6-isopropyl-3-{[3-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide (219 mg) as an orange solid.

[0202] Tables 7 to 47 show the chemical structures of the compounds prepared in the above preparation examples, and the chemical structures of the compounds of preparation examples prepared by the same manner as shown in the above preparation examples using corresponding starting materials. Tables 48 to 84 show the preparation processes and physical and chemical data of these preparation examples compounds.

Example 4

[0203] A mixture of 4-{[2-(isopropylsulfonyl)phenyl]amino}-2-(methylsulfanyl)-6-oxo-1,6-dihydropyrimidine-5-carboxamide (Preparation Example 294) (200 mg), 1-(aminomethyl)-N,N-dimethylcyclohexylamine (409 mg) and NMP (1 mL) was heated at 180°C for 10 minutes using a microwave reaction system. After cooling, the reaction liquid was diluted with ethyl acetate, and the precipitated crystal was collected by filtration and washed with ethyl acetate to give a white solid. To the white solid, a mixed solvent of ethanol and water was added, heated and then cooled, and the precipitated solid was collected by filtration to give 2-({[1-(dimethylamino)cyclohexyl]methyl}amino)-4-{[2-(isopropylsulfonyl)phenyl]amino}-6-oxo-1,6-dihydropyrimidine-5-carboxamide (136 mg) as a white solid.

Example 19

[0204] A mixture of 4-{[2-(isopropylsulfonyl)phenyl]amino}-2-(methylsulfanyl)-6-oxo-1,6-dihydropyrimidine-5-carboxamide (Preparation Example 294) (200 mg), tert-butyl 2-(aminomethyl)piperidine-1-carboxylate (1.12 g) and NMP (1 mL) was heated at 180°C for 10 minutes using a microwave reaction system. After cooling, the reaction liquid was diluted with ethyl acetate and washed with water and saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was distilled off, and the residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 to 20:1) to give a white amorphous. To a mixture of the white amorphous, ethyl acetate (10 mL) and ethanol (5 mL), 4M hydrogen chloride in ethyl acetate (5 mL) was added under ice cooling and stirred at room temperature for 4 hours. The precipitated solid was collected by filtration and dried to give 4-{[2-(isopropylsulfonyl)phenyl]amino}-6-oxo-2-[(piperidin-2-ylmethyl)amino]-1,6-dihydropyrimidine-5-carboxamide hydrochloride (126 mg) as a white solid.

Example 29

[0205] To a mixture of tert-butyl 3-[(5-carbamoyl-4-{[2-(isopropylsulfonyl)phenyl]amino}-6-oxo-1,6-dihydropyrimidine-2-yl)amino]piperidine-1-carboxylate (Example 28) (299 mg) and ethyl acetate (3 mL), 4M hydrogen chloride in ethyl acetate (2.7 mL) was added under ice cooling and stirred at room temperature for 1 hour. The precipitated solid was collected by filtration and dried to give 4-{[2-(isopropylsulfonyl)phenyl]amino}-6-oxo-2-(piperidin-3-ylamino)-1,6-dihydropyrimidine-5-carboxamide dihydrochloride (194 mg) as a white solid.

Example 31

[0206] To a mixture of 4-{[2-(isopropylsulfonyl)phenyl]amino}-6-oxo-2-(piperidin-3-ylamino)-1,6-dihydropyrimidine-5-carboxamide dihydrochloride (Example 29) (67 mg) and pyridine (1.3 mL), mesyl chloride (0.10 mL) was added under ice cooling and stirred for 1 hour. After ethanol was added to the reaction system, the reaction system was concentrated. The resulting residue was partitioned using chloroform and saturated aqueous sodium hydrogen carbonate, and the organic layer was dried. The organic layer was concentrated, followed by an azeotropic process with toluene. The resulting residue was solidified with ethyl acetate-hexane. The resulting solid was recrystallized from ethanol to give 4-{[2-(isopropylsulfonyl)phenyl]amino}-2-{[1-(methylsulfonyl)piperidin-3-yl]amino}-6-oxo-1,6-dihydropyrimidine-5-carboxamide (43 mg).

Example 37

[0207] A mixture of 4-{[3-(methylcarbamoyl)phenyl]amino}-2-(methylsulfinyl)-6-oxo-1,6-dihydropyrimidine-5-carboxamide (Preparation Example 311) (234 mg), 1-(aminomethyl)cyclohexaneamine (172 mg) and NMP (2 mL) was stirred at 80°C for 30 minutes. After cooling, the reaction liquid was diluted with ethyl acetate, and the precipitated solid was collected by filtration. This solid was heated with ethanol-water and washed to give 2-{[(1-aminocyclohexyl)methyl]amino}-4-{[3-(methylcarbamoyl)phenyl]amino}-6-oxo-1,6-dihydropyrimidine-5-carboxamide (215 mg) as a white solid.

Example 84

[0208] A mixture of 5-chloro-6-ethyl-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (Preparation Example 353) (150 mg), 1-(aminomethyl)cyclohexaneamine (163 mg) and NMP (1 mL) was heated at 180°C for 20 minutes using a microwave reaction system. The reaction liquid was cooled, and ethyl acetate and water were added and stirred for 30 minutes. Thereafter, the precipitated powder was collected by filtration. This powder was heated with ethanol-water (1:1) and washed to give 5-{[(1-aminocyclohexyl)methyl]amino}-6-ethyl-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (112 mg) as a white solid.

Example 146

[0209] A mixture of 3,5-dichloro-6-ethylpyrazine-2-carboxamide (200 mg), 3-chloro-4-methylsulfonylaniline (374 mg) and NMP (1 mL) was stirred at 230°C for 1 hour using a microwave reaction system. Thereafter, trans-4-aminocyclohexanol (524 mg) was added to the reaction liquid and stirred at 190°C for 30 minutes using a microwave reaction system. After cooling, the reaction liquid was partitioned using ethyl acetate and water, and the organic layer was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol = 10:0 to 30:1) to give a crude product. This product was heated with ethanol and washed to give a light yellow solid. To the light yellow solid, ethyl acetate was added and heated, and insoluble materials were separated by filtration and the filtrate was concentrated. After the filtrate was concentrated, the residue was heated and washed with ethanol to give 3-{[3-chloro-4-(methylsulfonyl)phenyl]amino}-6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]pyrazine-2-carboxamide (39 mg) as a light yellow solid.

Example 159

[0210] To a mixture of 5-[(trans-4-hydroxycyclohexyl)amino]-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (Example 111) (298 mg), chloroform (40 mL) and acetonitrile (10 mL), N-chlorosuccinimide (108 mg) was added and stirred at 70°C for 8 hours. After the reaction liquid was cooled, silica gel was added, and the solvent was distilled off, followed by purification by silica gel column chromatography (eluent; chloroform:methanol = 10:0 to 10:1). The resulting crude product was solidified from chloroform and collected by filtration. The resulting solid was heated with ethyl acetate and washed with ethyl acetate to give 6-chloro-5-[(trans-4-hydroxycyclohexyl)amino]-3-{(3-(methylsulfo-

nyl)phenyl]amino}pyrazine-2-carboxamide (189 mg) as a white solid.

Example 181

[0211] To a mixture of 5-[(trans-4-hydroxycyclohexyl)amino]-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (Example 111) (150 mg), chloroform (40 mL) and acetonitrile (20 mL), N-bromosuccinimide (69 mg) was added and stirred at room temperature for 2 hours. To the reaction liquid, silica gel was added, and the solvent was distilled off, followed by purification by silica gel column chromatography (eluent; chloroform:methanol = 10:0 to 10:1). The resulting crudeproduct was solidified with ethyl acetate and washed with ethyl acetate to give 6-bromo-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (130 mg) as a light yellow solid.

Example 190

[0212] To a mixture of 5-[(trans-4-hydroxycyclohexyl)amino]-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (Example 111) (150 mg), chloroform (40 mL) and acetonitrile (20 mL), N-iodosuccinimide (87 mg) was added and stirred at room temperature for 2 hours. To the reaction liquid, silica gel was added, and the solvent was distilled off, followed by purification by silica gel column chromatography (eluent; chloroform:methanol = 10:0 to 10:1). The resulting crude product was solidified with ethyl acetate and washed with ethyl acetate to give 5-[(trans-4-hydroxycyclohexyl)amino]-6-iodo-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (153 mg) as a light yellow solid.

Example 196

[0213] A mixture of 5-chloro-6-ethyl-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (Preparation Example 353) (8.8 mg), 1-methyl-piperidin-3-ylamine (8.0 mg) and NMP (0.5 mL) was heated at 190°C for 30 minutes using a microwave reaction system. After the reaction liquid was cooled, the organic layer was distilled off under reduced pressure, and the residue was separated and purified by HPLC (column: SunFire® C18, 5 μm, 19 mm x 100 mm, solvent: MeOH/0.1% HCOOH-H_2O = 10/90 (0 min)-10/90 (1 min)-95/5 (9 min)-95/5 (12 min), flow rate: 25 mL/min) to give (6-ethyl-5-[(1-methylpiperidin-3-yl)amino]-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (2.4 mg).

Example 302

[0214] To a mixture of 5-[(4-amino-4-methylcyclohexyl)amino]-3-{[3-(methylsulfonyl)phenyl]amino}-6-propylpyrazine-2-carboxamide (Example 301) (89 mg) and dichloromethane (5 mL), formalin (0.30 mL) and sodium triacetoxyborohydride (82 mg) were added and stirred at room temperature for 1.5 hours. After the reaction liquid was diluted with chloroform, it was washed with saturated aqueous sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. After the drying agent was separated by filtration, silica gel was added, and the solvent was distilled off, followed by purification of the residue by silica gel column chromatography (eluent; chloroform:methanol:saturated aqueous ammonia = 10:0:0 to 10:1:0.1). The resulting residue was washed with ethyl acetate to give 5-{[4-(dimethylamino)-4-methylcyclohexyl]amino}-3-{[3-(methylsulfonyl)phenyl]amino}-6-propylpyrazine-2-carboxamide (31 mg) as a light yellow solid.

Example 309

[0215] To a mixture of 6-ethyl-5-[(cis-4-hydroxy-4-methylcyclohexyl)amino]-3-[(4-methyl-3-nitrophenyl)amino]pyrazine-2-carboxamide (Example 308) (242 mg) and methanol (10 mL), 5% palladium on carbon (25 mg) was added and stirred under a hydrogen atmosphere at room temperature for 4 hours. After filtration of the reaction liquid, the filtrate was concentrated under reduced pressure to give 3-[(3-amino-4-methylphenyl)amino]-6-ethyl-5-[(cis-4-hydroxy-4-methylcyclohexyl)amino]pyrazine-2-carboxamide (162 mg) as a green solid.

Example 310

[0216] To a mixture of 3-[(3-amino-4-methylphenyl)amino]-6-ethyl-5-[(cis-4-hydroxy-4-methylcyclohexyl)amino]pyrazine-2-carboxamide (Example 309) (150 mg), THF (2 mL) and DMF (2 mL), N,N-diisopropylethylamine (49 mg) and acrylic acid chloride (34 mg) were added under ice cooling and stirred for 30 minutes. The reaction liquid was poured into water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride sequentially and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent; chloroform:methanol) to give 3-{[3-(acryloylamino)-4-methylphenyl]amino}-6-ethyl-5-[(cis-4-hydroxy-4-methylcyclohexyl)amino]pyrazine-2-carboxamide (48 mg) as a light yellow powder.

Example 343

[0217] To a mixture of 5-[(trans-4-hydroxycyclohexyl)amino]-6-isopropenyl-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide (Example 342) (205 mg), ethanol (20 mL) and THF (10 mL), 10% palladium on carbon (100 mg) was added under a hydrogen atmosphere and stirred at room temperature for 18 hours. After the catalyst was separated by filtration, the solvent was distilled off, and the residue was purified by basic silica gel column chromatography (eluent: chloroform). The resulting yellow solid was washed with ethyl acetate to give 5-[(trans-4-hydroxycyclohexyl)amino]-6-isopropyl-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide (136 mg) as a yellow solid.

Example 381

[0218] To a mixture of tert-butyl 4-[4-({3-carbamoyl-5-ethyl-6-[(trans-4-hydroxycyclohexyl)amino]pyrazin-2-yl}amino)-2-methoxyphenyl]piperidine-1-carboxylate (Example 382) (270 mg) and ethyl acetate (10 mL), 4M hydrogen chloride in ethyl acetate (4 mL) was added under ice cooling and stirred at room temperature for 1 hour. The reaction liquid was concentrated under reduced pressure, and saturated aqueous sodium hydrogen carbonate and chloroform were added to the residue. The precipitated solid was collected by filtration and dried to give 6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-[(3-methoxy-4-piperidin-4-ylphenyl)amino]pyrazine-2-carboxamide (85 mg) as a light yellow solid.

Example 405

[0219] To a mixture of 6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-[(4-piperidin-4-ylphenyl)amino]pyrazine-2-carboxamide (Example 358) (43 mg) and dichloroethane (1 mL), pyridine (0.01 mL) and acetic anhydride (0.01 mL) were added under ice cooling and stirred at room temperature for 20 minutes. After addition of saturated aqueous sodium hydrogen carbonate, the reaction liquid was partitioned using chloroform and saturated aqueous sodium hydrogen carbonate. After drying over anhydrous sodium sulfate, the organic layer was concentrated, and the resulting residue was solidified with ethyl acetate-hexane to give 3-{[4-(1-acetylpiperidin-4-yl)phenyl]amino}-6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]pyrazine-2-carboxamide (26 mg) as a white solid.

Example 436

[0220] To a mixture of methyl 4-[(5-carbamoyl-3-ethyl-6-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}pyrazin-2-yl)amino]cyclohexanecarboxylate (Example 435) (126 mg), THF (2 mL) and methanol (2 mL), 10 % aqueous sodium hydroxide (1 mL) was added and heated under reflux for 2 hours. To the reaction liquid, 10 % hydrochloric acid was added to give a pH of about 7, and the resulting solid was collected by filtration. This solid was purified by silica gel column chromatography (eluent; chloroform:methanol) to give 4-[(5-carbamoyl-3-ethyl-6-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}pyrazin-2-yl)amino]cyclohexanecarboxylic acid (Example 436) (47 mg), which was a low-polarity product, as a light yellow white powder and 4-[(5-carbamoyl-3-ethyl-6-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}pyrazin-2-yl)amino]cyclohexanecarboxylic acid (Example 437) (59 mg), which was a high-polarity product, as a light yellow powder.

Example 438

[0221] To a mixture of 4-[(5-carbamoyl-3-ethyl-6-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}pyrazin-2-yl)amino]cyclohexanecarboxylic acid (Example 436) (62 mg), o-anisidine (42 mg) and DMF (2 mL), 1-hydroxy-1H-benzotriazole monohydrate (46 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (65 mg) were added and stirred at room temperature for 7 hours. The reaction liquid was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride sequentially and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent; chloroform:methanol) to give 6-ethyl-5-({4-[(2-methoxy-phenyl)carbamoyl]cyclohexyl}amino)-3-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}pyrazine-2-carboxamide (33 mg) as a yellow powder.

Example 495

[0222] A mixture of 6-chloro-3-{[3-(1,4-dioxa-8-azaspiro[4.5]deca-8-yl)-4-methoxyphenyl]amino}-5-[(trans-4-hydroxycyclohexyl)amino]pyrazine-2-carboxamide (Example 482) (0.80 g), acetic acid (4 mL) and water (4 mL) was stirred at 80°C for 3 hours. To the reaction liquid, concentrated hydrochloric acid (1 mL) was added and stirred at 80°C for 2 hours. The reaction liquid was cooled and concentrated under reduced pressure, and then chloroform was added, followed by

washing with saturated aqueous sodium hydrogen carbonate. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was distilled off, followed by purification by silica gel column chromatography (eluent; chloroform:methanol = 10:1 to 30:1) to give 6-chloro-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-methoxy-3-(4-oxopiperidin-1-yl)phenyl]amino}pyrazine-2-carboxamide (0.74 g) as a yellow amorphous.

Example 499

[0223] To a mixture of 6-chloro-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-methoxy-3-(4-oxopiperidin-1-yl)phenyl]amino}pyrazine-2-carboxamide (Example 495) (0.346 mg), N-methylpiperazine (0.12 mL) and 1,2-dichloroethane (10 mL), sodium triacetoxyborohydride (225 mg) was added and stirred at room temperature for 5 hours. After addition of saturated aqueous sodium hydrogen carbonate, the reaction liquid was extracted with chloroform, and the organic layer was washed with saturated aqueous sodium chloride. After drying over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol:saturated aqueous ammonia = 100:0:0 to 20:1:0.1) to give a crude product. The crude product was solidified with ethyl acetate-diisopropyl ether and then washed with ethyl acetate to give 6-chloro-5-[(trans-4-hydroxycyclohexyl)amino]-3-({4-methoxy-3-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide (39 mg) as a light yellow solid.

Example 508

[0224] A mixture of 6-bromo-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (Example 181) (50 mg), cyclopropylboronic acid (18 mg), tetrakistriphenylphosphine palladium (24 mg), potassium carbonate (71 mg), dioxane (2.5 mL) and water (0.5 mL) was stirred at 115°C overnight. After cooling, the reaction liquid was partitioned using chloroform, saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. After drying, the organic layer was concentrated, and the resulting residue was purified by silica gel column chromatography (eluent; chloroform:methanol:saturated aqueous ammonia = 100:0:0 to 10:1:0.1). The resulting residue was solidified with ethyl acetate-hexane to give 6-cyclopropyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[3-(methylsulfonyl)phenyl]amino}pyrazine-2-carboxamide (10 mg) as a yellow solid.

Example 534

[0225] To a mixture of 5-[(1-benzylpiperidin-4-yl)amino]-6-ethyl-3-({3-methyl-4-[4(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide (Example 507) (1.31 g), ethanol (26 mL) and acetic acid (13 mL), palladium hydroxide (0.65 g) was added and stirred under a hydrogen atmosphere at room temperature for 3 days. After the catalyst was separated by filtration, the solvent was concentrated and partitioned using chloroform and saturated aqueous sodium hydrogen carbonate. The organic layer was concentrated to give 6-ethyl-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(piperidin-4-ylamino)pyrazine-2-carboxamide (0.73 g) as a light yellow solid.

[0226] Tables 85 to 164 show the chemical structures of the compounds prepared in the above examples, and the chemical structures of the examples compounds prepared by the same manner as shown in the above examples using corresponding starting materials. Tables 165 to 183 show the preparation processes and physical and chemical data of these examples compounds.

[Table 7]

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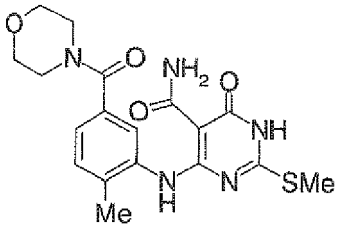
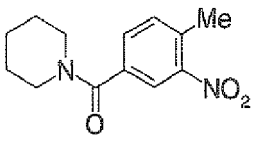
1		8	

(continued)

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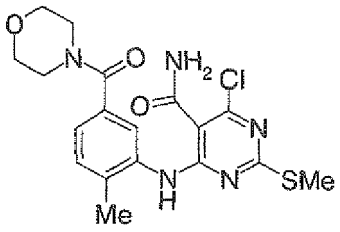
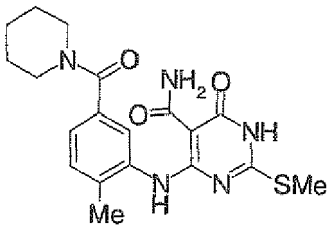
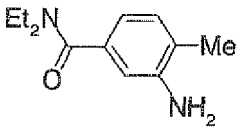
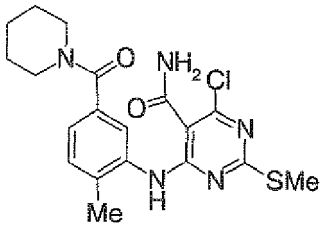
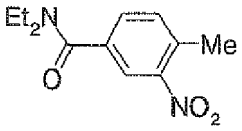
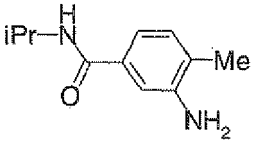
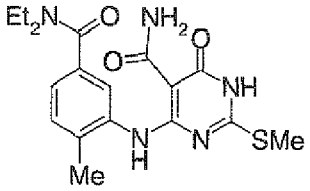
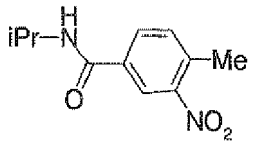
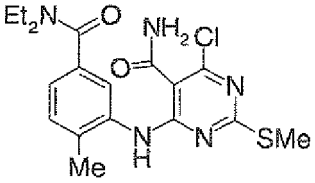
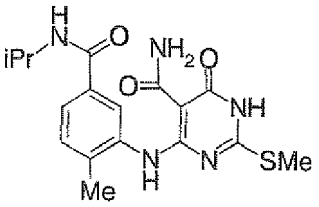
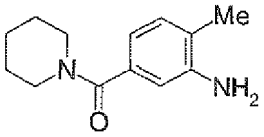
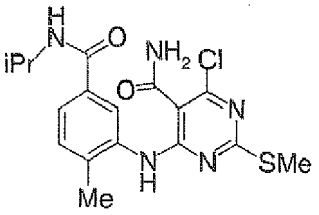
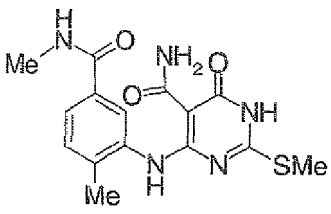
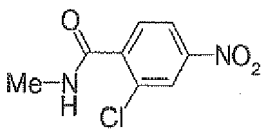
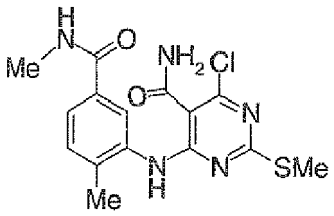
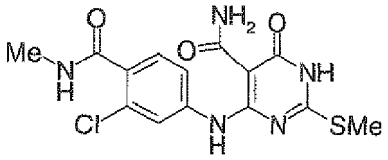
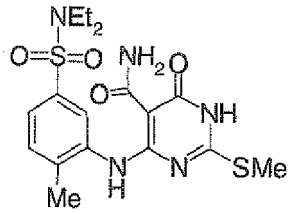
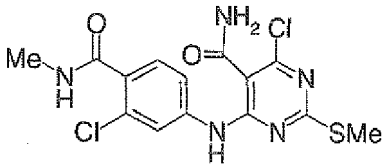
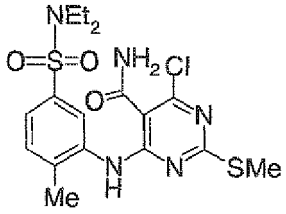
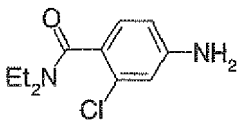
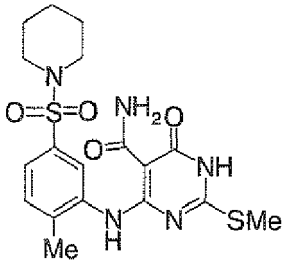
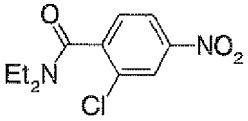
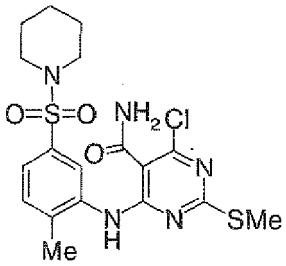
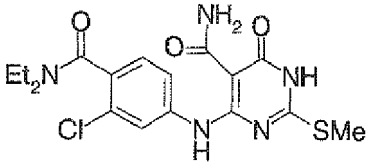
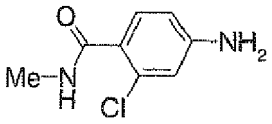
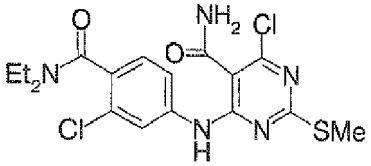
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

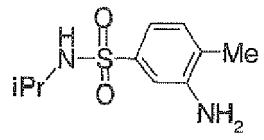
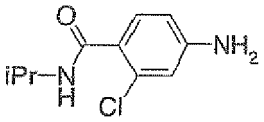
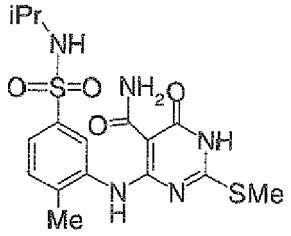
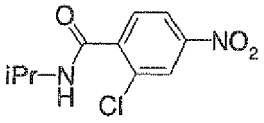
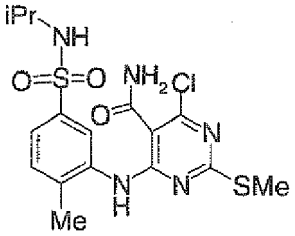
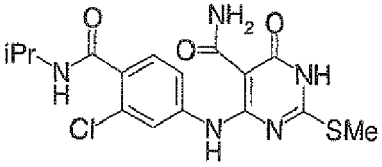
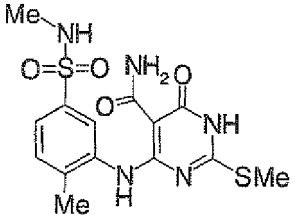
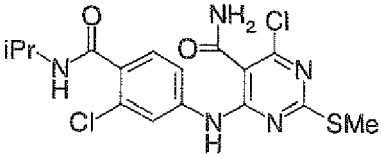
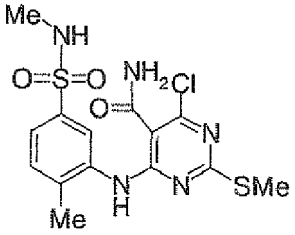
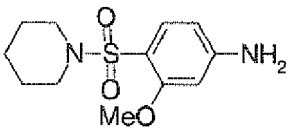
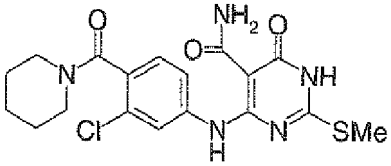
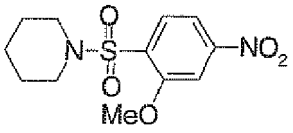
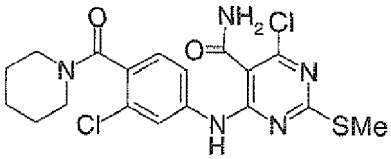
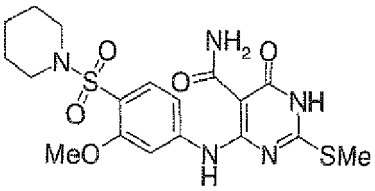
[Table 8]

Rex	Structure	Rex	Structure
15		22	

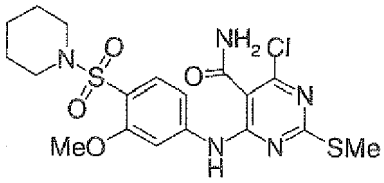
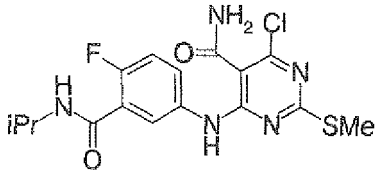
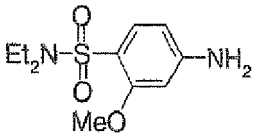
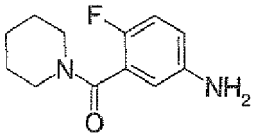
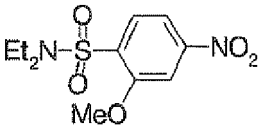
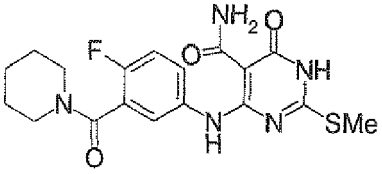
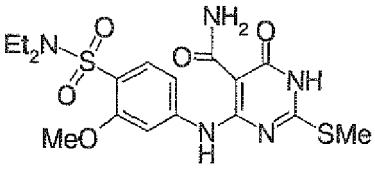
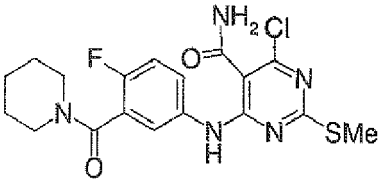
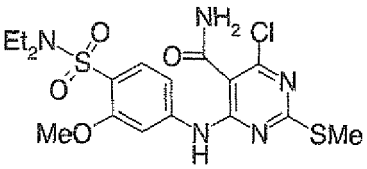
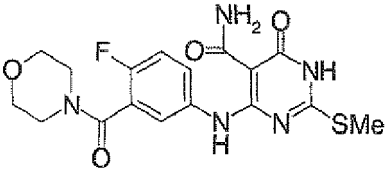
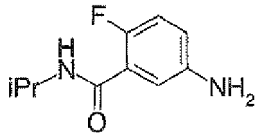
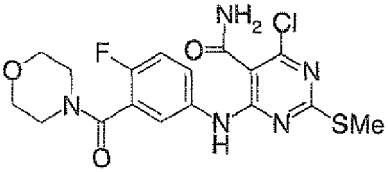
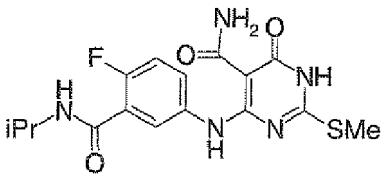
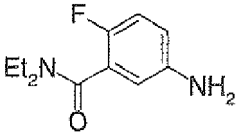
(continued)

Rex	Structure	Rex	Structure
16		23	
17		24	
18		25	
19		26	
20		27	
21		28	

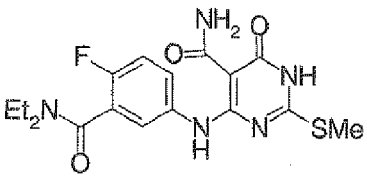
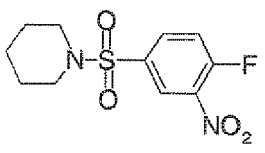
[Table 9]

Rex	Structure	Rex	Structure
29		36	
30		37	
31		38	
32		39	
33		40	
34		41	
35		42	

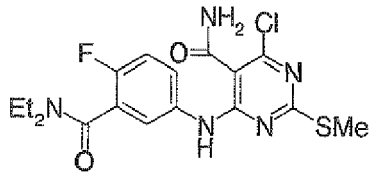
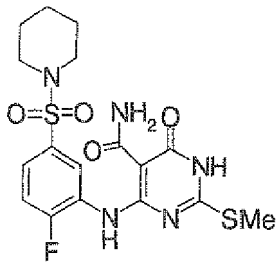
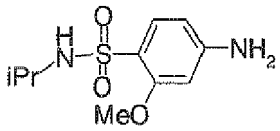
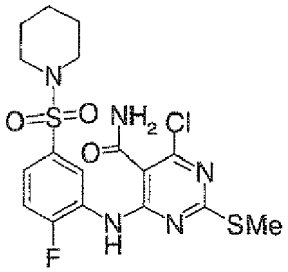
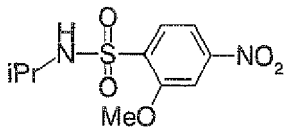
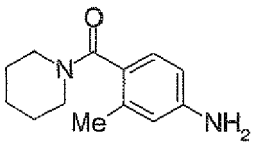
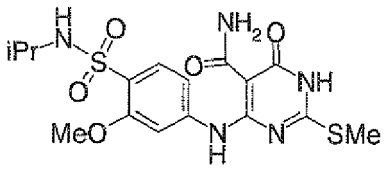
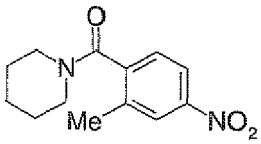
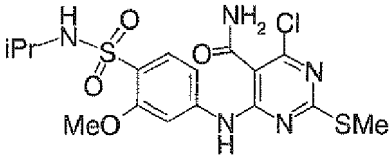
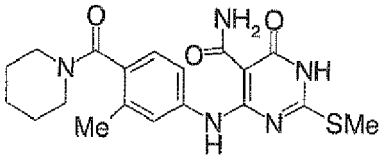
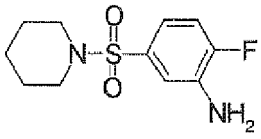
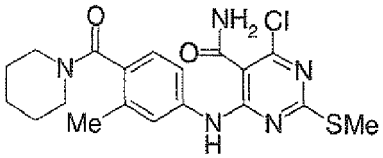
[Table 10]

Rex	Structure	Rex	Structure
43		50	
44		51	
45		52	
46		53	
47		54	
48		55	
49		56	

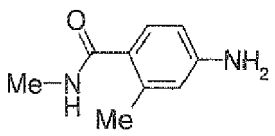
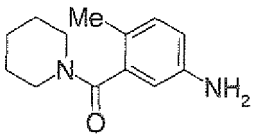
[Table 11]

Rex	Structure	Rex	Structure
57		64	

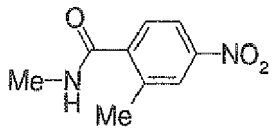
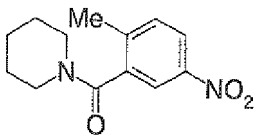
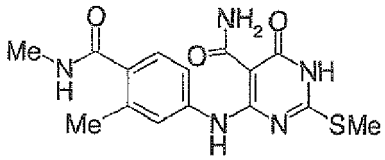
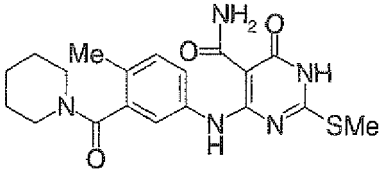
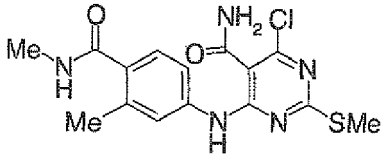
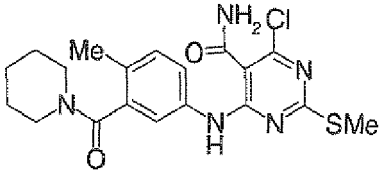
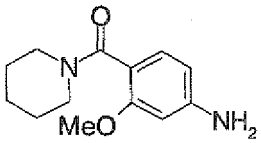
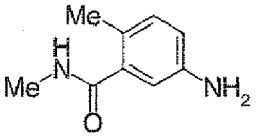
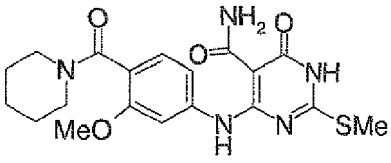
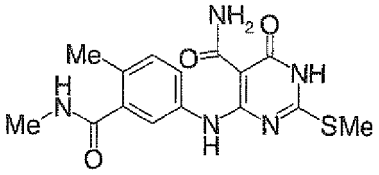
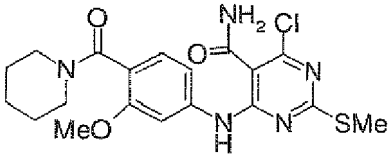
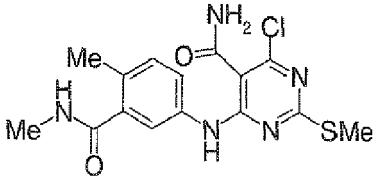
(continued)

Rex	Structure	Rex	Structure
58		65	
59		66	
60		67	
61		68	
62		69	
63		70	

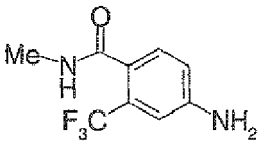
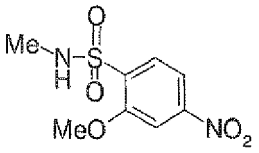
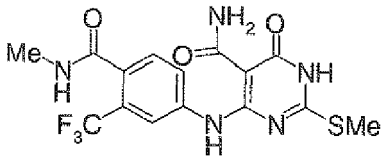
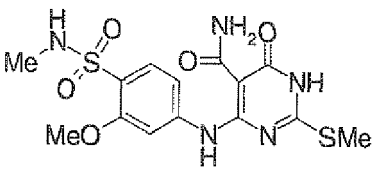
[Table 12]

Rex	Structure	Rex	Structure
71		78	

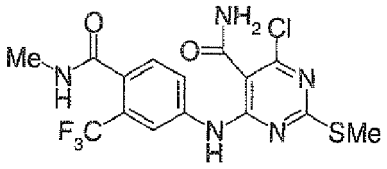
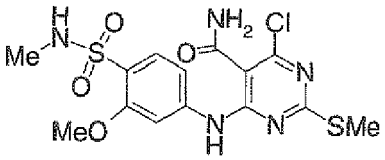
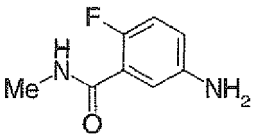
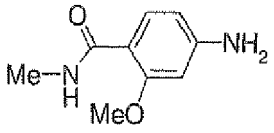
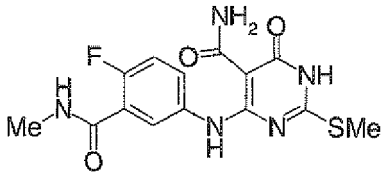
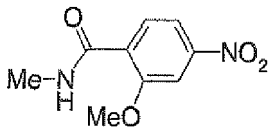
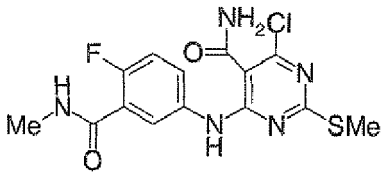
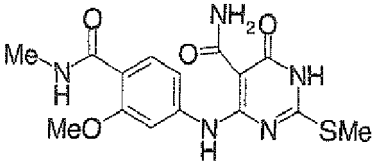
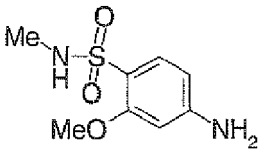
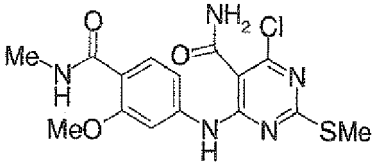
(continued)

Rex	Structure	Rex	Structure
72		79	
73		80	
74		81	
75		82	
76		83	
77		84	

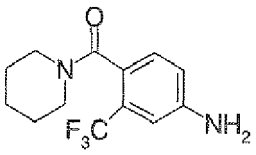
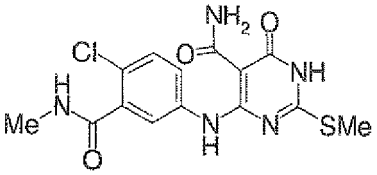
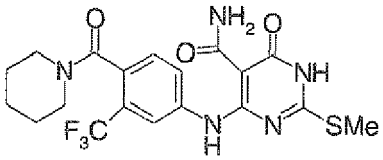
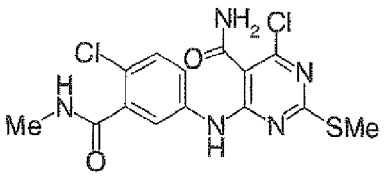
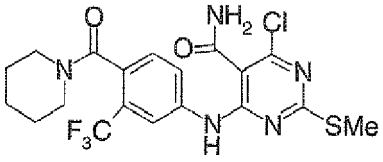
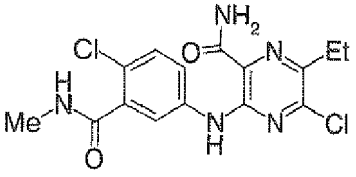
[Table 13]

Rex	Structure	Rex	Structure
85		92	
86		93	

(continued)

Rex	Structure	Rex	Structure
87		94	
88		95	
89		96	
90		97	
91		98	

[Table 14]

Rex	Structure	Rex	Structure
99		106	
100		107	
101		108	

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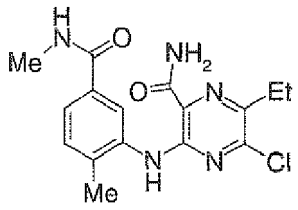
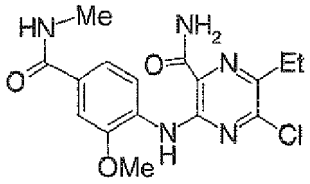
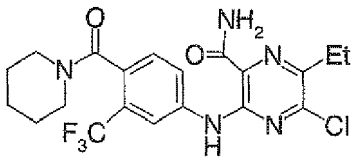
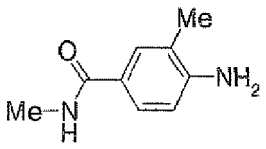
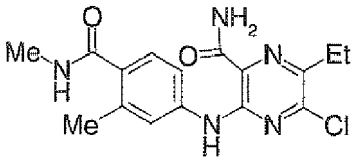
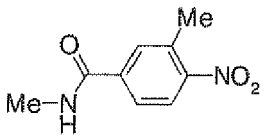
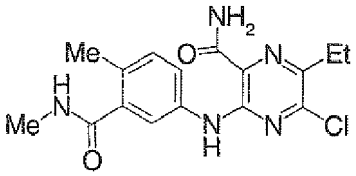
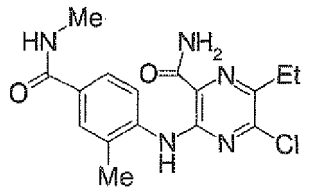
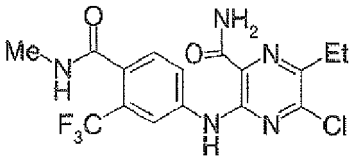
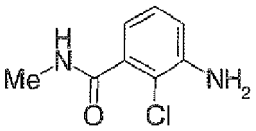
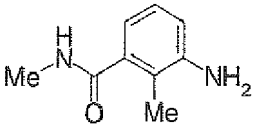
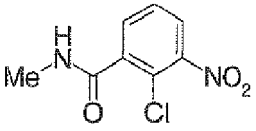
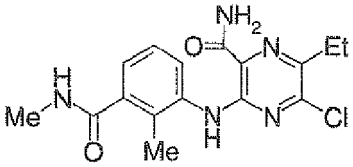
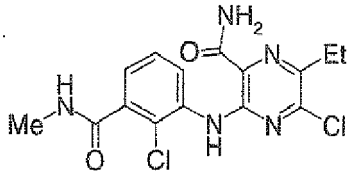
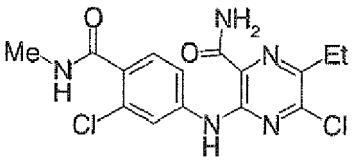
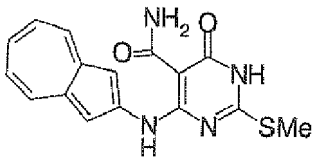
Rex	Structure	Rex	Structure
102		109	
103		110	
104		111	
105		112	

[Table 15]

Rex	Structure	Rex	Structure
113		120	
114		121	
115		122	
116		123	

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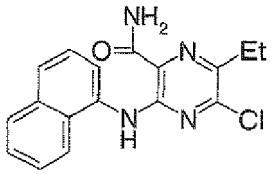
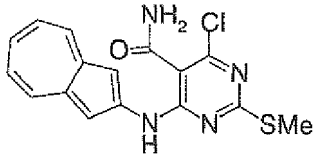
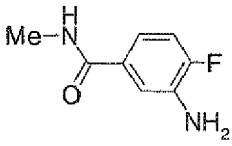
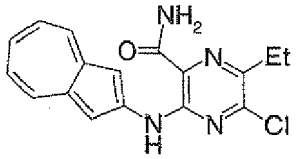
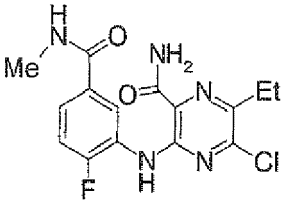
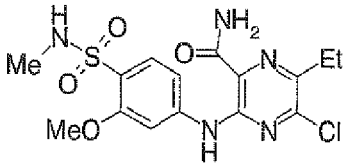
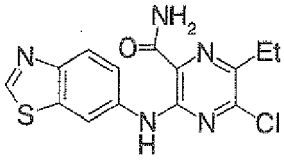
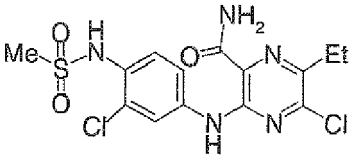
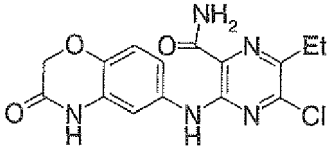
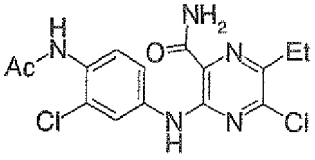
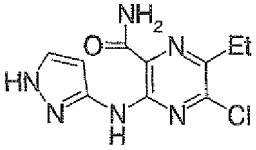
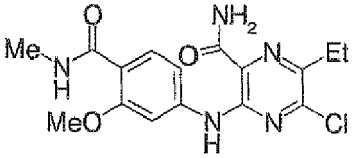
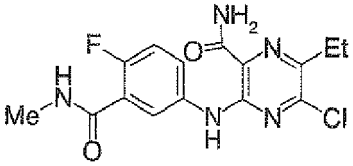
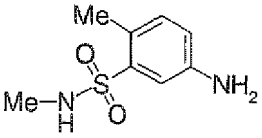
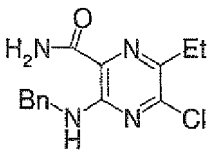
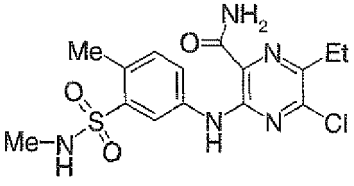
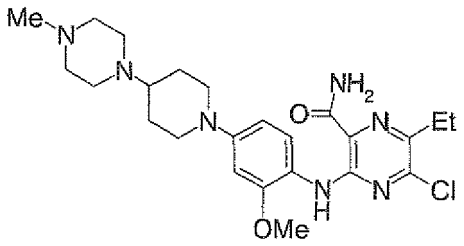
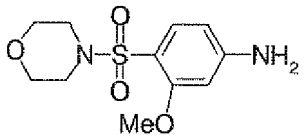
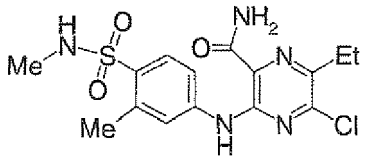
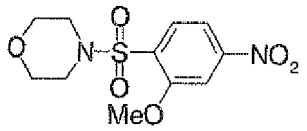
Rex	Structure	Rex	Structure
117		124	
118		125	
119		126	

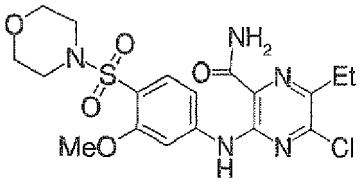
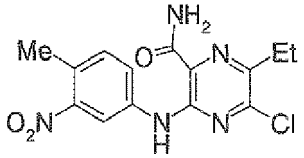
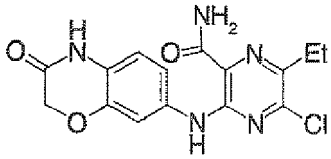
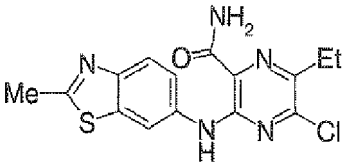
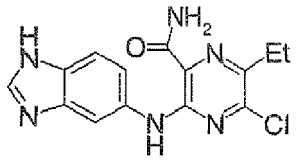
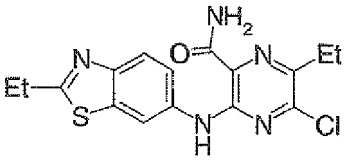
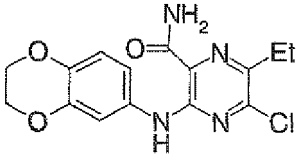
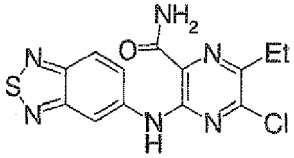
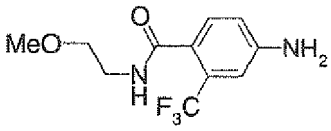
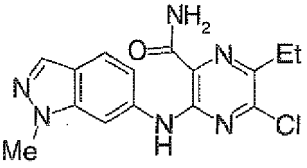
[Table 16]

Rex	Structure	Rex	Structure
127		134	
128		135	
129		136	
130		137	
131		138	

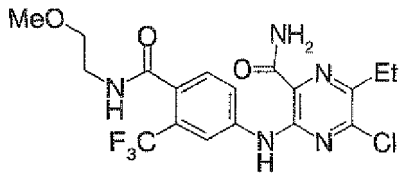
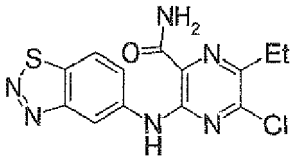
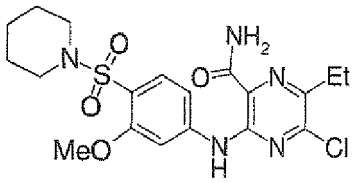
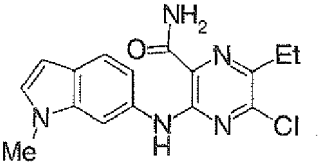
(continued)

Rex	Structure	Rex	Structure
132		139	
133		140	

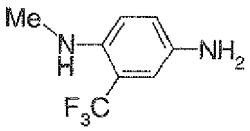
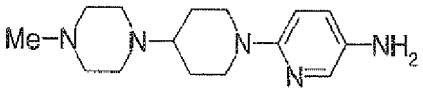
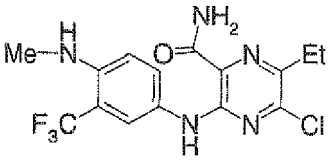
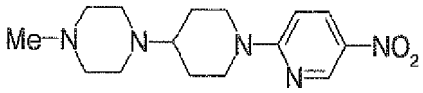
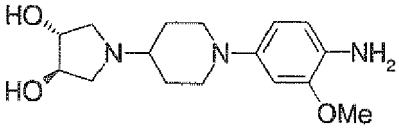
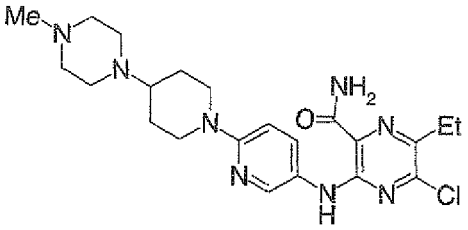
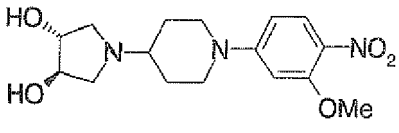
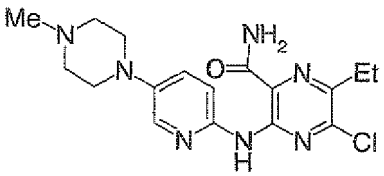
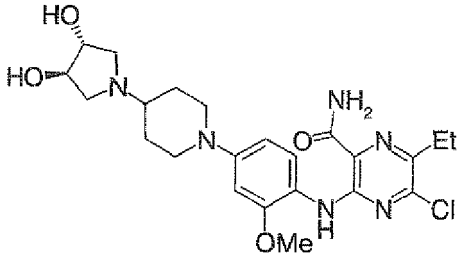
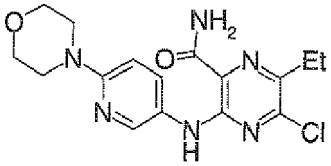
[Table 17]

Rex	Structure	Rex	Structure
141		148	
142		149	
143		150	
144		151	
145		152	

(continued)

Rex	Structure	Rex	Structure
146		153	
147		154	

[Table 18]

Rex	Structure	Rex	Structure
155		162	
156		163	
157		164	
158		165	
159		166	

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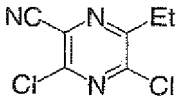
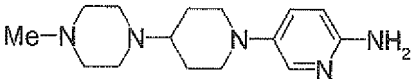
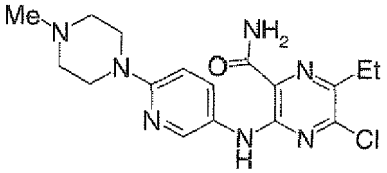
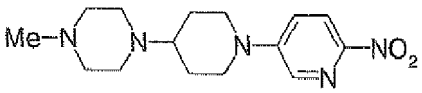
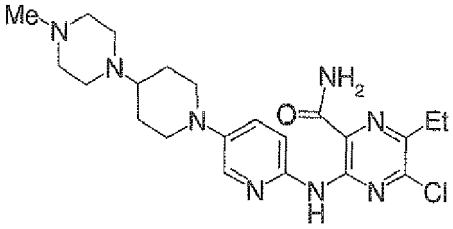
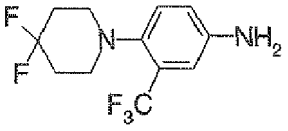
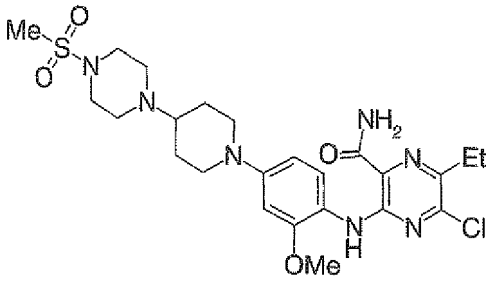
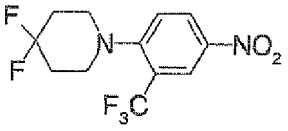
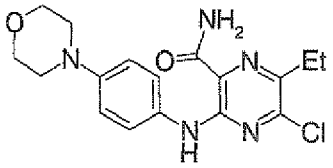
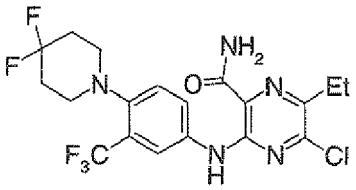
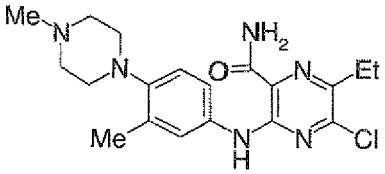
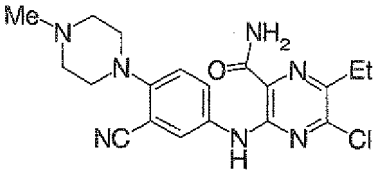
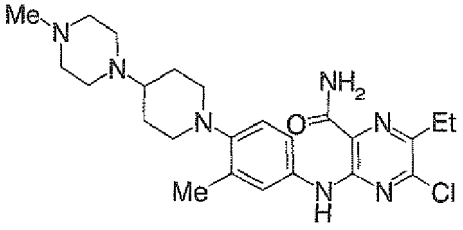
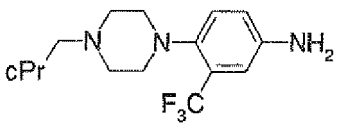
Rex	Structure	Rex	Structure
160		167	
161		168	

[Table 19]

Rex	Structure	Rex	Structure
169		176	
170		177	
171		178	
172		179	
173		180	

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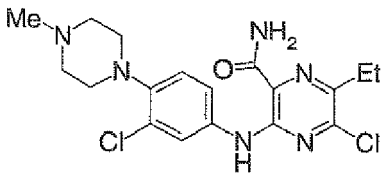
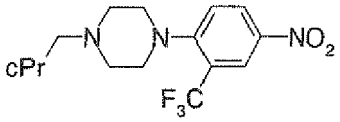
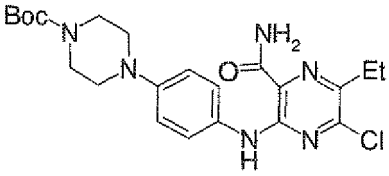
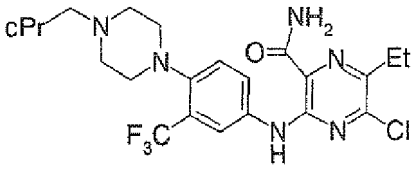
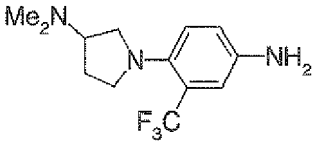
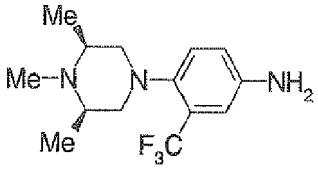
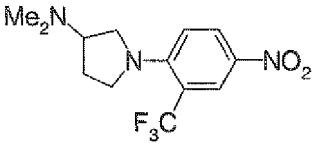
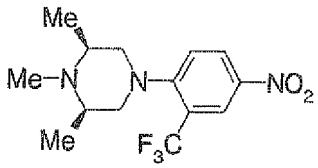
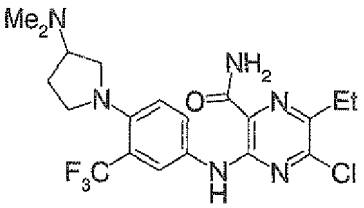
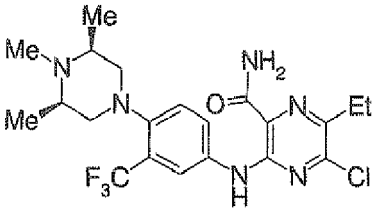
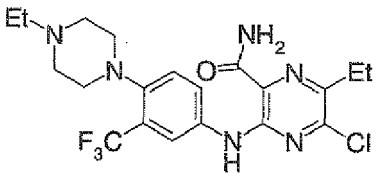
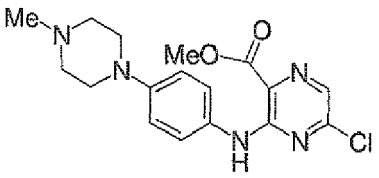
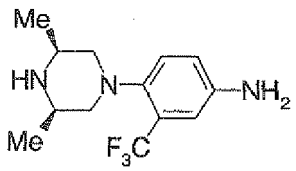
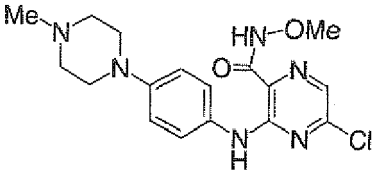
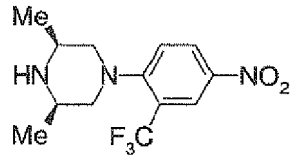
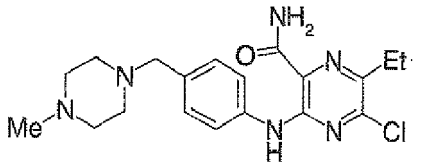
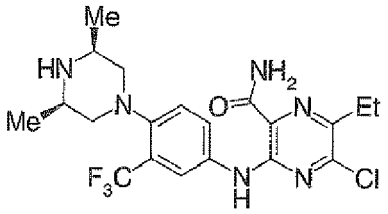
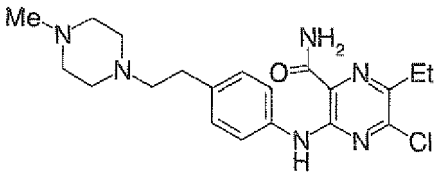
Rex	Structure	Rex	Structure
174		181	
175		182	

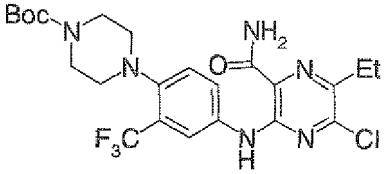
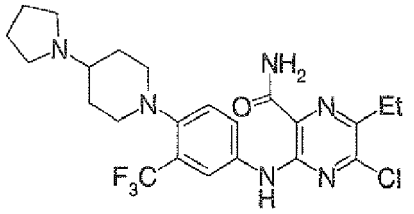
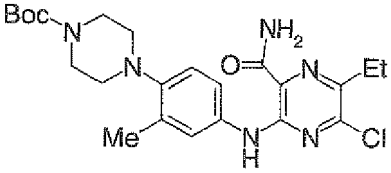
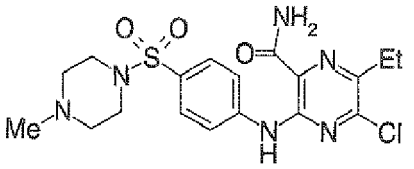
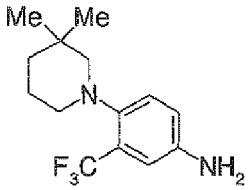
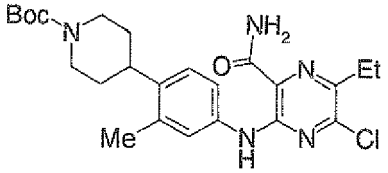
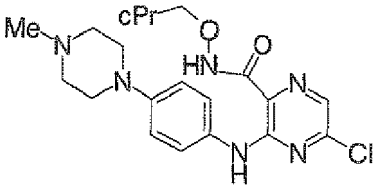
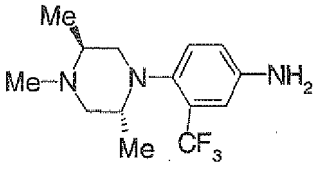
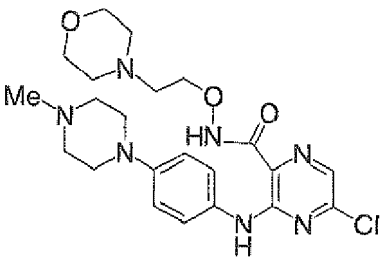
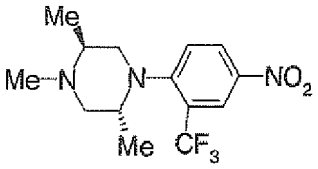
[Table 20]

Rex	Structure	Rex	Structure
183		190	
184		191	
185		192	
186		193	
187		194	

(continued)

Rex	Structure	Rex	Structure
188		195	
189		196	

[Table 21]

Rex	Structure	Rex	Structure
197		204	
198		205	
199		206	
200		207	
201		208	

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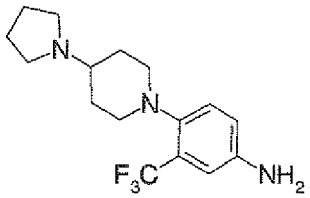
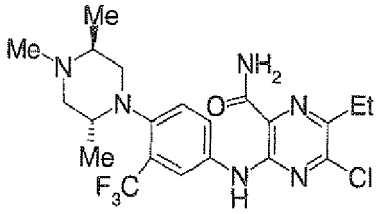
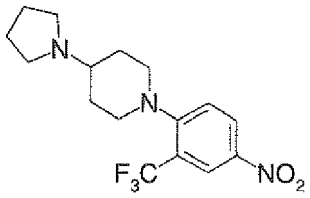
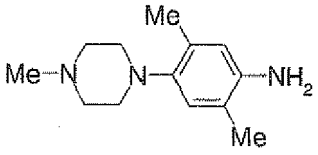
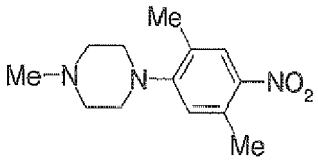
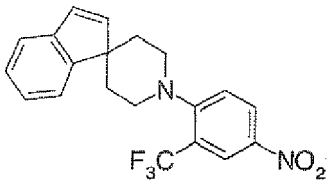
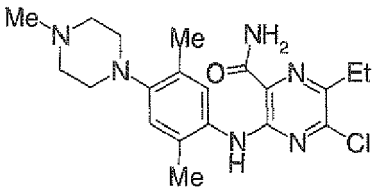
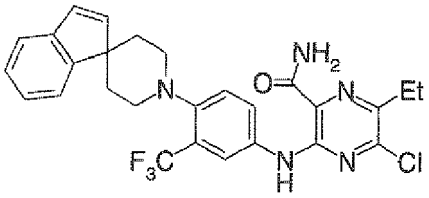
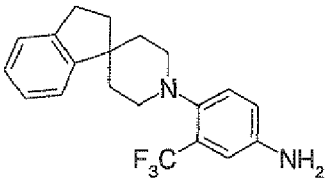
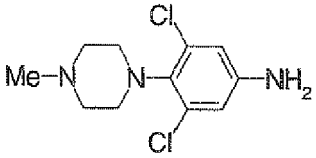
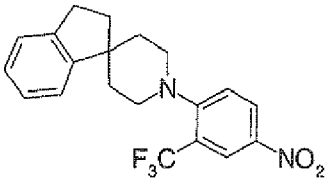
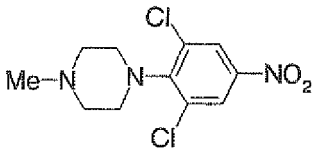
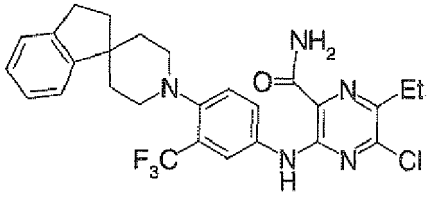
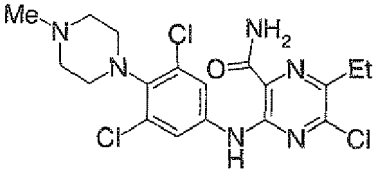
Rex	Structure	Rex	Structure
202		209	
203		210	

[Table 22]

Rex	Structure	Rex	Structure
211		218	
212		219	
213		220	
214		221	
215		222	

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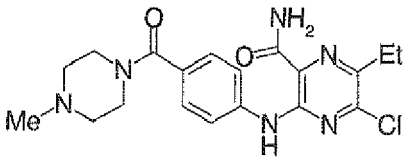
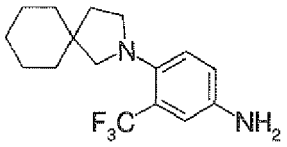
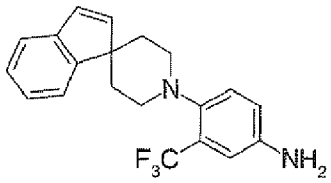
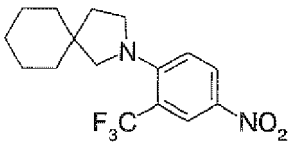
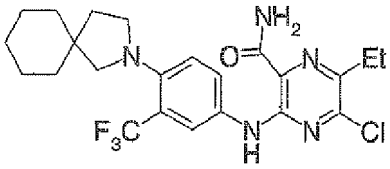
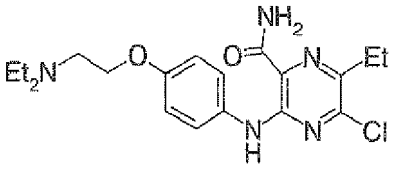
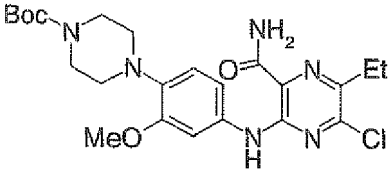
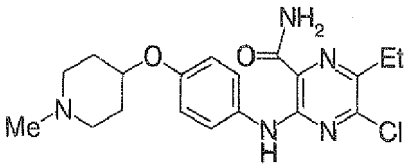
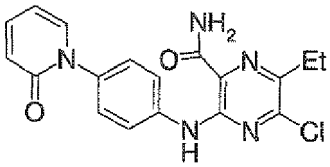
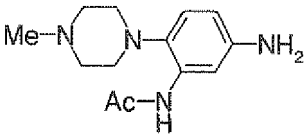
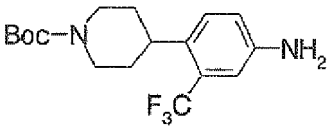
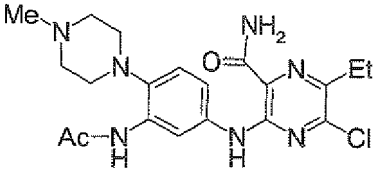
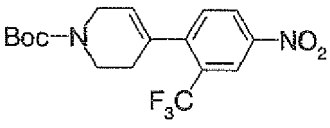
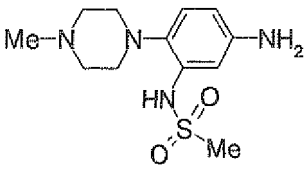
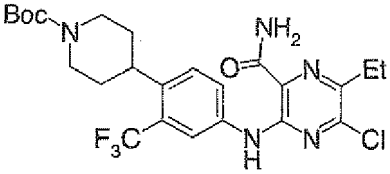
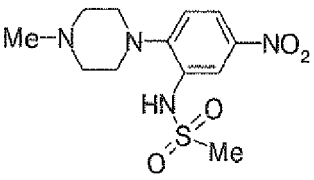
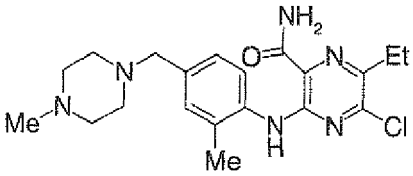
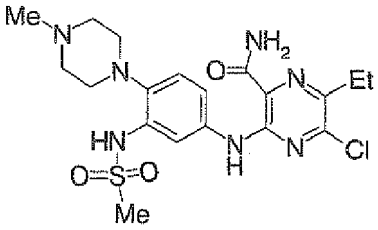
Rex	Structure	Rex	Structure
216		223	
217		224	

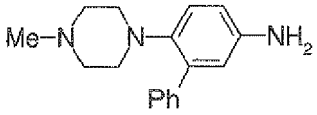
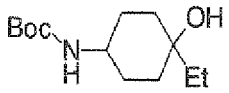
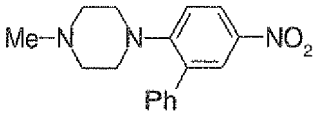
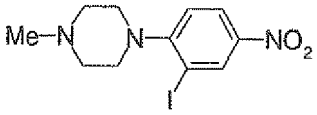
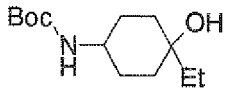
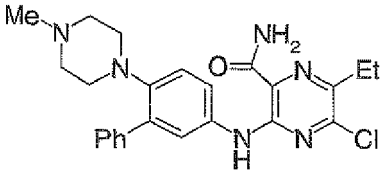
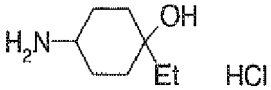
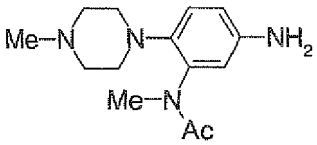
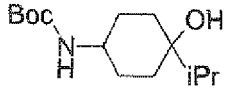
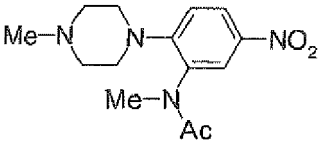
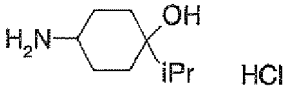
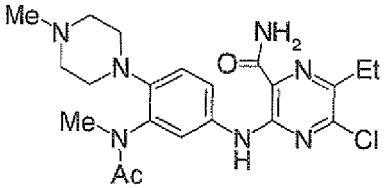
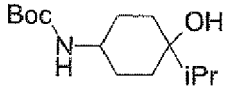
[Table 23]

Rex	Structure	Rex	Structure
225		232	
226		233	
227		234	
228		235	
229		236	
230		237	

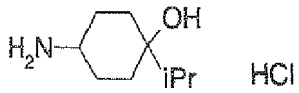
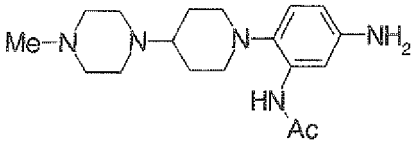
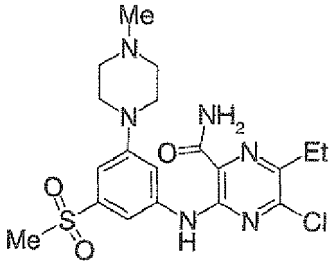
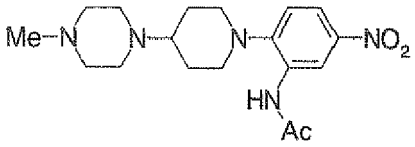
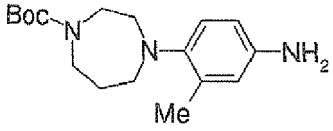
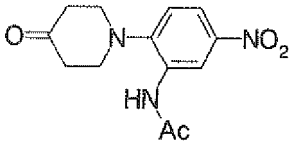
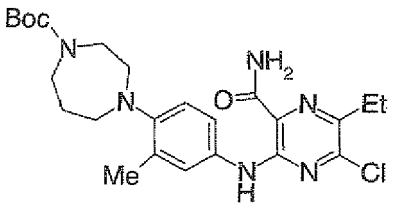
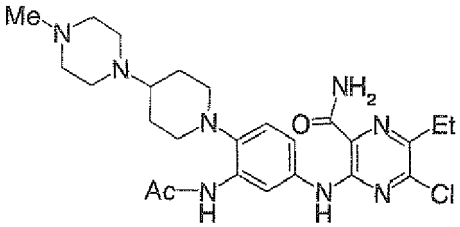
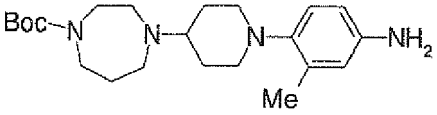
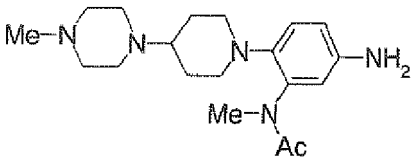
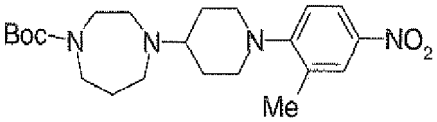
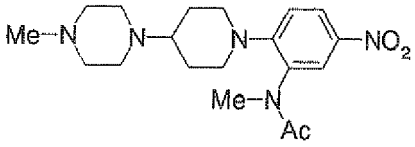
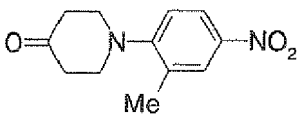
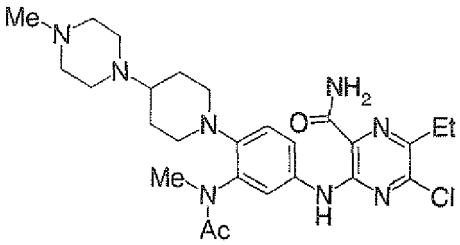
(continued)

Rex	Structure	Rex	Structure
231		238	

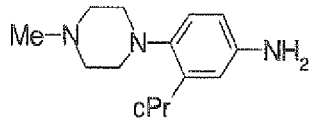
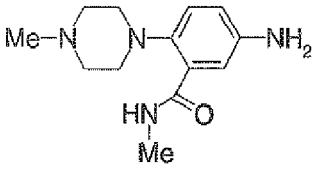
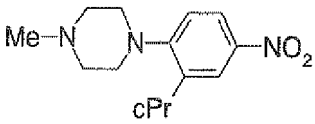
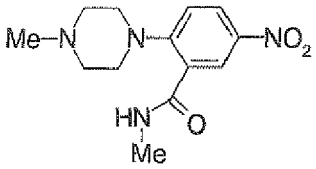
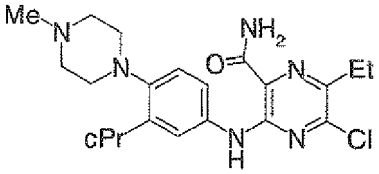
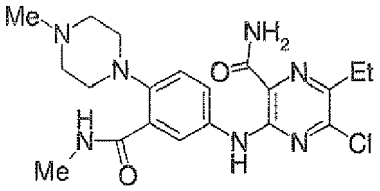
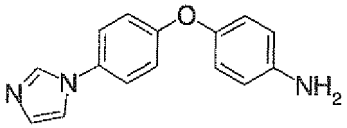
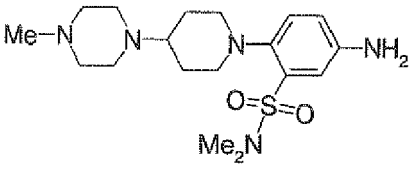
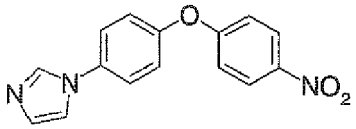
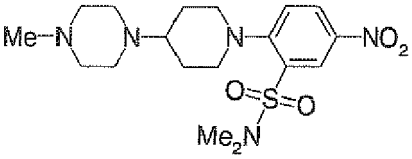
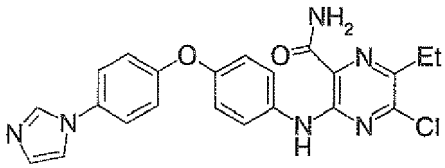
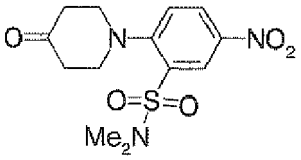
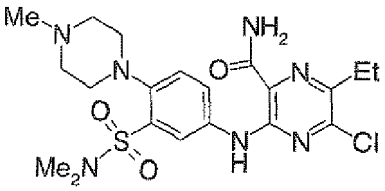
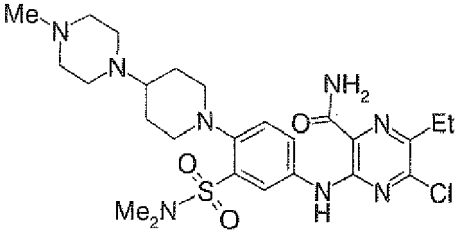
[Table 24]

Rex	Structure	Rex	Structure
239		246*1	
240		247*2	
241		248*1	
242		249*2	
243		250*3	
244		251*4	
245		252*3	

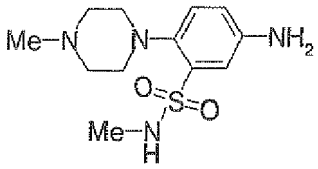
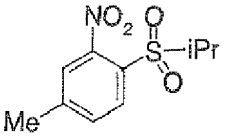
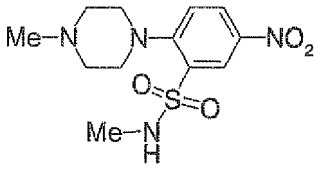
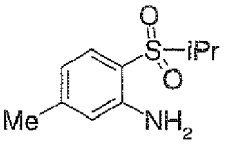
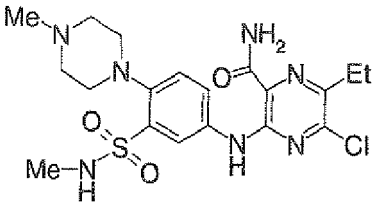
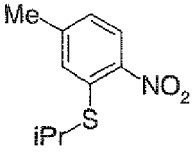
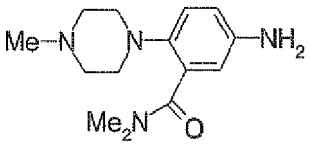
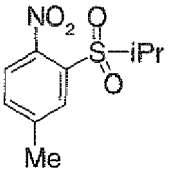
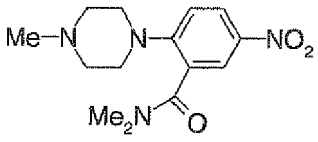
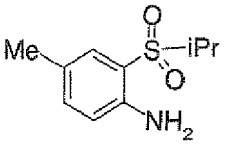
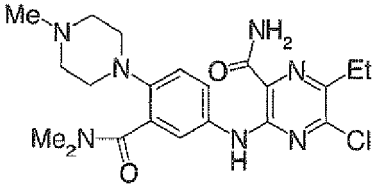
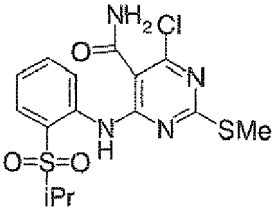
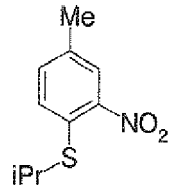
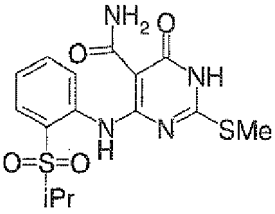
[Table 25]

Rex	Structure	Rex	Structure
253 *4		260	
254		261	
255		262	
256		263	
257		264	
258		265	
259		266	

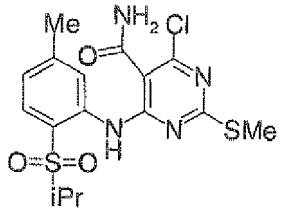
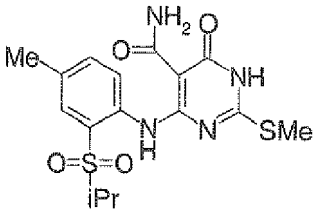
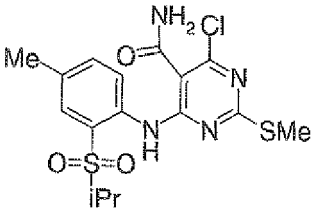
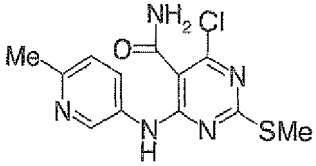
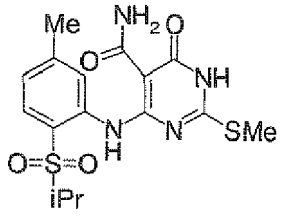
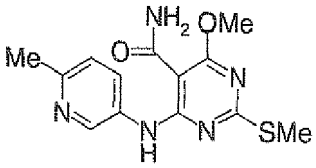
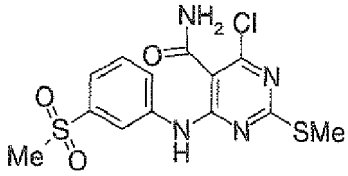
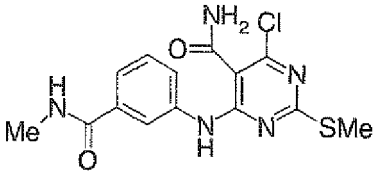
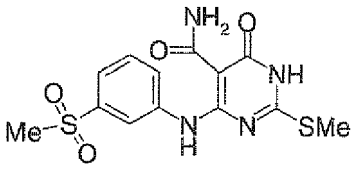
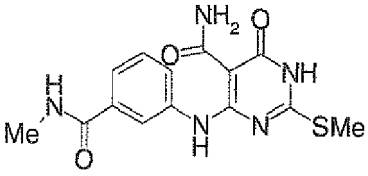
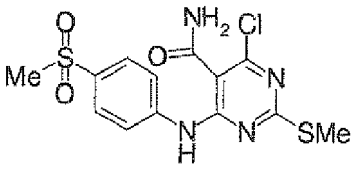
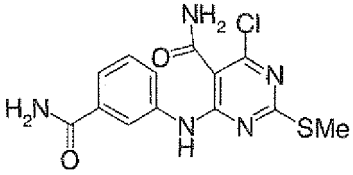
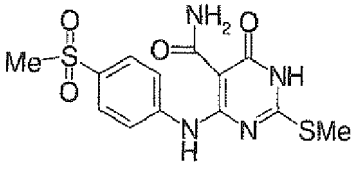
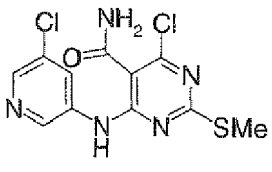
[Table 26]

Rex	Structure	Rex	Structure
267		274	
268		275	
269		276	
270		277	
271		278	
272		279	
273		280	

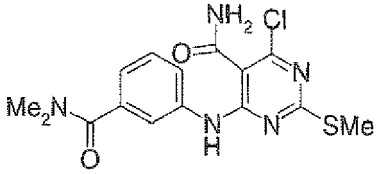
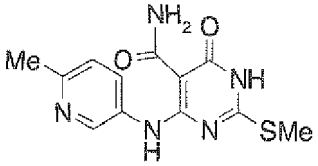
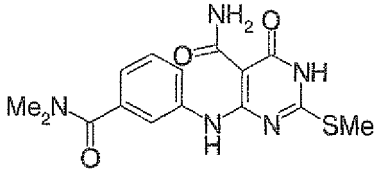
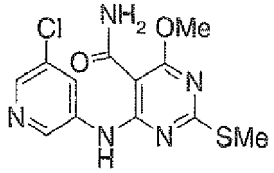
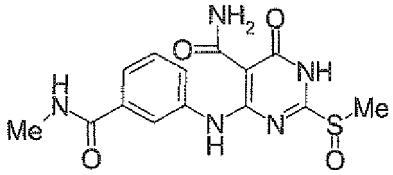
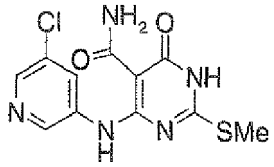
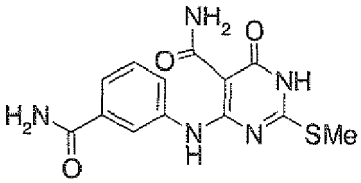
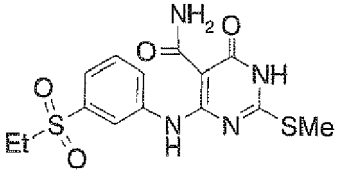
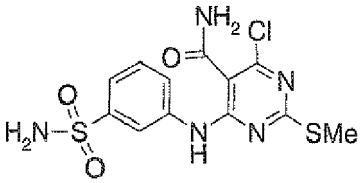
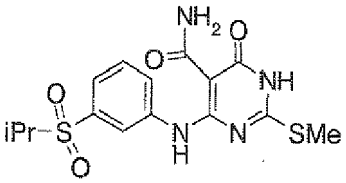
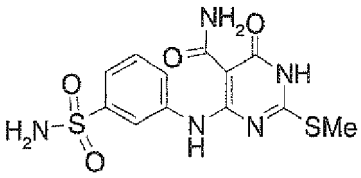
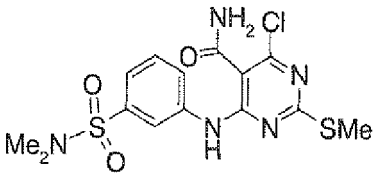
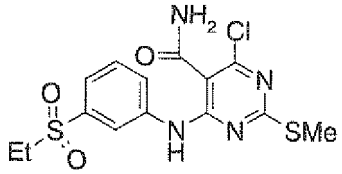
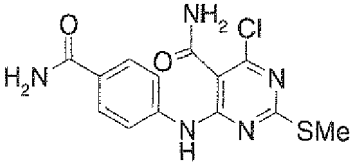
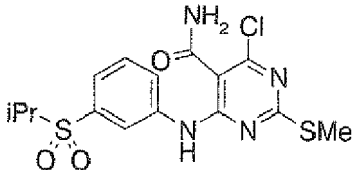
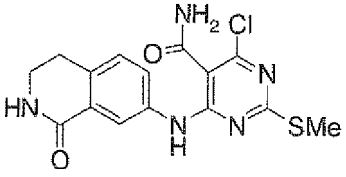
[Table 27]

Rex	Structure	Rex	Structure
281		288	
282		289	
283		290	
284		291	
285		292	
286		293	
287		294	

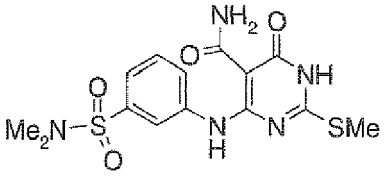
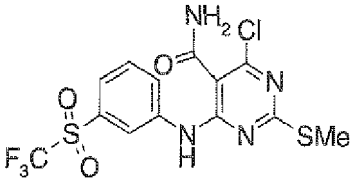
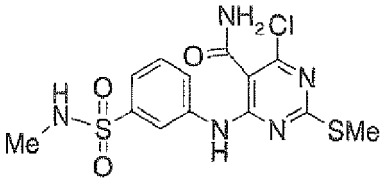
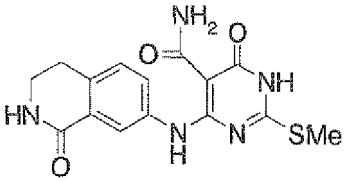
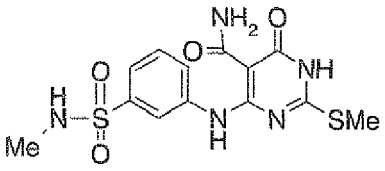
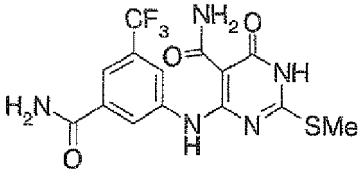
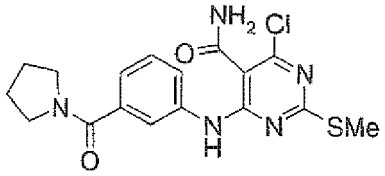
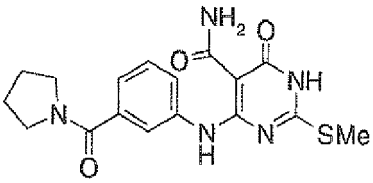
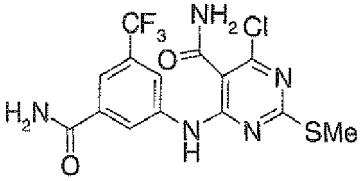
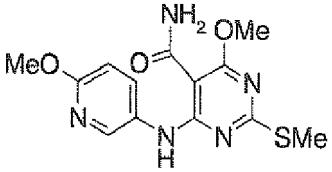
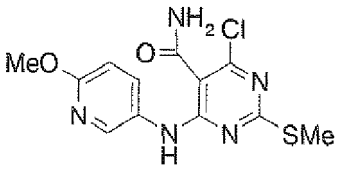
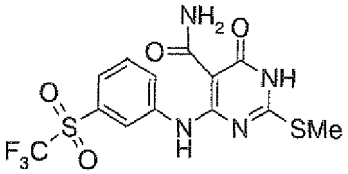
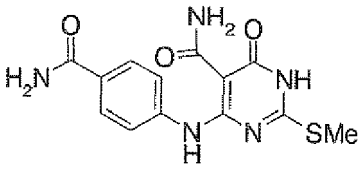
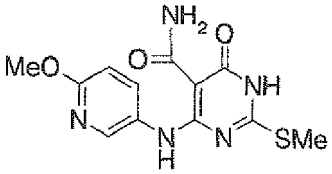
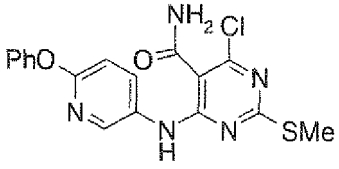
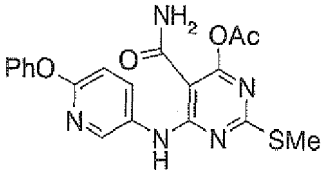
[Table 28]

Rex	Structure	Rex	Structure
295		302	
296		303	
297		304	
298		305	
299		306	
300		307	
301		308	

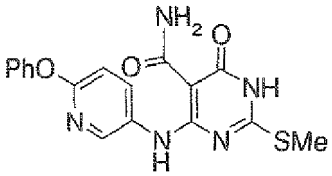
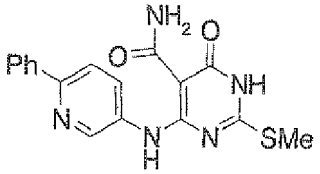
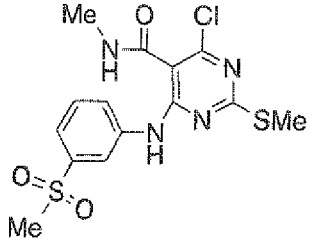
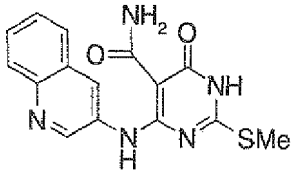
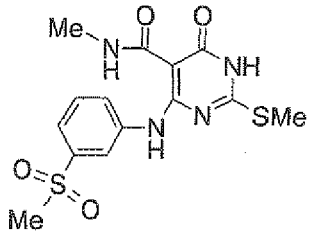
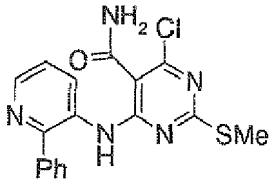
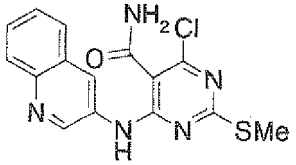
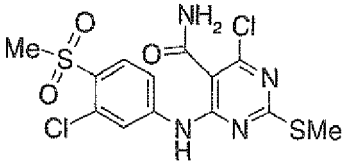
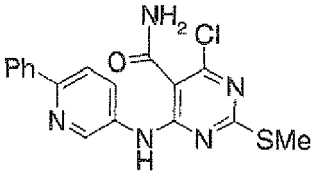
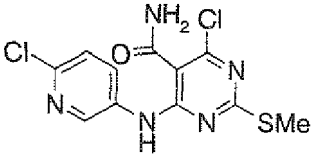
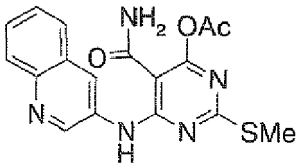
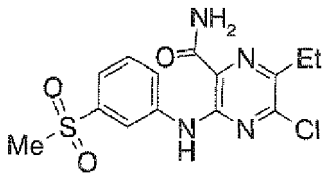
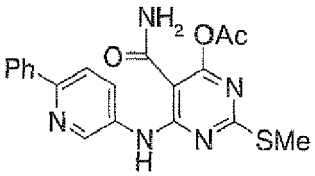
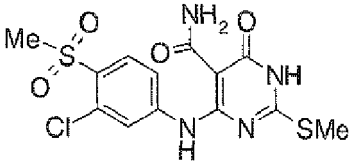
[Table 29]

Rex	Structure	Rex	Structure
309		317	
310		318	
311		319	
312		320	
313		321	
314		322	
315		323	
316		324	

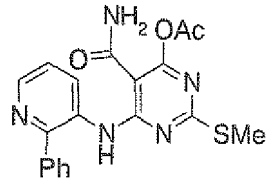
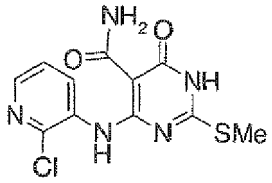
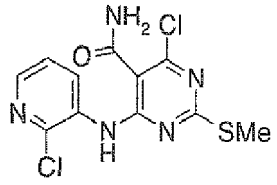
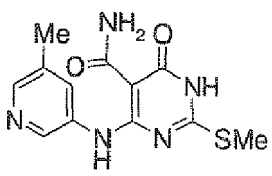
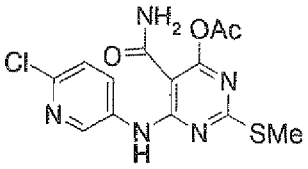
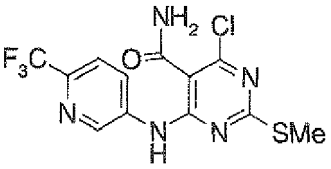
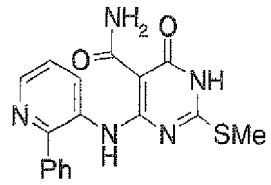
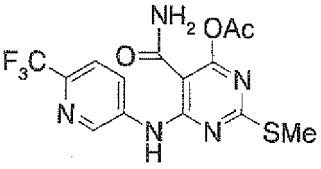
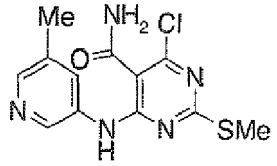
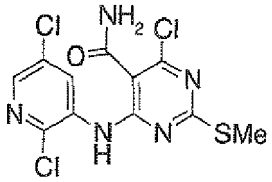
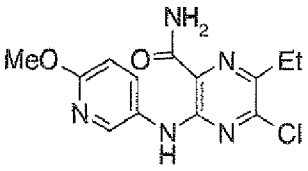
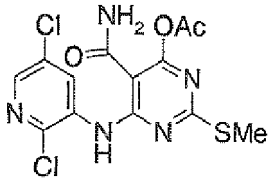
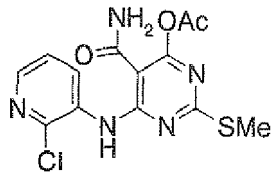
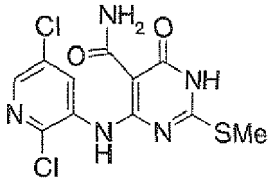
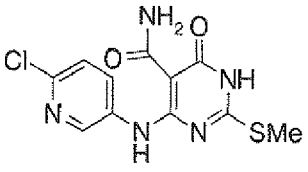
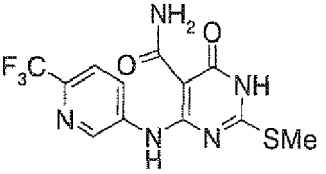
[Table 30]

Rex	Structure	Rex	Structure
325		333	
326		334	
327		335	
328		336	
329		337	
330		338	
331		339	
332		340	

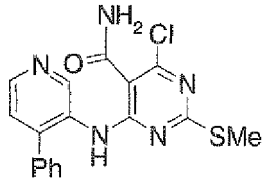
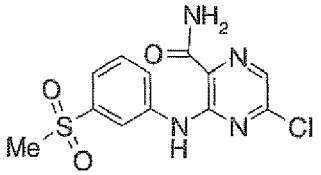
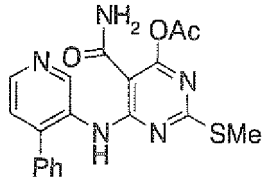
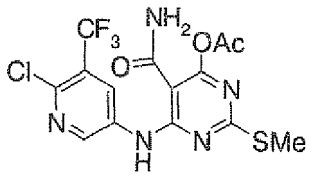
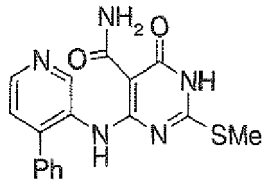
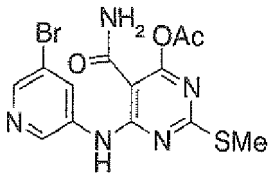
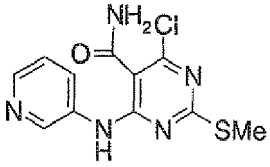
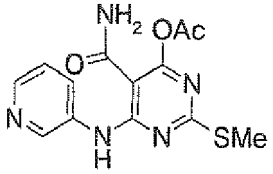
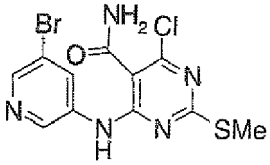
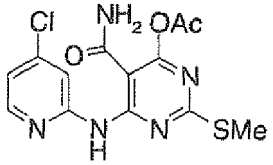
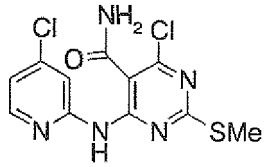
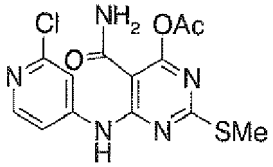
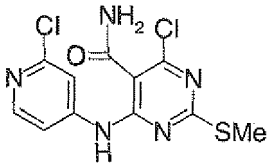
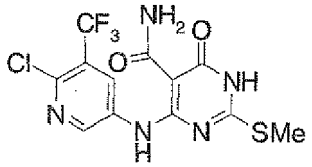
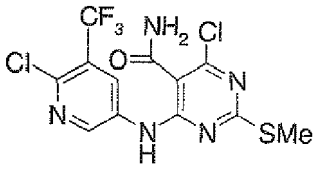
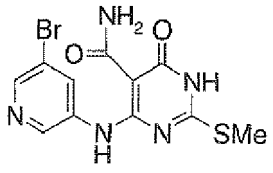
[Table 31]

Rex	Structure	Rex	Structure
341		348	
342		349	
343		350	
344		351	
345		352	
346		353	
347		354	

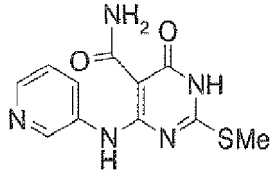
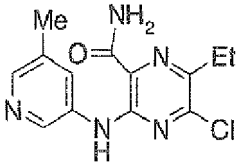
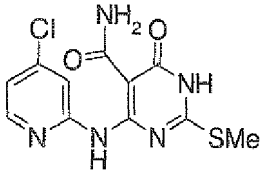
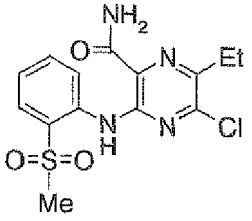
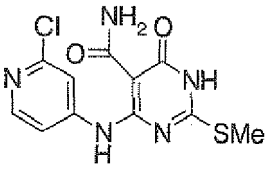
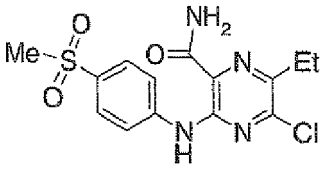
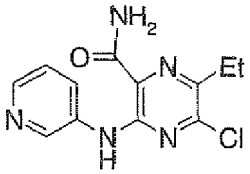
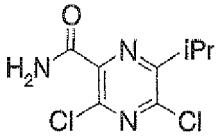
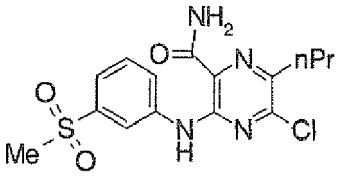
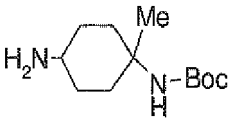
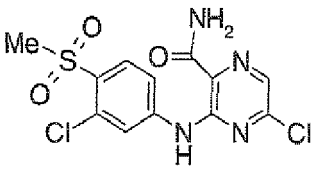
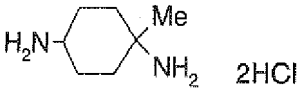
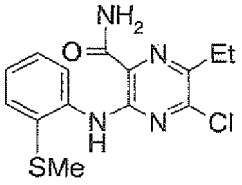
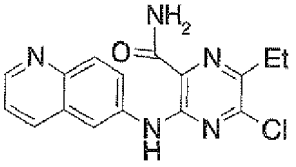
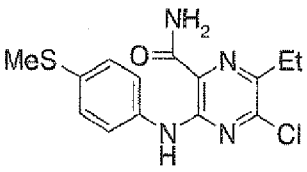
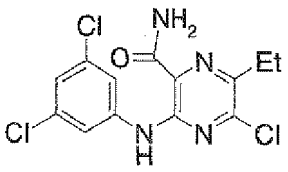
[Table 32]

Rex	Structure	Rex	Structure
355		363	
356		364	
357		365	
358		366	
359		367	
360		368	
361		369	
362		370	

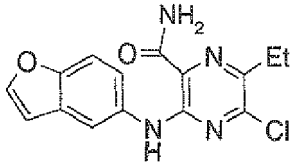
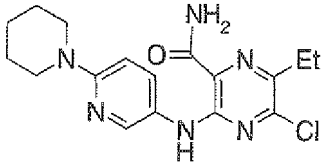
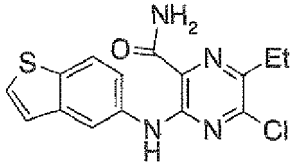
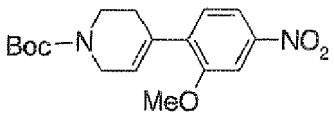
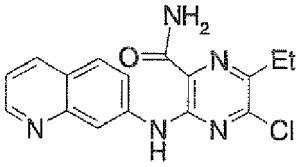
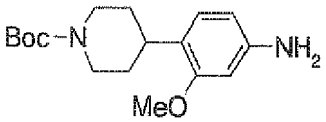
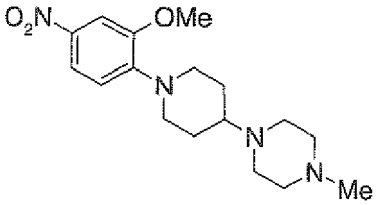
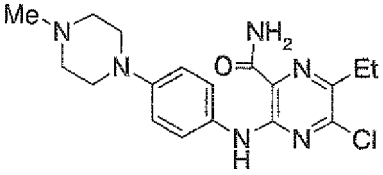
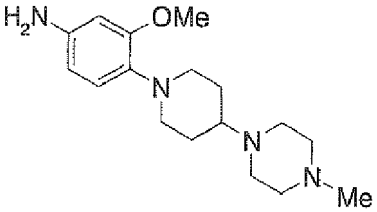
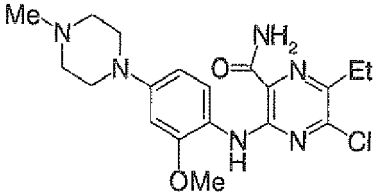
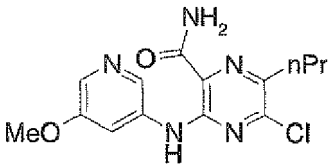
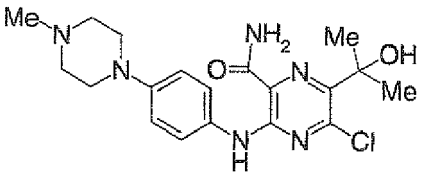
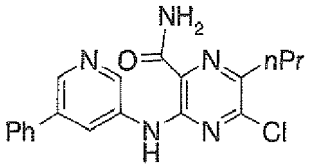
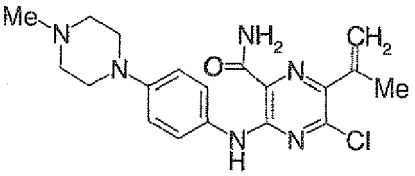
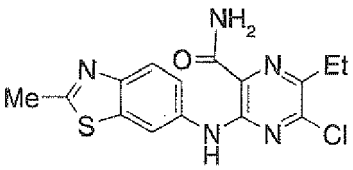
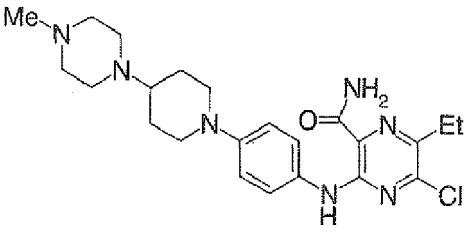
[Table 33]

Rex	Structure	Rex	Structure
371		379	
372		380	
373		381	
374		382	
375		383	
376		384	
377		385	
378		386	

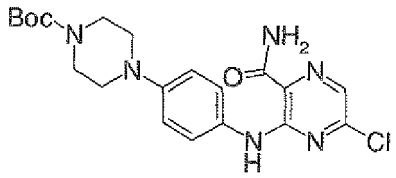
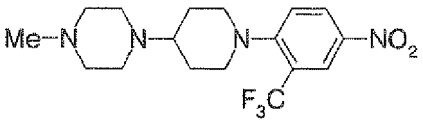
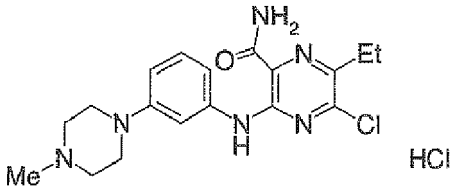
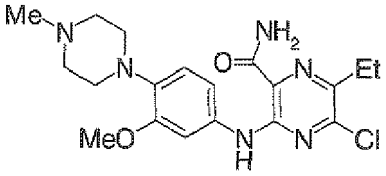
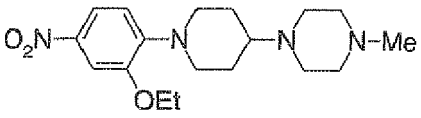
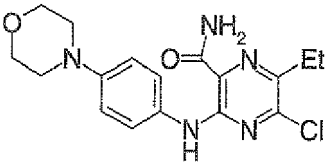
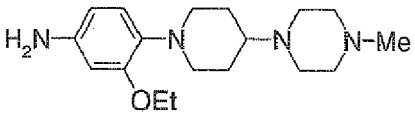
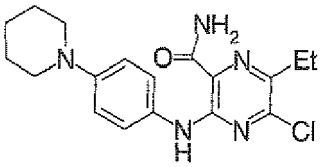
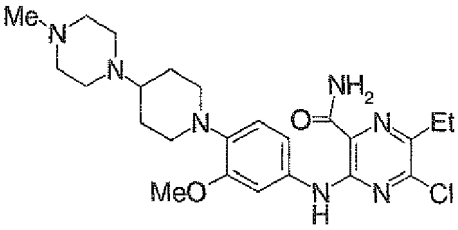
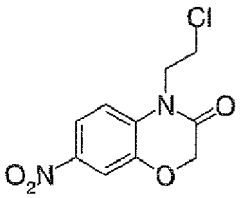
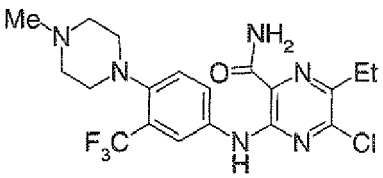
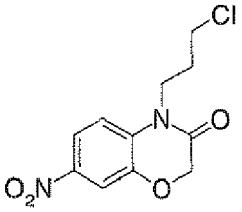
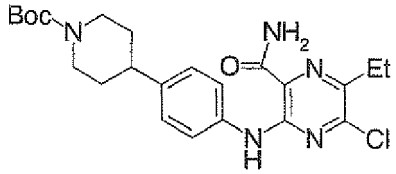
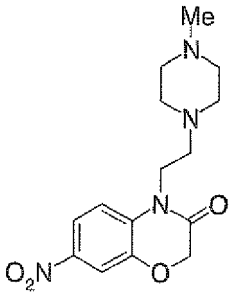
[Table 34]

Rex	Structure	Rex	Structure
387		395	
388		396	
389		397	
390		398	
391		399	
392		400	
393		401	
394		402	

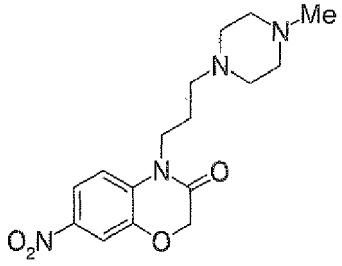
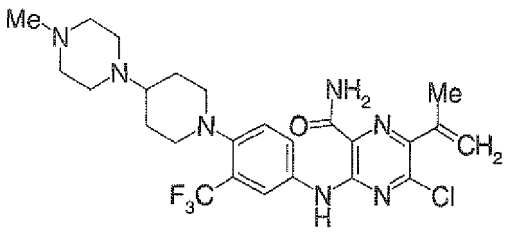
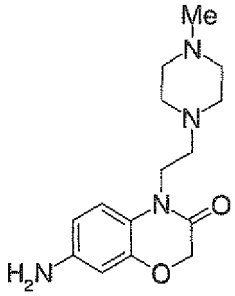
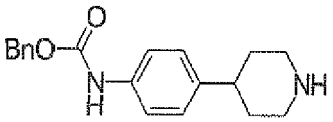
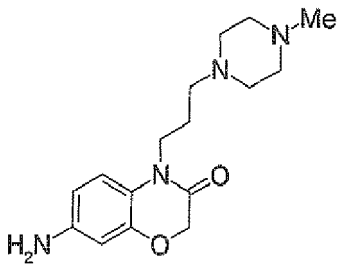
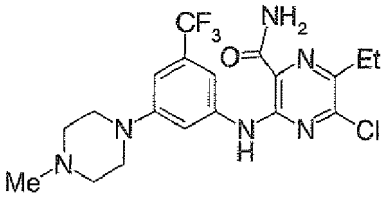
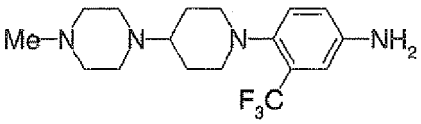
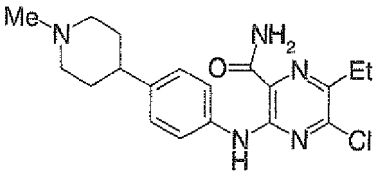
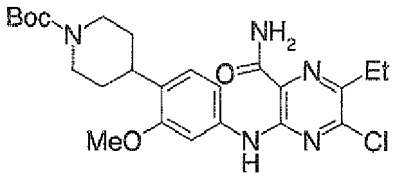
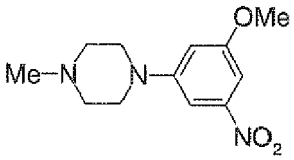
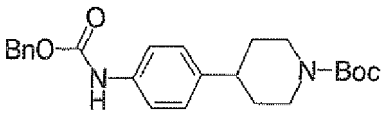
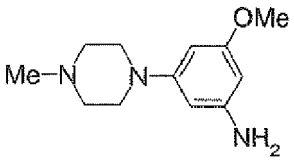
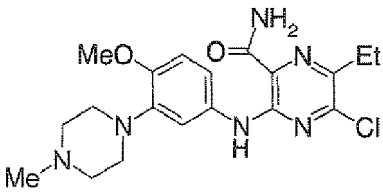
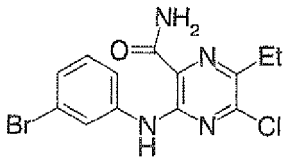
[Table 35]

Rex	Structure	Rex	Structure
403		411	
404		412	
405		413	
406		414	
407		415	
408		416	
409		417	
410		418	

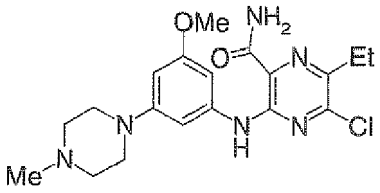
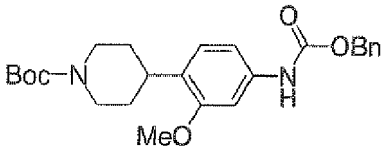
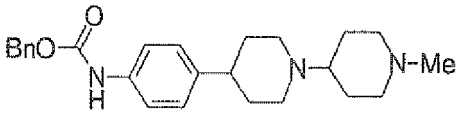
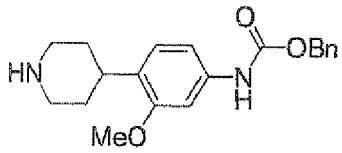
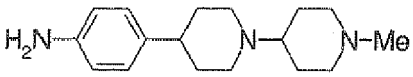
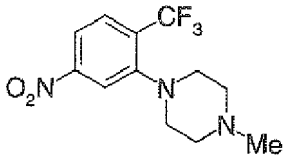
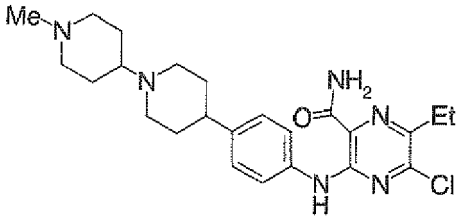
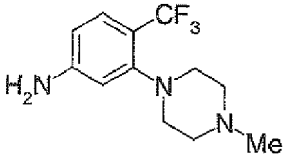
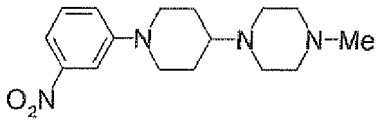
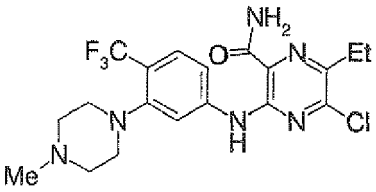
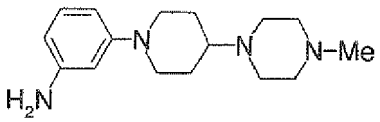
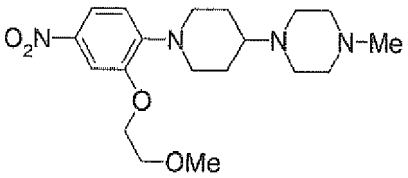
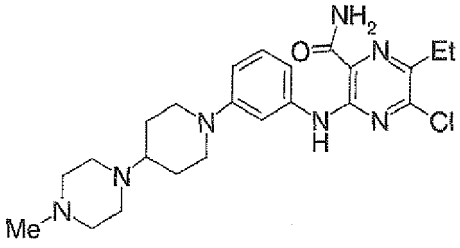
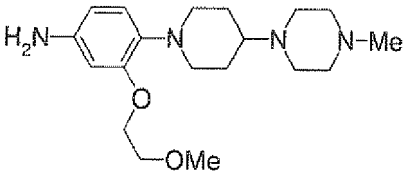
[Table 36]

Rex	Structure	Rex	Structure
419		426	
420		427	
421		428	
422		429	
423		430	
424		431	
425		432	

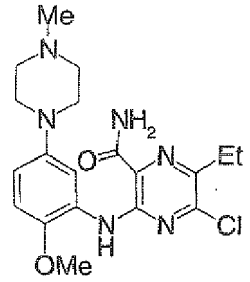
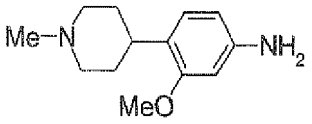
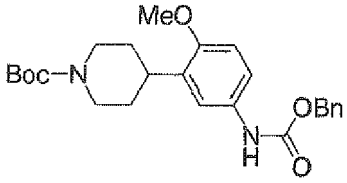
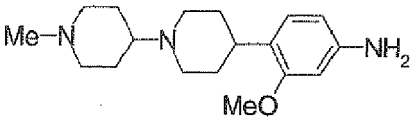
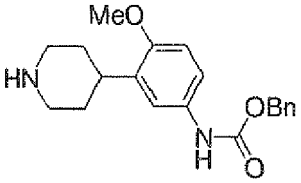
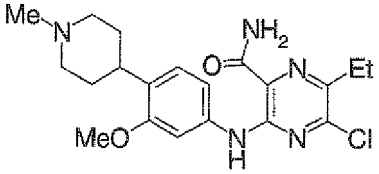
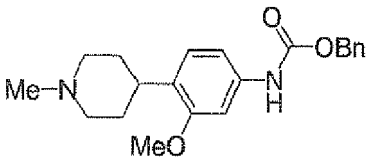
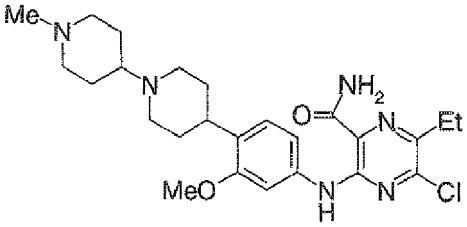
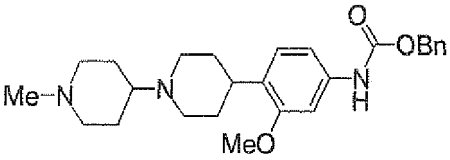
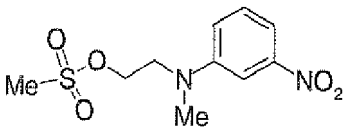
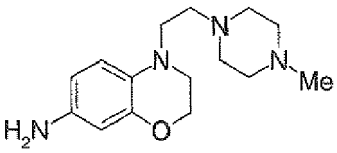
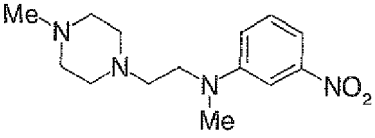
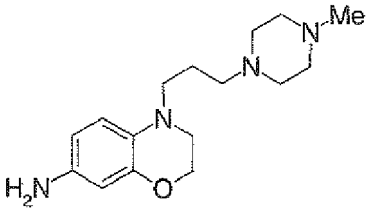
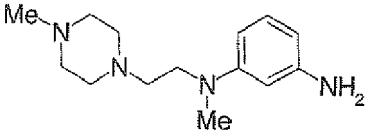
[Table 37]

Rex	Structure	Rex	Structure
433		440	
434		441	
435		442	
436		443	
437		444	
438		445	
439		446	

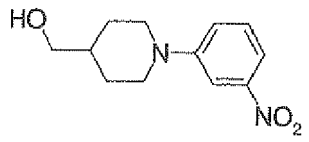
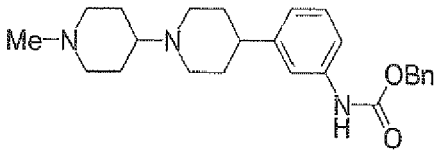
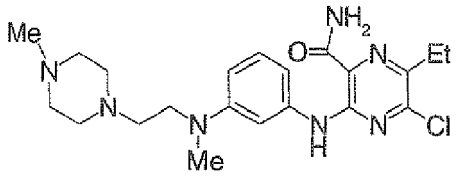
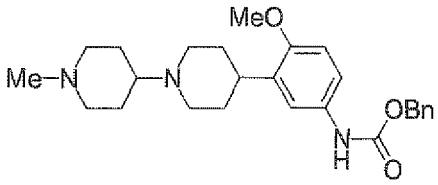
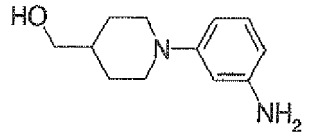
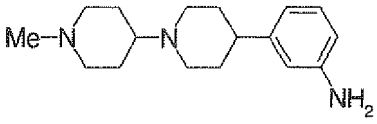
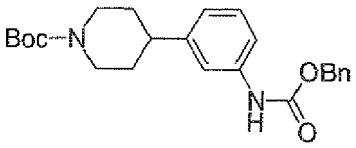
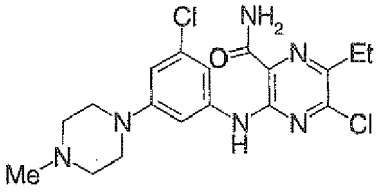
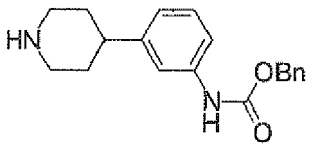
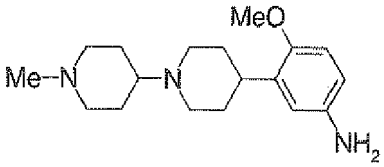
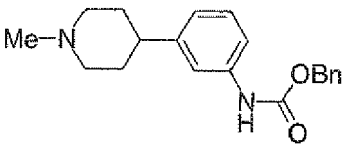
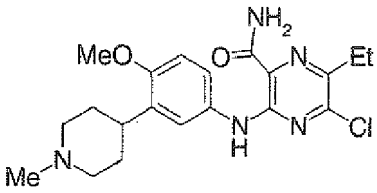
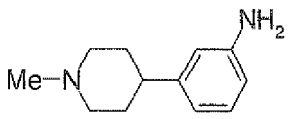
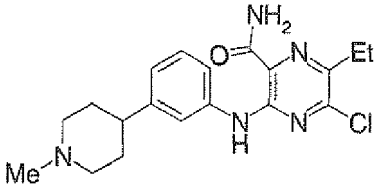
[Table 38]

Rex	Structure	Rex	Structure
447		454	
448		455	
449		456	
450		457	
451		458	
452		459	
453		460	

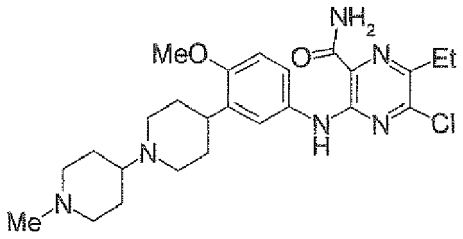
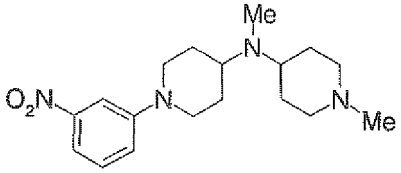
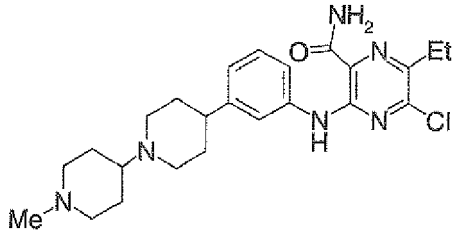
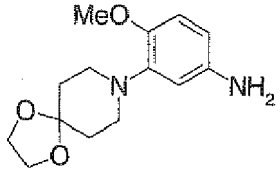
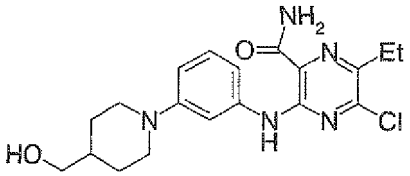
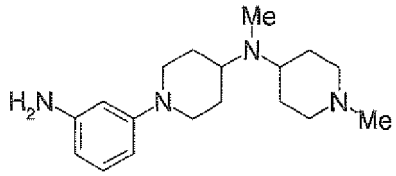
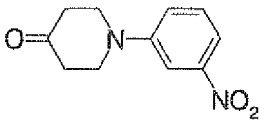
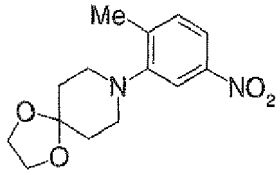
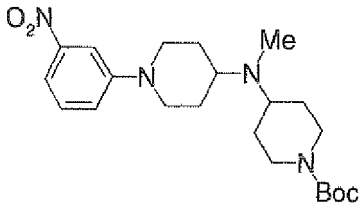
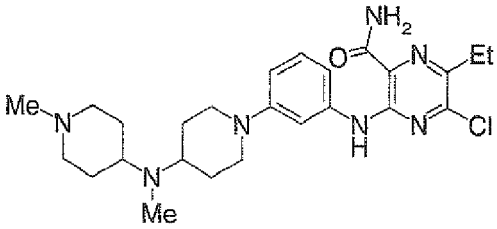
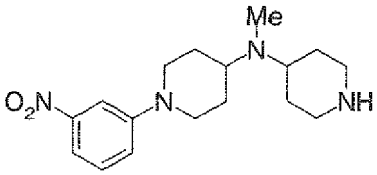
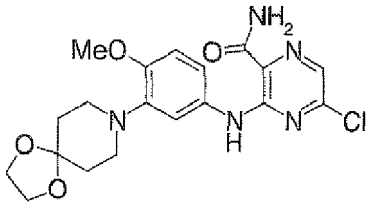
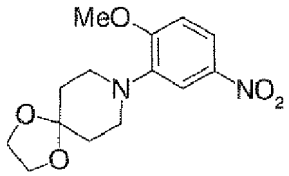
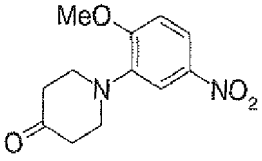
[Table 39]

Rex	Structure	Rex	Structure
461		468	
462		469	
463		470	
464		471	
465		472	
466		473	
467		474	

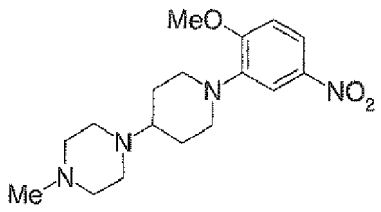
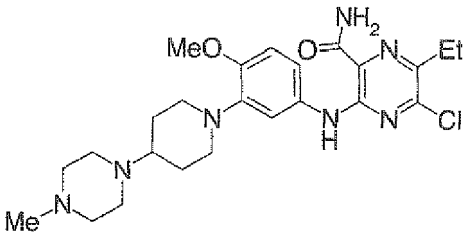
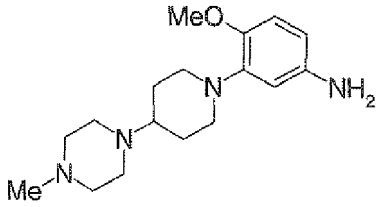
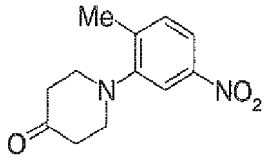
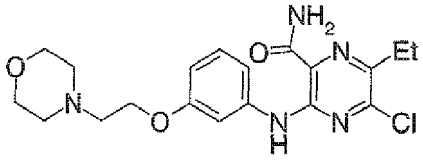
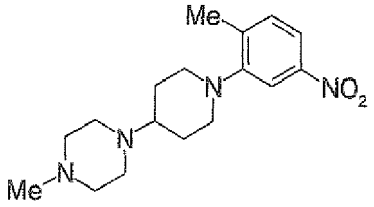
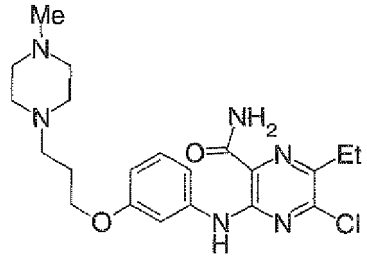
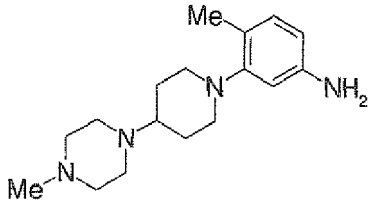
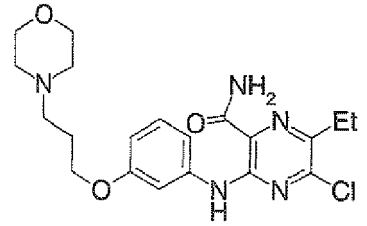
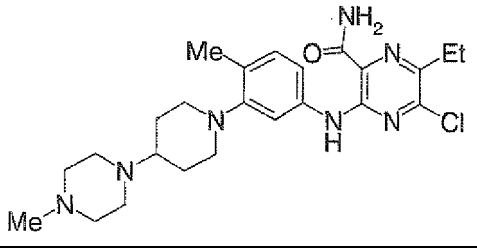
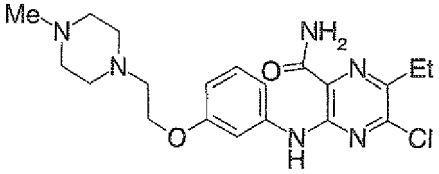
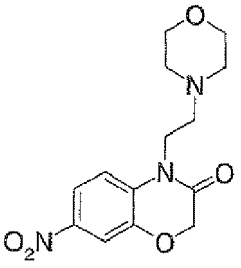
[Table 40]

Rex	Structure	Rex	Structure
475		482	
476		483	
477		484	
478		485	
479		486	
480		487	
481		488	

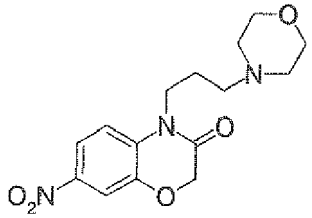
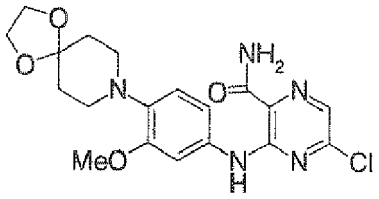
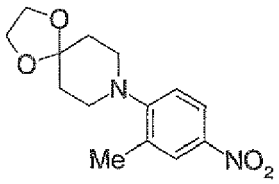
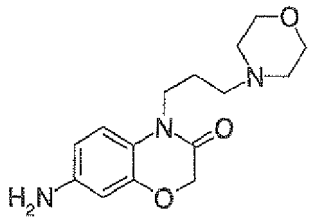
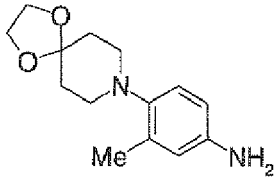
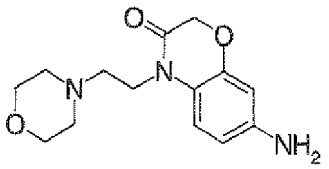
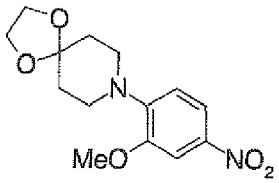
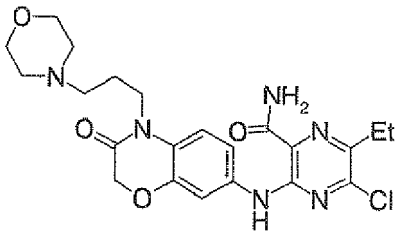
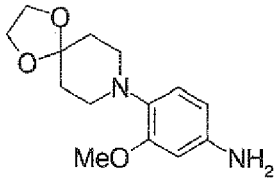
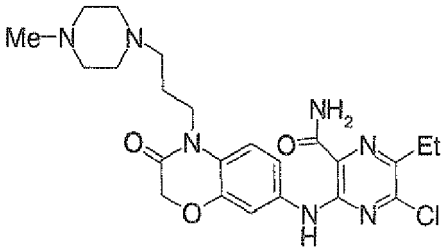
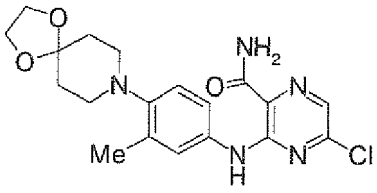
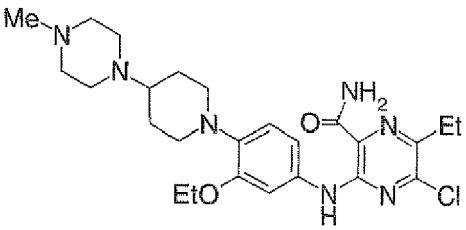
[Table 41]

Rex	Structure	Rex	Structure
489		496	
490		497	
491		498	
492		499	
493		500	
494		501	
495		502	

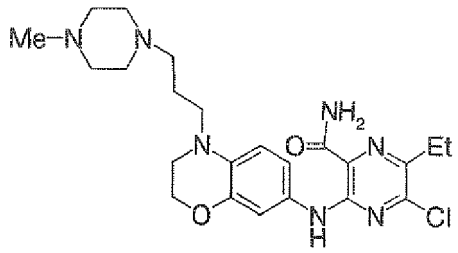
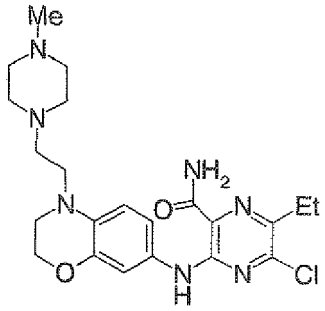
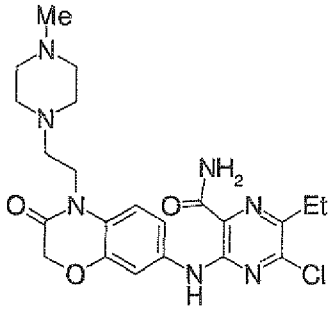
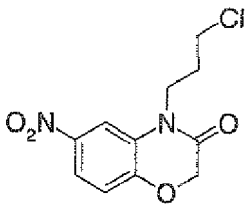
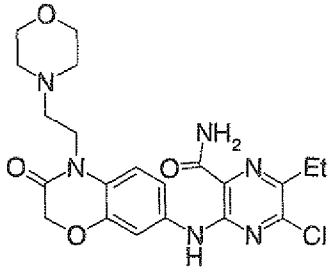
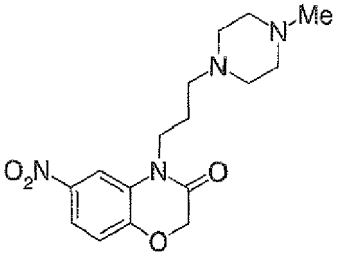
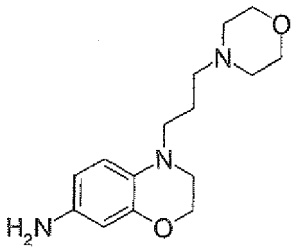
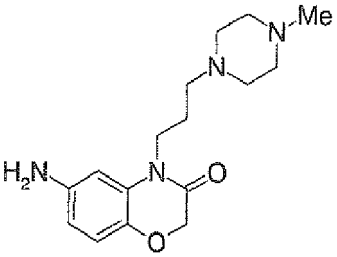
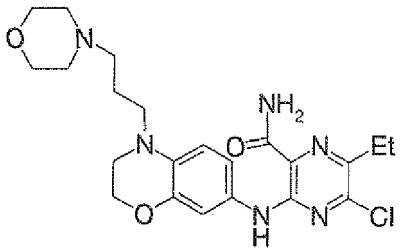
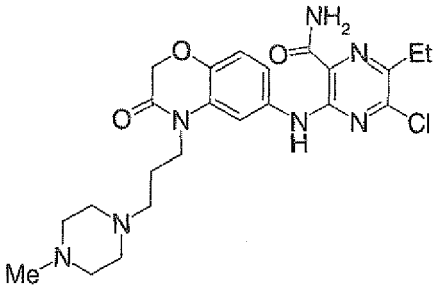
[Table 42]

Rex	Structure	Rex	Structure
503		509	
504		510	
505		511	
506		512	
507		513	
508		514	

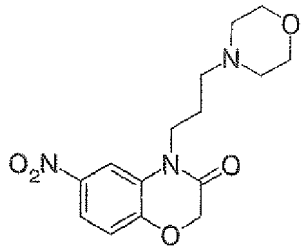
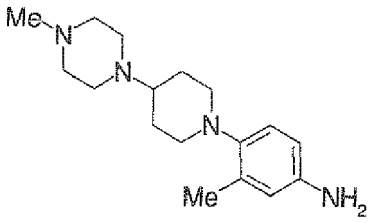
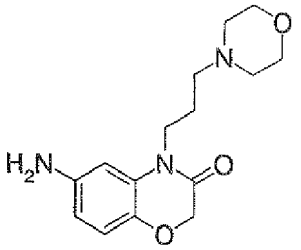
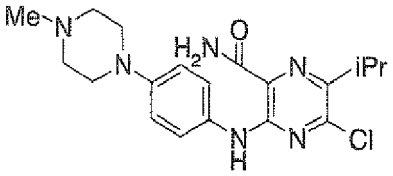
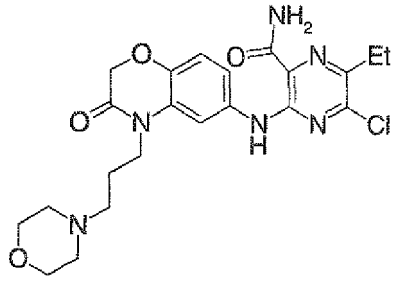
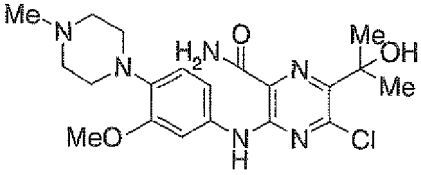
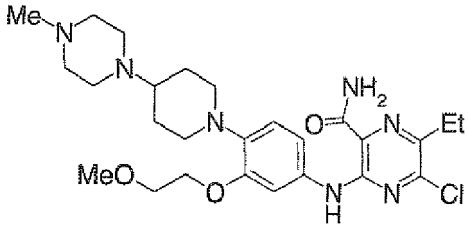
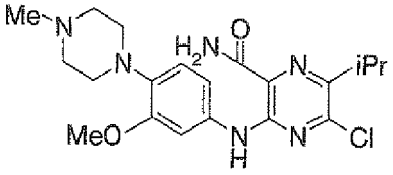
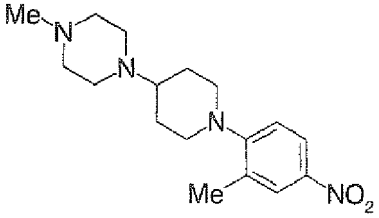
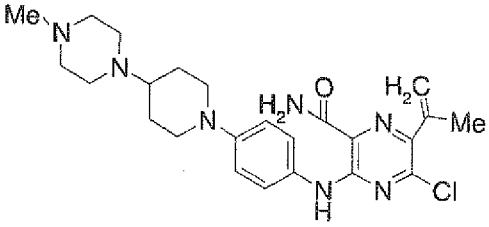
[Table 43]

Rex	Structure	Rex	Structure
515		521	
516		522	
517		523	
518		524	
519		525	
520		526	

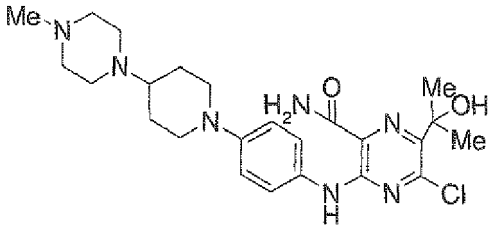
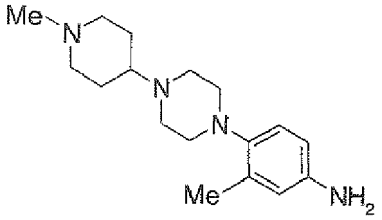
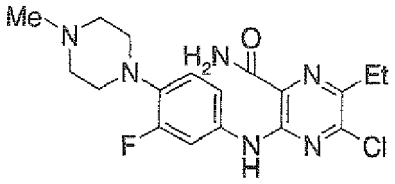
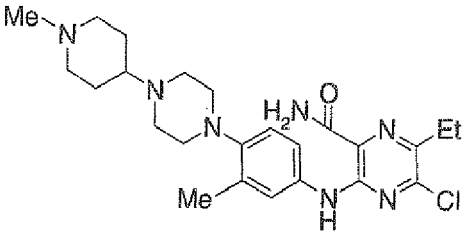
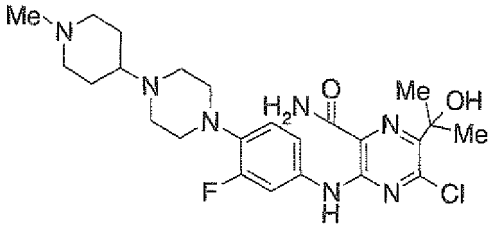
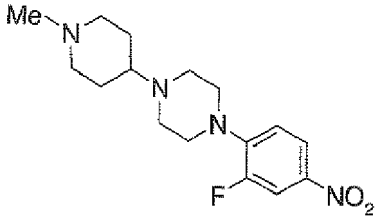
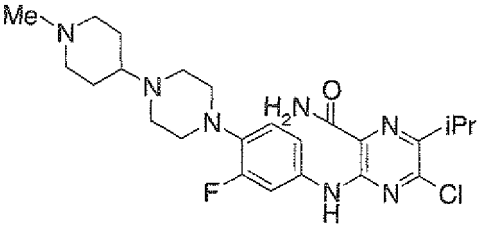
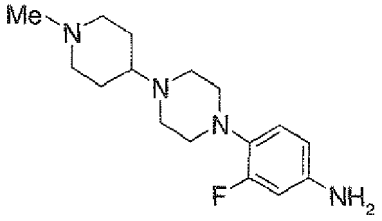
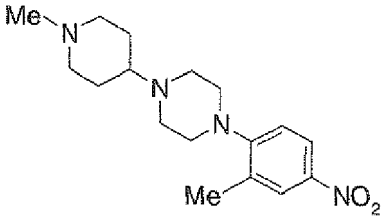
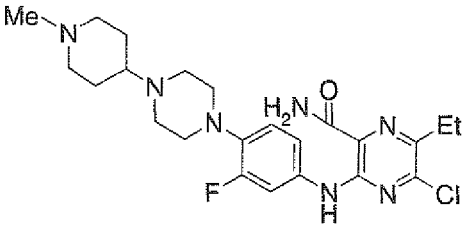
[Table 44]

Rex	Structure	Rex	Structure
527		532	
528		533	
529		534	
530		535	
531		536	

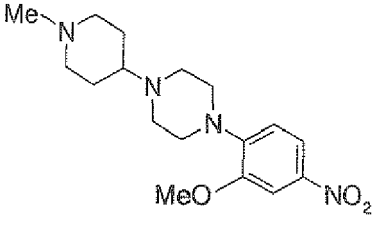
[Table 45]

Rex	Structure	Rex	Structure
537		542	
538		543	
539		544	
540		545	
541		546	

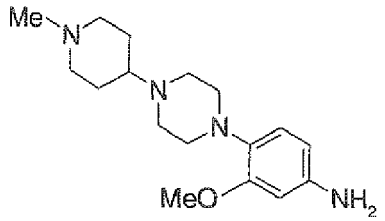
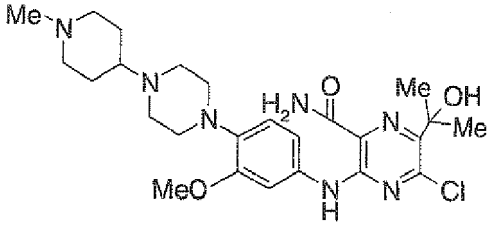
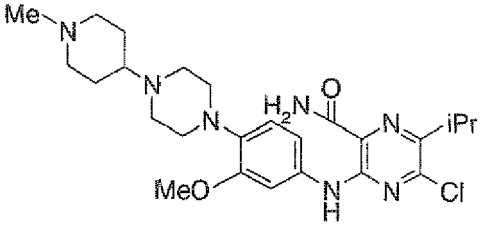
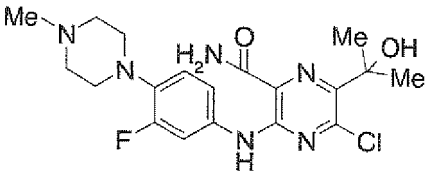
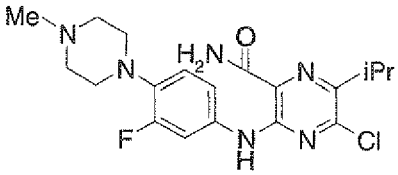
[Table 46]

Rex	Structure	Rex	Structure
547		552	
548		553	
549		554	
550		555	
551		556	

[Table 47]

Rex	Structure
557	

(continued)

Rex	Structure
558	
559	
560	
561	
562	

[Table 48]

Rex	Syn	Data
1	Rex299	ESI-: 402
2	Rex298	ESI-: 420
3	Rex292	^{1}H-NMR (CDCl3): 1.11 (3H, br-s), 1.21 (3H, br-s), 2.17 (3H, s), 3.28 (2H, br-s), 3.51 (2H, br-s), 3.66 (2H, br-s), 6.66-6.68 (2H, m), 7.03 (1H, dd, J = 0.8Hz, 8.0Hz).
4	Rex4	EI: 236
5	Rex299	ESI-: 388
6	Rex298	ESI-: 406
7	Rex292	^{1}H-NMR (CDCl3): 1.50-1.65 (6H, m), 2.16 (3H, s), 3.36 (2H, br-s), 3.71 (4H, m), 6.66-6.69 (2H, m), 7.02 (1H, d, J = 7.6Hz).
8	Rex4	EI: 248

(continued)

Rex	Syn	Data
9	Rex299	^{1}H-NMR (DMSO-d6): 1.48-1.59 (6H, m), 2.30 (3H, s), 2.41 (3H, s), 3.33 (2H, br-s), 3.54 (2H, br-s), 7.02 (1H, dd, J = 1.2Hz, 8.0Hz),7.28 (1H, d, J = 8.0Hz), 7.47 (1H, d, J = 4.0Hz), 7.99 (1H, d, J = 1.2Hz), 9.16 (1H, d, J = 4.4Hz), 12.68 (1H, s), 12.84 (1H, s).
10	Rex298	ESI-: 418
11	Rex292	^{1}H-NMR (CDCl3): 1.24 (6H, d, J = 6.8Hz), 2.19 (3H, s), 3.70 (2H, br-s), 4.23-4.29 (1H, m), 5.85 (1H, br-s), 6.97 (1H, dd, J = 1.6Hz, 7.6Hz), 7.06 (1H, d, J = 7.6Hz), 7.13(1H, d, J = 1.6Hz).
12	Rex4	^{1}H-NMR (CDCl3): 1.29 (6H, d, J = 6.4Hz), 2.65 (3H, s), 4.25-4.34 (1H, m), 5.99 (1H, br-s), 7.42 (1H, d, J = 8.0Hz), 7.94 (1H, dd, d = 2.0Hz, 8.0Hz), 8.30 (1H, d, J = 1.6Hz).

[Table 49]

Rex	Syn	Data
13	Rex299	^{1}H-NMR (DMSO-d6): 1.14 (6H, d, J = 6.4Hz), 2.31 (3H, s), 2.43 (3H, s), 4.06-4.11 (1H, m), 7.31 (1H, d, J = 8.0Hz), 7.47 (1H, d, J = 4.4Hz), 7.54 (1H, dd, J = 1.6Hz, 8.0Hz), 8.14 (1H, d, J = 7.6Hz), 8.47 (1H, d, J = 1.6Hz), 9.17 (1H, d, J = 4.4Hz), 12.69 (1H, s), 12.84 (1H, s).
14	Rex298	ESI-: 392
15	Rex299	^{1}H-NMR (DMSO-d6): 2.31 (3H, s), 2.44 (3H, s), 2.76 (3H, d, J = 4.4Hz), 7.31 (1H, d, J = 8.0Hz), 7.47 (1H, d, J = 4.4Hz), 7.52 (1H, dd, J = 1.6Hz, 8.0Hz), 8.36 (1H, d, J = 4.8Hz), 8.49 (1H, d, J = 1.6Hz), 9.19 (1H, d, J = 4.4Hz), 12.70 (1H, s), 12.85 (1H, s).
16	Rex298	ESI-: 364
17	Rex299	ESI-: 424
18	Rex298	ESI-: 442
19	Rex299	ESI-: 436
20	Rex298	ESI-: 454
21	Rex292	^{1}H-NMR (CDCl3): 3.00 (3H, d, J = 4.9Hz), 3.94 (2H, m), 6.44 (1H, m), 6.58 (1H, dd, J = 2.4Hz, 8.5Hz), 6.64 (1H, d, J = 2.4Hz), 7.67 (1H, d, J = 8.5Hz).
22	Rex4	^{1}H-NMR (CDCl3): 3.07 (3H, d, J = 4.9Hz), 6.15 (1H, m), 7.82 (1H, d, J = 8.3Hz), 8.17 (1H, dd, J = 2.2Hz, 8.3Hz),8.29 (1H, d, J = 2.2Hz).
23	Rex299	ESI-: 366
24	Rex298	ESI-: 384
25	Rex292	^{1}H-NMR (CDCl3): 1.05 (3H, t, J = 7.1Hz), 1.24 (3H, t, J = 7.1Hz), 3.18 (2H, q, J = 7.1Hz), 3.35 (1H, m), 3.83 (3H, m), 6.56 (1H, dd, J = 2.2Hz, 8.1Hz), 6.67 (1H, d, J = 2.2Hz), 7.03 (1H, d, J = 8.1Hz).

[Table 50]

Rex	Syn	Data
26	Rex4	^{1}H-NMR (CDCl3): 1.09(3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1Hz), 3.06-3.21 (2H, m), 3.35-3.44 (1H, m), 3.76-3.85 (1H, m), 7.74 (1H, d, J = 8.3Hz), 8.18 (1H, dd, J = 2.2Hz, 8.3Hz), 8.29 (1H, d, J = 2.2Hz).
27	Rex299	ESI-: 408
28	Rex298	ESI-: 426
29	Rex292	^{1}H-NMR (CDCl3): 1.08 (6H, d, J = 6.4Hz), 2.21 (1H, s), 3.40-3.47 (1H, m), 4.21 (1H, d, J = 6.8Hz), 7.14-7.18 (1H, m).

(continued)

Rex	Syn	Data
30	Rex299	^{1}H-NMR (DMSO-d_6): 0.86-0.96(6H, m), 2.43 (1H, s), 3.15-3.20 (1H, m), 3.35 (3H, s), 7.43-7.70 (4H, m), 8.23 (1H, s), 9.18 (1H, s), 12.79 (1H, s), 13.06(1H, s).
31	Rex298	ESI-: 428
32	Rex299	^{1}H-NMR (DMSO-d6): 2.32-2.54 (9H, m), 7.33-7.70 (4H, m), 8.52 (1H, s), 9.18 (1H, s), 12.81 (1H, s), 13.09 (1H, s).
33	Rex298	ESI-: 400
34	Rex299	^{1}H-NMR (DMSO-d6): 1.45-1.59 (6H, m), 2.54 (3H, s), 3.12 (2H, m), 3.56-3.63 (2H, m), 7.28-7.30 (1H, m), 7.38-7.41 (1H, m), 7.58-7.59 (1H, m), 7.99-7.99 (1H, m), 9.16-9.17 (1H, m), 12.85 (1H, br-s), 13.13 (1H, br-s).
35	Rex298	ESI-: 438
36	Rex292	^{1}H-NMR (CDCl3): 1.25 (6H, d,J = 6.6Hz), 3.94 (2H, m), 4.20-4.32 (1H, m), 6.22 (1H, m), 6.55-6.58 (1H, m), 6.63 (1H, d, J = 2.2Hz), 7.61 (1H, dd, J = 1.2Hz, 8.3Hz).

[Table 51]

Rex	Syn	Data
37	Rex4	^{1}H-NMR (CDCl3): 1.30 (6H, d,J = 6.6Hz), 4.28-4.36 (1H, m), 5.90 (1H, m), 7.78 (1H, d, J = 8.5Hz), 8.16 (1H, dd, J = 2.2Hz, 8.3Hz), 8.28 (1H, d, J = 2.2Hz).
38	Rex299	^{1}H-NMR(DMSO-d6): 1.14 (6H, d, J = 6.6Hz), 2.56 (3H, s), 4.01-4.02 (1H, m), 7.36-7.37 (2H, m), 7.58-7.59 (1H, m), 7.94-7.95 (1H, m), 8.24-8.26 (1H, m), 9.17 (1H, m), 12.85 (1H, br-s), 13.14 (1H, br-s).
39	Rex298	ESI-: 412
40	Rex292	^{1}H-NMR (CDCl3): 1.43-1.50 (2H, m), 1.57-1.63 (4H, m), 3.11-3.13 (4H, m), 3.84 (1H, s), 6.16-6.25 (2H, m), 7.62-7.66 (1H, m).
41	Rex41	^{1}H-NMR ($CDCl_3$): 1.54-1.63 (6H, m), 3.25 (4H, t, J = 5.6Hz), 4.04 (1H, s), 7.83 (1H, d, J = 0.2Hz), 7.88 (1H, dd, J = 0.2Hz, 8.8Hz), 8.07 (1H, d,J = 8.8Hz).
42	Rex299	ESI-: 452
43	Rex298	^{1}H-NMR (DMSO-d6): 1.44-1.50 (6H, m), 3.30-3.04 (4H, m), 3.10 (1H, s), 3.85 (1H, s), 7.46-7.48 (1H, m), 7.55-7.56 (1H, m), 7.64-7.66 (1H, m), 7.93 (1H, br-s), 9.53 (1H, br-s).
44	Rex292	^{1}H-NMR (CDCl3): 1.09 (6H, t, J = 7.2Hz), 2.28 (4H, q, J = 7.2Hz), 3.84 (1H, s), 6.17-6.23 (2H, m), 7.67-7.71 (1 H, m).
45	Rex41	^{1}H-NMR (CDCl3): 1.13 (6H, t, J = 7.2Hz), 3.37 (4H, q, J = 7.2Hz), 4.04 (3H, s), 7.82 (1H, d, J = 2.8Hz), 7.87 (1H, dd, J = 2.8Hz, 8.8Hz), 8.12 (1H, d, J = 8.8Hz).
46	Rex299	ESI-: 440
47	Rex298	ESI-: 458

[Table 52]

Rex	Syn	Data
48	Rex48	^{1}H-NMR (CDCl3): 1.26 (6H, d, J = 6.4Hz), 3.66 (2H, br-s), 4.25-4.31 (1H, m), 6.57 (1H, br-s), 6.69-6.73 (1H, m), 6.89 (1H, dd, J = 8.4Hz, 11.6Hz), 7.35 (1H, dd, J = 3.2Hz, 6.8Hz).
49	Rex299	^{1}H-NMR (DMSO-d6): 1.14 (6H, d,J = 6.4Hz), 2.39 (3H, s), 4.01-4.06 (1H, m), 7.24 (1H, t, J = 9.2Hz), 7.49-7.53 (2H, m), 7.88 (1H, dd, J = 2.8Hz, 6.4Hz), 8.18 (1H, d, J = 8.0Hz), 9.16 (1H, d, J = 4.4Hz), 12.74 (1H, s), 12.96 (1H, s).

(continued)

Rex	Syn	Data
50	Rex298	^{1}H-NMR (DMSO-d6): 1.14 (6H, d, J = 6.8Hz), 2.41 (3H, S), 4.01-4.07 (1H, m), 7.24 (1H, t, J = 9.2Hz), 7.62-7.66 (1H, m), 7.82-7.84 (1H, m), 7.87 (1H, s), 8.14 (1H, s), 8.15 (1H, m), 9.38 (1H, s).
51	Rex48	^{1}H-NMR (CDCl3): 1.50-1.65 (6H, m), 3.28 (2H, br-s), 3.63 (2H, br-s), 3.71 (2H, br-s), 6.61-6.65 (2H, m), 6.86 (1H, t, J = 7.6Hz).
52	Rex299	^{1}H-NMR (DMSO-d6): 1.44-1.61 (6H, m), 2.45 (3H, s), 3.21 (2H, br-s), 3.59 (2H, br-s), 7.26 (1H, t, J = 8.8Hz), 7.49-7.53 (2H, m), 7.63 (1 H, dd, J = 2.4Hz, 6.4Hz), 9.14 (1H, d, J = 4.4Hz), 12.72 (1H, s), 12.89 (1H, s).
53	Rex298	^{1}H-NMR (DMSO-d6): 1.45-1.62 (6H, m), 2.33 (3H, s), 3.22 (2H, m), 3.59 (2H, br-s), 7.26 (1H, t, J = 8.8Hz), 7.57-7.62 (2H, m), 7.86 (1H, s), 8.13 (1H, s), 9.35 (1H, s).
54	Rex299	^{1}H-NMR (DMSO-d6): 2.45 (3H, s), 3.26 (2H, br-s), 3.53 (2H, t, J = 4.8Hz), 3.63 (4H, br-s), 7.28 (1H, t, J = 8.8Hz), 7.51-7.57 (2H, m), 7.65 (1H, dd, J = 2.8Hz, 6.0Hz), 9.14 (1H, d, J = 4.4Hz), 12.73 (1H, s), 12.89 (1H, s).

[Table 53]

Rex	Syn	Data
55	Rex298	^{1}H-NMR (DMSO-d6): 2.41 (3H, s), 3.27 (2H, m), 3.54 (2H, t, J = 4.8H), 3.64 (4H, br-s), 7.28 (1H, t, J = 8.8Hz), 7.61-7.64 (2H, m), 7.88 (1H, br-s), 8.14 (1H, br-s), 9.38 (1H, s).
56	Rex292	^{1}H-NMR (CDC3): 1.08 (3H, t, J = 7.2Hz), 1.23 (3H, t, J = 7.2Hz), 3.24 (2H, q, J = 7.2Hz), 3.55 (2H, m), 3.70 (2H, br-s), 6.56 (1H, dd, J = 3.2Hz, 5.6Hz), 6.62 (1H, m), 6.85 (1H, t, J = 8.8Hz).
57	Rex299	^{1}H-NMR (DMSO-d6): 1.01 (3H, t, J = 7.2Hz), 1.13 (3H, t, J = 7.2Hz), 2.45 (3H, s), 3.17 (2H, q, J = 7.2Hz), 3.44 (2H, m), 7.26 (1 H, t, J = 8.8Hz), 7.46 (1H, m), 7.52 (1H, d, J = 4.4Hz), 7.67 (1H, dd, J = 2.8Hz, 6.0Hz), 9.15 (1H, d, J = 4.4Hz), 12.73 (1H, s), 12.94 (1H, s).
58	Rex298	^{1}H-NMR (DMSO-d6): 1.02 (3H, t, J = 7.2Hz), 1.13 (3H, t, J = 7.2Hz), 2.40 (3H, s), 3.18 (2H, q, J = 7.2Hz), 3.45 (2H, q, J = 7.2Hz), 7.27 (1H, t, J = 9.2Hz), 7.58-7.61 (2H, m), 7.87 (1H, br-s), 8.14 (1H, br-s), 9.35 (1H, s).
59	Rex292	^{1}H-NMR (CDCl3): 1.05 (6H, d, J = 6.4Hz), 3.27-3.49 (1H, m), 3.90 (1H, s), 4.55 (1H, d, J = 6.4Hz), 6.62-6.28 (2H, m), 7.65-7.69 (1H, m).
60	Rex41	^{1}H-NMR (CDCl3): 1.08 (6H, t, J = 6.8Hz), 3.48 (1H, q, J = 7.6Hz), 4.11 (1H, s), 4.75 (1H, d, J = 7.6Hz), 7.88 (1H, d, J = 2.0Hz), 7.94 (1H, dd, J = 2.0Hz, 8.4Hz), 8.12 (1H, d, J = 8.4Hz).
61	Rex299	^{1}H-NMR (DMSO-d6): 0.94-0.99 (6H, m), 3.18-3.24 (1H, m), 2.49 (1H, s), 3.92 (1H, s), 7.06-7.08 (1H, m), 7.20-7.23 (1H, m), 7.39-7.40 (1H, m), 7.61-7.69 (2H, m), 9.20 (1H, br-s), 12.88 (1H, br-s), 13.28 (1H, br-s).

[Table 54]

Rex	Syn	Data
62	Rex298	ESI-: 444
63	Rex292	^{1}H-NMR (CDCl3): 1.40-1.46 (2H, m), 1.62-1.67 (4H, m), 2.96-2.99 (4H, m), 3.97 (1H, br-s), 7.06-7.10 (2H, m), 7.15-7.18 (1H, m).
64	Rex41	^{1}H-NMR (CDCl3): 1.45-1.71 (7H, m), 3.06 (4H, t, J = 5.6Hz), 7.46-7.52 (1H, m), 8.00-8.04 (1H, m), 8.43-8.46 (1H, m).
65	Rex299	ESI-: 440
66	Rex298	^{1}H-NMR (DMSO-d6): 1.31-1.38 (4H, m), 1.51-1.55 (7H, m), 2.44 (1H, s), 2.83-2.92 (7H, m), 7.56-7.58 (2H, m), 8.14-8.26 (3H, m), 9.77 (1H, br-s).

(continued)

Rex	Syn	Data
67	Rex292	^{1}H-NMR (CDCl3): 1.43-1.45 (2H, m), 1.64 (4H, m), 2.22 (1H, s), 3.21 (2H, m), 3.66-3.76 (4H, m), 6.48-6.51 (2H, m), 6.94 (1H, d, J = 8.0Hz).
68	Rex4	^{1}H-NMR (CDCl3): 1.43-1.87 (6H, m), 2.42 (3H, s), 3.13-3.15 (2H, m), 3.69-3.83 (2H, m), 7.32 (1H, d, J = 8.4Hz), 8.07-8.11 (2H, m).
69	Rex299	ESI-: 400
70	Rex298	ESI-: 418
71	Rex292	^{1}H-NMR (CD3OD): 2.23 (3H, s), 2.84 (3H, s), 6.50-6.55 (2H, m), 7.14 (1H, d, J = 8.4Hz).
72	Rex4	^{1}H-NMR (CDCl3): 2.54 (3H, s), 3.04 (3H, d, J = 4.8Hz), 5.80 (1H, br-s), 7.49 (1H, d, J = 8.4Hz), 8.04-8.12 (1H,m).
73	Rex299	ESI-: 346
74	Rex298	ESI-: 364
75	Rex292	^{1}H-NMR (CDCl3): 1.54-1.62 (6H, m), 3.20-3.23 (2H, m), 3.62-3.64 (1H, m), 3.77 (5H, m), 6.20 (1H, d, J = 2.0Hz), 6.27 (1H, dd, J = 2.0Hz, 8.1Hz), 7.02 (1H, d, J = 8.1Hz).
76	Rex299	ESI-: 416

[Table 55]

Rex	Syn	Data
77	Rex298	ESI-: 434
78	Rex292	^{1}H-NMR (CDCl3): 1.45-1.47 (2H, m), 1.65 (4H, m), 2.17 (3H, s), 3.18-3.21 (2H, m), 3.59-3.66 (3H, m), 3.78-3.82 (1H, m), 6.49 (1H, d, J = 2.7Hz), 6.60 (1H, dd, J = 2.7Hz, 8.3Hz), 6.97 (1H, d, J = 8.3Hz).
79	Rex4	^{1}H-NMR (CDCl3): 1.48-1.54 (2H, m), 1.70 (4H, m), 2.42 (3H, s), 3.16-3.20 (2H, m), 3.73-3.80 (2H, m), 7.39 (1H, d, J = 8.5Hz), 8.05 (1H, d, J = 2.2Hz), 8.12 (1H, dd, J = 2.2Hz,8.5Hz).
80	Rex299	ESI-: 400
81	Rex298	ESI-: 418
82	Rex292	^{1}H-NMR (CDCl3): 2.31 (3H, s), 2.98 (3H, d, J = 4.9Hz), 3.60 (2H, m), 5.69 (1H, m), 6.64 (1H, dd, J = 2.7Hz, 8.1Hz), 6.70 (1H, d, J = 2.7Hz), 6.98 (1H, d, J = 8.1 Hz).
83	Rex299	ESI-: 346
84	Rex298	ESI-: 364
85	Rex48	^{1}H-NMR (CDCl3): 2.97 (3H, d, J = 4.8Hz), 4.03 (2H, br-s), 5.76 (1H, br-s), 6.77 (1H, dd, J = 2.4Hz, 8.0Hz), 6.90 (1H, d, J = 2.4Hz), 7.33 (1H, d, J = 8.0Hz).
86	Rex299	^{1}H-NMR (DMSO-d6): 2.51 (3H, s), 2.73 (3H, d, J = 4.4Hz), 7.48 (1H, d, J = 8.4Hz), 7.63-7.65 (2H, m), 8.22 (1H, d, J = 1.6Hz), 8.38 (1H, d, J = 4.8Hz), 9.18 (1H, d, J = 4.4Hz), 12.89 (1H, s), 13.27 (1H, s).
87	Rex298	^{1}H-NMR (DMSO-d6): 2.45 (3H, s), 2.73 (3H, d, J = 4.8Hz), 7.48 (1H, d, J = 8.4Hz), 7.88 (1H, d, J = 8.8Hz), 7.89 (1H, s), 8.12 (1H, d, J = 2.0Hz), 8.17 (1H, s), 8.38 (1H, m), 9.62 (1H, s).

[Table 56]

Rex	Syn	Data
88	Rex48	^{1}H-NMR (CDCl3): 3.01 (3H, dd, J = 1.2Hz, 5.2Hz), 3.69 (2H, br-s), 6.70-6.74 (1H, m), 6.77 (1H, br-s), 6.90 (1H, dd, J = 8.4Hz, 11.6Hz), 7.38 (1H, dd, J = 3.2Hz, 6.4Hz).

(continued)

Rex	Syn	Data
89	Rex299	^{1}H-NMR (DMSO-d6): 2.49 (3H, s), 2.77 (3H, d, J = 4.4Hz), 7.26 (1H, t, J = 8.8Hz), 7.53-7.58 (2H, m), 7.95 (1H, dd, J = 2.8Hz, 6.4Hz), 8.24 (1H, br-s), 9.16 (1H, d, J = 4.4Hz), 12.75 (1H, s), 12.96 (1H, s).
90	Rex298	^{1}H-NMR (DMSO-d6): 2.40 (3H, s), 2.77 (3H, d, J = 4.8Hz), 7.26 (1H, t, J = 10.0Hz), 7.64-7.68 (1H, m), 7.87 (1H, br-s), 7.92 (1H, dd, J = 2.4Hz, 6.4Hz), 8.14 (1H, br-s), 8.21 (1H, br-s), 9.39 (1H, br-s).
91	Rex292	^{1}H-NMR (CDCl3): 2.55 (3H, s), 3.91 (3H, s), 6.22-6.30 (2H, m), 7.65-7.69 (1H, m).
92	Rex41	^{1}H-NMR (CDCl3): 2.66 (3H, d, J = 5.2Hz), 4.11 (3H, s), 4.84 (1H, d, J = 5.2Hz), 7.89 (1H, d, J = 2.0Hz), 7.94 (1H, dd, J = 2.0Hz, 8.8Hz), 8.12 (1H, d, J = 8.8Hz).
93	Rex299	ESI-: 398
94	Rex298	ESI-: 416
95	Rex292	^{1}H-NMR (CDCl3): 2.97 (3H, d, J = 4.6Hz), 3.90 (3H, s), 3.96 (2H, m), 6.20 (1H, d, J = 2.2Hz), 6.34 (1H, dd, J = 2.2Hz, 8.5Hz), 7.66 (1 H, m), 8.04 (1H, d, J = 8.5Hz).
96	Rex4	^{1}H-NMR (CDCl3): 3.04 (3H, d, J = 4.9Hz), 4.09 (3H, s), 7.74 (1H, m), 7.84 (1H, d, J = 2.2Hz), 7.93 (1H, dd, J = 2.2Hz, 8.5Hz), 8.39 (1H, d, J = 8.5Hz).
97	Rex299	ESI-: 362

[Table 57]

Rex	Syn	Data
98	Rex298	ESI-: 380
99	Rex48	^{1}H-NMR (CDCl3): 0.83-0.88 (1H, m), 1.42-1.65 (5H, m), 3.15 (2H, dd, J = 9.2Hz, 15.2Hz), 3.64-3.76 (2H, m), 4.01 (2H, br-s), 6.78 (1H, dd, J = 2.4Hz, 8.4Hz), 6.90 (1H, d, J = 2.8Hz), 7.05 (1H, d, J = 8.4Hz).
100	Rex299	^{1}H-NMR (DMSO-d6): 1.37-1.59 (6H, m), 2.54 (3H, s), 3.06-3.11 (2H, m), 3.51-3.62 (2H, m), 7.40 (1H, d, J = 8.4Hz), 7.61-7.66 (2H, m), 8.27 (1H, d, J = 2.0Hz), 9.18 (1H, d, J = 4.0Hz), 12.89 (1H, s), 13.28 (1H, s).
101	Rex298	^{1}H-NMR (DMSO-d6): 1.37-1.59 (6H, m), 2.45 (3H, s), 3.06-3.11 (2H, m), 3.52-3.62 (2H, m), 7.40 (1H, d, J = 8.0Hz), 7.90 (1H, br-s), 7.92 (1H, m), 8.16 (1H, br-s), 8.19 (1H, d, J = 2.0Hz), 9.62 (1H, s).
102	Rex353	ESI-: 346
103	Rex353	ESI-: 454
104	Rex353	ESI-: 346
105	Rex353	ESI-: 346
106	Rex299	^{1}H-NMR (DMSO-d6): 2.53 (3H, s), 2.72 (3H, d, J = 4.4Hz), 7.41 (1H, d, J = 8.8Hz), 7.48-7.56 (2H, m), 8.36 (1H, d, J = 4.6Hz), 9.16 (1H, d, J = 3.7Hz), 12.80 (1H, s), 13.10 (1H, s).
107	Rex298	^{1}H-NMR (DMSO-d6): 2.43 (3H, s), 2.73 (3H, d, J = 4.6Hz), 7.41 (1H, d, J = 8.5Hz), 7.65 (1H, dd, J = 2.7Hz, 8.8Hz), 7.77 (1H, d, J = 2.4Hz), 7.88 (1H, s), 8.14 (1H, s), 8.35 (1 H, d, J = 4.6Hz), 9.43 (1H, s).

[Table 58]

Rex	Syn	Data
108	Rex353	^{1}H-NMR (CDCl3): 1.29 (3H, t, J = 7.6Hz), 2.87 (2H, q, J = 7.3Hz), 3.04 (3H, s), 5.56 (1H, br-s), 6.25 (1H, br-s), 7.34 (1H, d, J = 8.8Hz), 7.74 (1H, br-), 7.81 (1H, dd, J = 2.9Hz, 8.8Hz), 7.93 (1H, d, J = 2.7Hz), 10.95 (1H, br-s).
109	Rex353	^{1}H-NMR (CDCl3): 1.31 (3H, t, J = 7.6Hz), 2.89 (2H, q, J = 7.3Hz), 3.03 (3H, d, J = 4.9Hz), 4.04 (3H, s), 5.53 (1H, br-s), 6.12 (1H, br-s), 7.28 (1H, m), 7.49 (1H, s), 7.74 (1H, br-s), 8.58 (1H, d, J = 8.3Hz), 11.43 (1H, br-s).
110	Rex292	^{1}H-NMR (CDCl3): 2.18 (3H, s), 2.98 (3H, d, J = 4.9Hz), 3.88 (2H, m), 5.97 (1H, m), 6.64 (1H, d, J = 8.1 Hz), 7.44 (1H, dd, J = 2.0Hz, 8.3Hz), 7.51 (1H, m).
111	Rex4	^{1}H-NMR (CDCl3): 2.64(3H, s), 3.05 (3H, d, J = 4.9H), 6.17 (1H, m), 7.67 (1H, dd, J = 2.0Hz, 8.3Hz), 7.76 (1H, d, J = 2.0Hz), 8.00 (1H, d, J = 8.3Hz).
112	Rex353	ESI-: 346
113	Rex353	ESI-: 400
114	Rex292	^{1}H-NMR (CDCl3): 2.21 (3H, s), 2.99 (3H, d, J = 4.9Hz), 3.70 (2H, m), 5.72 (1H, m), 6.71-6.77 (2H, m), 7.00-7.04 (1H, m).
115	Rex353	^{1}H-NMR (CDCl3): 1.30 (3H, t, J = 7.3Hz), 2.42 (3H, s), 2.87 (2H, q, J = 7.3Hz), 3.02 (3H, d, J = 4.9Hz), 5.50 (1H, m), 5.75 (1H, m), 7.09-7.11 (1H, m), 7.75 (1H, m), 8.16-8.18 (1H, m), 10.74 (1H, m).
116	Rex353	ESI-: 366
117	Rex353	ESI-: 325

[Table 59]

Rex	Syn	Data
118	Rex292	^{1}H-NMR (CDCl3): 2.98 (3H, d, J = 4.9Hz), 3.85 (2H, br-s), 6.06 (1H, br-s), 6.98-7.01 (2H, m), 7.25-7.29 (1H, m).
119	Rex353	^{1}H-NMR (CDCl3): 1.31 (3H, t, J = 7.6Hz), 2.92 (2H, q, J = 7.3Hz), 3.05 (3H, d, J = 4.9Hz), 5.57 (1H, br-s), 6.13 (1H, br-s), 7.18 (1H, m), 7.52 (1H, m), 7.73 (1H, s), 8.87 (1H, d, J = 8.5Hz), 11.15 (1H, br-s).
120	Rex292	^{1}H-NMR (CDCl3): 3.00 (3H, d, J = 4.9Hz), 4.19 (2H, br-s), 5.92 (1H, br-s), 6.80 (1H, dd, J = 1.7Hz, 7.6Hz), 6.87 (1H, dd, J = 1.7Hz, 7.6Hz), 7.08 (1H, d, J = 7.6Hz).
121	Rex4	^{1}H-NMR (CDCl3): 3.06 (3H, s), 5.57 (1H, br-s), 6.04 (1H, br-s), 7.42 (1H, d, J = 8.1H), 7.74 (1H, dd, J = 1.5Hz, 7.6H), 7.83 (1H, dd, J = 2.0Hz, 8.1Hz).
122	Rex353	^{1}H-NMR (CDCl3): 1.31 (3H, t, J = 7.6Hz), 2.91 (2H, q, J = 7.3Hz), 3.04 (3H, d, J = 4.9Hz), 5.56 (1H, br-s), 5.95 (1H, br-s), 7.21 (1H, m), 7.34 (1H, m), 7.74 (1H, br-s), 8.56 (1H, m), 11.40 (1H, br-s).
123	Rex299	^{1}H-NMR (DMSO-d6): 2.84 (3H, s), 7.21 (2H, t, J = 9.6H), 7.52 (1H, t, J = 9.6Hz), 7.53 (2H, s), 7.64 (1H, d, J = 4.0Hz), 8.22 (2H, d, J = 9.2Hz), 9.24 (1H, d, J = 4.0Hz), 12.92 (1H, br-s), 13.73 (1H, s).
124	Rex298	ESI-: 343
125	Rex353	ESI-: 325
126	Rex353	ESI-: 398
127	Rex353	ESI+: 334

[Table 60]

Rex	Syn	Data
128	Rex353	^{1}H-NMR (DMSO-d6): 1.24 (3H, t, J = 7.6Hz), 2.89 (2H, q, J = 7.3Hz), 4.53 (2H, s), 6.92 (1H, d, J = 8.5Hz), 7.11-7.16 (2H, m), 8.02 (1H, br-s), 8.25 (1H, br-s), 10.78 (1H, br-s), 11.06 (1H, br-s).
129	Rex353	ESI-: 265
130	Rex353	ESI-: 350
131	Rex353	ESI-: 289
132	Rex353	ESI+: 488
133	Rex353	^{1}H-NMR (CDCl3): 1.31 (3H, t, J = 7.2Hz), 2.64 (6H, s), 2.91 (2H, q, J = 7.2H), 4.30 (1H, br-s), 5.60 (1H, br-s), 7.56 (1H, br-s), 7.77 (1H, m), 7.95 (1H, d, J = 8.0Hz), 11.12 (1H, br-s).
134	Rex353	^{1}H-NMR (CDCl3): 1.30 (3H, t, J = 7.2Hz), 2.89 (2H, q, J = 7.6Hz), 2.99 (3H, s), 5.59 (1H, br-s), 6.60 (1H, br-s), 7.53 (1H, dd, J = 2.4H, 9.2Hz), 7.60 (1H, d, J = 8.8Hz), 7.75 (1H, br-s), 7 96 (1H, d, J = 2.4Hz), 10.95(1H, s).
135	Rex353	ESI+: 368
136	Rex353	ESI+: 364
137	Rex292	^{1}H-NMR (CDCl3): 2.44(3H, s), 2.50 (3H, s), 6.79 (1H, dd, J = 2.4Hz, 8.4Hz), 7.06 (1H, d, J = 8.4Hz), 7.25 (1H, d, J = 2.4Hz).
138	Rex353	ESI-: 382
139	Rex292	^{1}H-NMR (CDCl3): 3.15-3.17 (4H, m), 3.70-3.72 (4H, m), 3.85 (3H, s), 4.13 (2H, br-s), 6.19 (1H, d, J = 2.0Hz), 6.23 (1H, dd, J = 2.0Hz, 8.4Hz), 7.01 (1H, d, J = 8.4Hz).
140	Rex41	^{1}H-NMR (CDCl3): 3.28-3.30 (4H, m), 3.72-3.74 (4H, m), 4.06 (3H, s), 7.86 (1H, d, J = 2.0Hz), 7.89 (1H, dd, J = 2.0Hz, 8.4Hz), 8.80 (1H, d, J = 8.4Hz,).

[Table 61]

Rex	Syn	Data
141	Rex353	ESI-: 454
142	Rex353	^{1}H-NMR (DMSO-d6): 1.24 (3H, t, J = 7.6Hz), 2.79 (2H, q, J = 7.3Hz), 4.56 (2H, s), 6.84 (1H, d, J = 8.5Hz), 6.98 (1H, dd, J = 2.4Hz, 8.5Hz), 7.46 (1H, d, J = 2.2Hz), 8.01 (1H, br-s), 8.24 (1H, br-s), 10.65 (1H, br-s), 11.11 (1H, br-s).
143	Rex353	ESI+: 317
144	Rex353	^{1}H-NMR (DMSO-d6): 1.24 (3H, t, J = 7.6Hz), 2.78 (2H, q, J = 7.3Hz), 4.20-4.24 (4H, m), 6.81-6.89 (2H, m), 7.29 (1H, d, J = 2.4Hz), 7.98 (1H, br-s), 8.21 (1H, br-s), 10.98 (1H, br-s).
145	Rex48	^{1}H-NMR ($CDCl_3$): 3.36 (3H, s), 3.53 (2H, t, J = 5.1 Hz), 3.61 (2H, m), 4.01 (2H, br-s), 6.14 (1H, br-s), 6.76 (1H, dd, J = 2.0Hz, 8.3Hz), 6.91 (1H, d, J = 2.2Hz), 7.33 (1H, d, J = 8.3Hz).
146	Rex353	^{1}H-NMR (CDCl3): 1.31 (3H, t, J = 7.6Hz), 2.90 (2H, q, J = 7.3Hz), 3.39 (3H, s), 3.58 (2H, m), 3.64 (2H, m), 5.79 (1H, br-s), 6.38 (1H, br-s), 7.52 (1H, d, J = 3.7Hz), 7.75 (1H, br-s), 7.87 (1H, dd, J =2.0Hz, 8.3Hz), 11.05 (1H, br-s).
147	Rex353	^{1}H-NMR (CDCl3): 1.24-1.59 (9H, m), 2.90 (2H, q, J = 7.6Hz), 3.10-3.17 (4H, m), 3.95 (3H, s), 5.59 (1H, br-s), 7.13 (1H, d, J = 8.8Hz), 7.63 (1H, d, J = 8.4Hz), 7.75-7.81 (3H, m), 11.16 (1H, br-s).
148	Rex353	^{1}H-NMR (CDCl3): 1.25 (3H, t, J = 7.6Hz), 2.60 (3H, s), 2.92 (2H, q, J = 7.6Hz), 5.59 (1H, br-s), 7.28 (1H, m), 7.73 (1H, br-s), 7.75 (1H, m), 8.44 (1H, d, J = 2.0Hz), 10.99 (1H, br-s).
149	Rex353	^{1}H-NMR (CDCl3): 1.21-1.34 (3H, m), 2.82-2.92 (5H, m), 5.61 (1H, br-s), 7.51 (1H, d, J = 6.8Hz), 7.72-7.75 (1H, m), 7.87 (1H, d, J = 6.8Hz), 8.42 (1H, d, J = 2.8Hz), 10.99 (1H, br-s).

[Table 62]

Rex	Syn	Data
150	Rex353	ESI+: 364
151	Rex353	^{1}H-NMR (CDCl3): 1.25 (3H, t, J = 7.6Hz), 2.92 (3H, q, J = 7.6Hz), 5.63 (1H, br-s), 7.53 (1H, dd, J = 3.6Hz, 6.9Hz), 7.76 (1H, br-s), 7.90 (1H, d, J = 6.0Hz), 8.78 (1H, d, J = 3.6Hz), 11.27 (1H, br-s).
152	Rex353	ESI+: 329
153	Rex353	^{1}H-NMR (CDCl3): 1.34 (3H, t, J = 7.6Hz), 2.95 (2H, q, J = 7.6Hz), 5.65 (1H, br-s), 7.74 (1H, dd, J = 2.0Hz, 9.2Hz), 7.79 (1H, br-s), 8.02 (1H, d, J = 9.2Hz), 9.28 (1H, d, J = 2.0Hz), 11.25 (1H, br-s).
154	Rex353	^{1}H-NMR (CDCl3): 1.30 (3H, t, J = 7.6Hz), 2.86 (2H, q, J = 7.6Hz), 3.79 (3H, s), 5.49 (1H, m), 6.44 (1H, d, J = 3.2Hz), 7.01 (1H, d, J = 3.2Hz), 7.15 (1H, dd, J = 0.2Hz, 8.4Hz), 7.54 (1H, d, J = 8.4Hz), 7.74 (1H, m), 7.98 (1H, s), 10.84 (1H, m).
155	Rex292	^{1}H-NMR (CDC3): 2.84 (3H, s), 3.37 (2H, br-s), 3.99 (1H, br-s), 6.62 (1H, d, J = 8.4Hz), 6.82 (1H, dd, J = 2.8Hz, 8.4Hz), 6.86 (1H, d, J = 2.8Hz).
156	Rex353	^{1}H-NMR (CDCl3): 1.28 (3H, t, J = 7.6Hz), 2.85 (2H, q, J = 7.6Hz), 2.91 (3H, d, J = 4.8Hz), 4.32 (1H, br-s), 5.51 (1H, br-s), 6.73 (1H, d, J = 8.4Hz), 7.66-7.70 (3H, m), 10.50 (1H, br-s).
157	Rex292	^{1}H-NMR (DMSO-d6): 1.67-1.78 (2H, m), 2.07 (2H, m), 3.03-3.27 (8H, m), 3.73 (3H, s), 3.90-4.16 (3H, m), 5.79 (2H, br-s), 6.29 (1H, d, J = 8.5Hz), 6.50-6.54 (2H, m).
158	Rex503	ESI+: 338
159	Rex353	ESI+: 491
160	Rex160	^{1}H-NMR (CDCl3): 1.35(3H, t, J = 7.6Hz), 3.02 (2H, q, J=7.6Hz).
161	Rex353	ESI+: 375

[Table 63]

Rex	Syn	Data
162	Rex292	ESI+: 276
163	Rex444	ESI+: 306
164	Rex353	ESI+: 459
165	Rex353	ESI+: 376
166	Rex353	^{1}H-NMR (CDCl3): 1.28(3H, t, J = 7.6Hz), 2.84 (2H, q, J = 7.6Hz), 3.46-3.48 (4H, m), 3.83-3.85 (4H, m), 5.55 (1H, br-s), 6.67 (1H, d, J = 8.8Hz), 8.43 (1H, d, J = 2.4Hz), 10.45 (1H, br-s).
167	Rex292	ESI+: 276
168	Rex444	ESI+: 306
169	Rex353	ESI+: 459
170	Rex353	ESI+: 552
171	Rex353	^{1}H-NMR (CDCl3): 1.28 (3H, t, J = 7.2Hz), 2.84 (2H, q, J = 7.2Hz), 3.12-3.14 (4H, m), 3.86-3.88 (4H, m), 5.51 (1H, br-s), 6.91 (1H, dd, J = 2.4Hz, 7.2Hz), 7.55 (1H, dd, J = 2.4Hz, 7.2Hz), 7.71 (1H, br-s), 10.58 (1H, br-s).
172	Rex353	^{1}H-NMR (CDCl3): 1.28 (3H, t, J = 7.6Hz), 2.31 (3H, s), 2.36 (3H, s), 2.84 (2H, q, J = 7.6Hz), 2.92-2.94 (4H, m), 5.48 (1H, br-s), 7.02 (1H, d, J = 8.8Hz), 7.34 (1H, d, J = 2.4Hz), 7.55 (1H, dd, J = 2.7Hz, 8.5Hz), 7.71 (1H, br-s), 10.60 (1H, br-s).
173	Rex353	^{1}H-NMR (CDCl3): 1.28 (3H, t, J = 7.6Hz), 1.68-1.74 (6H, m), 1.92-1.95 (2H, m), 2.29-2.36 (7H, m), 2.50-2.65 (8H, m), 2.84 (2H, q, J = 7.6Hz), 3.13-3.16 (2H, m), 5.54 (1H, br-s), 6.98 (1H, d, J = 6.5Hz), 7.33 (1H, d, J = 2.6Hz), 7.51 (1H, d, J = 2.7Hz), 7.71 (1H, br-s), 10.58 (1H, br-s).

[Table 64]

Rex	Syn	Data
174	Rex353	^{1}H-NMR (CDCl3): 1.29 (3H, t, J = 7.3Hz), 2.37 (3H, s), 2.62 (4H, m), 2.85 (2H, q, J = 7.3Hz), 3.03 (4H, m), 5.53 (1H, br-s), 7.05 (1H, d, J = 8.8Hz), 7.51 (1H, dd, J = 2.7Hz, 8.8Hz), 7.72 (1H, d, J = 2.4Hz), 10.70 (1H, br-s).
175	Rex353	^{1}H-NMR(CDCl3):1.28(t,J=7.2Hz,3H),1.49(s,9H),2.84(q,J=7.2Hz,2H),3.09(m,4H),3.58(m,4H),5.62(br-s,1H),6.92(d,J=9.2Hz,2H),7.54(d,J=9.2Hz,2H),7.7 1(br-s,1H),10.60(s,1H).
176	Rex292	^{1}H-NMR (CDCl3): 1.60 (2H, br-s), 2.04-2.17 (4H, m), 2.91-2.94 (4H, m), 6.80 (1H, dd, J = 2.8Hz, 8.4Hz), 6.91 (1H, d, J = 2.8Hz), 7.17 (1H, d, J = 8.4H).
177	Rex516	^{1}H-NMR (CDCl3): 2.13-2.22 (4H, m), 3.18-3.20 (4H, m), 7.36 (1H, d, J = 8.8Hz), 8.35 (1H, dd, J = 2.4Hz, 9.2Hz), 8.53 (1H, d, J = 2.4Hz).
178	Rex353	ESI-: 462
179	Rex353	ESI+: 400
180	Rex292	^{1}H-NMR (CDCl3): 0.16-0.20 (2H, m), 0.55-0.59 (2H, m), 0.97 (1H, m), 2.40 (2H, d, J = 6.4Hz), 2.75 (2H, m), 2.96 (4H, m), 3.72 (2H, m), 6.79 (1H, dd, J = 2.8Hz, 8.4Hz), 6.89 (1H, d, J = 2.8Hz), 7.24 (1H, d, J = 8.4Hz).
181	Rex516	EI: 329
182	Rex353	ESI+: 483
183	Rex292	^{1}H-NMR (CDCl3): 1.80-1.88 (1H, m), 2.06-2.14 (1H, m), 2.24 (6H, s), 2.85-3.20 (5H, m), 3.65 (2H, br-s), 6.78 (1H, dd, J = 2.9Hz, 8.5Hz), 6.90 (1H, d, J = 2.7Hz), 7.14 (1H, d, J = 8.5Hz).

[Table 65]

Rex	Syn	Data
184	Rex516	^{1}H-NMR (CDCl3): 1.90-1.97 (1H, m), 2.21-2.29 (1H, m), 2.32 (3H, s), 2.77-2.82 (1H, m), 3.43-3.53 (1H, m), 3.62-3.67 (3H, m), 6.79 (1H, d, J = 9.5Hz), 8.16 (1H, dd, J = 2.7Hz, 9.5Hz), 8.53 (1H, d, J = 2.7Hz).
185	Rex353	^{1}H-NMR (CDCl3): 1.29 (3H, t, J = 7.3Hz), 1.84-1.89 (1H, m), 2.12-2.16 (1H, m), 2.26 (6H, s), 2.83-2.89 (3H, m), 3.20-3.41 (4H, m), 5.57 (1H, br-s), 7.09 (1H, d, J = 8.8Hz), 7.71-7.82 (3H, m), 10.68 (1H, br-s).
186	Rex353	^{1}H-NMR (CDCl3): 1.10-1.15 (3H, m), 1.30 (3H, t, J = 7.3Hz), 2.45-2.52 (2H, m), 2.85-2.97 (10H, m), 5.57 (1H, br-s), 7.37-7.39 (1H, m), 7.73 (1H, br-s), 7.87-7.88 (2H, m), 10.86 (1 H, br-s).
187	Rex292	^{1}H-NMR (CDCl3): 1.04 (6H, d, J = 6.3Hz), 2.28-2.33 (2H, m), 2.81 (2H, dd, J = 2.0Hz, 9.0Hz), 3.02-3.07 (2H, m), 3.69 (2H, br-s), 6.78 (1H, dd, J = 2.7Hz, 8.5Hz), 6.89 (1H, d, J = 2.9Hz), 7.15 (1H, d, J = 8.5Hz).
188	Rex516	^{1}H-NMR (CDCl3): 1.10(3H, s), 1.11 (3H, s), 2.48-2.53 (2H, m), 3.08-3.13 (2H, m), 3.22 (2H, d, J = 10.7Hz), 7.22 (1H, d, J = 9.0Hz), 8.29 (1H, dd, J = 2.7Hz, 9.0Hz), 8.50 (1H, d, J = 2.7Hz).
189	Rex353	^{1}H-NMR ($CDCl_3$): 1.05-1.09 (6H, m), 1.22-1.46 (3H, m), 2.34-2.40 (2H, m), 2.71-3.76 (6H, m), 5.57 (1H, br-s), 7.32 (1H, d, J = 8.5Hz), 7.74 (1H, br-s), 7.85-7.88 (2H, m), 10.85 (1H, br-s).

[Table 66]

Rex	Syn	Data
190	Rex292	^{1}H-NMR (CDCl3): 1.41 (3H, s), 1.42 (3H, s), 2.68 (3H, s), 2.87-2.90 (2H, m), 2.81 (2H, dd, J = 2.0Hz, 9.0Hz,2H),3.00(m,2H),3.23(m,2H),3.81 (br-s), 6.80 (1H, dd, J = 2.9Hz, 8.5Hz), 6.88 (1H, d, J = 2.9Hz), 7.24 (1H, d, J = 7.8Hz).

(continued)

Rex	Syn	Data
191	Rex516	^{1}H-NMR (CDCl3): 1.15 (3H, s), 1.16 (3H, s), 2.36 (3H, s), 2.46-2.50 (2H, m), 2.79-2.85 (2H, m), 3.19 (2H, dd, J = 2.7Hz, 9.0Hz), 7.22-7.24 (1H, m), 8.30 (1H, dd, J = 2.7H, 9.0Hz), 8.50 (1H, d, J = 2.7Hz).
192	Rex353	^{1}H-NMR (CDCl3): 1.11 (6H, m), 1.30 (3H, t, J = 7.3Hz), 2.33-2.44 (5H, m), 2.67-2.79 (2H, m), 2.85-2.91 (4H, m), 5.54 (1H, br-s), 7.33 (1H, d, J = 8.3Hz), 7.73 (1H, br-s), 7.85-7.87 (2H, m), 10.85 (1H, br-s).
193	Rex353	ESI+: 362
194	Rex194	ESI+: 377
195	Rex353	ESI+: 389
196	Rex353	ESI+: 403
197	Rex353	^{1}H-NMR (CDCl3): 1.30 (3H, t, J = 7.6Hz), 1.48 (9H, s), 2.76-2.91 (6H, m), 3.55 (4H, m), 5.57 (1H, br-s), 7.31 (1H, d, J = 8.8Hz), 7.74 (1H, br-s), 7.86-7.90 (2H, m), 10.89 (1H, br-s).
198	Rex353	^{1}H-NMR (CDCl3): 1.28 (3H, t, J = 7.6Hz), 1.48 (9H, s), 2.32 (3H, s), 2.82-2.88 (6H, m), 3.56 (4H, t, J = 4.9Hz), 5.52 (1H, br-s), 6.98 (1H, d, J = 8.5Hz), 7.36 (1H, d, J = 2.7Hz), 7.55 (1H, dd, J = 2.7Hz, 8.5Hz), 7.72 (1H, br-s), 10.62 (1H, br-s).

[Table 67]

Rex	Syn	Data
199	Rex516	1H-NMR(CDCl3):0.99(s,6H),1.29(t,J=5.6Hz,2H),1.59-1.67(m,2H),2.46(s,2H),2.67(m,2H),3.67(br-s,2H),6.77(dd,J=2.9Hz,8.5Hz,1H),6.89(d,J=2.7Hz, 1H),7.16(d,J=6.5Hz,1H).
200	Rex194	ESI+: 417
201	Rex194	ESI+: 476
202	Rex292	^{1}H-NMR (CDCl3): 1.81-1.85 (2H, m), 1.99-2.03 (2H, m), 2.18-2.21 (4H, m), 2.79-2.84 (2H, m), 3.01-3.04 (2H, m), 3.12-3.34 (4H, m), 3.66-3.69 (2H, m), 9.92 (1H, dd, J = 2.4Hz, 8.0Hz), 6.98 (1H, d, J = 2.4Hz), 7.24 (1H, d, J = 8.0Hz).
203	Rex516	EI : 343
204	Rex353	ESI+: 497
205	Rex353	ESI-: 437
206	Rex353	ESI-: 472
207	Rex292	^{1}H-NMR (CDCl3): 0.81 (3H, d, J = 6.4Hz), 1.48 (3H, d, J = 6.6Hz), 2.68 (2H, q, J = 11.0Hz), 2.81 (2H, d, J = 4.9Hz), 2.93 (1H, dd, J = 2.9Hz, 12.9Hz), 3.17 (1H, br-s), 3.29-3.44 (2H, m), 3.87 (2H, br-s), 6.83 (1H, dd, J = 2.7Hz, 8.5H), 6.89 (1H, d, J = 2.7Hz), 7.29 (1H, d, J = 8.3Hz).
208	Rex516	^{1}H-NMR (CDCl3): 0.79 (3H, d, J = 6.3Hz), 1.04 (3H, d, J = 6.4Hz), 2.16-2.21 (2H, m), 2.28-2.34 (4H, m), 2.44-2.50 (1H, m), 2.86-2.90 (2H, m), 7.56 (1H, d, J = 8.8Hz), 8.40 (1H, dd, J = 2.7Hz, 8.8Hz), 8.55 (1H, d, J = 2.7Hz).
209	Rex353	ESI+: 471
210	Rex292	EI: 219
211	Rex516	EI: 249
212	Rex353	ESI+: 403

[Table 68]

Rex	Syn	Data
213	Rex292	^{1}H-NMR (CDCl3): 1.52-1.55 (2H, m), 2.01 (2H, dt, J = 4.4Hz, 8.4Hz), 2.12-2.16 (2H, m), 2.84-2.94 (6H, m), 6.87 (1H, dd, J = 2.4Hz, 8.4Hz), 6.94 (1H, d, J = 2.4Hz), 7.10-7.21 (4H, m), 7.29 (1H, d, J = 8.4Hz).
214	Rex516	^{1}H-NMR (CDCl3): 1.52-1.55 (2H, m), 2.01 (2H, dt, J = 4.4Hz, 12.8Hz), 2.12-2.16 (2H, m), 2.84-3.31 (6H, m), 6.86-6.89 (1H, m), 6.95 (1H, m), 7.10-7.19 (4H, m), 7.30 (1H, d, J = 8.4Hz).
215	Rex353	ESI-: 528
216	Rex353	ESI+: 403
217	Rex292	EI: 344
218	Rex516	EI: 374
219	Rex353	ESI-: 526
220	Rex292	^{1}H-NMR (CDCl3): 2.34 (3H, s), 2.51 (4H, t, J = 4.8Hz), 3.17 (4H, t, J = 4.8Hz), 3.63 (2H, br-s), 6.58 (2H, s).
221	Rex516	^{1}H-NMR (CDCl3): 2.38 (3H, s), 2.58 (4H, m), 3.36 (4H, t, J = 4.8Hz), 8.15 (2H, s).
222	Rex353	ESI-: 441
223	Rex292	^{1}H-NMR (CDCl3): 1.41-1.53 (10H, m), 1.69 (2H, t, J = 7.1Hz), 2.86 (2H, s), 3.10 (2H, t, J = 6.8Hz), 3.59 (2H, br-s), 6.77 (1H, d, J = 2.7H, 8.5Hz), 6.90 (1H, dd, J = 2.5Hz, 9.5Hz), 7.08 (1H, d, J = 8.8Hz).
224	Rex516	^{1}H-NMR (CDCl3): 1.42-1.57 (10H, m), 1.85 (2H, t, J = 7.1 Hz), 3.33 (2H, s), 3.61 (2H, t, J = 7.0Hz), 6.77 (1H, d, J = 9.5Hz), 8.14 (1H, dd, J = 2.7Hz, 9.5Hz), 8.53 (1H, d, J = 2.9Hz).

[Table 69]

Rex	Syn	Data
225	Rex353	^{1}H-NMR (CDCl3): 1.28 (3H, t, J = 7.6Hz), 1.43-1.55 (10H, m), 2.32 (3H, s), 1.75 (2H, t, J = 7.1Hz), 2.85 (2H, q, J = 7.6Hz), 3.06 (2H, s), 3.32 (2H, t, J = 6.8Hz), 5.50 (1H, br-s), 7.02 (1H, d, J = 9.0Hz), 7.69-7.71 (2H, m), 7.80 (1H, d, J = 2.7Hz), 10.61 (1H, br-s).
226	Rex353	^{1}H-NMR (CDCl3): 1.29 (3H, t, J = 7.6Hz), 1.49 (9H, s), 2.85 (2H, q, J = 7.6Hz), 2.98 (4H, m), 3.61 (4H, t, J = 5.1Hz), 3.90 (3H, s), 5.52 (1H, br-s), 6.87 (1H, d, J = 8.5Hz), 7.14 (1H, dd, J = 2.4Hz, 8.5Hz), 7.38 (1H, d, J = 2.2Hz), 7.73 (1H, br-s), 10.70 (1H, br-s).
227	Rex353	ESI+: 370
228	Rex413	ESI-: 343
229	Rex412	^{1}H-NMR (CDCl3): 1.50 (9H, s), 2.37 (2H, m), 3.63-3.65 (2H, m), 4.06 (2H, m), 5.66 (1H, m), 7.44 (1H, d, J = 8.3Hz), 8.35 (1H, dd, J = 2.2Hz, 8.3Hz), 8.54 (1H, d, J = 2.2Hz).
230	Rex353	^{1}H-NMR (CDCl3): 1.30 (3H, t, J = 7.3Hz), 1.49 (9H, s), 1.60-1.78 (2H, m), 2.81 (2H, m), 2.88 (2H, q, J = 7.3Hz), 3.00-3.06 (1H, m), 4.24 (1H, m), 5.56 (1H, m), 7.37 (1H, d, J = 8.5Hz), 7.74 (1H, m), 7.85 (1H, dd, J = 2.4Hz, 8.5Hz), 7.92 (1H, d, J = 2.4Hz), 10.90 (1H, br-s).
231	Rex353	ESI+: 403
232	Rex353	ESI+: 392
233	Rex353	ESI+: 390
234	Rex292	^{1}H-NMR (CDCl3): 2.18 (3H, s), 2.38 (3H, s), 2.58 (4H, br-s), 2.83 (4H, br-s), 3.63 (2H, br-s), 6.35 (1H, dd, J = 2.8Hz, 8.4Hz), 6.98 (1H, d, J = 8.4Hz), 7.81 (1H, d, J = 2.8H), 8.66 (1H, br-s).

[Table 70]

Rex	Syn	Data
235	Rex353	ESI+: 432
236	Rex292	^{1}H-NMR (CDCl3+CD3OD): 2.42 (3H, s), 2.69 (4H, br-s), 2.86 (4H, br-s), 3.05 (3H, s), 6.44 (1H, dd, J = 2.8Hz, 8.4Hz), 6.87 (1H, d, J=2.8Hz), 7.08 (1H, d, J = 8.8Hz).
237	Rex516	^{1}H-NMR (CDCl3): 2.39 (3H, s), 2.64 (4H, br-s), 2.97 (4H, t, J = 4.8Hz), 3.19 (3H, s), 7.28 (1H, d, J = 8.8Hz), 7.53 (1H, br-s), 7.97 (1H, dd, J = 2.4Hz, 8.4Hz), 8.31 (1H, d, J = 2.4Hz).
238	Rex353	ESI+: 468
239	Rex292	^{1}H-NMR (CDCl3): 2.35 (3H, s), 2.45 (4H, br-s), 2.85 (4H, t, J = 4.8Hz), 3.54 (2H, br-s), 6.62-6.65 (2H, m), 6.92 (1H, d, J = 9.2Hz), 7.29 (1H, t, J = 7.6Hz), 7.36 (2H, t, J = 7.6Hz), 7.57 (2H, d, J = 7.2Hz).
240	Rex240	^{1}H-NMR (CDCl3): 2.27 (3H, s), 2.34 (4H, br-s), 2.99 (4H, t, J = 4.8Hz), 7.01 (1H, d, J = 9.2Hz), 7.35 (1H, t, J = 7.2Hz), 7.44 (2H, t, J = 7.2Hz), 7.58 (2H, d, J = 7.2Hz), 8.08 (1H, d, J = 2.8Hz), 8.14 (1H, dd, J = 2.8Hz, 9.2Hz).
241	Rex516	ESI+: 348
242	Rex353	ESI+: 451
243	Rex292	^{1}H-NMR (CDCl3): 1.91 (3H, s), 2.34 (3H, s), 2.55 (4H, br-s), 2.87 (4H, m), 3.22 (3H, s), 3.64 (2H, br-s), 6.47 (1H, s), 6.66 (1H, d, J = 8.8Hz), 6.95 (1H, d, J = 8.4Hz).
244	Rex244	^{1}H-NMR (CDCl3): 1.98 (3H, s), 2.35 (3H, s), 2.56 (4H, t, J = 4.8Hz), 3.18 (4H, dd, J = 3.6Hz, 5.6Hz), 3.26 (3H, s), 7.05 (1H, d, J = 9.2Hz), 7.98 (1H, d, J = 2.4Hz), 8.14 (1H, dd, J = 2.4Hz, 8.8Hz).

[Table 71]

Rex	Syn	Data
245	Rex353	ESI+: 446
246	Rex246	^{1}H-NMR (CDCl3): 0.90 (3H, t, J = 7.8Hz), 1.40-1.55 (15H, m), 1.61-1.64 (2H, m), 1.78-1.82 (2H, m), 3.39 (1H, m), 4.42 (1H, m).
247	Rex247	^{1}H-NMR (CD3OD): 0.90 (3H, t, J = 7.6Hz), 1.30-1.54 (6H, m), 1.62-1.65 (3H, m), 2.52-2.58 (1H, m).
248	Rex246	^{1}H-NMR (CDCl3): 0.91 (3H, t, J = 7.6Hz), 1.32-1.49 (13H, m), 1.54 (2H, q, J = 7.6Hz), 1.60-1.66 (2H, m), 1.88-1.93 (2H, m), 3.59 (1H, m), 4.55 (1H, m).
249	Rex249	^{1}H-NMR (CD3OD): 0.89 (3H, t, J = 7.6Hz), 1.20-1.31 (2H, m), 1.38-1.45 (2H, m), 1.55 (2H, q, J = 7.6Hz), 1.68-1.81 (4H, m), 2.70-2.75 (1H, m).
250	Rex250	^{1}H-NMR (CDCl3): 0.91 (6H, d, J = 6.8Hz), 1.43-1.49 (11H, m), 1.51-1.63 (5H, m), 1.81-1.83 (2H, m), 3.37 (1H, m), 4.41 (1H, m).
251	Rex251	^{1}H-NMR (DMSO-d6): 0.82 (6H, d, J = 6.8Hz), 1.24-1.31 (2H, m), 1.43-1.53 (3H, m), 1.65-1.67 (4H, m), 2.85-2.89 (1H, m), 3.87 (1H, m), 7.88 (2H, m).
252	Rex250	^{1}H-NMR (CDCl3): 0.92 (6H, d, J = 6.8Hz), 1.43-1.45 (11H, m), 1.52-1.55 (2H, m), 1.64-1.76 (3H, m), 1.88-1.92 (2H, m), 3.68 (1H, m), 4.53 (1H, m).
253	Rex253	^{1}H-NMR (DMSO-d6): 0.83 (6H, d, J = 6.8Hz), 1.25-1.32 (2H, m), 1.48 (2H, m), 1.62-1.68 (3H, m), 1.82-1.88 (2H, m), 3.17 (1H, m), 3.92 (1H, m), 7.84 (2H, m).
254	Rex353	ESI+: 453

[Table 72]

Rex	Syn	Data
255	Rex292	^{1}H-NMR (CDCl3): 1.48 (9H, s), 1.85-1.93 (2H, m), 2.23 (3H, s), 2.93-3.02 (4H, m), 3.45-3.59 (6H, m), 6.47 (1H, d, J = 8.3Hz), 6.53 (1H, s), 6.86 (1H, d, J = 8.3Hz).
256	Rex353	^{1}H-NMR (CDCl3): 1.28 (3H, t, J = 7.3Hz), 1.49 (9H, s), 1.91-1.96 (2H, m), 2.31 (3H, s), 2.84 (2H, q, J = 7.3Hz), 3.00-3.08 (4H, m), 3.56-3.61 (4H, m), 5.50 (1H, br-s), 7.01-7.04 (1H, m), 7.34 (1H, s), 7.52 (1H, m), 7.71 (1H, br-s), 10.60 (1H, br-s).
257	Rex292	^{1}H-NMR (CD3OD): 1.49 (9H, s), 2.02-2.20 (6H, m), 2.37 (3H, s), 2.77-2.86 (2H, m), 3.27-3.34 (6H, m), 3.48-3.65 (6H, m), 3.96 (1H, t, J = 15.4Hz), 7.18-7.23 (3H, m).
258	Rex503	^{1}H-NMR (CDCl3): 1.47 (9H, s), 1.69-1.90 (6H, m), 2.35 (3H, s), 2.61-2.80 (7H, m), 3.30-3.33 (2H, m), 3.42-3.50 (4H, m), 6.96 (1H, d, J = 8.3Hz), 8.00-8.03 (2H, m).
259	Rex516	ESI+: 235
260	Rex292	^{1}H-NMR (CDCl3): 1.63 (2H, m), 2.03-2.94 (21H, m), 3.63 (2H, br-s), 6.34 (1H, d, J = 8.4Hz), 6.93 (1H, d, J = 8.4Hz), 7.81 (1H, s), 8.61 (1H, br-s).
261	Rex503	^{1}H-NMR (CDCl3): 1.64-1.73 (2H, m), 2.12 (2H, d, J = 12.8Hz), 2.24 (3H, s), 2.29-2.38 (1H, m), 2.31 (3H, s), 2.50 (4H, br-s), 2.66 (4H, br-s), 2.75 (2H, t, J = 12.4Hz), 3.15 (2H, d, J = 12.0Hz), 7.16 (1H, d, J = 8.8Hz), 7.92 (1H, dd, J = 2.8Hz, 8.8Hz), 8.07 (1H, br-s), 9.16 (1H, d, J = 2.4Hz).
262	Rex516	^{1}H-NMR (CDCl3): 2.29 (3H, s), 2.68 (4H, t, J = 6.0Hz), 3.27 (4H, t, J = 6.0Hz), 7.23 (1H, d, J = 8.8Hz), 7.97 (1H, dd, J = 2.4Hz, 8.8Hz), 8.16 (1H, br-s), 9.22 (1H, br-s).

[Table 73]

Rex	Syn	Data
263	Rex353	ESI+: 515
264	Rex292	^{1}H-NMR (CDCl3): 1.63 (2H, m), 1.89 (3H, s), 1.97 (2H, m), 2.56-3.21 (19H, m), 3.61 (2H, br-s), 6.47 (1H, d, J = 2.8Hz), 6.61 (1H, dd, J = 2.8Hz, 8.4Hz), 6.91 (1H, d, J = 8.8Hz).
265	Rex244	^{1}H-NMR (CDCl3): 1.62 (2H, m), 1.96 (3H, s), 2.00 (2H, m), 2.29 (3H, s), 2.36 (1H, m), 2.48 (4H, br-s), 2.48 (4H, br-s), 2.61 (4H, br-s), 2.86 (4H, m), 3.48 (3H, s), 3.51 (2H, t, J = 10.8Hz), 7.03 (1H, d, J = 9.2Hz), 7.96 (1H, d, J = 2.8Hz), 8.11 (1H, dd, J = 2.8Hz, 9.2Hz).
266	Rex353	ESI+: 529
267	Rex292	^{1}H-NMR (CDCl3): 0.62-0.66 (2H, m), 0.91-0.96 (2H, m), 2.35 (1H, m), 2.35 (3H, s), 2.57 (4H, br-s), 2.96 (4H, s), 3.42 (2H, br-s), 6.08 (1H, d, J = 2.4Hz), 6.46 (1H, dd, J = 2.4Hz, 8.4Hz), 6.88 (1H, d, J = 8.4Hz).
268	Rex240	^{1}H-NMR (CDCl3): 0.83 (2H, m), 1.09 (2H, m), 2.15 (1H, m), 2.38 (3H, s), 2.62 (4H, br-s), 3.21 (4H, br-s), 6.99 (1H, d, J = 8.4Hz), 7.68 (1H, d, J = 2.8Hz), 7.99 (1H, dd, J = 2.4Hz, 8.8Hz).
269	Rex353	ESI+: 415
270	Rex292	EI :251
271	Rex516	EI:281
272	Rex353	ESI-: 433
273	Rex353	ESI+: 482
274	Rex292	^{1}H-NMR (CD3OD): 2.54 (3H, s), 2.57 (3H, s), 2.90-2.94 (4H, m), 2.99-3.02 (4H, m), 6.80 (1H, dd, J = 2.4Hz, 8.8Hz), 7.09 (1H, d, J = 8.8Hz), 7.22 (1H, d, J = 2.4Hz).

[Table 74]

Rex	Syn	Data
275	Rex516	^{1}H-NMR (CDCl3): 2.39 (3H, s), 2.60 (4H, m), 3.04 (3H, d, J = 4.8Hz), 3.12-3.15 (4H, m), 7.17 (1H, d, J = 8.8Hz), 8.23 (1H, dd, J = 2.4Hz, 8.8Hz), 8.80 (1H, d, J = 2.4Hz).
276	Rex353	ESI+: 432
277	Rex292	^{1}H-NMR (CD3OD): 1.69-1.71 (2H, m), 1.92-1.95 (2H, m), 2.35 (3H, s), 2.55 (3H, s), 2.57-2.82 (9H, m), 3.14 (2H, m), 3.31 (2H, m), 3.34 (6H, s), 6.86-6.88 (1H, m), 7.20-7.22 (2H, m).
278	Rex503	^{1}H-NMR (CDCl3): 1.71-1.80 (2H, m), 1.96-1.99 (2H, m), 2.30 (3H, s), 2.49-2.64 (9H, m), 2.80 (6H, s), 2.84 (2H, m), 3.57-3.60 (2H, m), 7.31 (1H, d, J = 9.2Hz), 8.30 (1H, dd, J = 2.8Hz, 9.2Hz), 8.71 (1H, d, J = 2.8Hz).
279	Rex516	^{1}H-NMR (CDCl3): 2.69-2.72 (4H, m), 2.86 (6H, s), 3.47-3.50 (4H, m), 7.39 (1H, d, J = 8.8Hz), 8.36 (1H, dd, J = 2.4Hz, 8.8Hz), 8.71 (1H, d, J = 2.4H).
280	Rex353	ESI+: 565
281	Rex292	^{1}H-NMR (CDCl3): 2.48 (3H, s), 2.98 (4H, m), 3.31 (7H, m), 6.90 (1H, dd, J = 2.8Hz, 8.4Hz), 7.21 (1H, d, J = 2.8Hz), 7.27 (1 H, d, J = 8.4Hz).
282	Rex516	EI: 328
283	Rex353	ESI+: 468
284	Rex292	^{1}H-NMR (CDCl3): 2.88 (3H, s), 2.96 (3H, s), 3.14 (3H, s), 3.19-3.56 (8H, m), 7.09 (1H, s), 7.29 (2H, m).
285	Rex516	^{1}H-NMR (CDCl3): 2.34 (3H, s), 2.49-2.51 (4H, m), 2.88 (3H, s), 3.13-3.16 (2H, m), 3.15 (3H, s), 3.38 (2H, m), 6.64 (1H, d, J = 8.8Hz), 8.14-8.18 (2H, m).

[Table 75]

Rex	Syn	Data
286	Rex353	ESI+: 446
287	Rex287	EI: 211
288	Rex291	ESI+: 244
289	Rex292	FAB+: 214
290	Rex287	EI: 211
291	Rex291	FAB+: 244
292	Rex292	FAB+: 214
293	Rex298	ESI+: 401
294	Rex299	ESI+: 383
295	Rex298	ESI+: 415
296	Rex298	ESI+: 415
297	Rex299	ESI+: 397
298	Rex298	ESI-: 371
299	Rex299	ESI-: 353
300	Rex298	ESI-: 371
301	Rex299	ESI-: 354
302	Rex299	ESI+: 397
303	Rex298	ESI+: 310

(continued)

Rex	Syn	Data
304	Rex304	ESI+: 306
305	Rex298	ESI+: 352
306	Rex299	FAB+: 334
307	Rex298	ESI+: 338
308	Rex298	ESI+: 330,332
309	Rex298	ESI+: 366
310	Rex299	ESI+: 348
311	Rex311	FAB+: 350
312	Rex299	ESI-: 318
313	Rex298	ESI+: 374
314	Rex299	ESI+: 56
315	Rex298	ESI+: 387
316	Rex298	ESI+: 401

[Table 76]

Rex	Syn	Data
317	Rex339	ESI+: 292
318	Rex304	ESI+: 326,328
319	Rex339	ESI-: 310
320	Rex299	APCI-: 367
321	Rex299	ESI-: 381
322	Rex298	APCI-: 400
323	Rex298	ESI-: 336
324	Rex298	ESI+: 364
325	Rex299	ESI+: 384
326	Rex298	ESI+: 388
327	Rex299	APCI-: 368
328	Rex298	ESI+: 392
329	Rex298	ESI+: 404
330	Rex298	ESI+: 326
331	Rex299	ESI-: 318
332	Rex298	ESI+: 388
333	Rex298	ESI+: 427
334	Rex299	ESI-: 344
335	Rex299	ESI-: 386
336	Rex299	ESI-: 373
337	Rex304	ESI+: 322

(continued)

Rex	Syn	Data
338	Rex299	ESI-: 407
339	Rex339	ESI+: 308
340	Rex346	ESI+: 412
341	Rex349	ESI+: 370
342	Rex342	ESI+: 387, 389
343	Rex342	FAB+: 369
344	Rex298	ESI+: 346
345	Rex298	ESI+: 372
346	Rex346	ESI+: 370
347	Rex346	ESI+: 396

[Table 77]

Rex	Syn	Data
348	Rex349	ESI+: 354
349	Rex349	ESI+: 328
350	Rex298	ESI+: 372
351	Rex298	ESI+: 407, 409
352	Rex298	ESI+: 330
353	Rex353	ESI+: 355
354	Rex299	ESI+: 389, 391
355	Rex346	ESI+: 396
356	Rex298	ESI+: 330
357	Rex346	ESI+: 354
358	Rex349	ESI+: 354
359	Rex298	ESI+: 310, 312
360	Rex353	ESI+: 308, 310
361	Rex346	ESI+: 354
362	Rex349	ESI+: 312
363	Rex349	ESI+: 312
364	Rex364	ESI+: 292
365	Rex298	ESI+: 364
366	Rex346	ESI+: 388
367	Rex298	ESI+: 364
368	Rex346	ESI+: 388
369	Rex349	ESI+: 346
370	Rex349	ESI+: 346
371	Rex298	ESI+: 372

(continued)

Rex	Syn	Data
372	Rex346	ESI+: 396
373	Rex349	ESI+: 354
374	Rex298	ESI+: 296
375	Rex298	ESI+: 374
376	Rex298	ESI+: 330
377	Rex298	ESI+: 330
378	Rex298	ESI+: 398

[Table 78]

Rex	Syn	Data
379	Rex353	FAB+: 327
380	Rex346	ESI+: 422
381	Rex346	ESI-: 396
382	Rex346	ESI+: 320
383	Rex346	ESI+: 354
384	Rex346	ESI+: 354
385	Rex349	ESI+: 380
386	Rex349	ESI+: 356
387	Rex349	ESI+: 278
388	Rex349	ESI+: 312
389	Rex349	ESI+: 312
390	Rex353	ESI+: 278
391	Rex353	ESI+: 369, 371
392	Rex353	ESI+: 361, 363
393	Rex353	ESI+: 323
394	Rex353	ESI+: 323
395	Rex353	ESI+: 292
396	Rex397	ESI+: 355
397	Rex397	ESI+: 355
398	Rex398	ESI+: 234, 236
399	Rex399	ESI+: 229
400	Rex400	ESI+: 129
401	Rex353	ESI+: 328
402	Rex353	ESI-: 343
403	Rex353	ESI+: 317
404	Rex353	ESI+: 333
405	Rex353	ESI+: 328

(continued)

Rex	Syn	Data
406	Rex516	ESI+: 335
407	Rex292	ESI+: 305
408	Rex353	ESI+: 322
409	Rex353	ESI+: 368

[Table 79]

Rex	Syn	Data
410	Rex353	ESI+: 348
411	Rex353	ESI+: 361
412	Rex412	FAB+: 335
413	Rex413	ESI+: 306
414	Rex353	ESI+: 375
415	Rex353	ESI+: 405
416	Rex353	ESI+: 405
417	Rex417	ESI+: 387
418	Rex353	ESI+: 458
419	Rex353	ESI+: 433
420	Rex353	ESI+: 375
421	Rex516	ESI+: 349
422	Rex292	ESI+: 319
423	Rex353	ESI+: 488, 490
424	Rex353	ESI+: 443
425	Rex353	ESI+: 460
426	Rex516	ESI+: 373
427	Rex353	ESI+: 405
428	Rex353	ESI+: 362
429	Rex353	ESI+: 360
430	Rex430	EI: 256, 258
431	Rex430	EI: 270, 272
432	Rex432	ESI+: 321
433	Rex432	ESI+: 335
434	Rex292	ESI+: 291
435	Rex292	ESI+: 305
436	Rex292	ESI+: 343
437	Rex353	FAB+: 489 491
438	Rex454	ESI-: 409
439	Rex353	ESI+: 405

(continued)

Rex	Syn	Data
440	Rex440	ESI+: 538

[Table 80]

Rex	Syn	Data
441	Rex455	ESI+: 311
442	Rex353	ESI+: 443
443	Rex353	ESI+: 374
444	Rex444	ESI+: 252
445	Rex292	ESI+: 222
446	Rex353	ESI+: 355, 357
447	Rex353	ESI+: 405
448	Rex464	ESI+: 408
449	Rex468	ESI+: 274
450	Rex353	ESI+: 457
451	Rex516	ESI+: 305
452	Rex292	ESI+: 275
453	Rex353	ESI+: 458
454	Rex454	ESI+: 441
455	Rex455	ESI+: 341
456	Rex516	ESI+: 290
457	Rex292	ESI+: 260
458	Rex353	ESI+: 443
459	Rex516	ESI+: 379
460	Rex292	ESI+: 349
461	Rex353	ESI+: 405
462	Rex454	ESI+: 441
463	Rex455	APCI/ESI+: 341
464	Rex464	ESI+: 355
465	Rex464	ESI+: 438
466	Rex467	ESI+: 277
467	Rex467	ESI+: 291
468	Rex468	ESI+: 221
469	Rex468	ESI+: 304
470	Rex353	ESI+: 404, 406
471	Rex353	ESI+: 487, 489

[Table 81]

Rex	Syn	Data
472	Rex472	ESI+: 275
473	Rex473	APCI/ESI+: 279
474	Rex292	APCI/ESI+: 249
475	Rex516	APCI/ESI+: 237
476	Rex353	APCI/ESI+: 432, 434
477	Rex292	APCI/ESI+: 207
478	Rex454	FAB+: 411
479	Rex455	ESI+: 311
480	Rex464	ESI+: 325
481	Rex468	ESI+: 191
482	Rex464	ESI+: 408
483	Rex464	ESI+: 438
484	Rex468	ESI+: 274
485	Rex353	ESI+: 409
486	Rex468	ESI+: 304
487	Rex353	ESI+: 404
488	Rex353	ESI+: 374
489	Rex353	ESI+: 487
490	Rex353	ESI+: 457
491	Rex353	APCI/ESI+: 390, 392
492	Rex502	EI:220
493	Rex503	ESI+: 419
494	Rex455	ESI+: 319
495	Rex444	ESI+:295
496	Rex464	ESI+: 333
497	Rex292	ESI+: 265
498	Rex292	ESI+: 303
499	Rex444	ESI+: 279
500	Rex353	APCI/ESI+: 486, 488
501	Rex353	ESI+: 420
502	Rex502	APCI/ESI+: 251

[Table 82]

Rex	Syn	Data
503	Rex503	APCI/ESI+: 335
504	Rex292	APCI/ESI+: 305
505	Rex353	APCI/ESI+: 406
506	Rex353	APCI/ESI+: 433

(continued)

Rex	Syn	Data
507	Rex353	APCI/ESI+: 420
508	Rex353	APCI/ESI+: 419
509	Rex353	APCI/ESI+: 488
510	Rex502	APCI/ESI+: 235
511	Rex503	APCI/ESI+: 319
512	Rex292	APCI/ESI+: 239
513	Rex353	ESI+: 472
514	Rex432	ESI+: 308
515	Rex432	ESI+: 322
516	Rex516	ESI+: 279
517	Rex292	ESI+: 249
518	Rex516	ESI+: 295
519	Rex292	APCI/ESI+: 265
520	Rex353	ESI+: 404
521	Rex353	ESI+: 420
522	Rex292	ESI+: 292
523	Rex292	ESI+: 278
524	Rex353	ESI+: 475, 477
525	Rex353	ESI+: 488, 490
526	Rex353	ESI+: 502, 504
527	Rex353	ESI+: 474, 476
528	Rex353	ESI+: 474
529	Rex353	ESI+: 461
530	Rex467	ESI+: 278
531	Rex353	ESI+: 461, 463
532	Rex353	ESI+: 460, 462
533	Rex430	EI: 270, 272

[Table 83]

Rex	Syn	Data
534	Rex432	ESI+: 335
535	Rex292	ESI+: 305
536	Rex353	ESI+: 488, 490
537	Rex432	ESI+: 322
538	Rex292	ESI+: 292
539	Rex353	ESI+: 475, 477
540	Rex353	ESI+: 532, 534

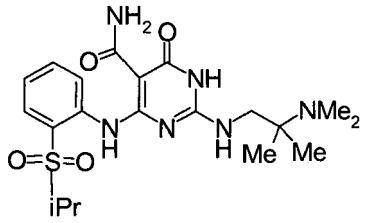
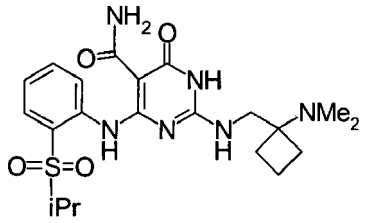
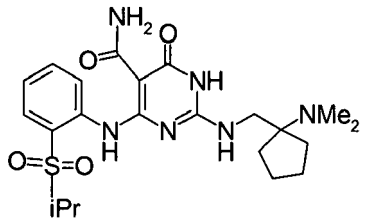
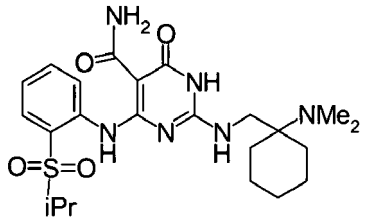
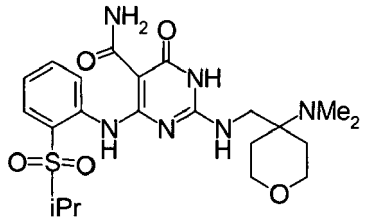
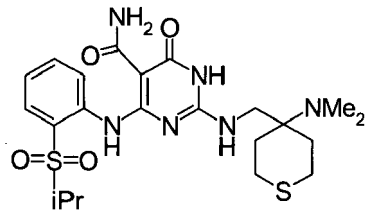
(continued)

Rex	Syn	Data
541	Rex516	ESI+: 319
542	Rex292	ESI+: 289
543	Rex545	ESI+: 389
544	Rex353	ESI+: 435
545	Rex545	APCI/ESI+: 419
546	Rex417	ESI+: 470
547	Rex353	APCI/ESI+: 488
548	Rex353	^{1}H-NMR (CDCl3):1.28(3H, t, J = 7.3Hz), 2.36(3H, S), 2.62 (4H, br-s), 2.85 (2H, q, J = 7.6Hz), 3.10 (4H, br-s), 5.50(1H, br-s), 6.91-6.99 (1H, m), 7.25 (1H, br-s), 7.53 (1H, d, J = 14.4Hz), 7.71 (1H, br-s), 10.71 (1H, br-s)
549	Rex353	ESI+: 506
550	Rex545	ESI+: 490
551	Rex516	ESI+:319
552	Rex292	ESI+:289
553	Rex353	ESI+: 472
554	Rex516	1H-NMR (CDCl3) :1.71-2.17 (6H, m), 2.35 (4H, m), 2.72-2.75 (4H, m), 2.99-3.02 (2H, m), 3.30-3.32 (4H, m), 6.87-6.92 (1H, m), 7.87-7.99 (2H, m)
555	Rex292	ESI+: 293

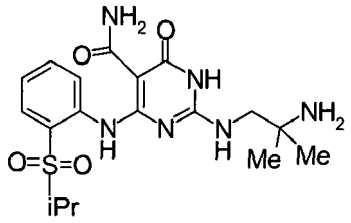
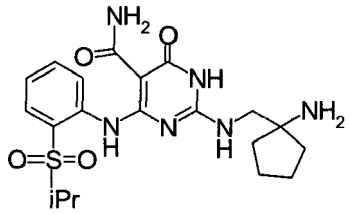
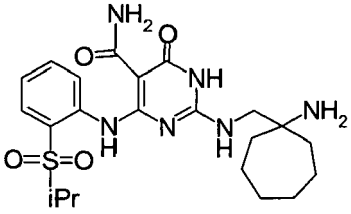
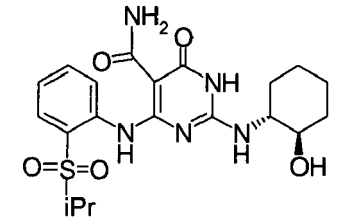
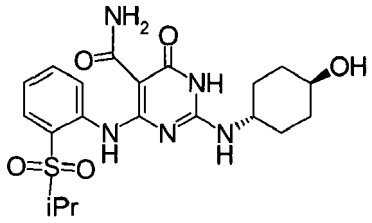
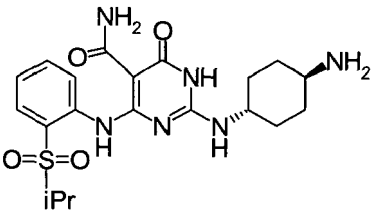
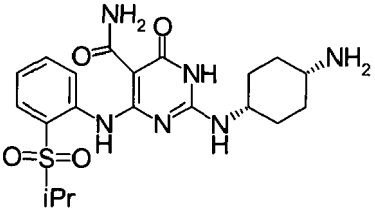
[Table 84]

Rex	Syn	Data
556	Rex353	1H-NMR (CDCl3): 1.26-1.32 (3H, m), 1.56-1.65 (2H, m), 1.84-1.97 (4H, m), 2.30 (4H, m), 2.72-3.09 (12H, m), 5.49 (1H, br-s), 6.90-6.95 (1H, m), 7.17-7.29 (1H, m), 7.52-7.56 (1H, m), 7.71 (1H, br-s), 10.71 (1H, br-s)
557	Rex516	1H-NMR (CDCl3): 1.59 (2H, m), 1.82-1.85 (2H, m), 1.93-1.98 (2H, m), 2.27 (4H, br-s), 2.75 (4H, t, J = 4.6Hz), 2.91-2.94 (2H, m), 3.24-3.26 (4H, m), 3.95 (3H, s), 6.87 (1H, d, J = 9.0Hz), 7.70 (1H, d, J = 2.4Hz), 7.85 (1H, dd, J = 2.7, 9.0Hz)
558	Rex292	1H-NMR (CDCl3): 1.65-2.00 (8H, m), 2.29 (4H, br-s), 2.75-2.76 (4H, m), 2.93-3.03 (6H, m), 3.83 (3H, s), 6.23-6.26 (2H, m), 6.76 (1H, d, J = 8.1 Hz)
559	Rex353	1H-NMR (CDCl3): 1.57-1.98 (11H, m), 2.29 (5H, m), 2.78 (4H, br-s), 2.94-2.96 (2H, m), 3.09 (4H, br-s), 3.71 (1H, br-s), 3.90 (3H, s), 5.56 (1H, br-s), 6.91 (1H, d, J = 8.5H), 7.13 (1H, dd, J = 2.4, 8.5Hz), 7.36 (1H, d, J = 2.4Hz), 7.41 (1H, br-s), 10.76 (1H, br-s)
560	Rex545	ESI+: 502
561	Rex353	ESI+: 423
562	Rex545	1H-NMR (CDCl3): 1.26 (6H, d, J = 6.8Hz), 2.37 (3H, S), 2.62 (4H, br-s), 3.10 (4H, br-s), 3.40-3.47 (1H, m), 5.52 (1H, br-s), 6.91-6.96 (1H, m), 7.24-7.26 (1H, m), 7.53 (1H, dd, J = 2.7, 14.6Hz), 7.69 (1H, br-s), 10.70 (1H, br-s)

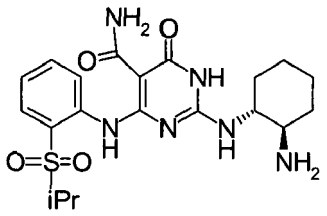
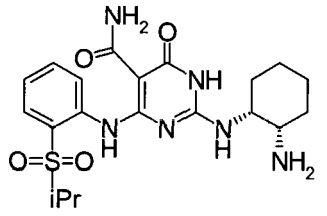
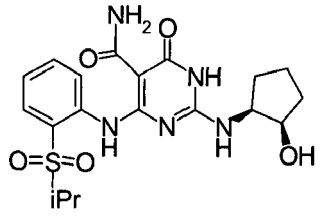
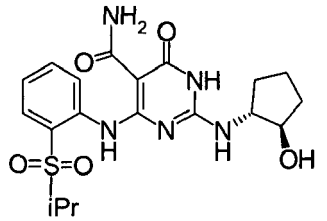
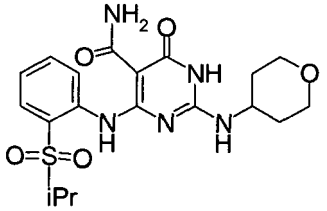
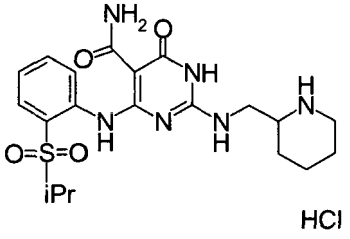
[Table 85] (# not part of the invention)

Ex	Structure
1#	
2#	
3#	
4#	
5#	
6#	

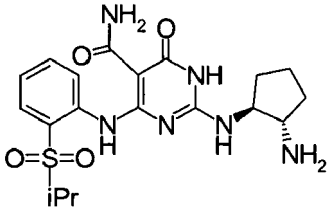
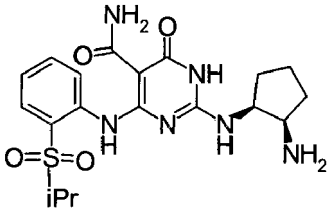
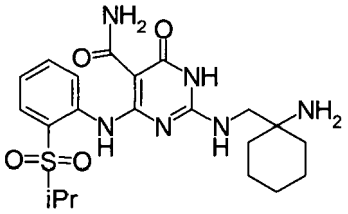
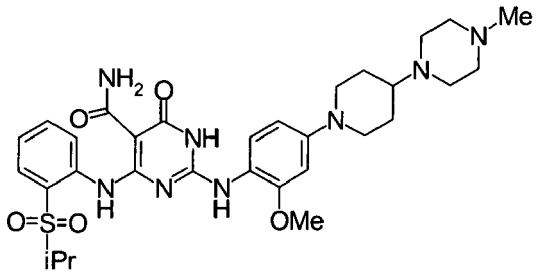
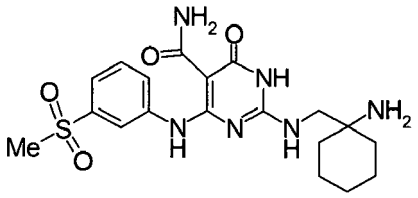
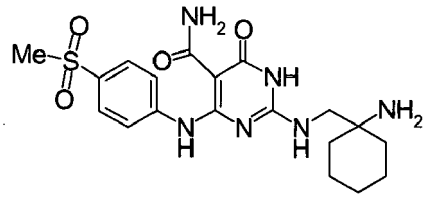
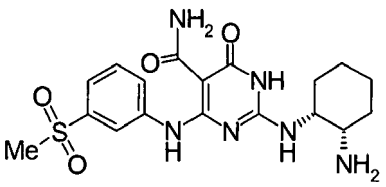
[Table 86] (# not part of the invention)

Ex	Structure
7#	
8#	
9#	
10#	
11#	
12#	
13#	

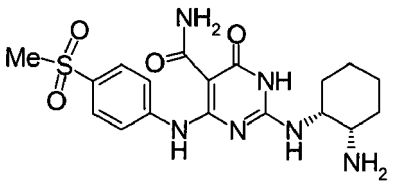
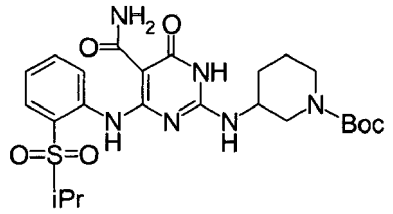
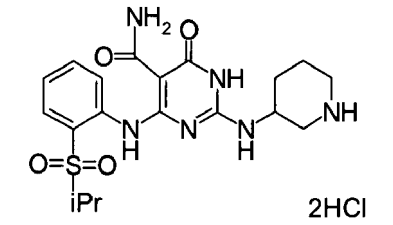
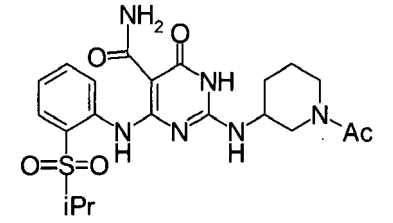
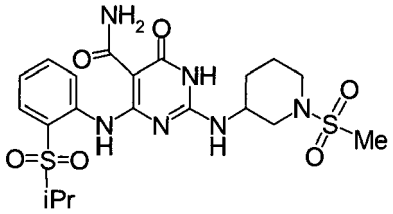
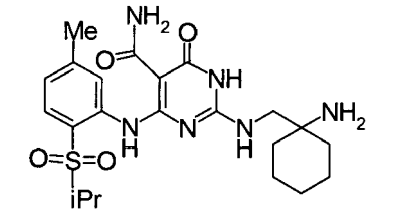
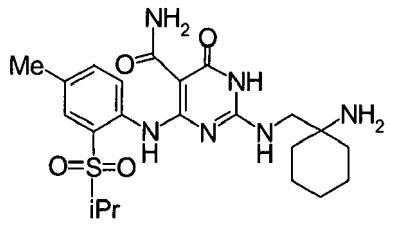
[Table 87] (# not part of the invention)

Ex	Structure
14#	
15#	
16#	
17#	
18#	
19#	

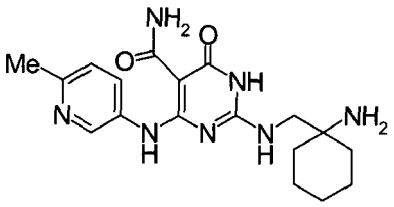
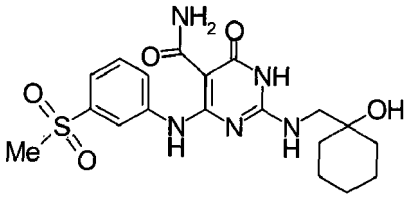
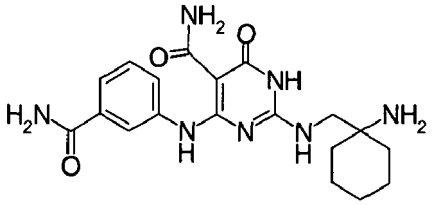
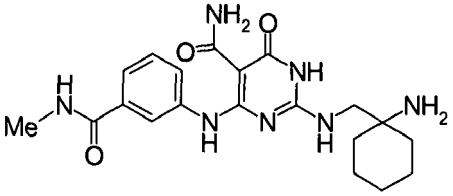
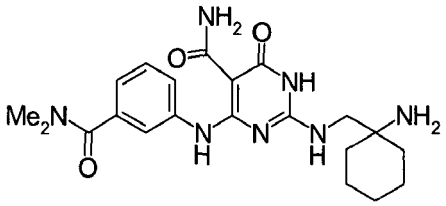
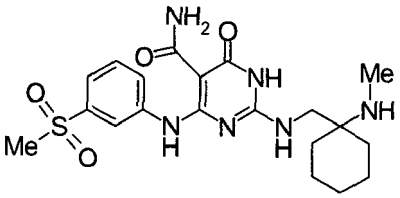
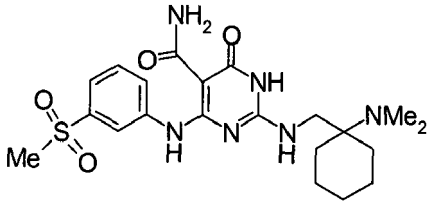
[Table 88] (# not part of the invention)

Ex	Structure
20#	
21#	
22#	
23#	
24#	
25#	
26#	

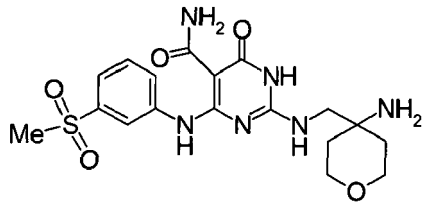
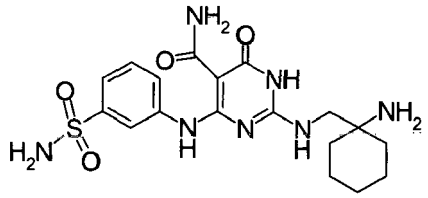
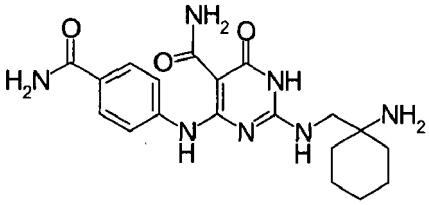
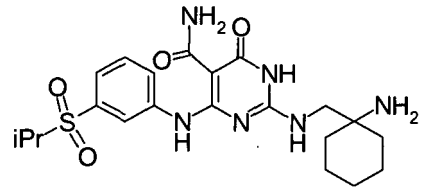
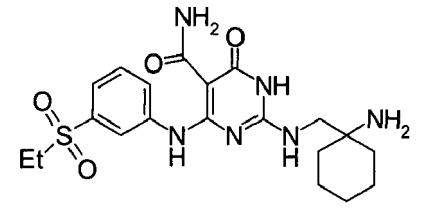
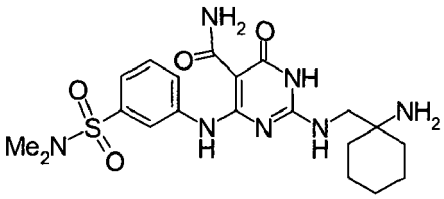
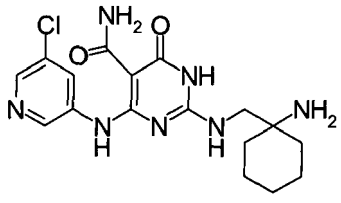
[Table 89] (# not part of the invention)

Ex	Structure
27#	
28#	
29#	
30#	
31#	
32#	
33#	

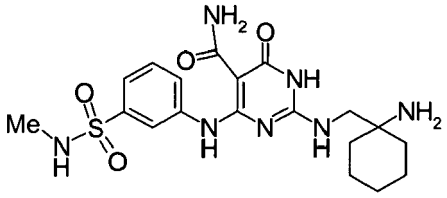
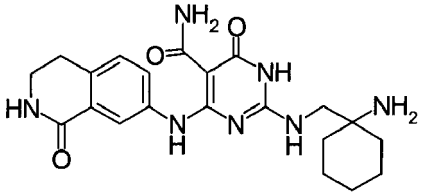
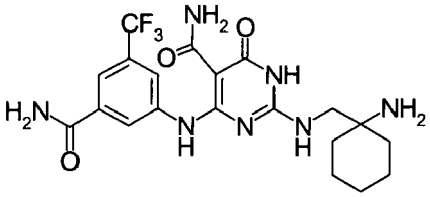
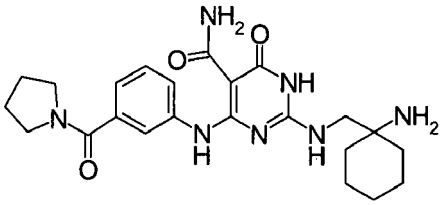
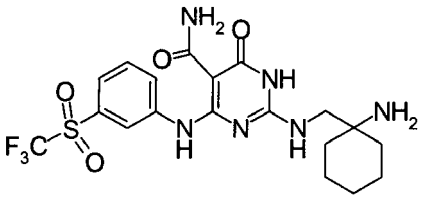
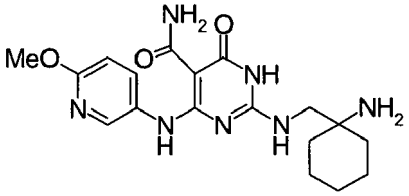
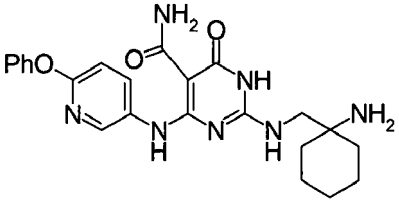
[Table 90] (# not part of the invention)

Ex	Structure
34#	
35#	
36#	
37#	
38#	
39#	
40#	
[0334] (# not part of the invention)	

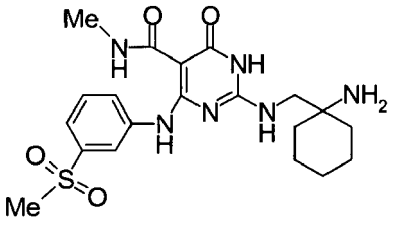
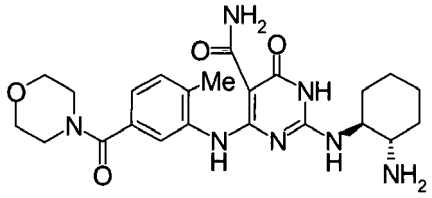
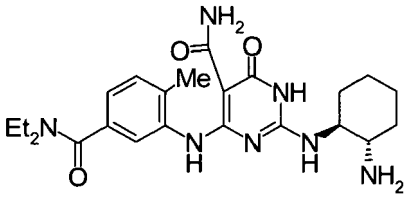
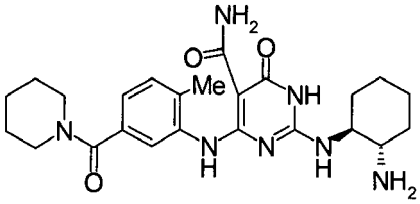
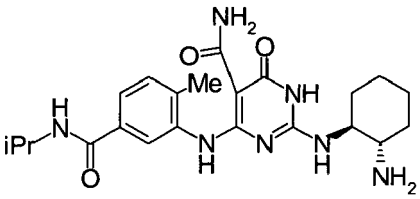
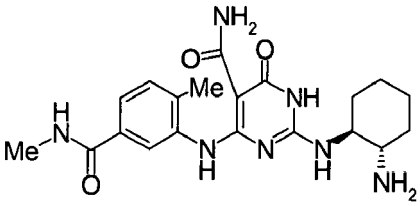
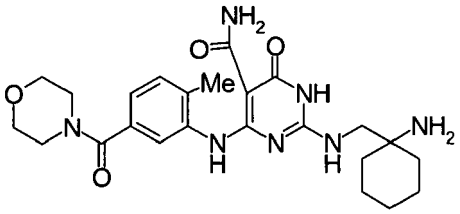
[Table 91] (# not part of the invention)

Ex	Structure
41#	
42#	
43#	
44#	
45#	
46#	
47#	

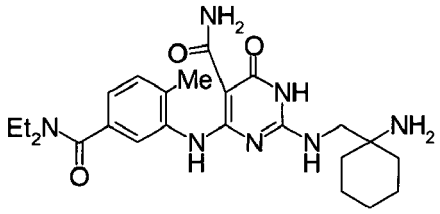
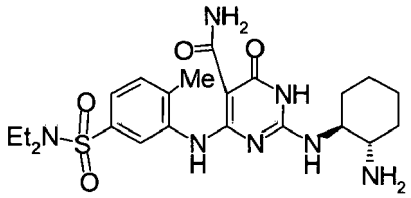
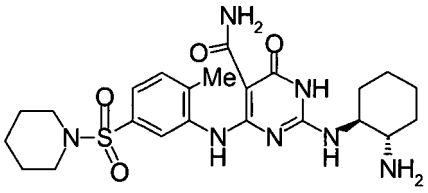
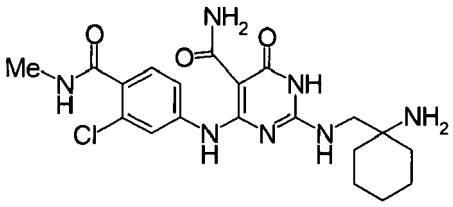
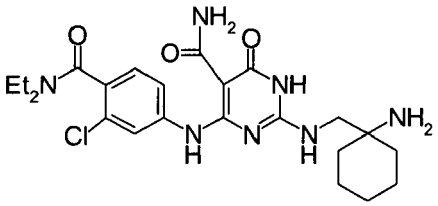
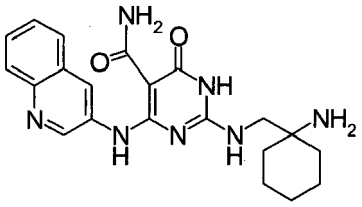
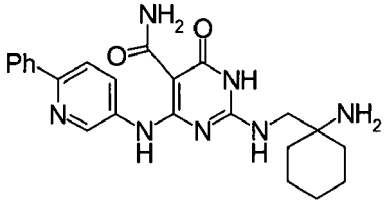
[Table 92] (# not part of the invention)

Ex	Structure
48#	
49#	
50#	
51#	
52#	
53#	
54#	

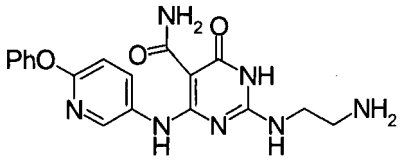
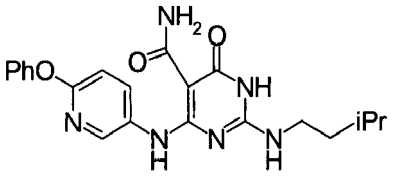
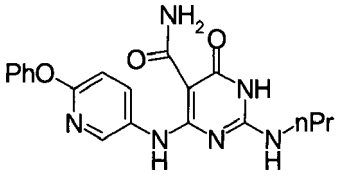
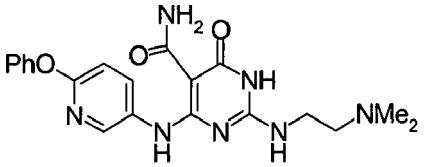
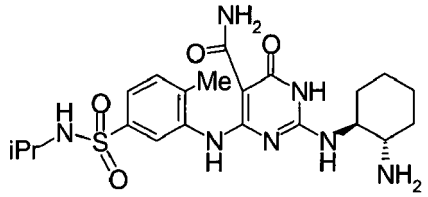
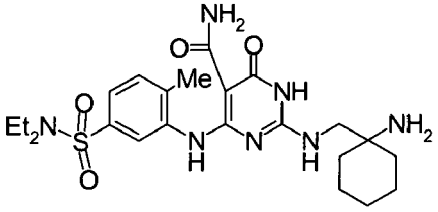
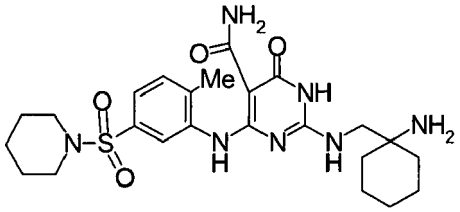
[Table 93] (# not part of the invention)

Ex	Structure
55#	
56#	
57#	
58#	
59#	
60#	
61#	

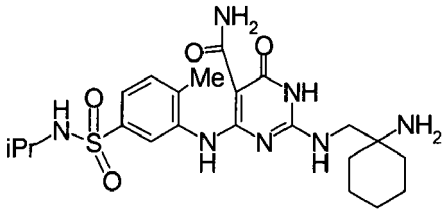
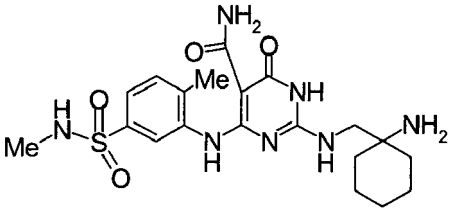
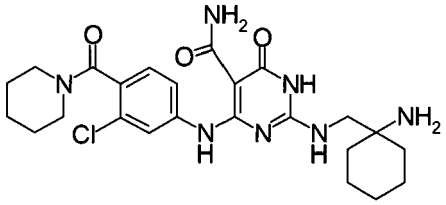
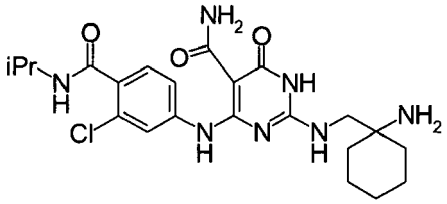
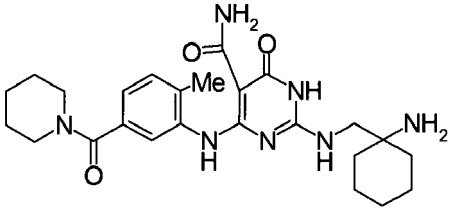
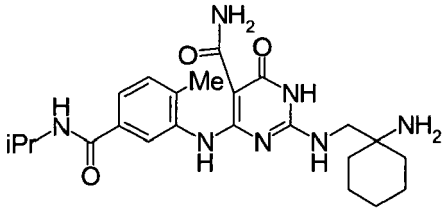
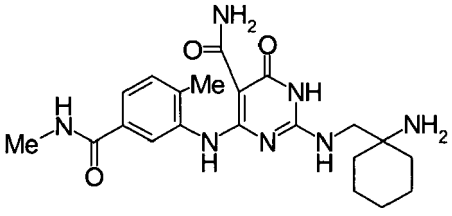
[Table 94] (# not part of the invention)

Ex	Structure
62#	
63#	
64#	
65#	
66#	
67#	
68#	

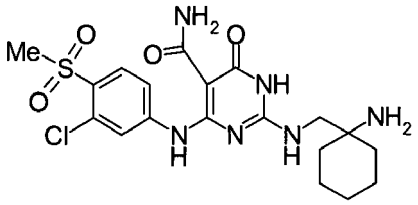
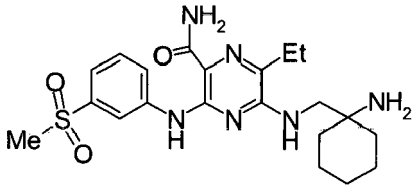
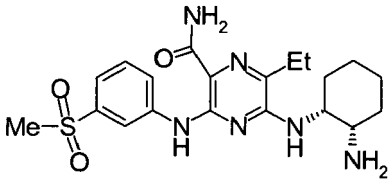
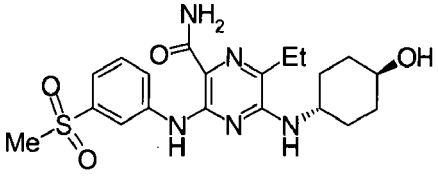
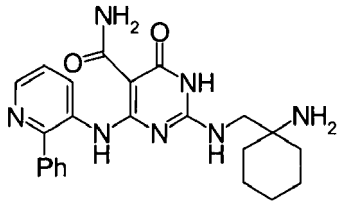
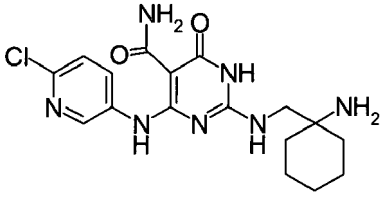
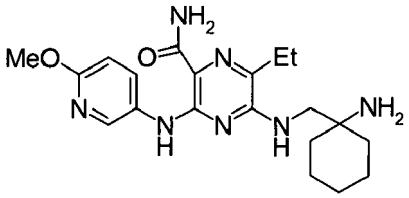
[Table 95] (# not part of the invention)

Ex	Structure
69#	
70#	
71#	
72#	
73#	
74#	
75#	

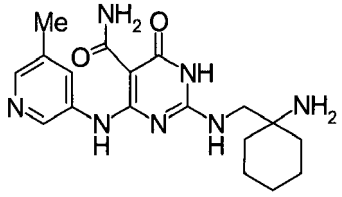
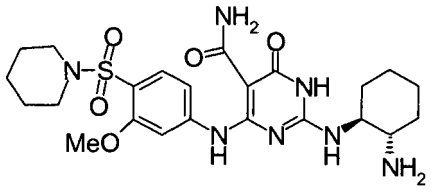
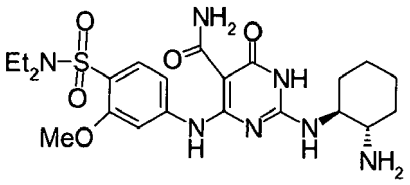
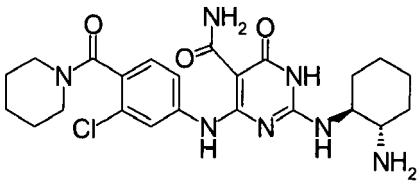
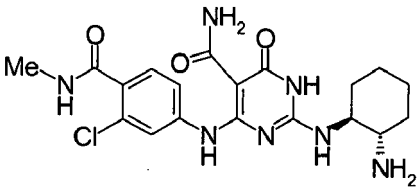
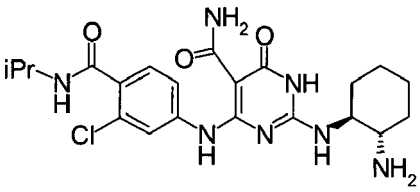
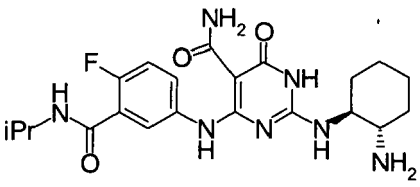
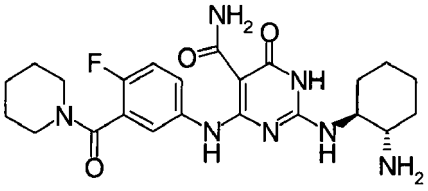
[Table 96] (# not part of the invention)

Ex	Structure
76#	
77#	
78#	
79#	
80#	
81#	
82#	

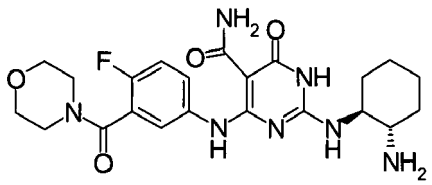
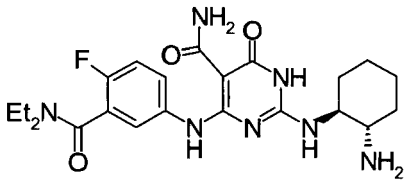
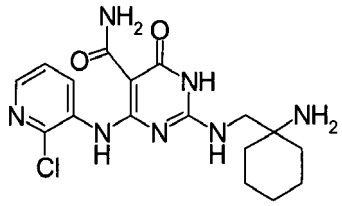
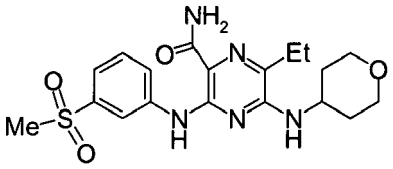
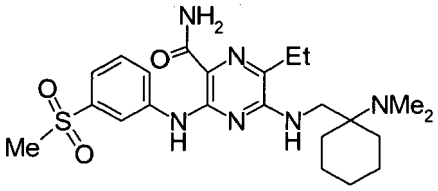
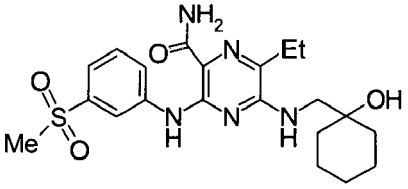
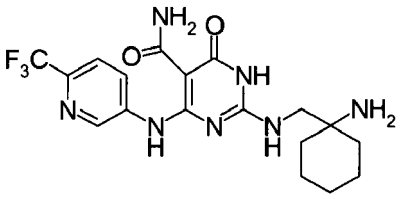
[Table 97] (# not part of the invention)

Ex	Structure
83#	
84#	
85#	
86#	
87#	
88#	
89#	

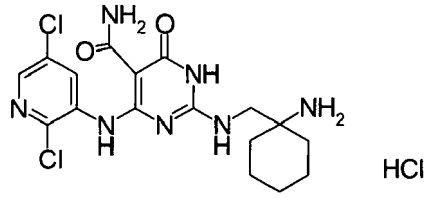
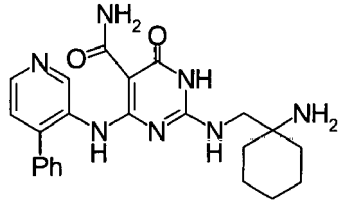
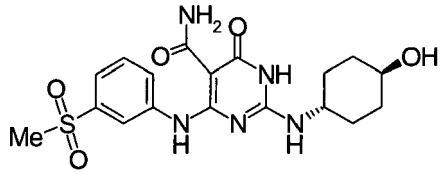
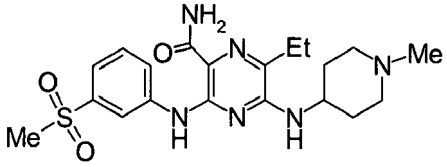
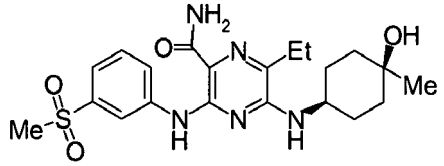
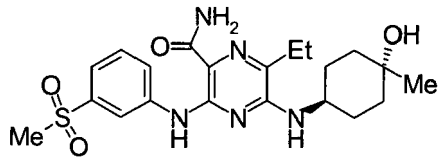
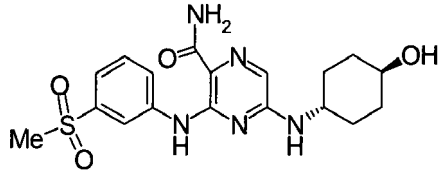
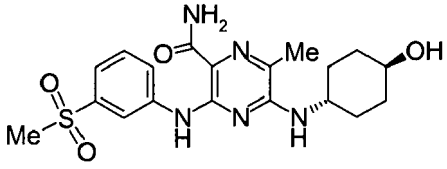
[Table 98] (# not part of the invention)

Ex	Structure
90#	
91#	
92#	
93#	
94#	
95#	
96#	
97#	

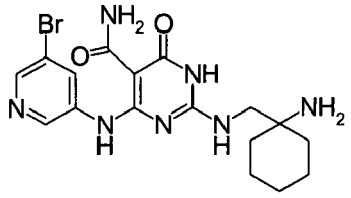
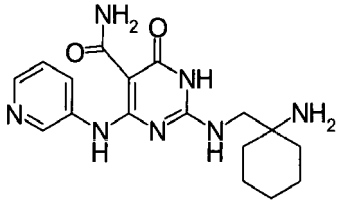
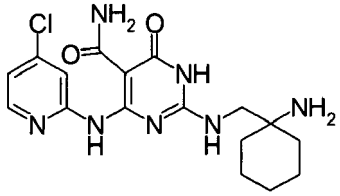
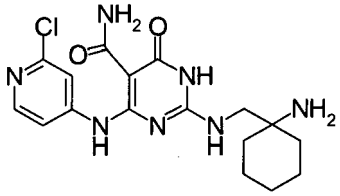
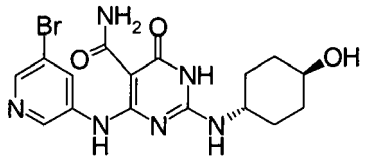
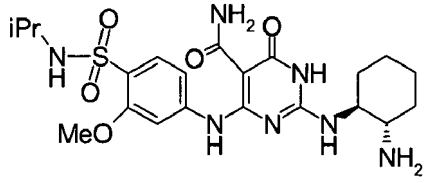
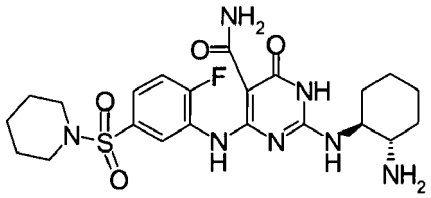
[Table 99] (# not part of the invention)

Ex	Structure
98#	
99#	
100#	
101#	
102#	
103#	
104#	

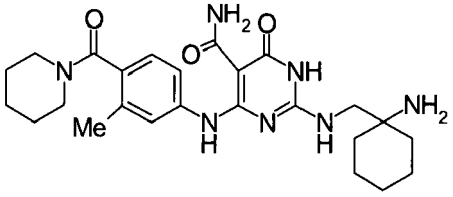
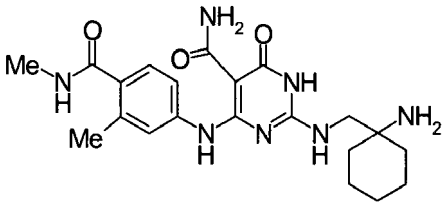
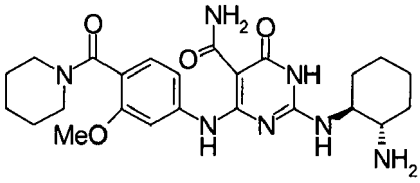
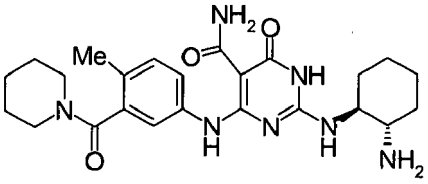
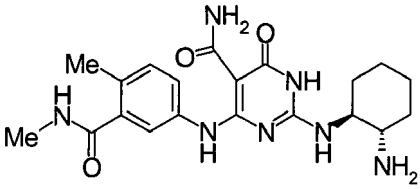
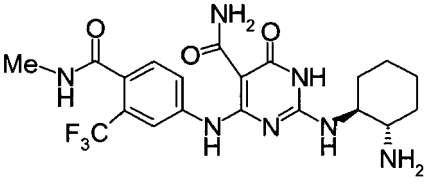
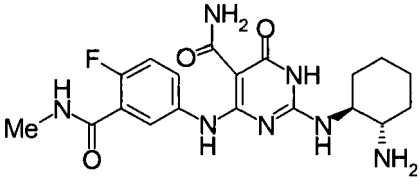
[Table 100] (# not part of the invention)

Ex	Structure
105#	
106#	
107#	
108#	
109#	
110#	
111#	
112#	

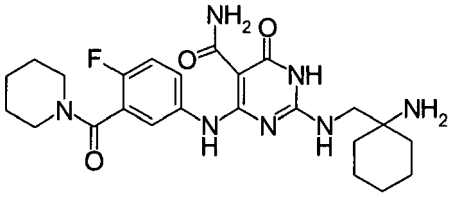
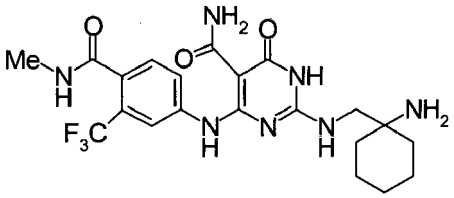
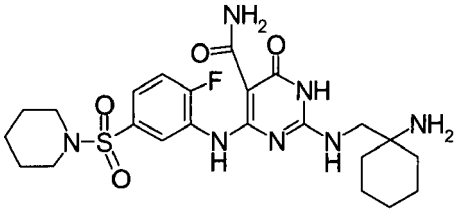
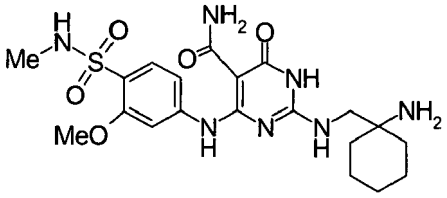
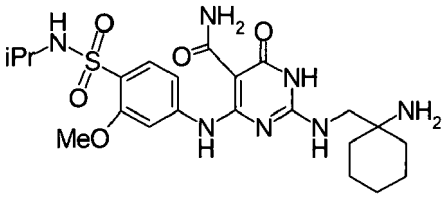
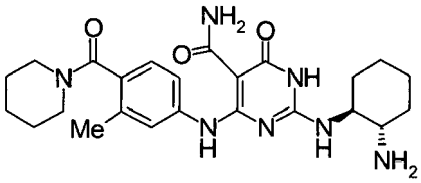
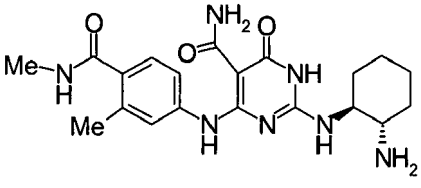
[Table 101] (# not part of the invention)

Ex	Structure
113#	
114#	
115#	
116#	
117#	
118#	
119#	

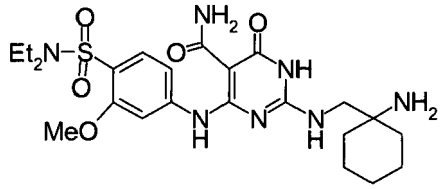
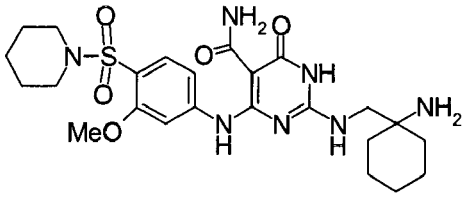
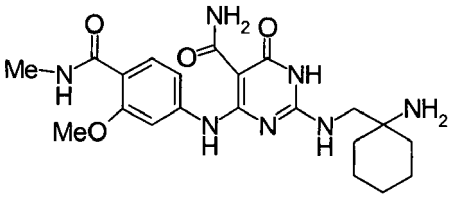
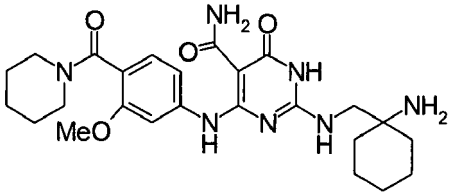
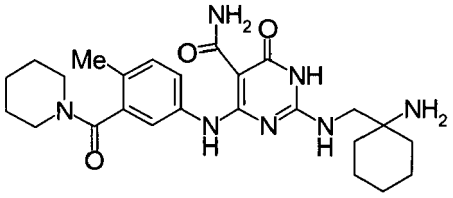
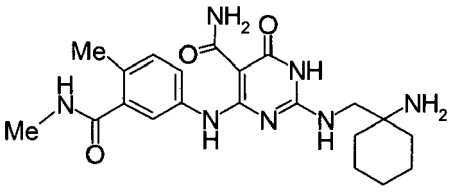
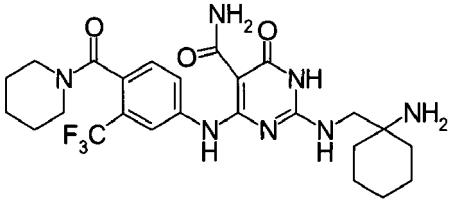
[Table 102] (# not part of the invention)

Ex	Structure
120#	
121#	
122#	
123#	
124#	
125#	
126#	

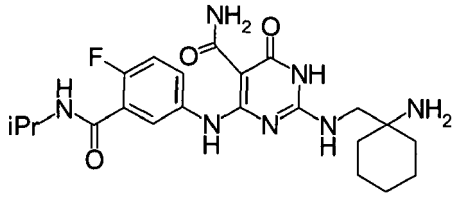
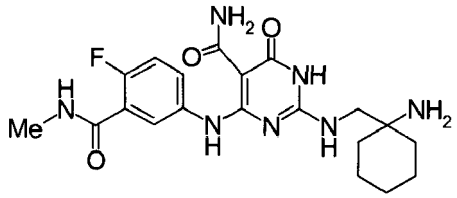
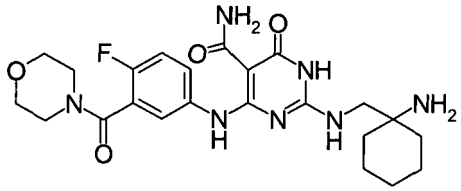
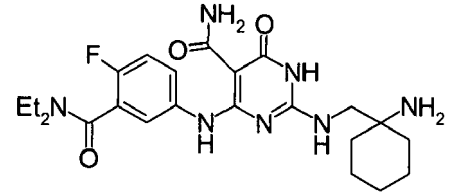
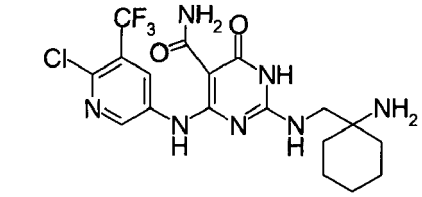
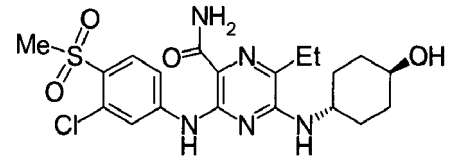
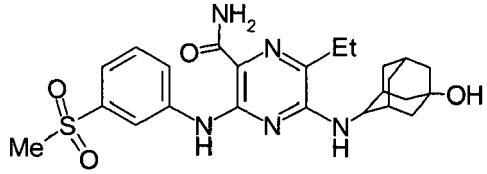
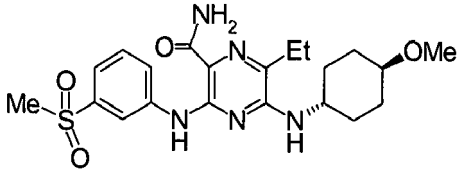
[Table 103] (# not part of the invention)

Ex	Structure
127#	
128#	
129#	
130#	
131#	
132#	
133#	

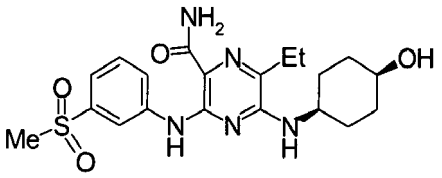
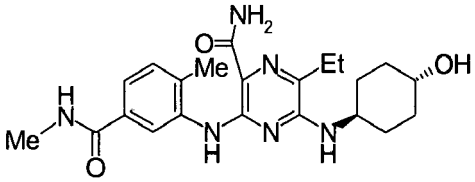
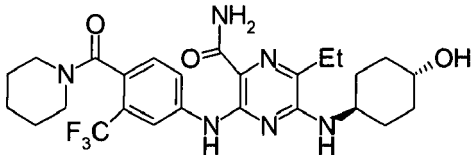
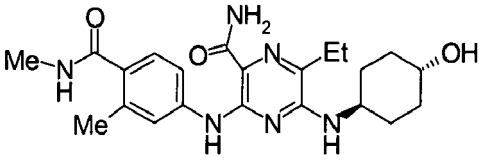
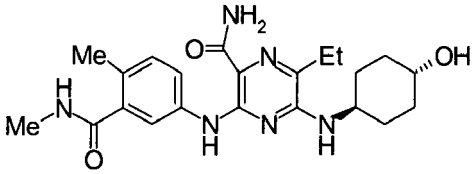
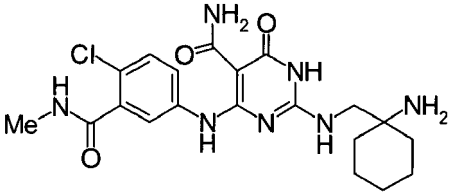
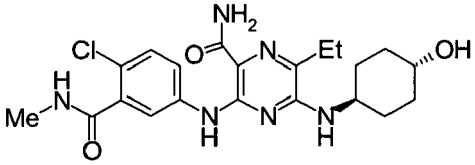
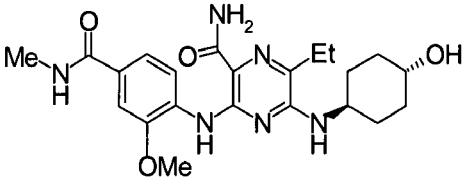
[Table 104] (# not part of the invention)

Ex	Structure
134#	
135#	
136#	
137#	
138#	
139#	
140#	

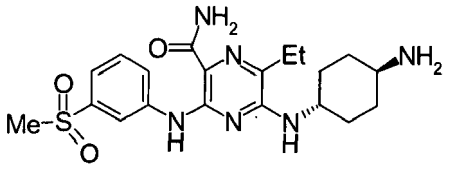
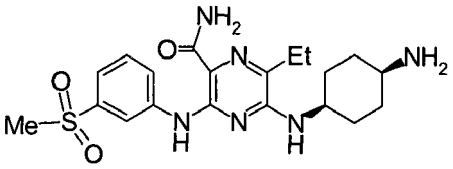
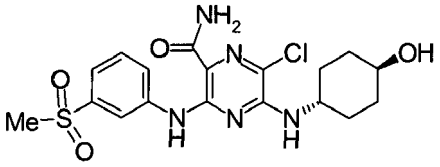
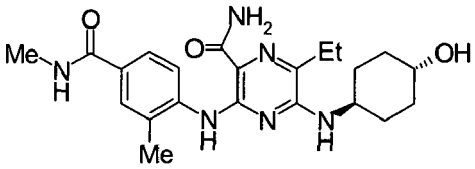
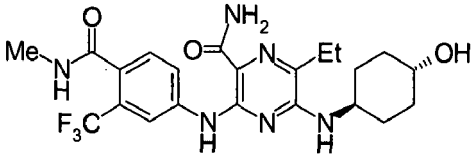
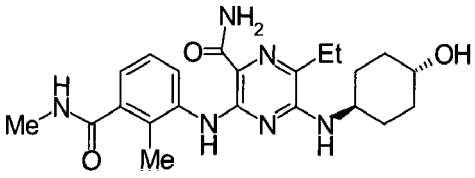
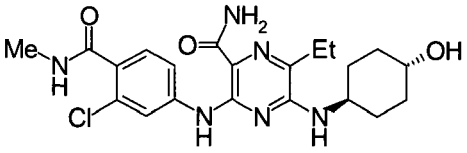
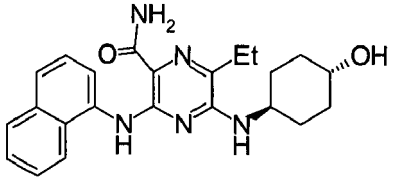
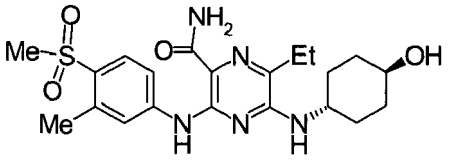
[Table 105] (# not part of the invention)

Ex	Structure
141#	
142#	
143#	
144#	
145#	
146#	
147#	
148#	

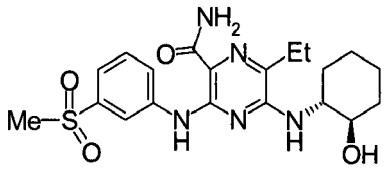
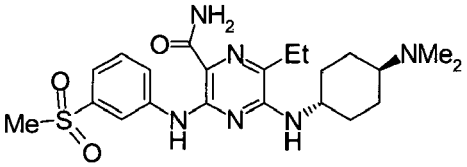
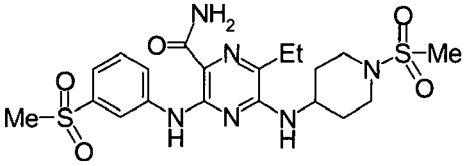
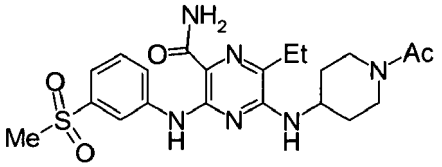
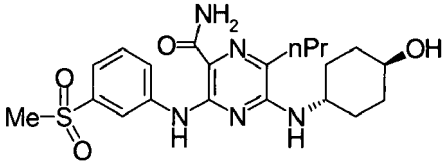
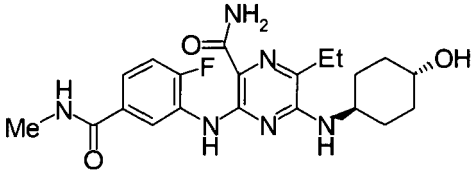
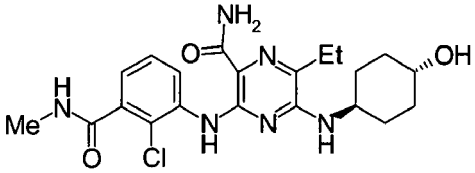
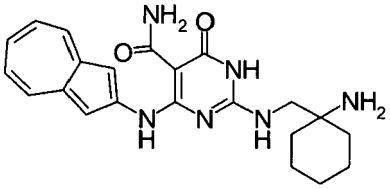
[Table 106] (# not part of the invention)

Ex	Structure
149#	
150#	
151#	
152#	
153#	
154#	
155#	
156#	

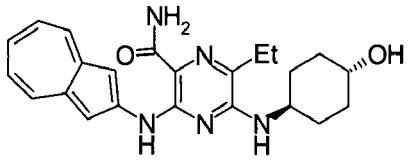
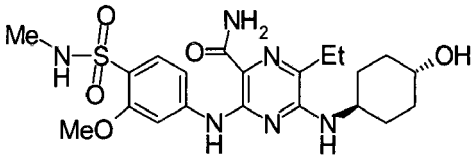
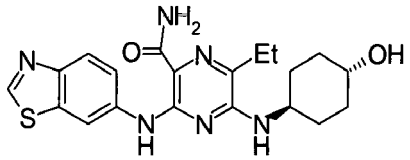
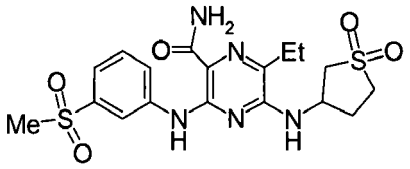
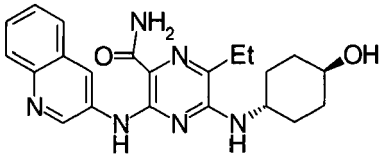
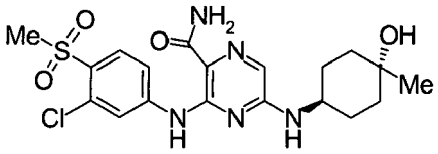
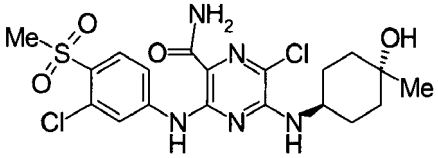
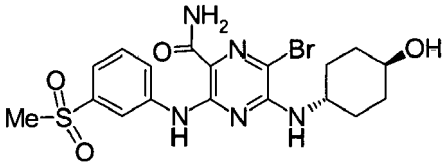
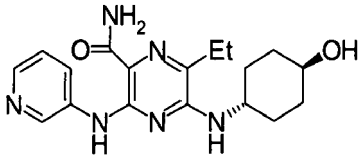
[Table 107] (# not part of the invention)

Ex	Structure
157#	
158#	
159#	
160#	
161#	
162#	
163#	
164#	
165#	

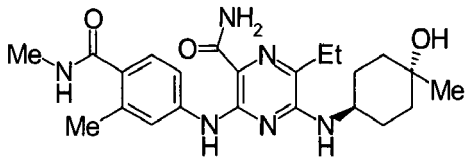
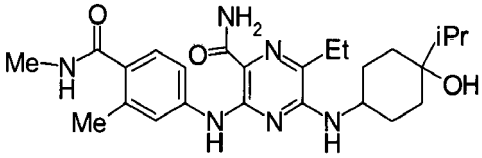
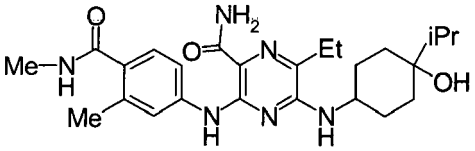
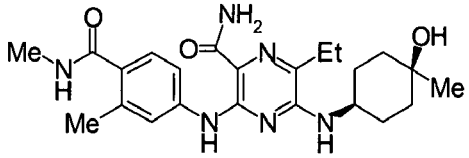
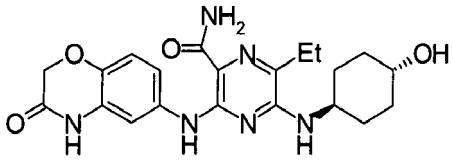
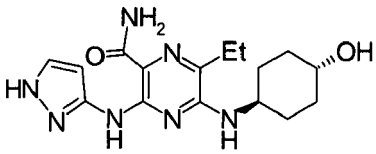
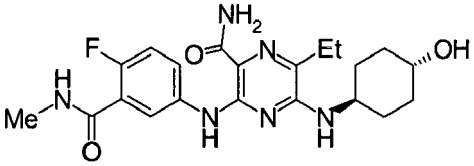
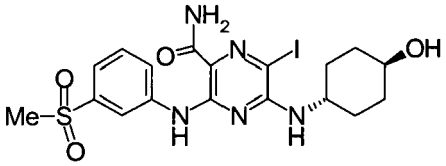
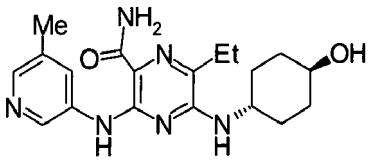
[Table 108] (# not part of the invention)

Ex	Structure
166#	
167#	
168#	
169#	
170#	
171#	
172#	
173#	

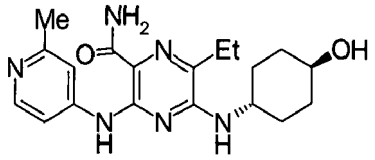
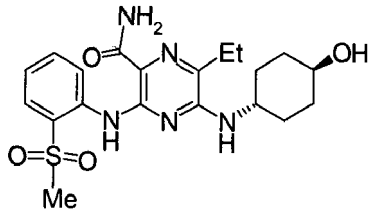
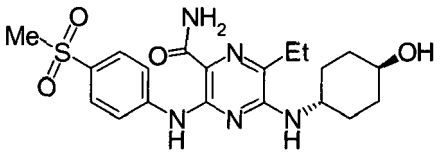
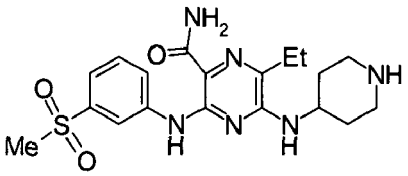
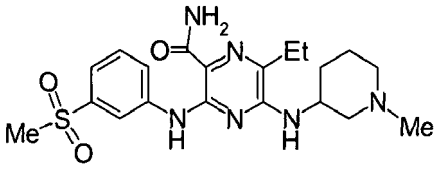
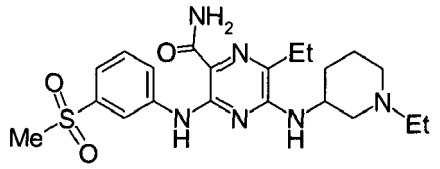
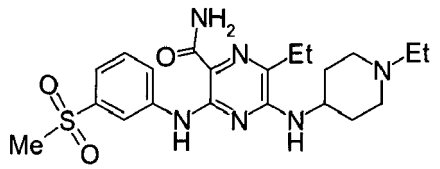
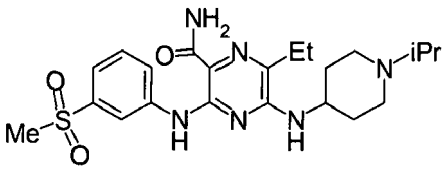
[Table 109] (# not part of the invention)

Ex	Structure
174#	
175#	
176#	
177#	
178#	
179#	
180#	
181#	
182#	

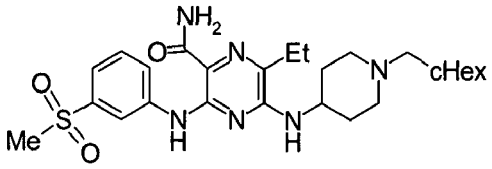
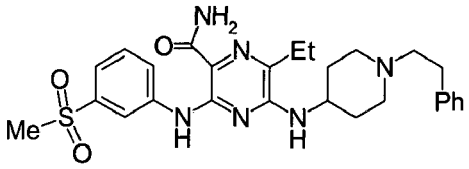
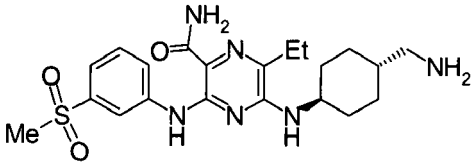
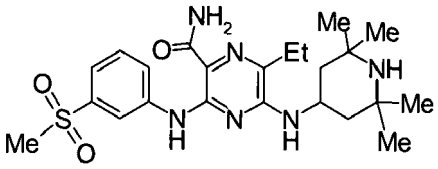
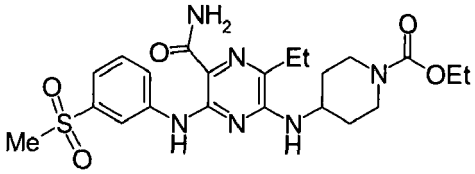
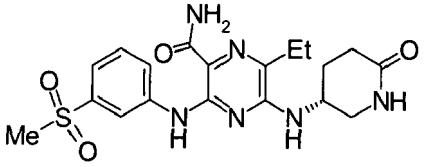
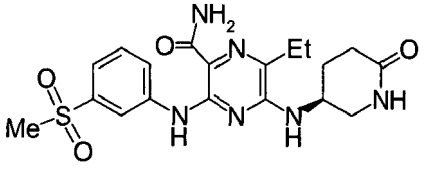
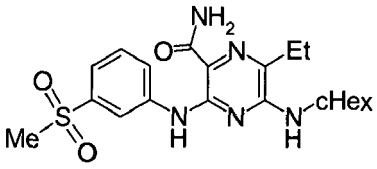
[Table 110] (# not part of the invention)

Ex	Structure
183#	
184# *5	
185# *5	
186#	
187#	
188#	
189#	
190#	
191#	

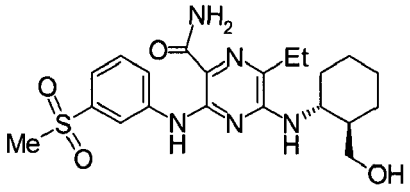
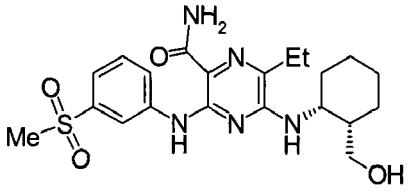
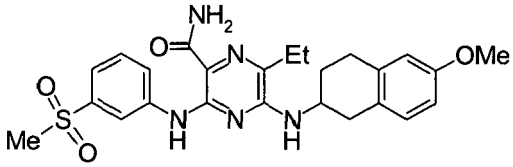
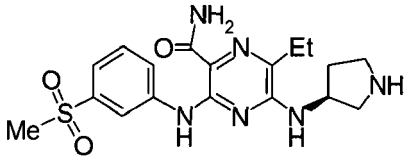
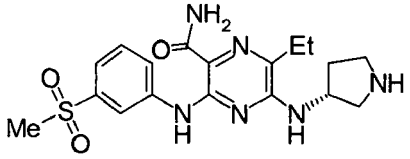
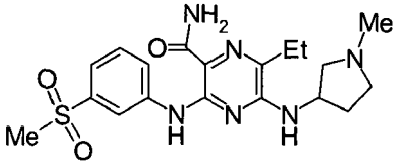
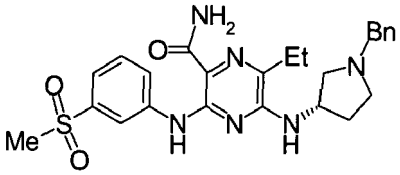
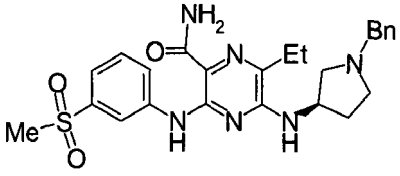
[Table 111] (# not part of the invention)

Ex	Structure
192#	
193#	
194#	
195#	
196#	
197#	
198#	
199#	

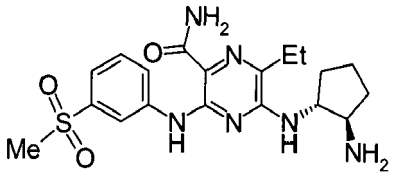
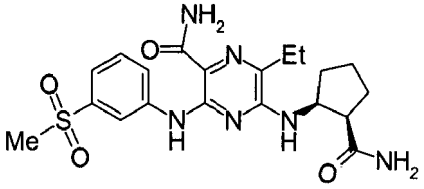
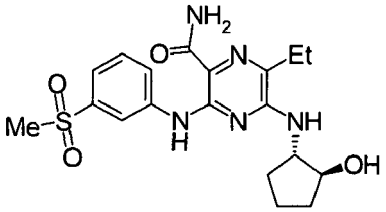
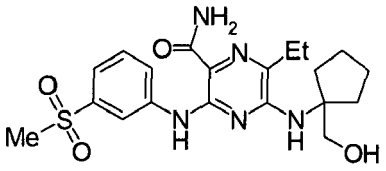
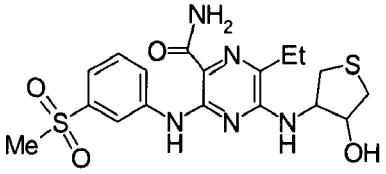
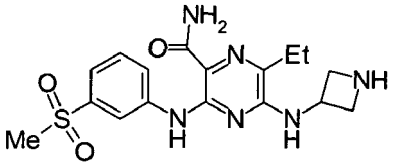
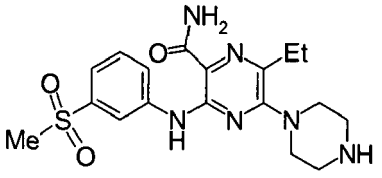
[Table 112] (# not part of the invention)

Ex	Structure
200#	
201#	
202#	
203#	
204#	
205#	
206#	
207#	

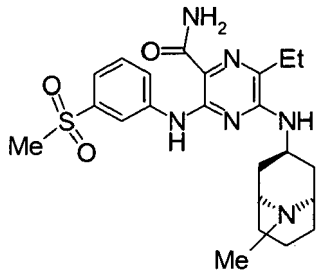
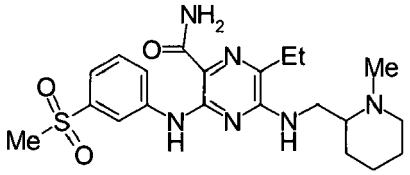
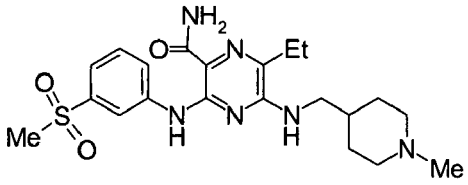
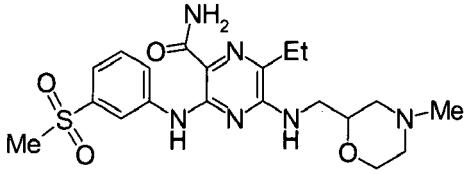
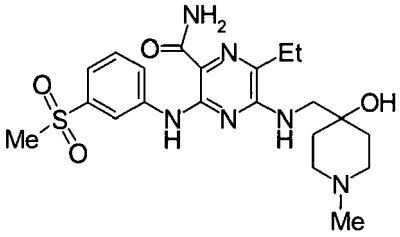
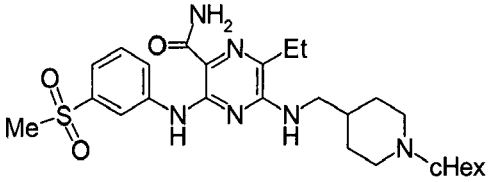
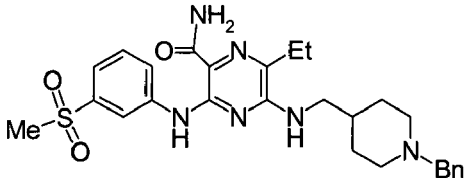
[Table 113] (# not part of the invention)

Ex	Structure
208#	
209#	
210#	
211#	
212#	
213#	
214#	
215#	

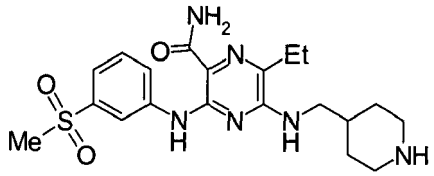
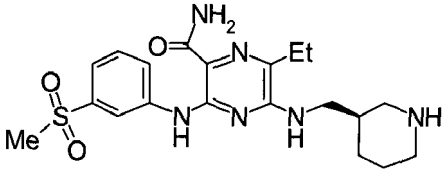
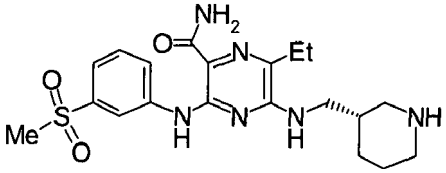
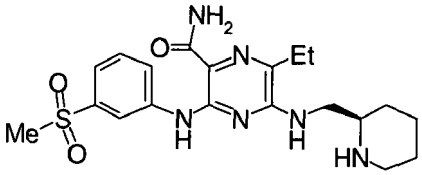
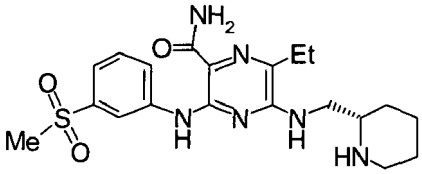
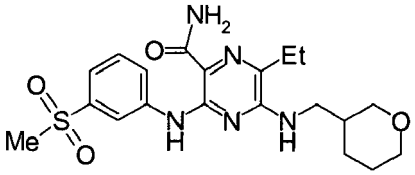
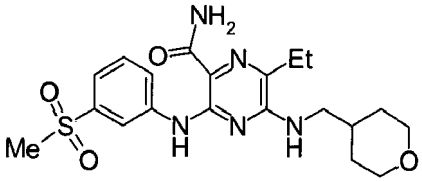
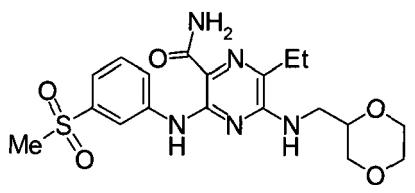
[Table 114] (# not part of the invention)

Ex	Structure
216#	
217#	
218#	
219#	
220#	
221#	
222#	

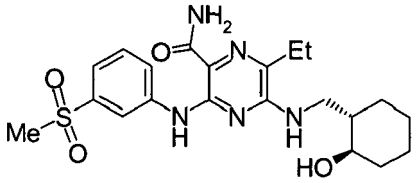
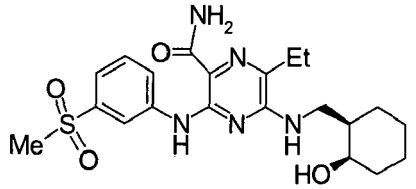
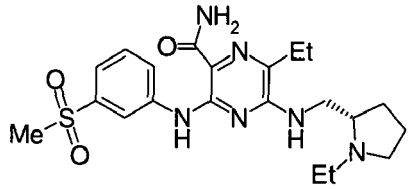
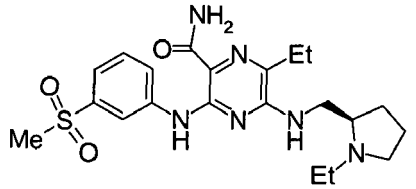
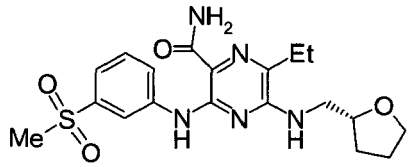
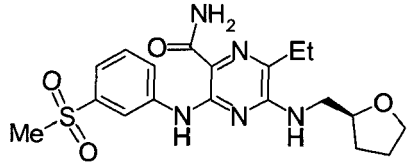
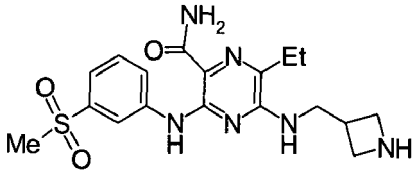
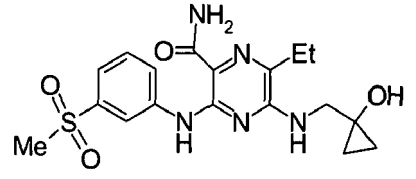
[Table 115] (# not part of the invention)

Ex	Structure
223#	
224#	
225#	
226#	
227#	
228#	
229#	

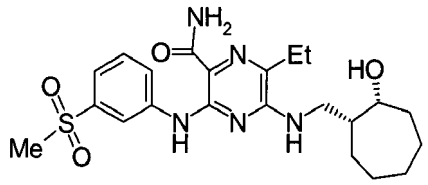
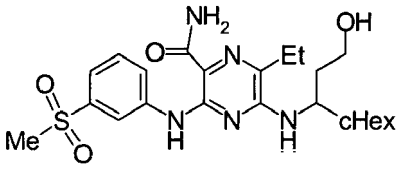
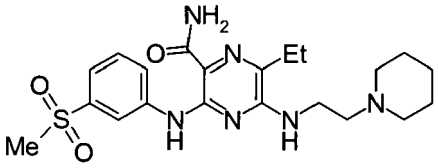
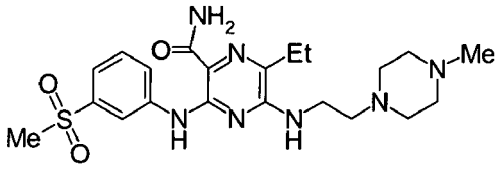
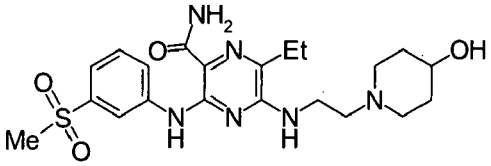
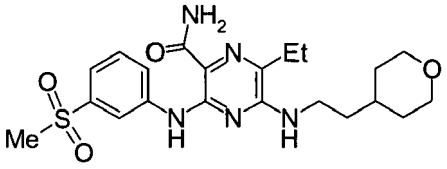
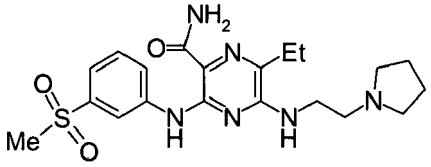
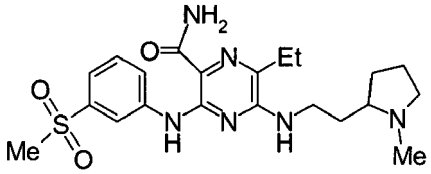
[Table 116] (# not part of the invention)

Ex	Structure
230#	
231#	
232#	
233#	
234#	
235#	
236#	
237#	

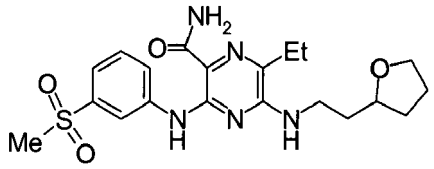
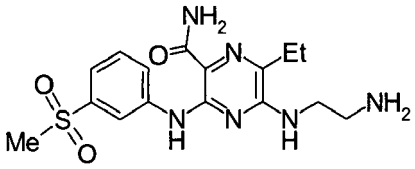
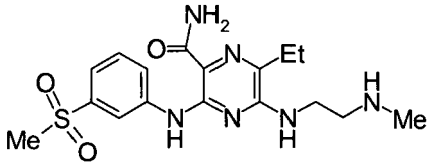
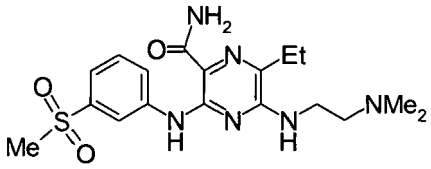
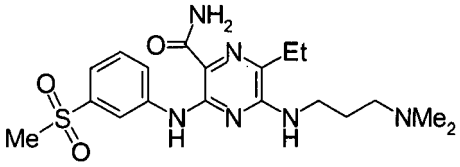
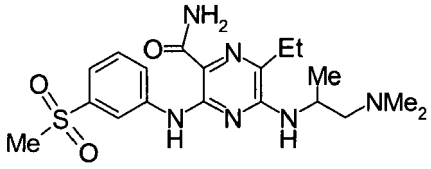
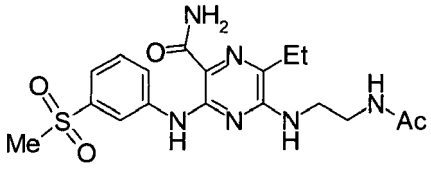
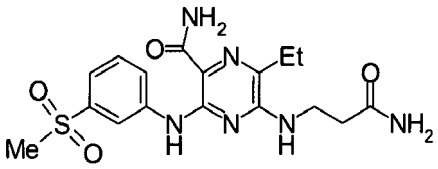
[Table 117] (# not part of the invention)

Ex	Structure
238#	
239#	
240#	
241#	
242#	
243#	
244#	
245#	

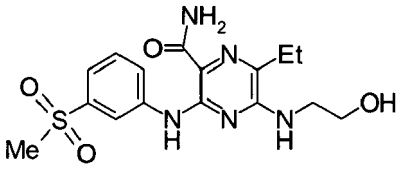
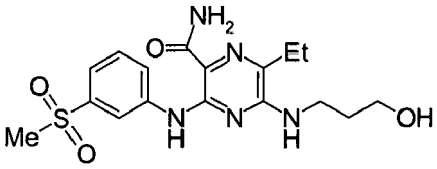
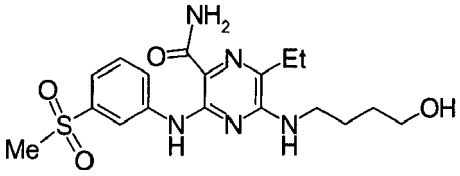
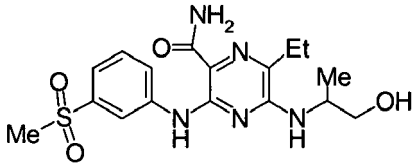
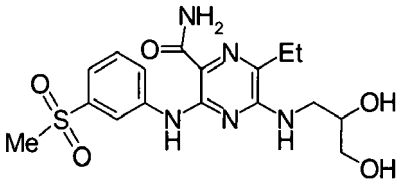
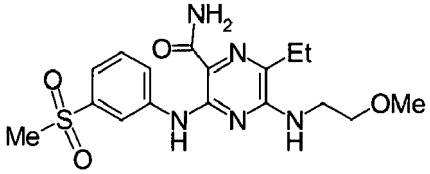
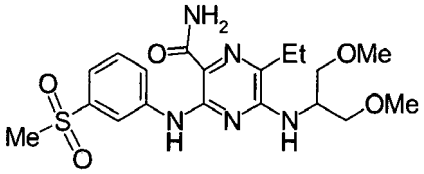
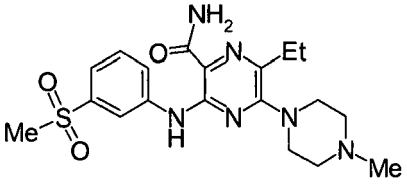
[Table 118] (# not part of the invention)

Ex	Structure
246#	
247#	
248#	
249#	
250#	
251#	
252#	
253#	

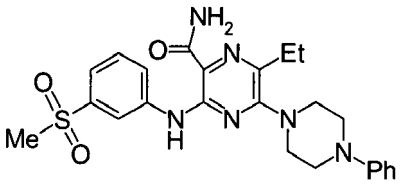
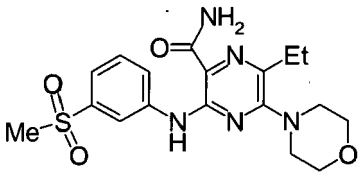
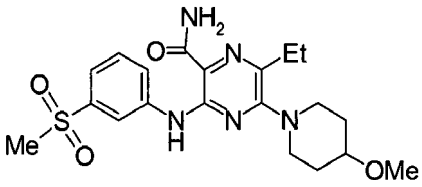
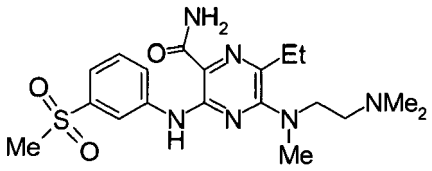
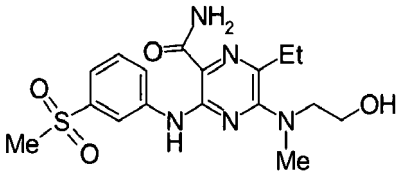
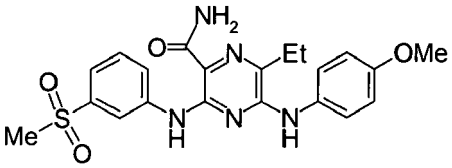
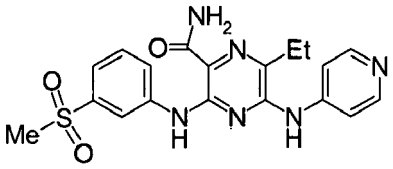
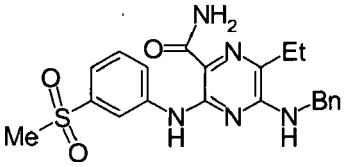
[Table 119] (# not part of the invention)

Ex	Structure
254#	
255#	
256#	
257#	
258#	
259#	
260#	
261#	

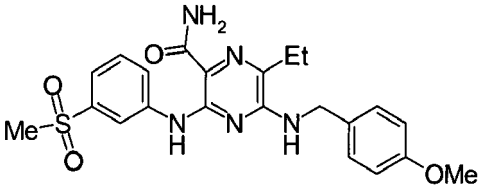
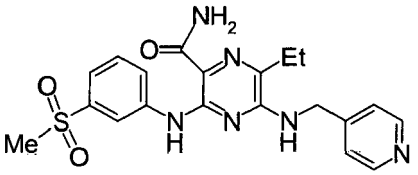
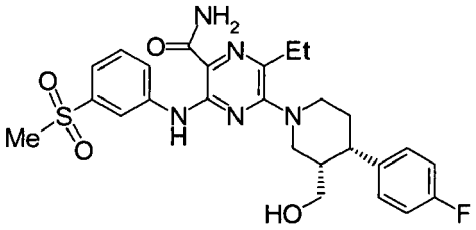
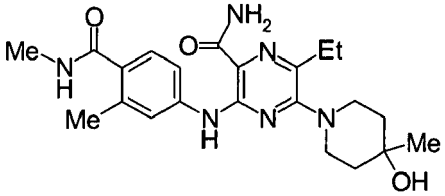
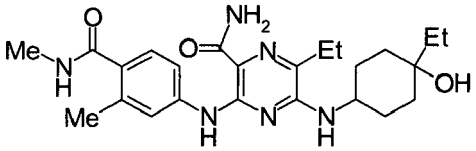
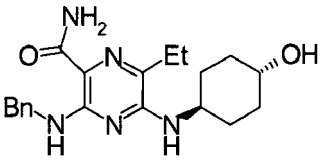
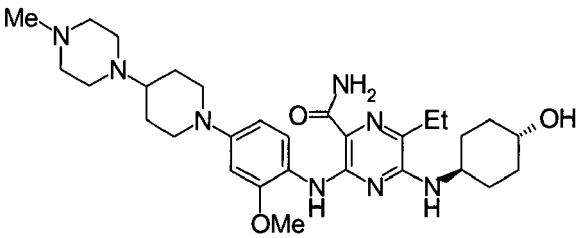
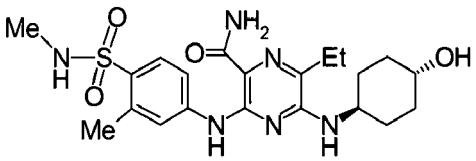
[Table 120] (# not part of the invention)

Ex	Structure
262#	
263#	
264#	
265#	
266#	
267#	
268#	
269#	

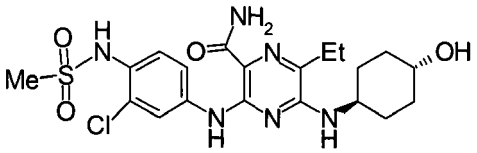
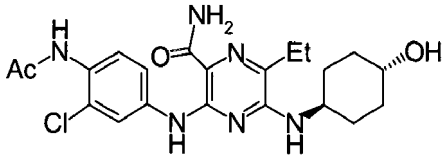
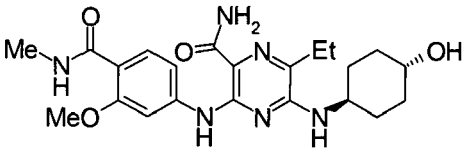
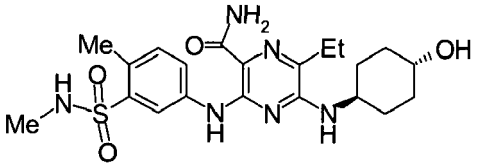
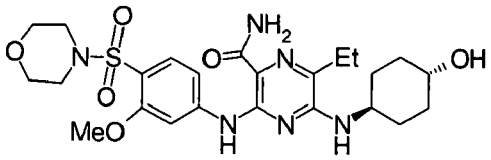
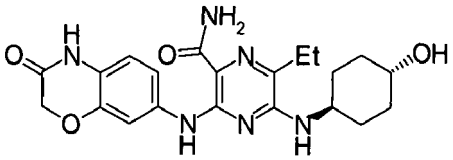
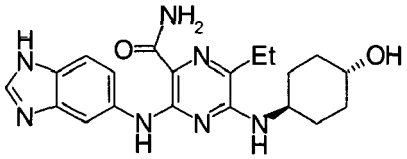
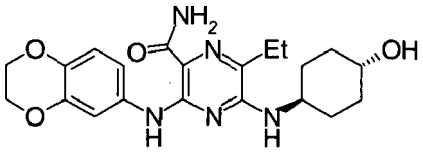
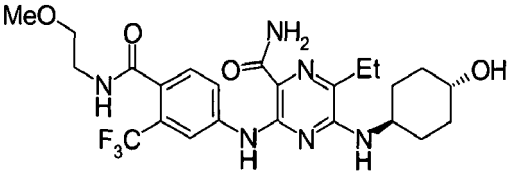
[Table 121] (# not part of the invention)

Ex	Structure
270#	
271#	
272#	
273#	
274#	
275#	
276#	
277#	

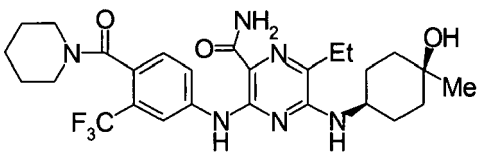
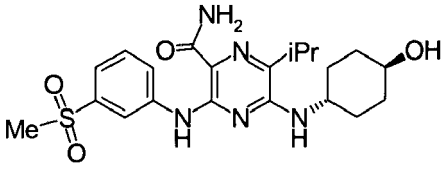
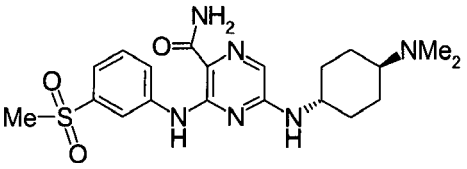
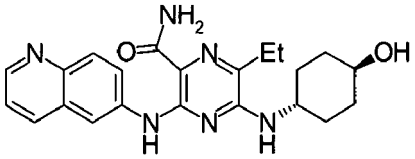
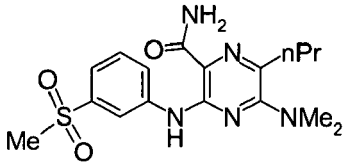
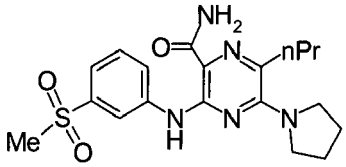
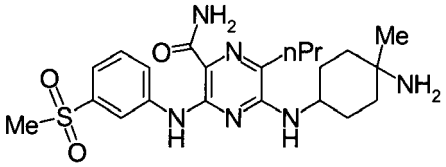
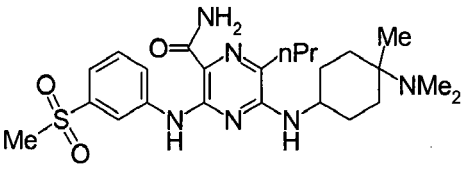
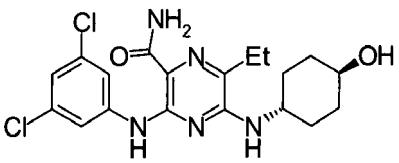
[Table 122] (# not part of the invention)

Ex	Structure
278#	
279#	
280#	
281#	
282# *	
283#	
284#	
285#	

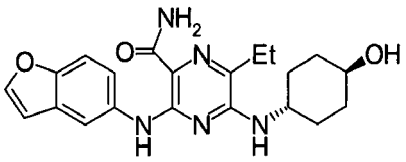
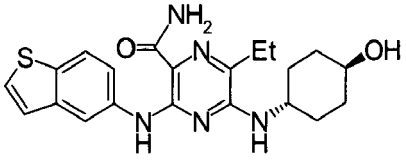
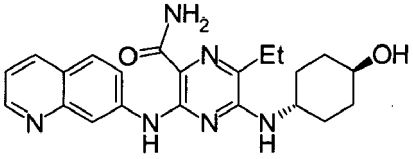
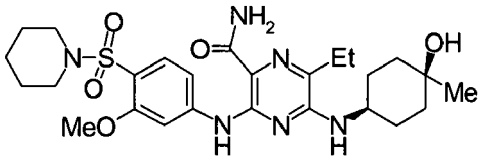
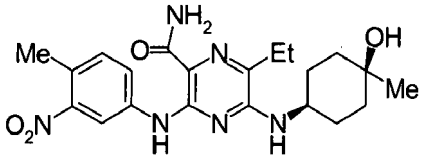
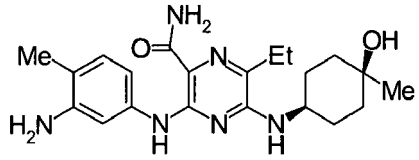
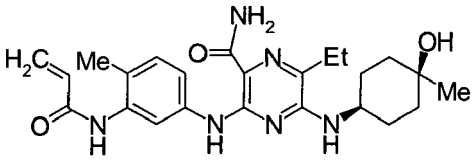
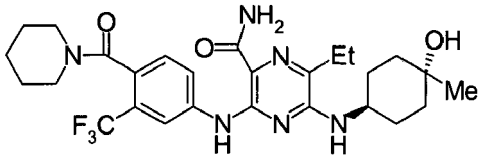
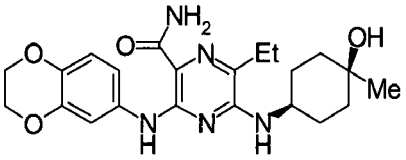
[Table 123] (# not part of the invention)

Ex	Structure
286#	
287#	
288#	
289#	
290#	
291#	
292#	
293#	
294#	

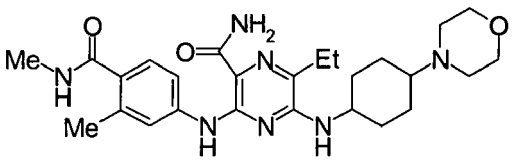
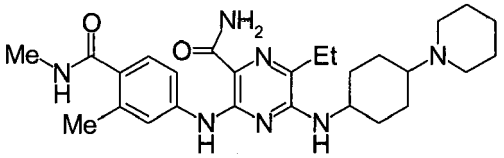
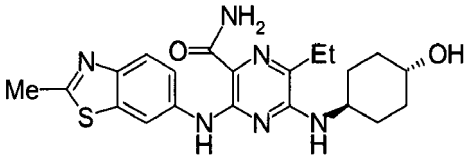
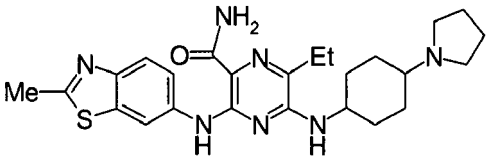
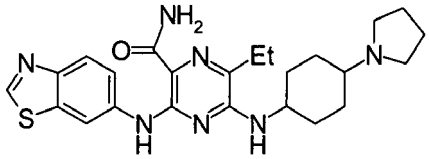
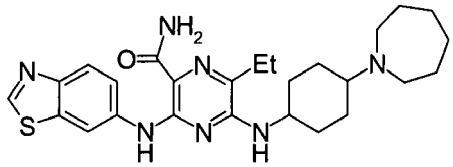
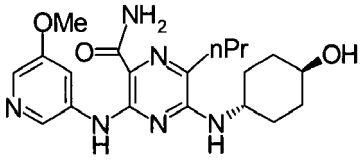
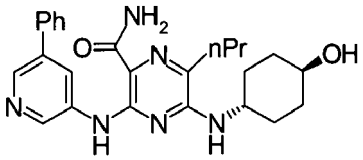
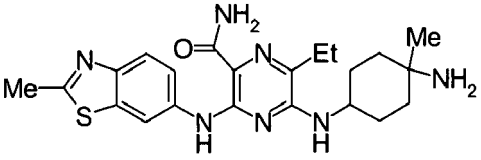
[Table 124] (# not part of the invention)

Ex	Structure
295#	
296#	
297#	
298#	
299#	
300#	
301# *	
302# *	
303#	

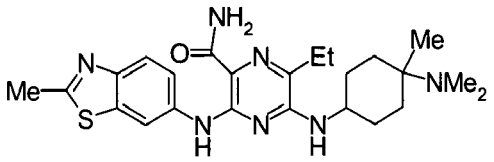
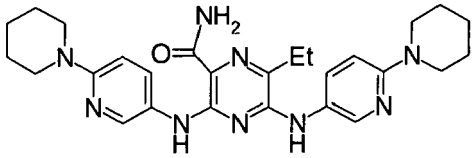
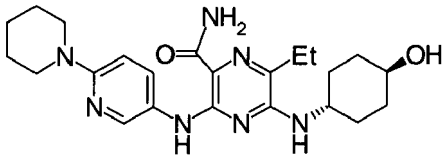
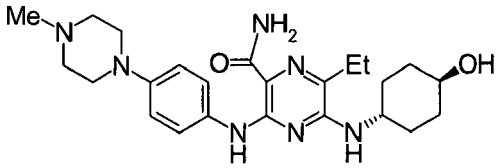
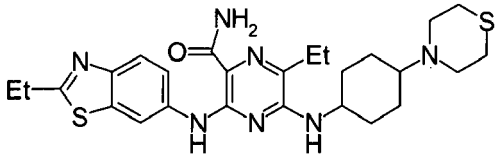
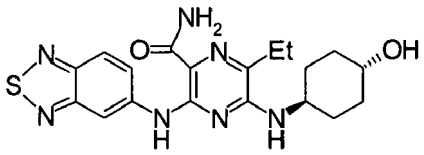
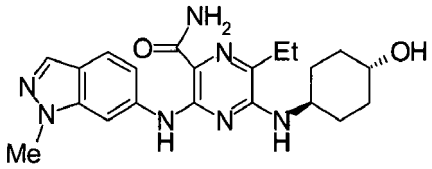
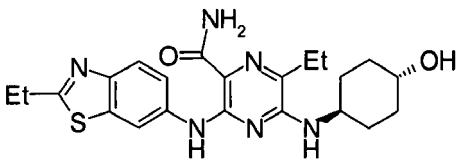
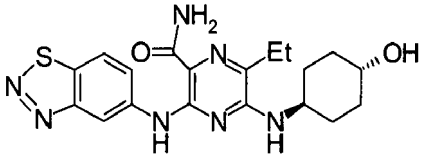
[Table 125] (# not part of the invention)

Ex	Structure
304#	
305#	
306#	
307#	
308#	
309#	
310#	
311#	
312#	

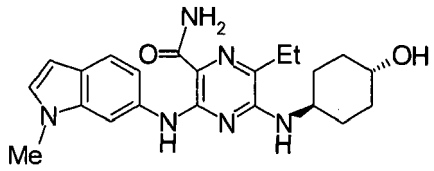
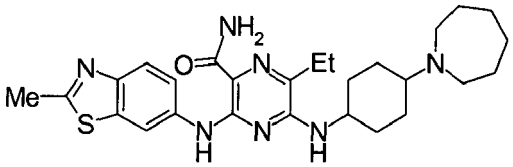
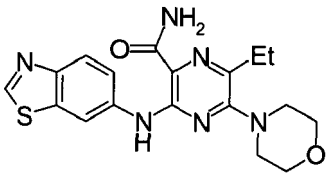
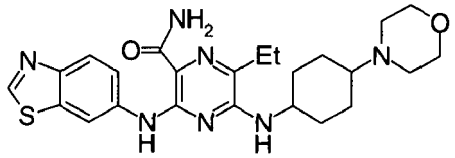
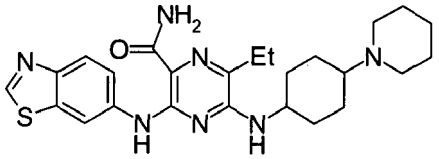
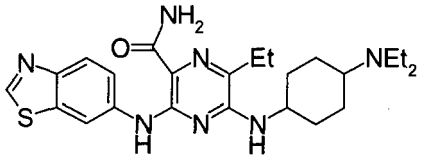
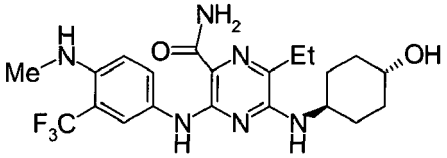
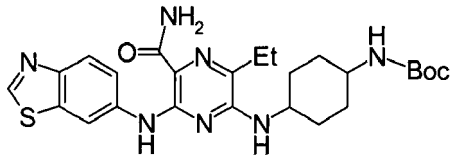
[Table 126] (# not part of the invention)

Ex	Structure
313#	
314# *	
315#	
316# *	
317# *	
318# *	
319#	
320#	
321#	

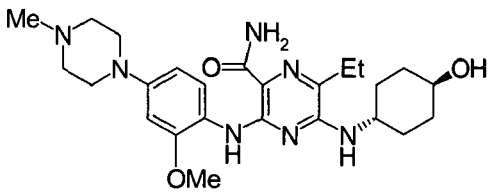
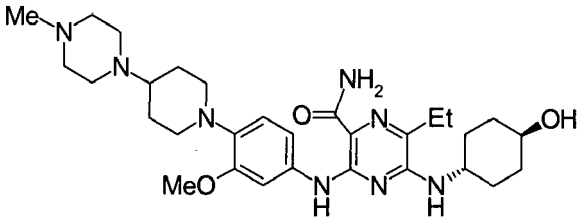
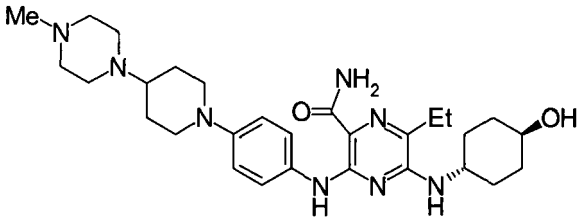
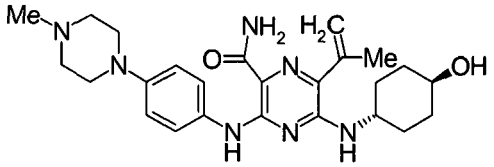
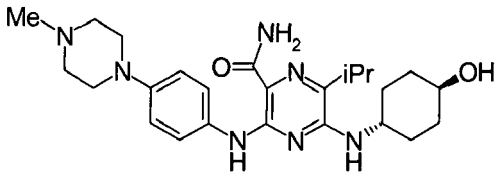
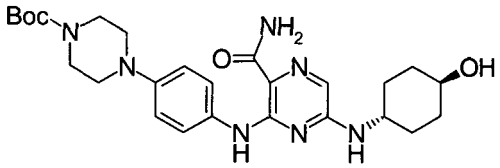
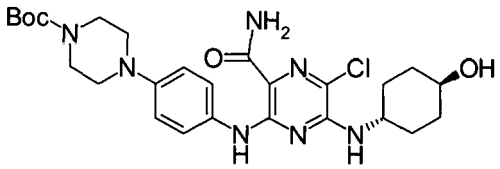
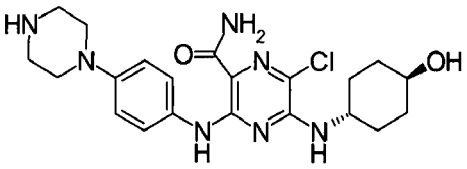
[Table 127] (# not part of the invention)

Ex	Structure
322#	
323#	
324#	
325	
326#	
327#	
328#	
329#	
330#	

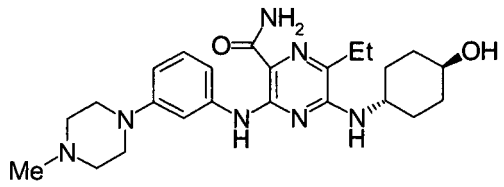
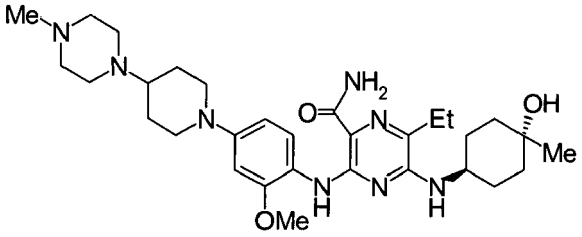
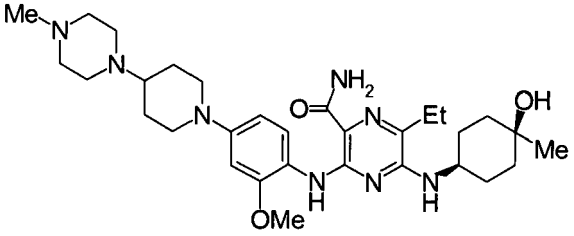
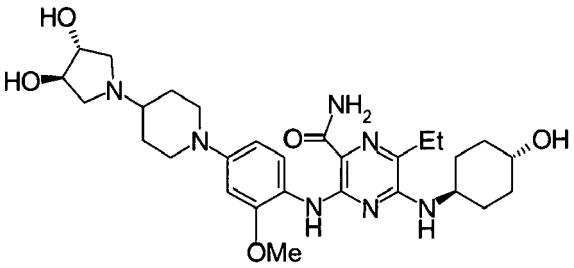
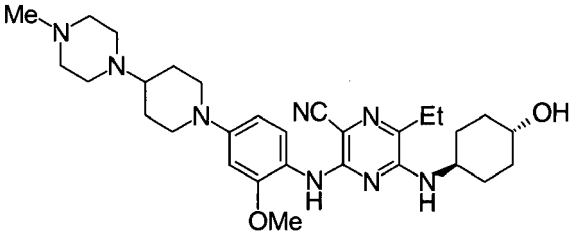
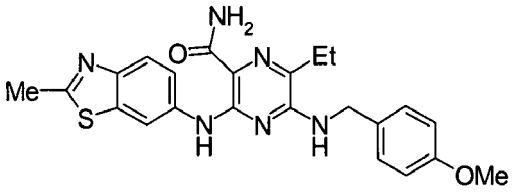
[Table 128] (# not part of the invention)

Ex	Structure
331#	
332#	
333#	
334#	
335#	
336# *	
337#	
338#	

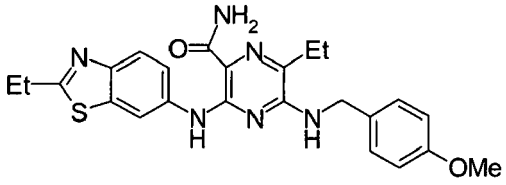
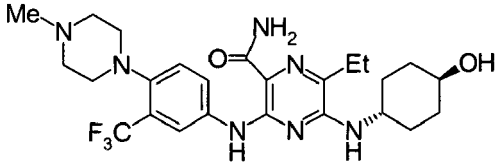
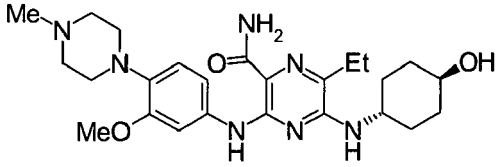
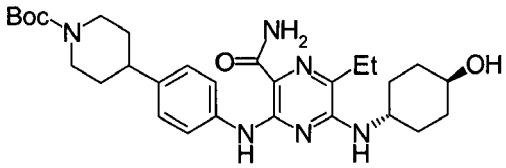
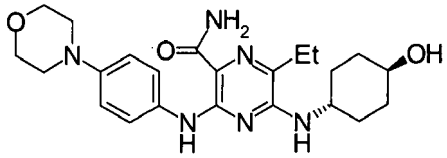
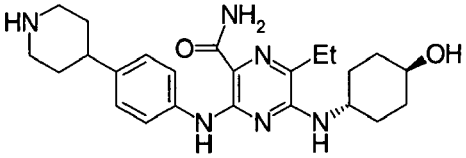
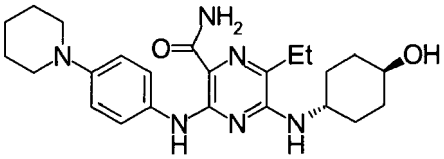
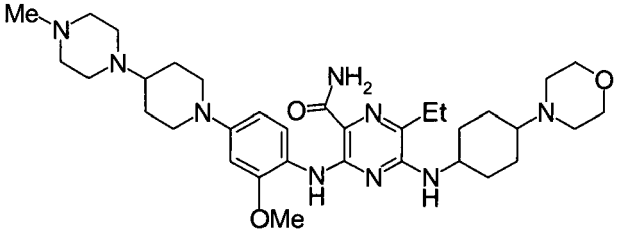
[Table 129] (# not part of the invention)

Ex	Structure
339#	
340	
341	
342#	
343	
344#	
345#	
346	

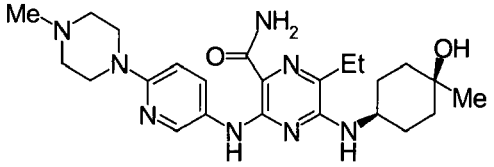
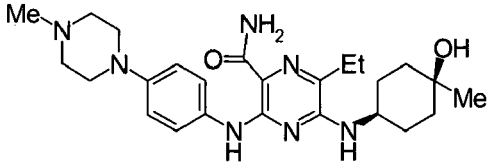
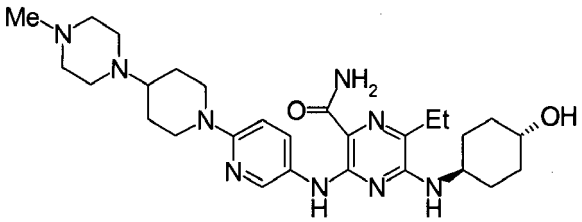
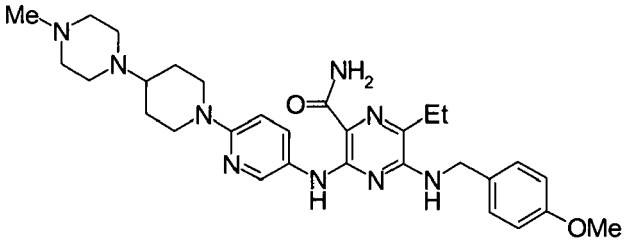
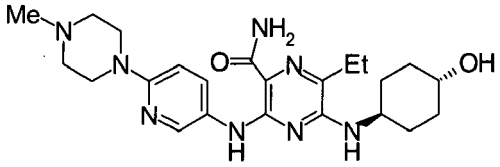
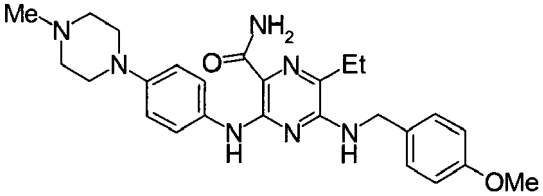
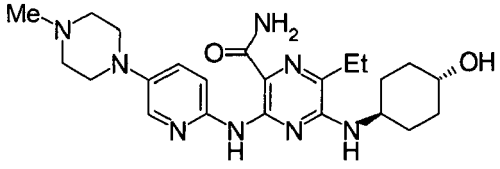
[Table 130] (# not part of the invention)

Ex	Structure
347#	
348#	
349#	
350#	
351#	
352#	

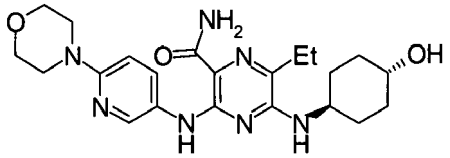
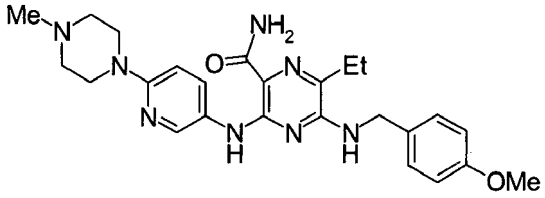
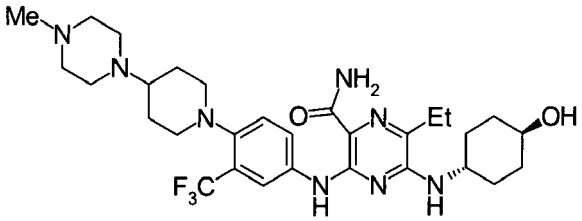
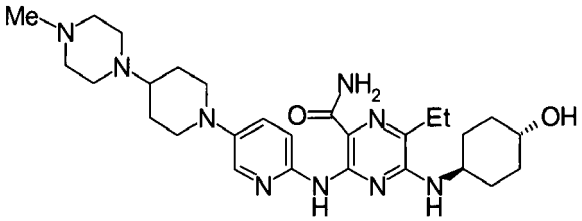
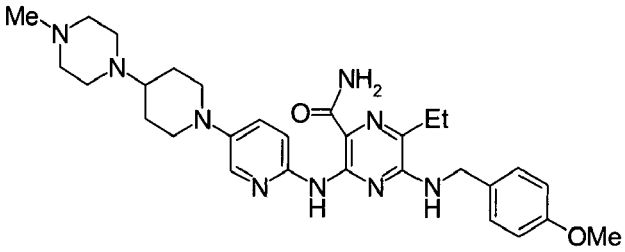
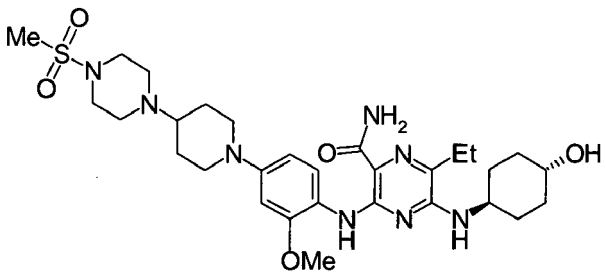
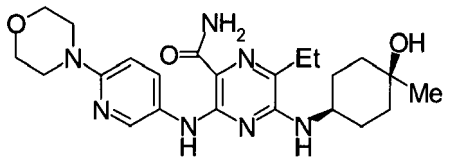
[Table 131] (# not part of the invention)

Ex	Structure
353#	
354	
355	
356#	
357	
358	
359	
360#	

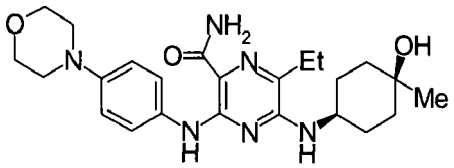
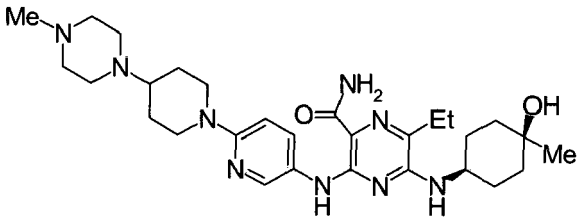
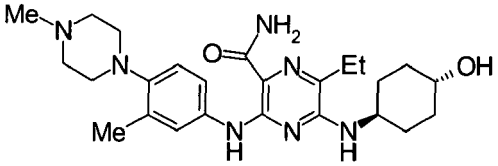
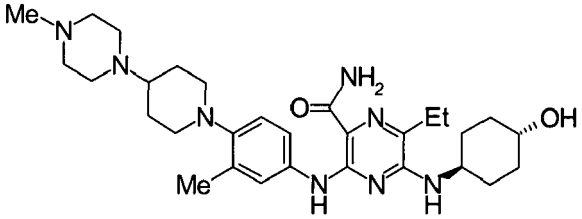
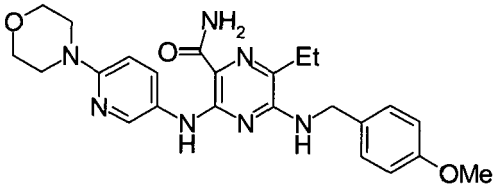
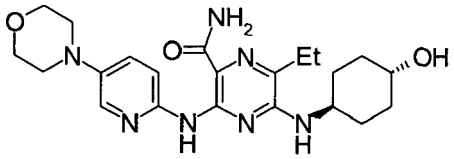
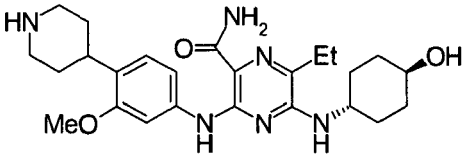
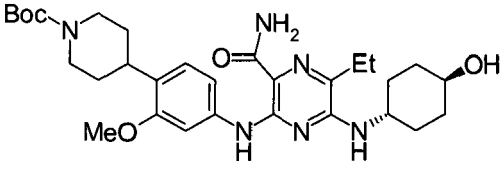
[Table 132] (# not part of the invention)

Ex	Structure
361#	
362	
363#	
364#	
365#	
366#	
367#	

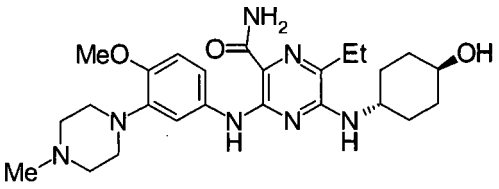
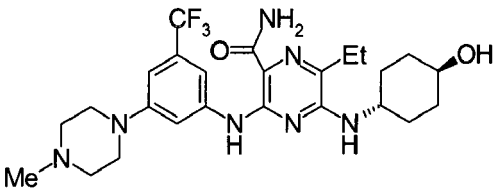
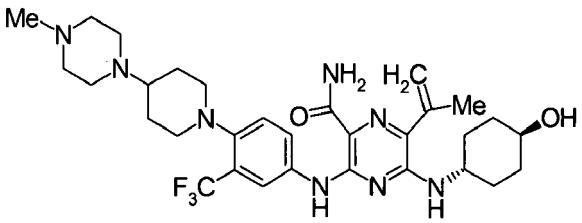
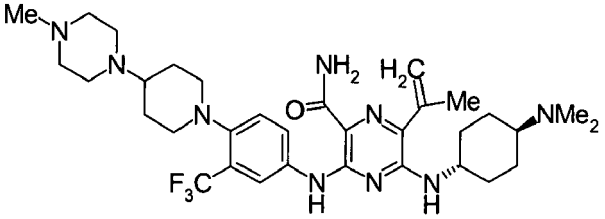
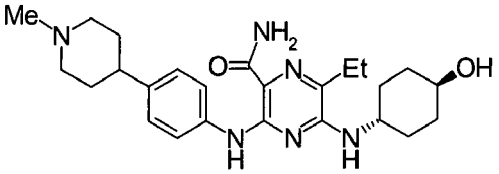
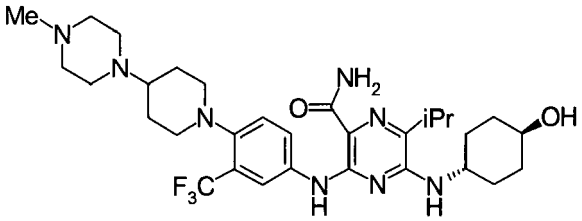
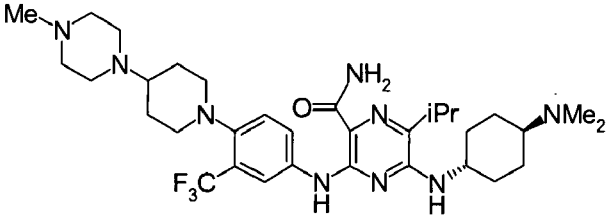
[Table 133] (# not part of the invention)

Ex	Structure
368#	
369#	
370	
371#	
372#	
373#	
374#	

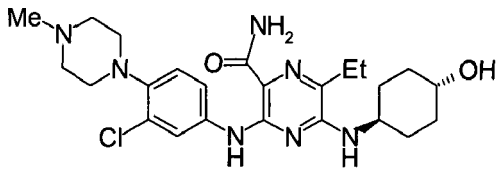
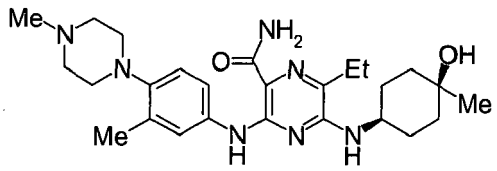
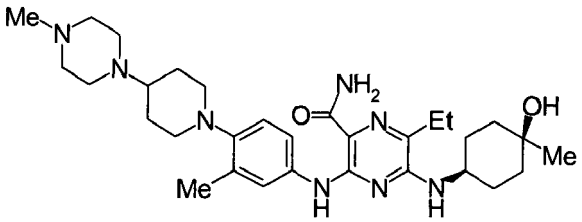
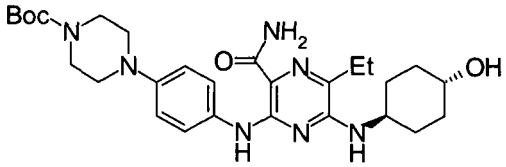
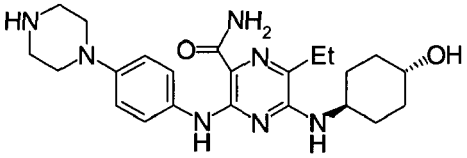
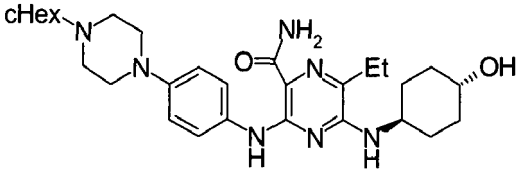
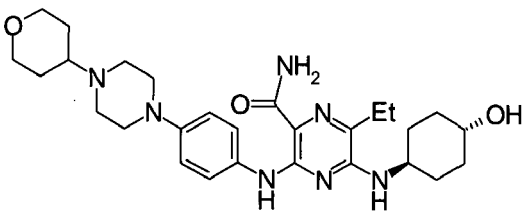
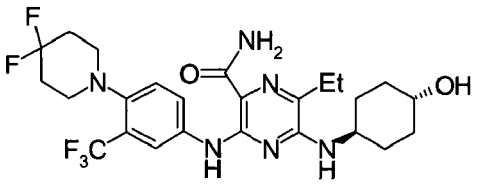
[Table 134] (# not part of the invention)

Ex	Structure
375	
376#	
377	
378	
379#	
380#	
381	
382#	

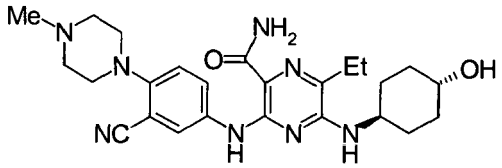
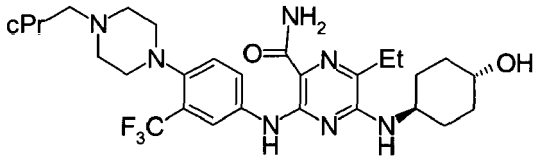
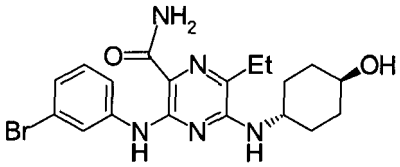
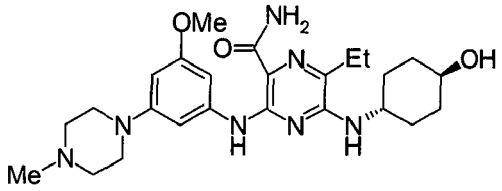
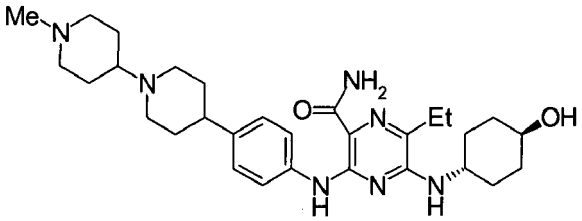
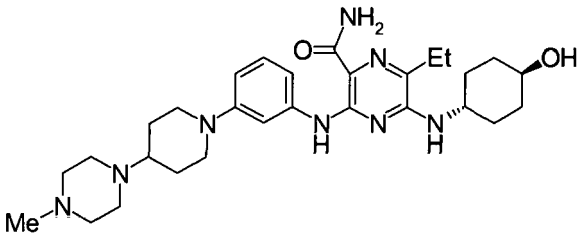
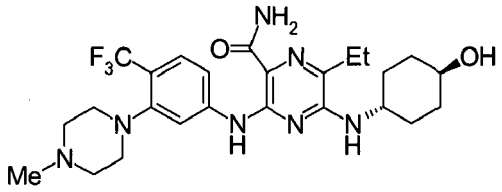
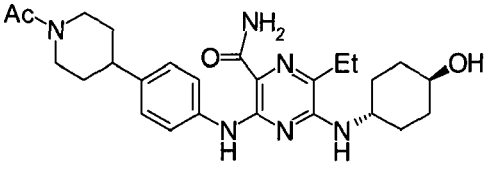
[Table 135] (# not part of the invention)

Ex	Structure
383#	
384#	
385#	
386#	
387	
388	
389	

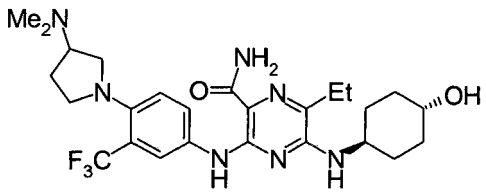
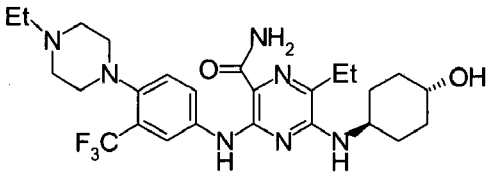
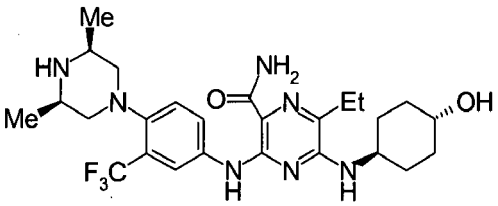
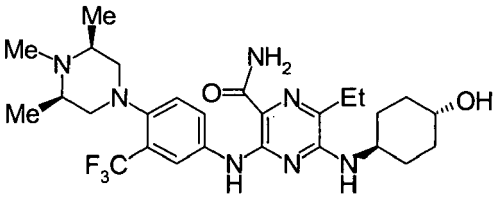
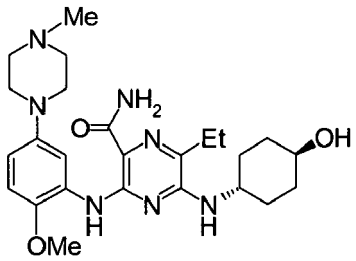
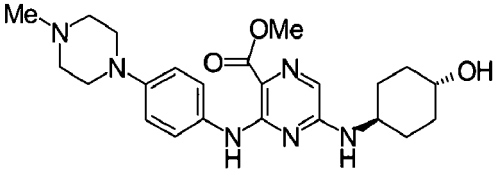
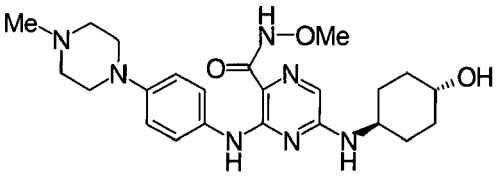
[Table 136] (# not part of the invention)

Ex	Structure
390	
391	
392	
393#	
394	
395#	
396	
397	

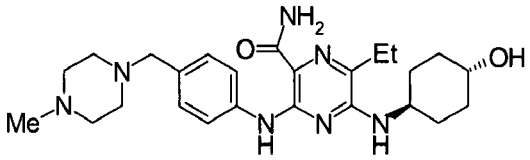
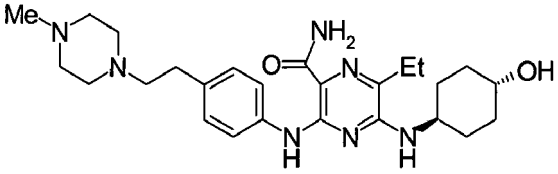
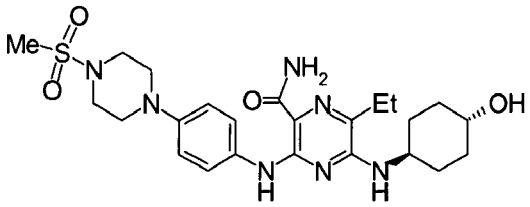
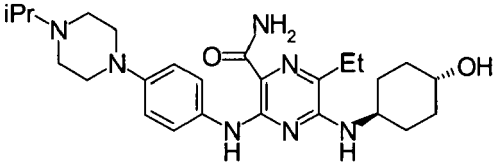
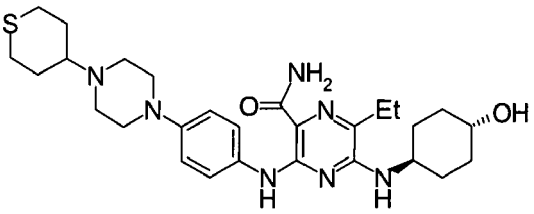
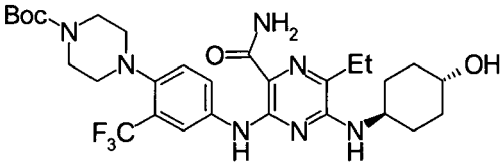
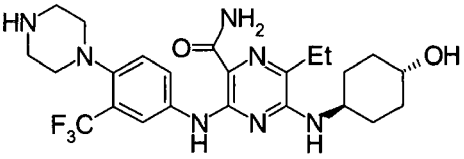
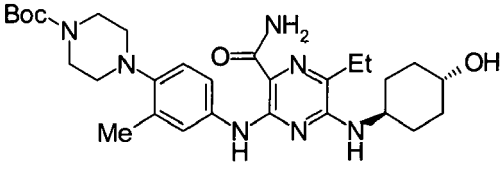
[Table 137] (# not part of the invention)

Ex	Structure
398#	
399#	
400#	
401#	
402	
403#	
404#	
405#	

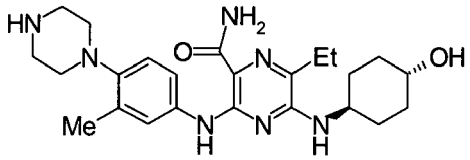
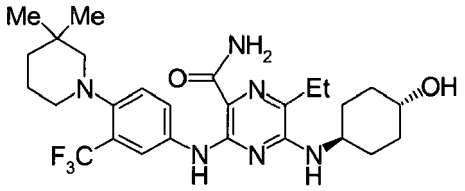
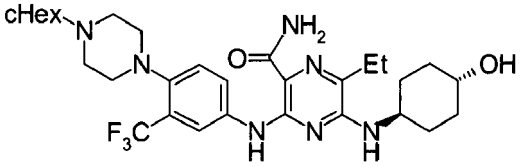
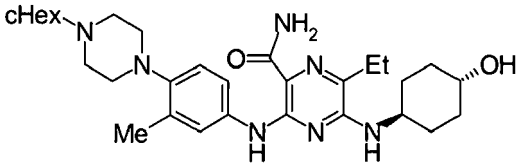
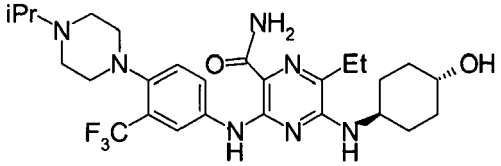
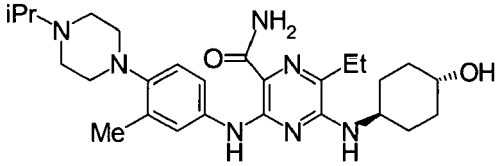
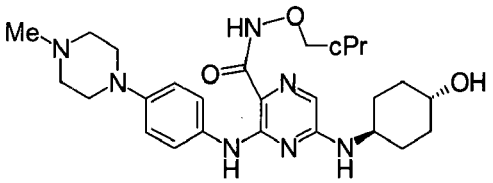
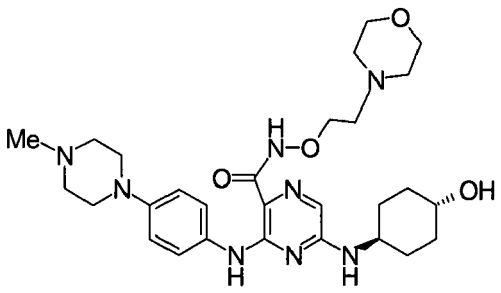
[Table 138] (# not part of the invention)

Ex	Structure
406#	
407	
408	
409	
410#	
411#	
412#	

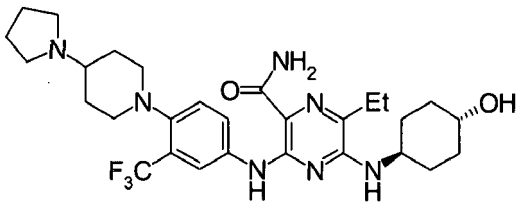
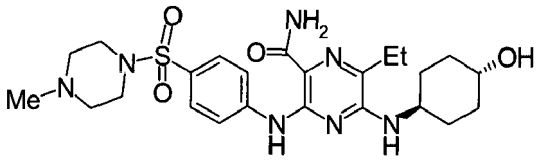
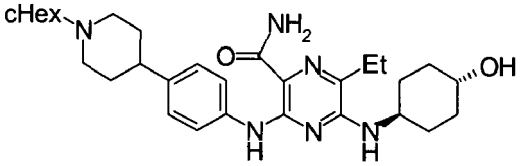
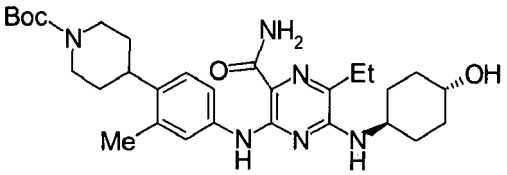
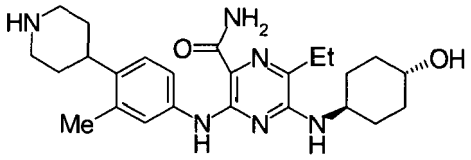
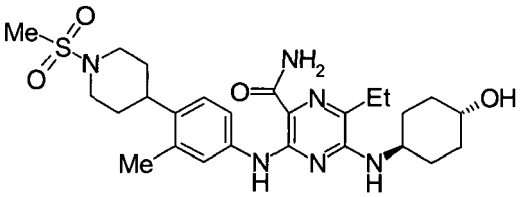
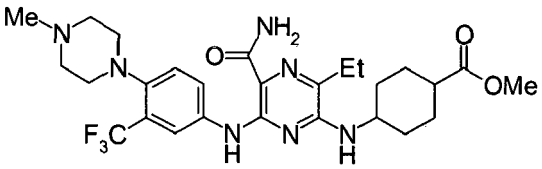
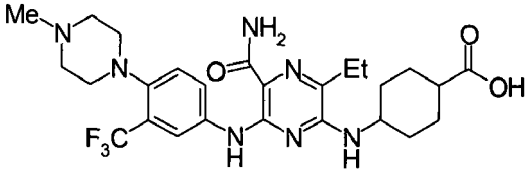
[Table 139] (# not part of the invention)

Ex	Structure
413#	
414#	
415#	
416	
417	
418#	
419	
420#	

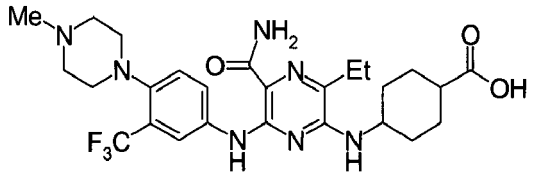
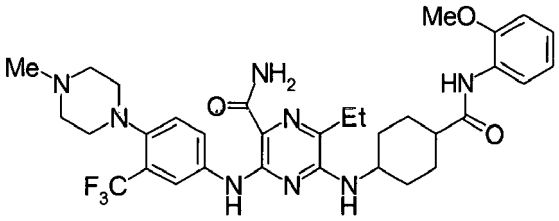
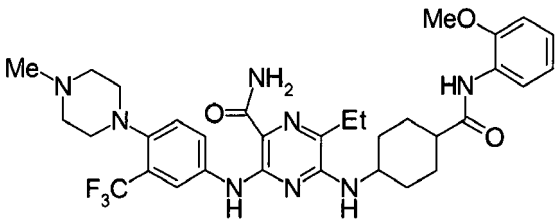
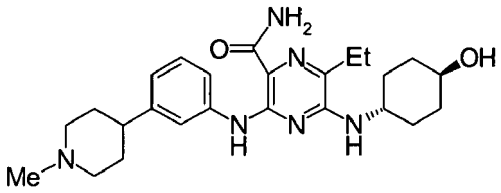
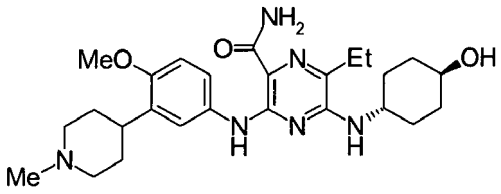
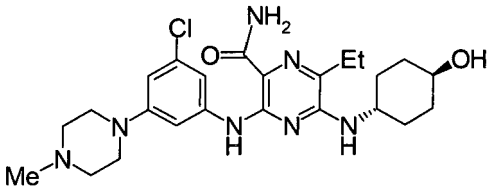
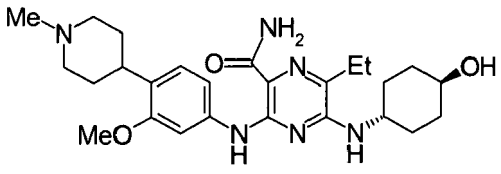
[Table 140] (# not part of the invention)

Ex	Structure
421	
422	
423#	
424#	
425	
426	
427#	
428#	

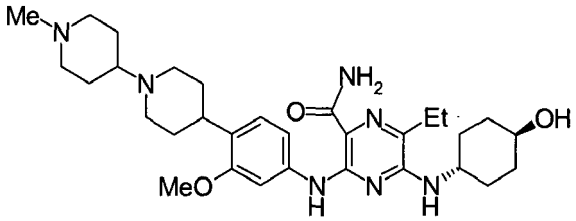
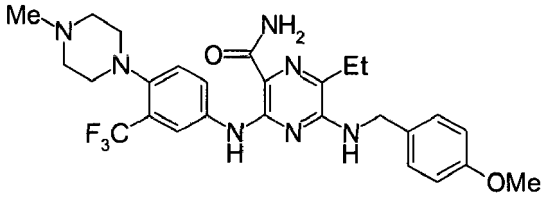
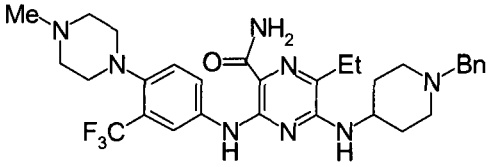
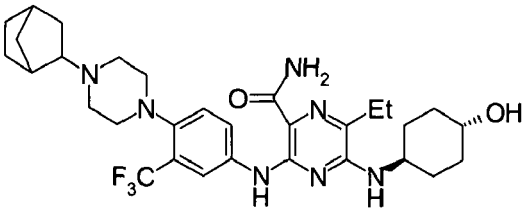
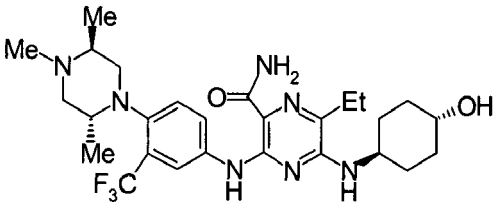
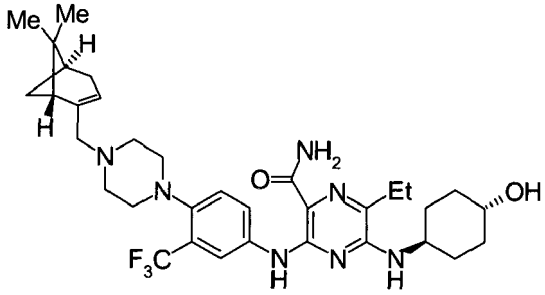
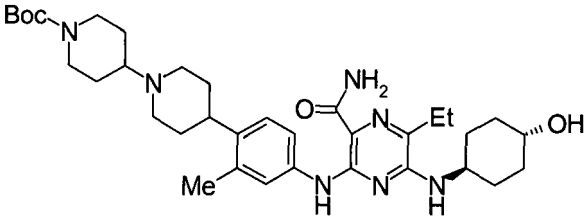
[Table 141] (# not part of the invention)

Ex	Structure
429	
430#	
431#	
432#	
433	
434#	
435	
436 *6	

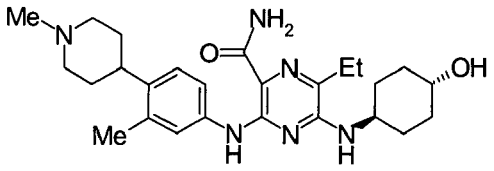
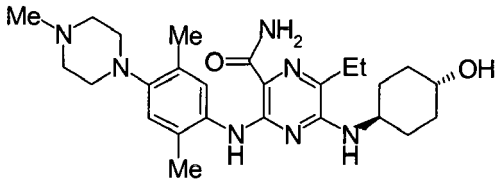
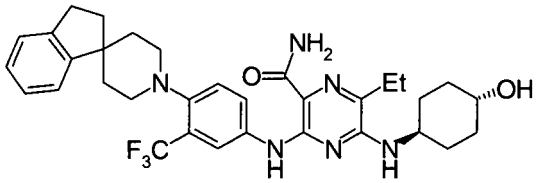
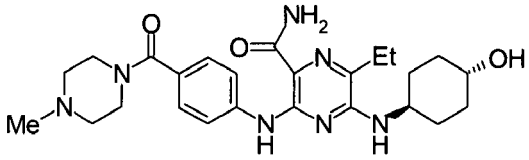
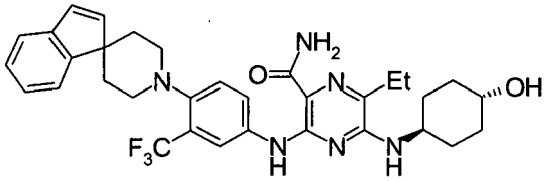
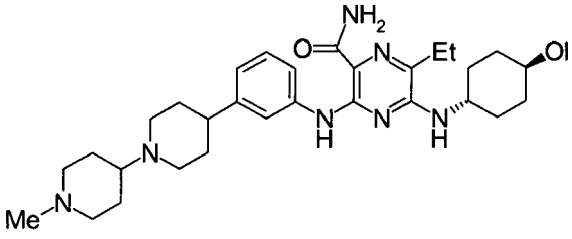
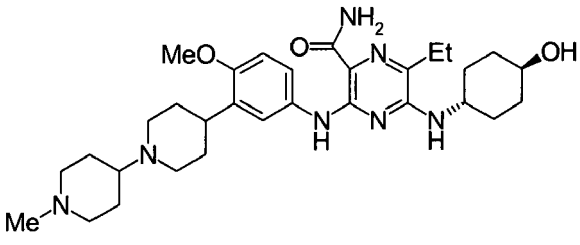
[Table 142] (# not part of the invention)

Ex	Structure
437 *6	
438 *7	
439 *7	
440#	
441#	
442#	
443	

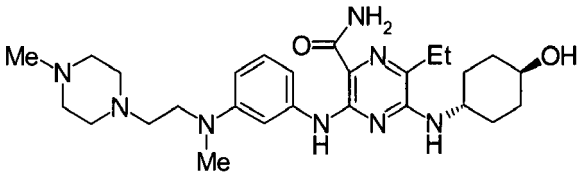
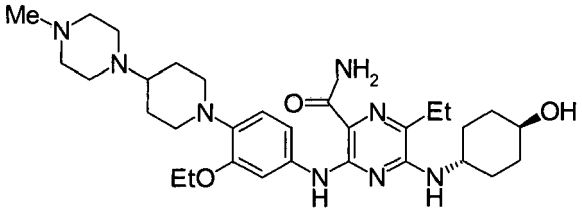
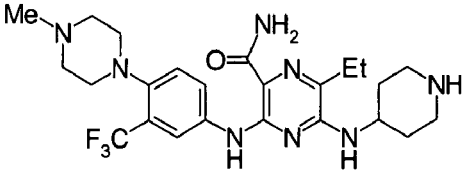
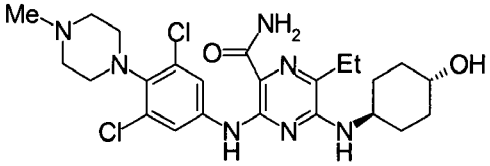
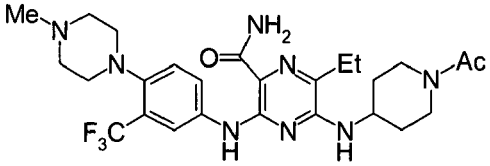
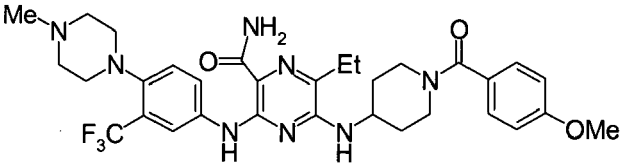
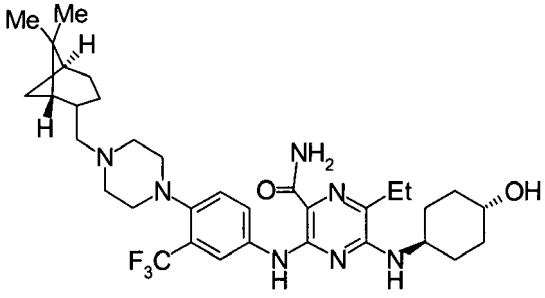
[Table 143] (# not part of the invention)

Ex	Structure
444	
445#	
446	
447#	
448	
449#	
450#	

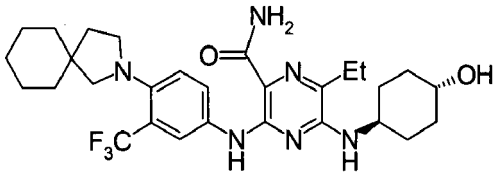
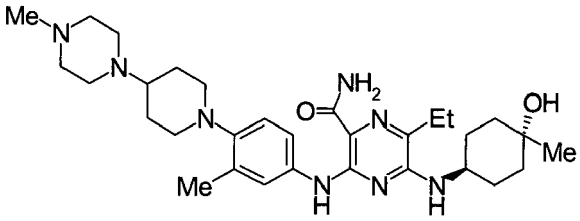
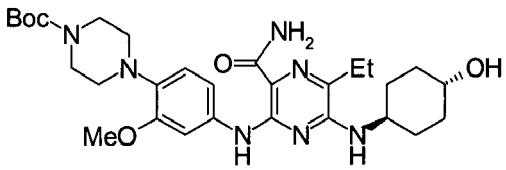
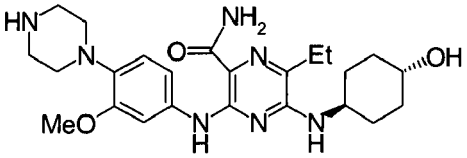
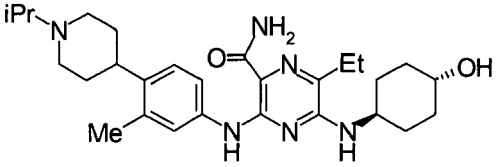
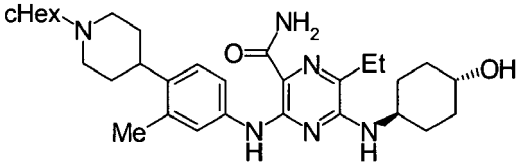
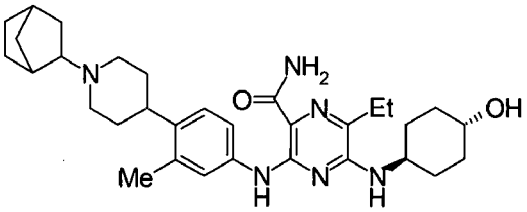
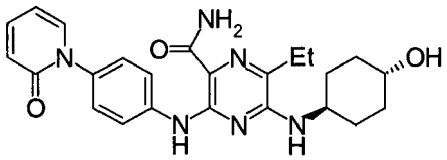
[Table 144] (# not part of the invention)

Ex	Structure
451	
452#	
453#	
454#	
455#	
456#	
457#	

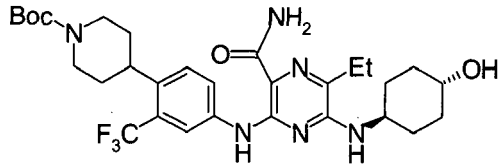
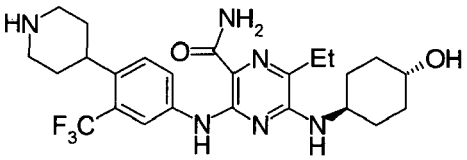
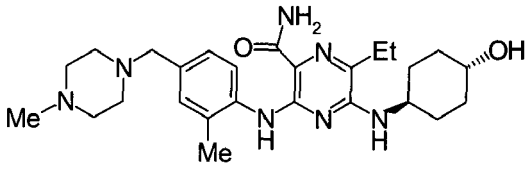
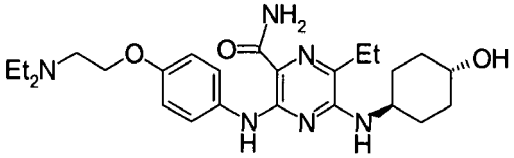
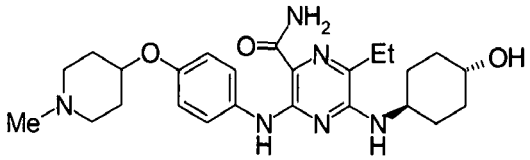
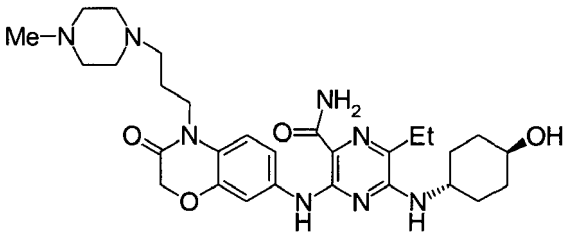
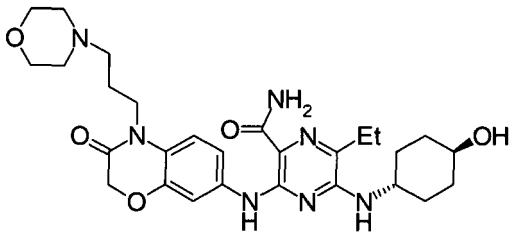
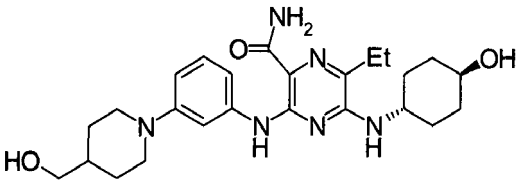
[Table 145] (# not part of the invention)

Ex	Structure
458#	
459	
460	
461#	
462	
463	
464#	

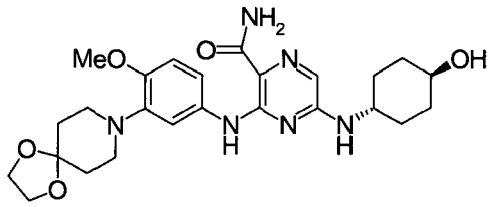
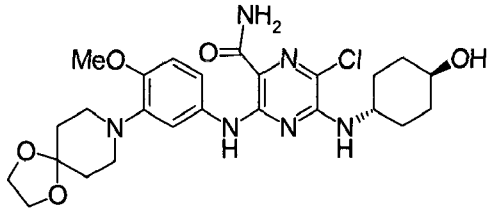
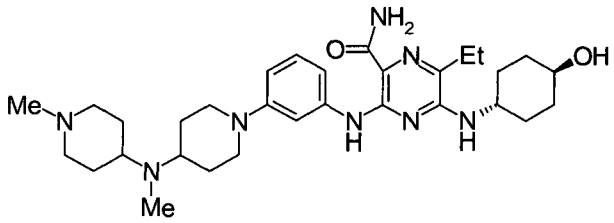
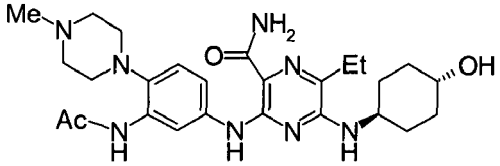
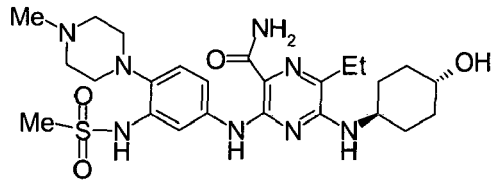
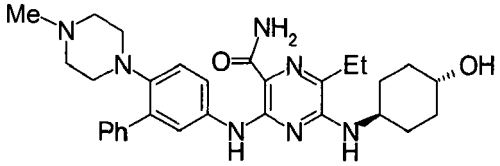
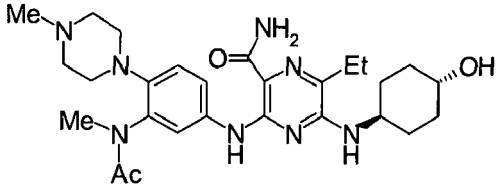
[Table 146] (# not part of the invention)

Ex	Structure
465#	
466	
467#	
468	
469	
470#	
471#	
472#	

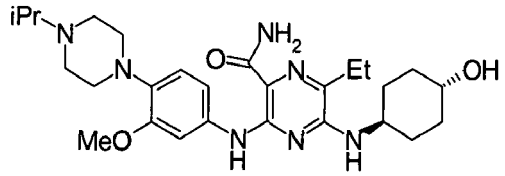
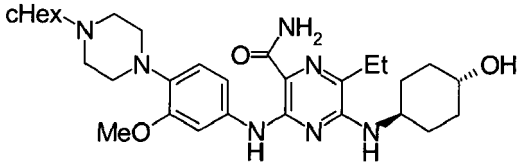
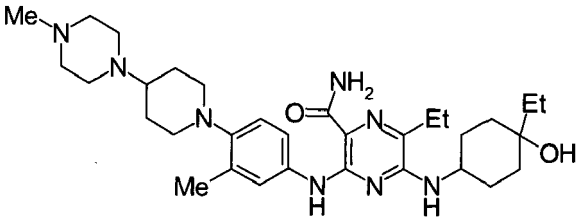
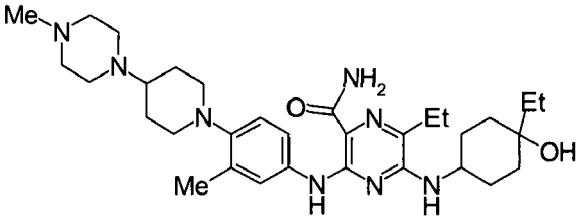
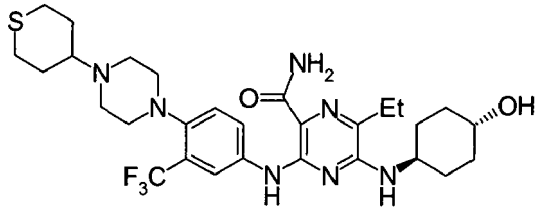
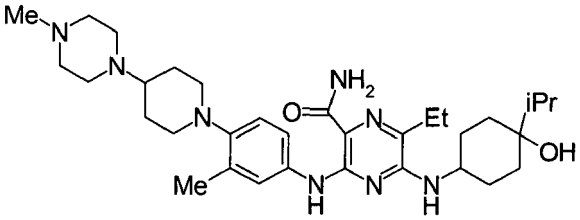
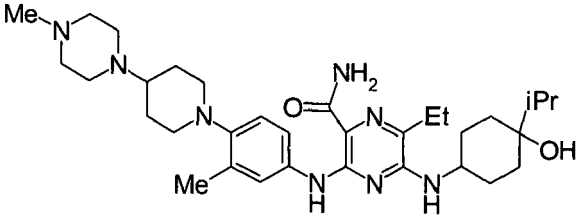
[Table 147] (# not part of the invention)

Ex	Structure
473#	
474	
475#	
476#	
477#	
478#	
479#	
480#	

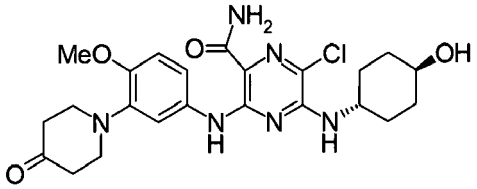
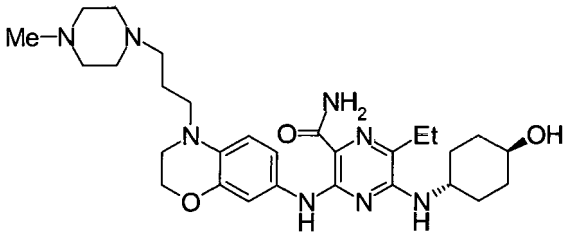
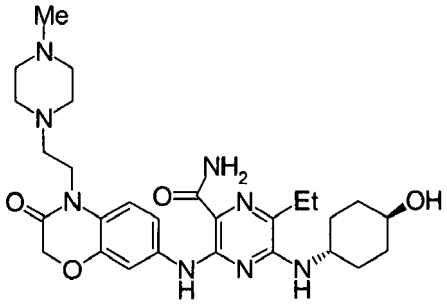
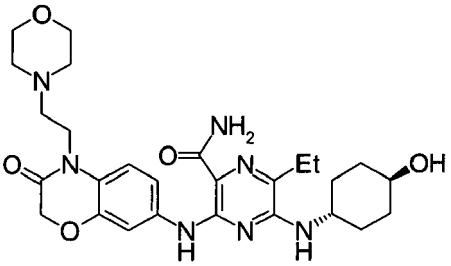
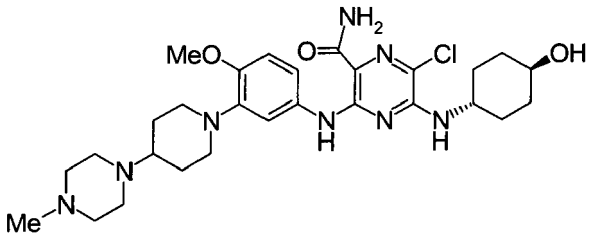
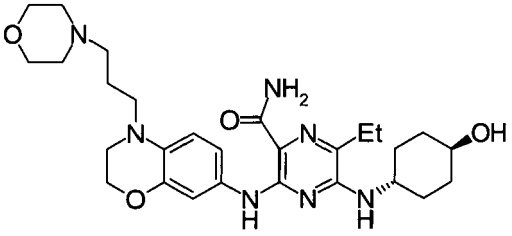
[Table 148] (# not part of the invention)

Ex	Structure
481#	
482#	
483#	
484#	
485#	
486#	
487#	

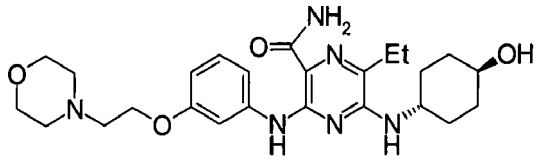
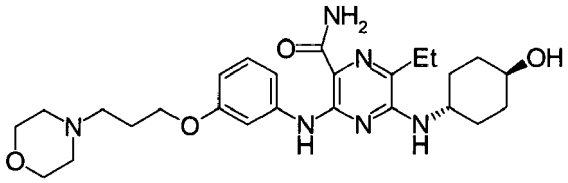
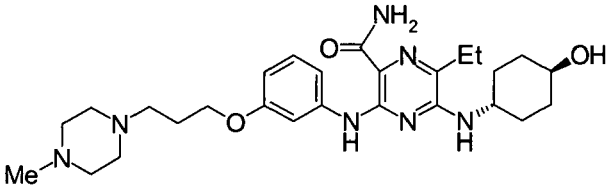
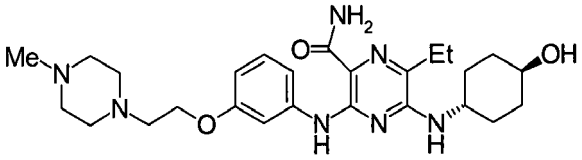
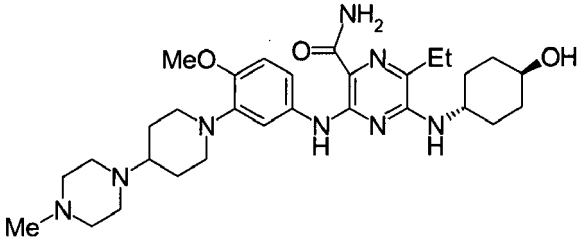
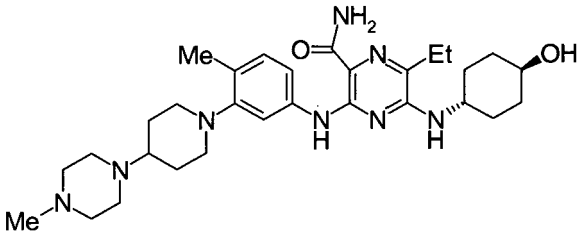
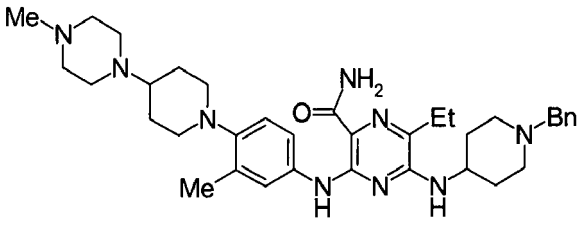
[Table 149] (# not part of the invention)

Ex	Structure
488	
489#	
490 *8	
491 *8	
492	
493 *9	
494 *9	

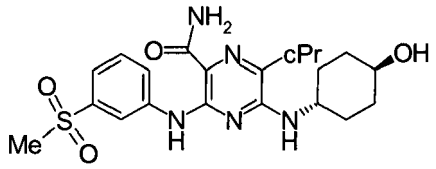
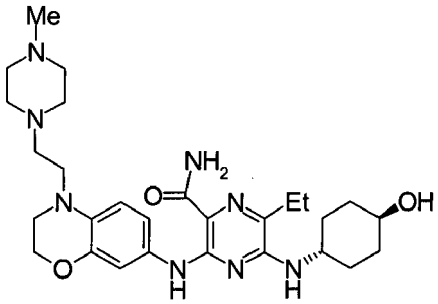
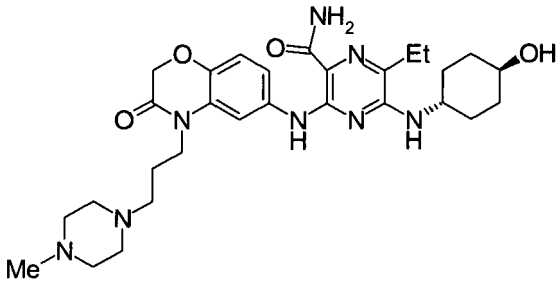
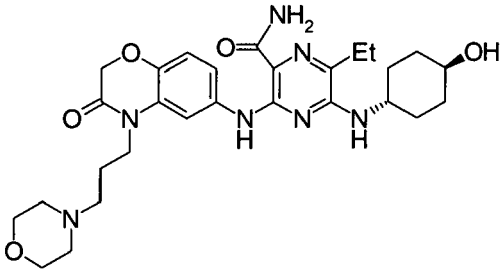
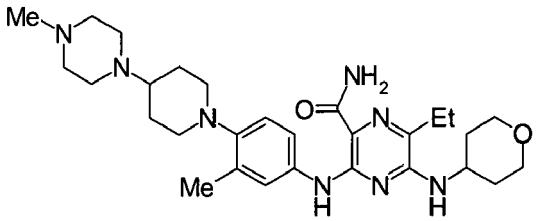
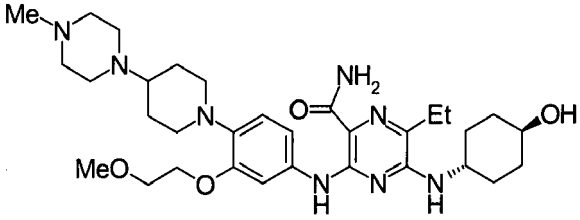
[Table 150] (# not part of the invention)

Ex	Structure
495#	
496#	
497#	
498#	
499#	
500#	

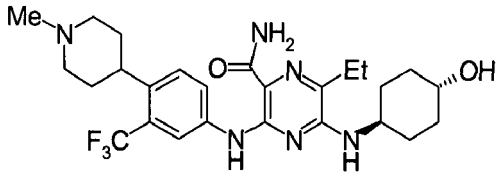
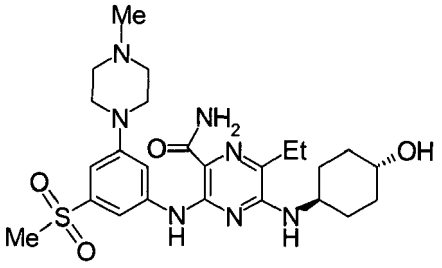
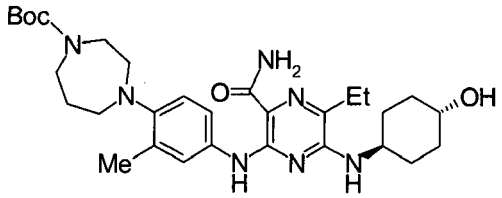
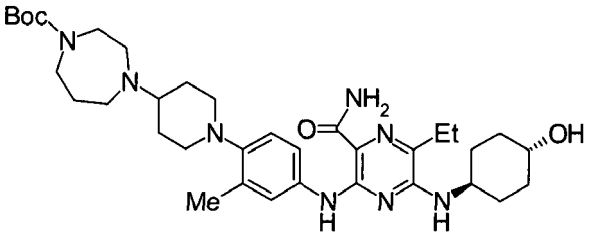
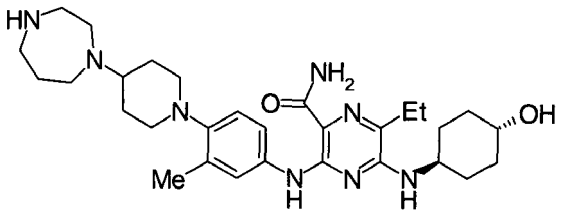
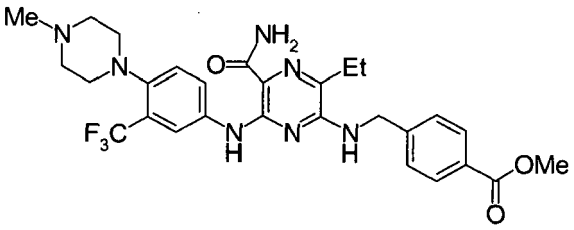
[Table 151] (# not part of the invention)

Ex	Structure
501#	
502#	
503#	
504#	
505#	
506#	
507	

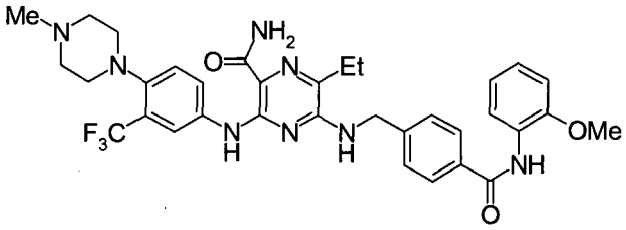
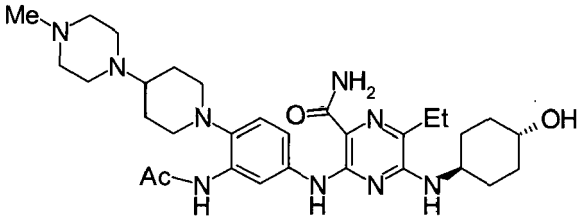
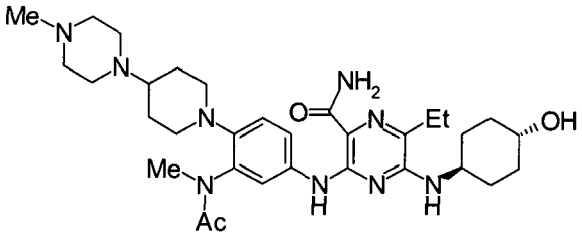
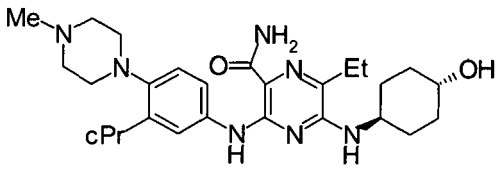
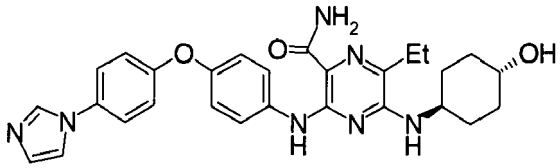
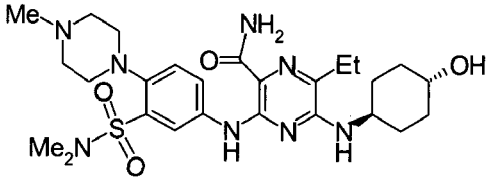
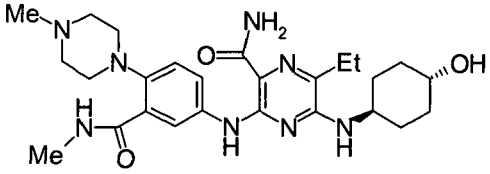
[Table 152]

Ex	Structure
508#	
509#	
510#	
511#	
512	
513#	

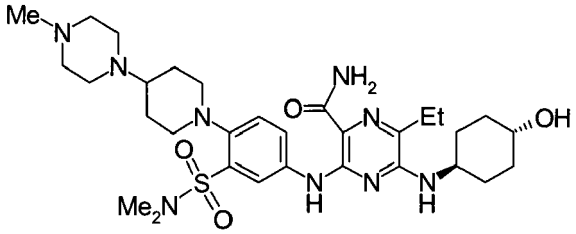
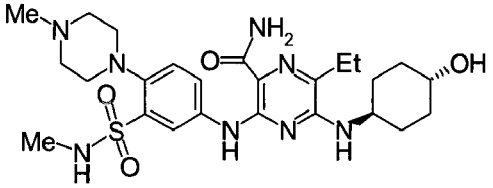
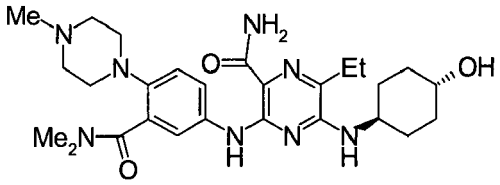
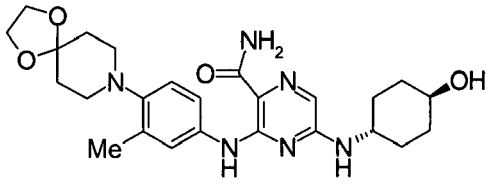
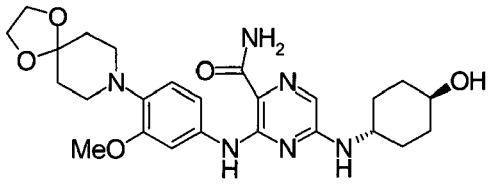
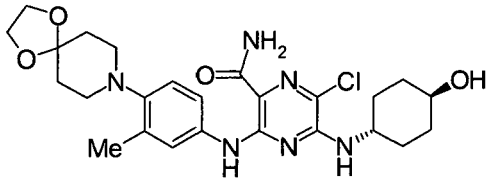
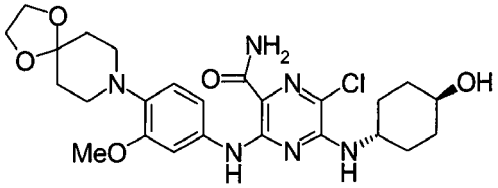
[Table 153] (# not part of the invention)

Ex	Structure
514	
515#	
516#	
517#	
518	
519#	

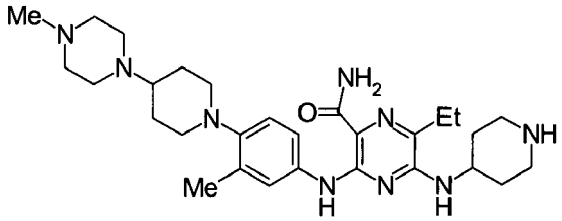
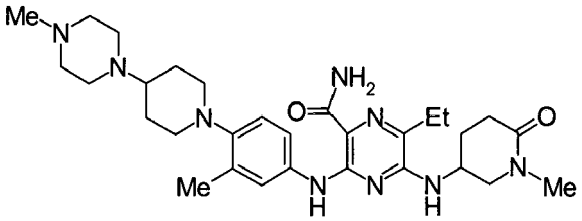
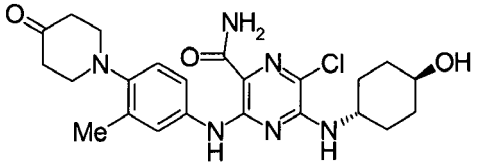
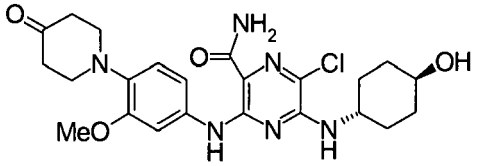
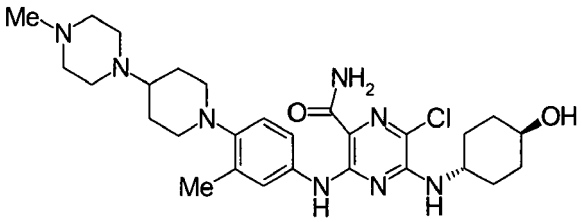
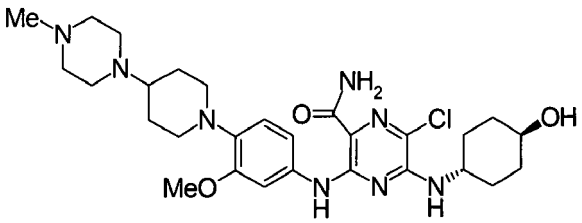
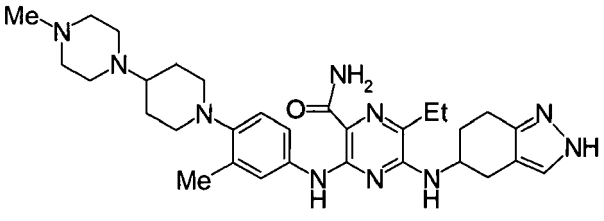
[Table 154] (# not part of the invention)

Ex	Structure
520#	
521#	
522#	
523#	
524#	
525#	
526#	

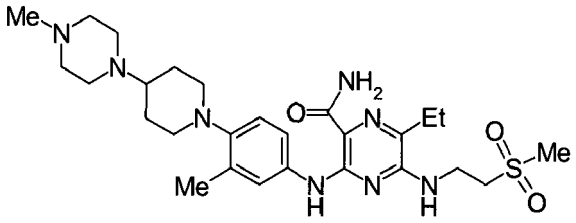
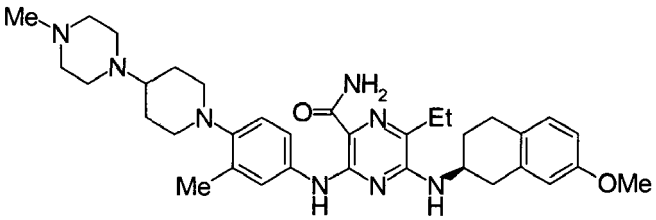
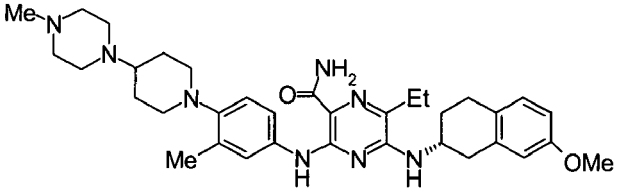
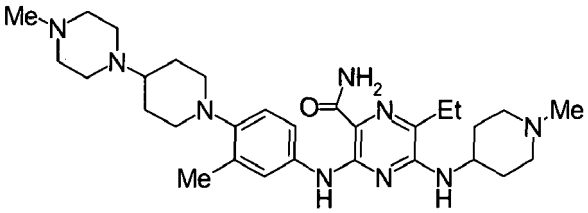
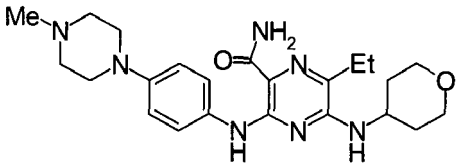
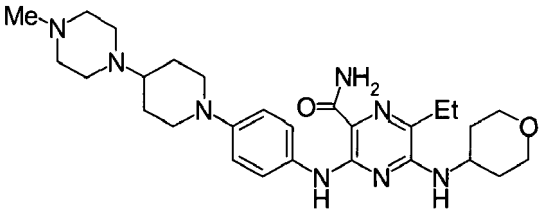
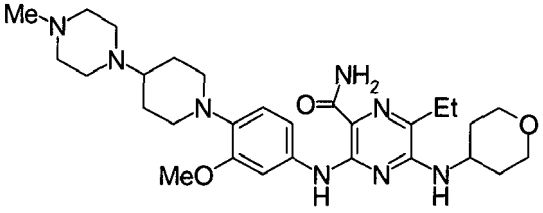
[Table 155] (# not part of the invention)

Ex	Structure
527#	
528#	
529#	
530#	
531#	
532#	
533#	

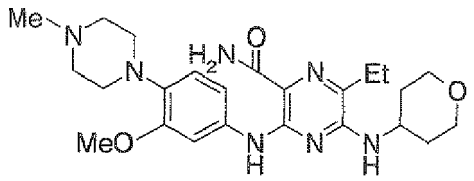
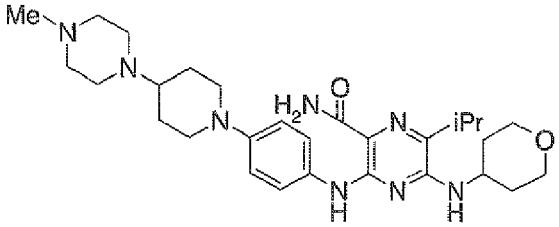
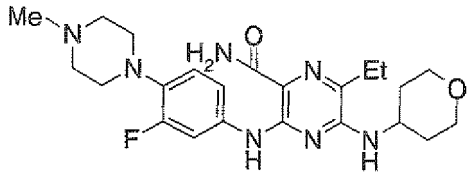
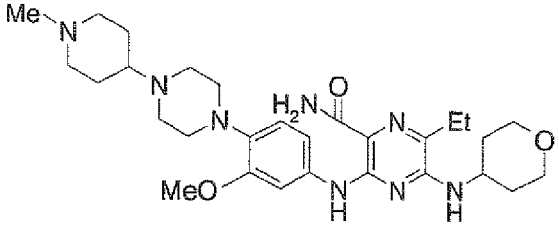
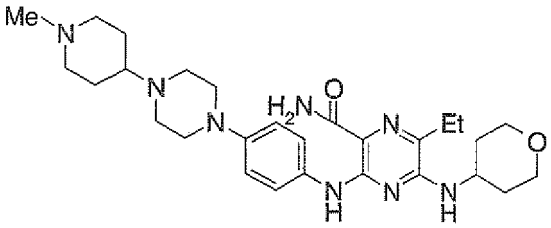
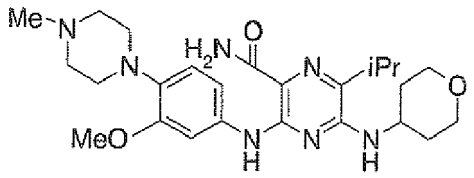
[Table 156] (# not part of the invention)

Ex	Structure
534	
535	
536#	
537#	
538	
539	
540#	

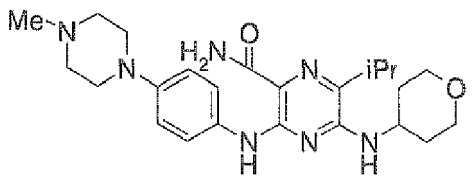
[Table 157] (# not part of the invention)

EX	STRUCTURE
541#	
542#	 2TsOH
543#	 2TsOH
544	
545	
546	
547	

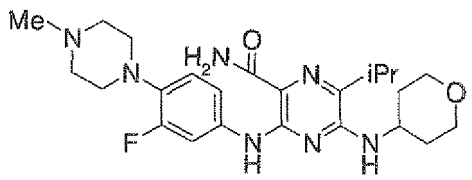
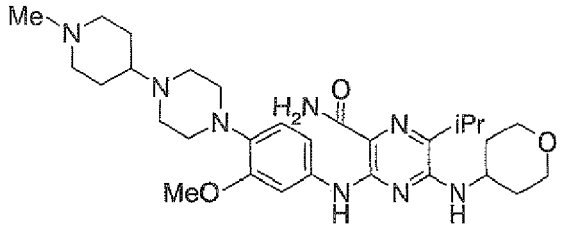
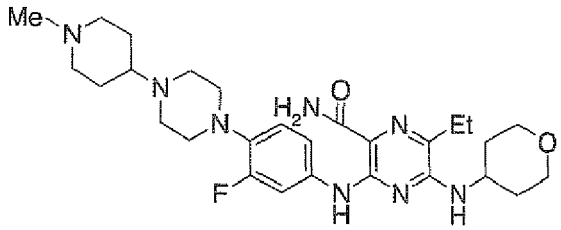
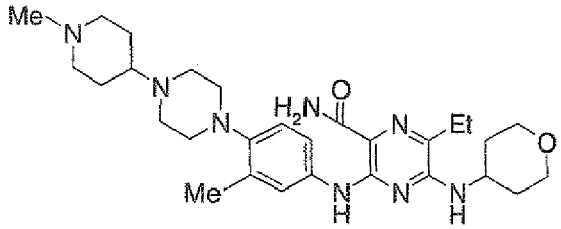
[Table 158]

EX	STRUCTURE
548	
549	
550	
551	
552	
553	

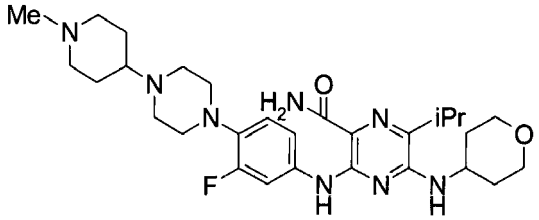
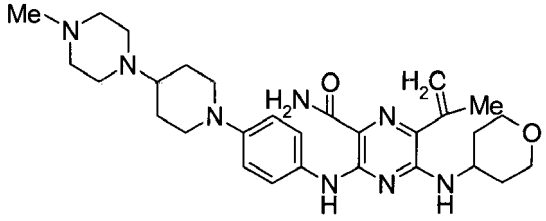
[Table 159]

EX	STRUCTURE
554	

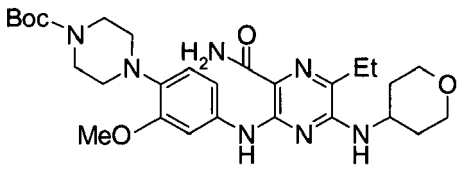
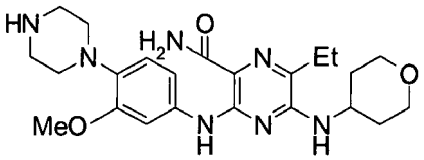
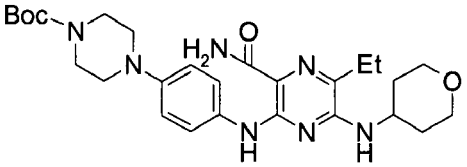
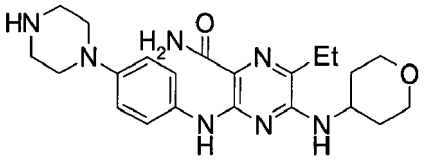
(continued)

EX	STRUCTURE
555	
556	
557	
558	

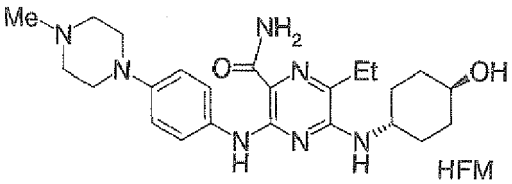
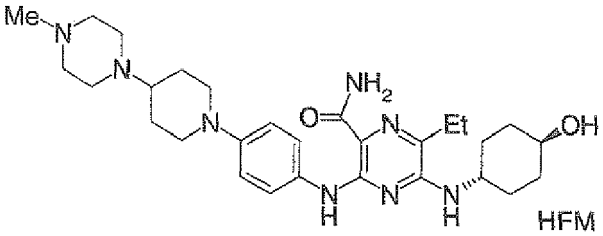
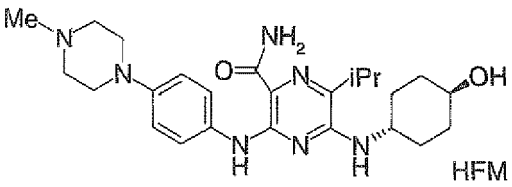
[Table 160] (# not part of the invention)

EX	STRUCTURE
559	
560#	

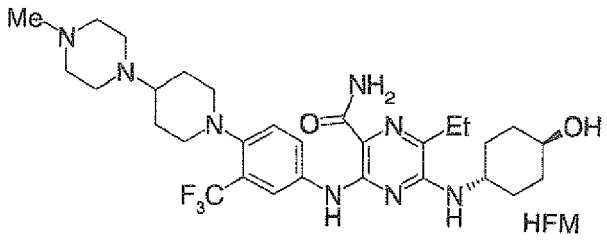
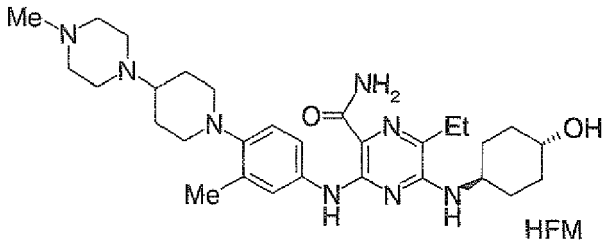
(continued)

EX	STRUCTURE
561#	
562	
563#	
564	

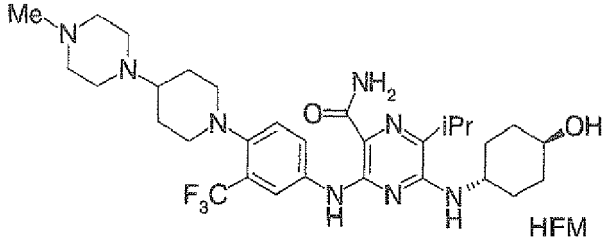
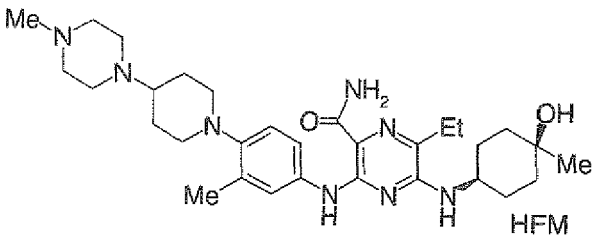
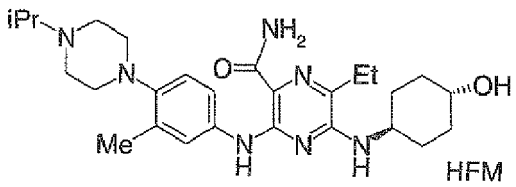
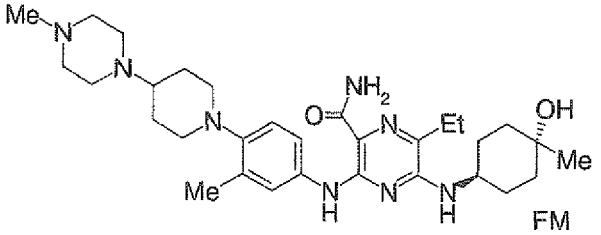
[Table 161]

EX	STRUCTURE
565	
566	
567	

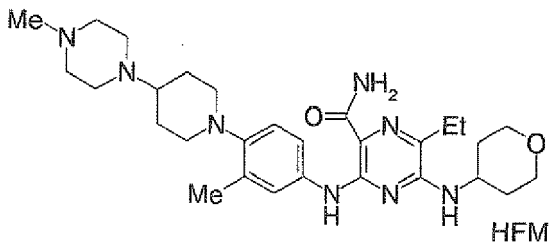
(continued)

EX	STRUCTURE
568	 HFM
569	 HFM

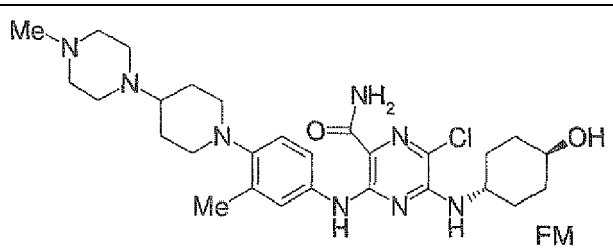
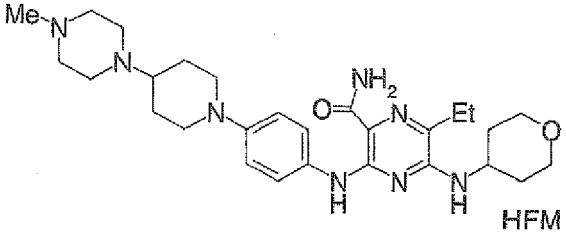
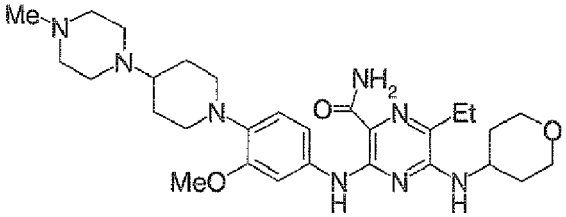
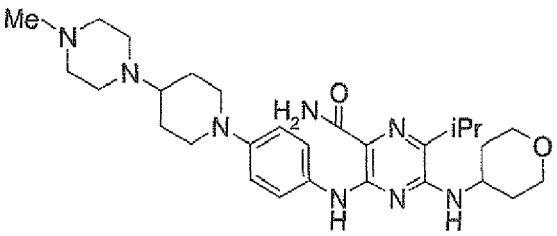
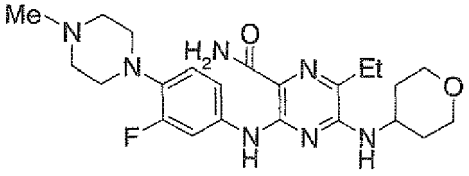
[Table 162]

EX	STRUCTURE
570	 HFM
571	 HFM
572	 HFM
573	 FM

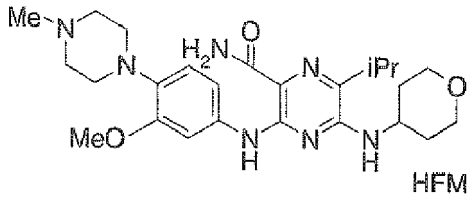
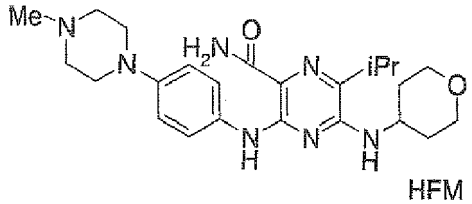
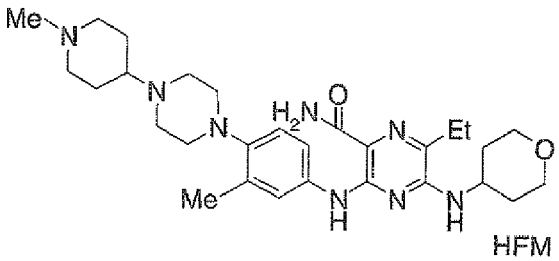
(continued)

EX	STRUCTURE
574	 HFM

[Table 163]

EX	STRUCTURE
575	 FM
576	 HFM
577	 HFM
578	 HFM
579	 HFM

[Table 164]

EX	STRUCTURE
580	 HFM
581	 HFM
582	 HFM

[Table 165]

Ex	Syn	Data
1	Ex4	ESI+: 451
2	Ex4	ESI+: 463
3	Ex4	ESI+: 477
4	Ex4	ESI+: 491
5	Ex4	ESI+: 493
6	Ex4	ESI+: 509
7	Ex4	ESI+: 423
8	Ex4	ESI+: 449
9	Ex4	ESI+: 477
10	Ex4	FAB+: 450
11	Ex4	FAB+: 450
12	Ex4	FAB+: 449
13	Ex4	ESI+: 449
14	Ex4	ESI+: 449
15	Ex4	ESI+: 449
16	Ex4	ESI+: 436
17	Ex4	ESI+: 436
18	Ex4	ESI+: 436

(continued)

Ex	Syn	Data
19	Ex19	ESI+: 449
20	Ex4	ESI+: 435
21	Ex4	ESI+: 435
22	Ex4	ESI+: 463
23	Ex37	ESI+: 639
24	Ex4	ESI+: 435
25	Ex4	ESI+: 435
26	Ex4	ESI+: 421
27	Ex4	ESI+: 421
28	Ex37	ESI+: 535
29	Ex29	ESI+: 435
30	Ex405	FAB+: 477
31	Ex31	FAB+: 513
32	Ex4	ESI+: 477
33	Ex4	ESI+: 477
34	Ex4	ESI+: 372
35	Ex4	FAB+: 436
36	Ex4	ESI+: 400
37	Ex37	ESI+: 414
38	Ex4	ESI+: 428
39	Ex4	ESI+: 449
40	Ex4	ESI+: 463
41	Ex4	ESI+: 437
42	Ex4	ESI+: 436
43	Ex4	ESI-: 400
44	Ex4	ESI+: 463
45	Ex4	ESI+: 449
46	Ex4	ESI+: 464
47	Ex4	ESI+: 392
48	Ex4	ESI+: 450
49	Ex4	ESI+: 426
50	Ex4	ESI+: 468
51	Ex4	ESI+: 454
52	Ex4	ESI+: 489
53	Ex4	FAB+: 388
54	Ex4	FAB+: 450
55	Ex4	ESI+: 449
56	Ex4	ESI+: 470

(continued)

Ex	Syn	Data
57	Ex4	ESI+: 456
58	Ex4	ESI+: 468
59	Ex4	ESI+: 442
60	Ex4	ESI+: 414
61	Ex4	ESI+: 484
62	Ex4	ESI+: 470
63	Ex4	ESI+: 492
64	Ex4	ESI+: 504
65	Ex4	ESI+: 448
66	Ex4	ESI+: 490

[Table 166]

Ex	Syn	Data
67	Ex4	ESI+: 408
68	Ex4	ESI+: 434
69	Ex4	FAB+: 382
70	Ex4	FAB+: 409
71	Ex4	ESI+: 381
72	Ex4	FAB+: 410
73	Ex4	ESI+: 478
74	Ex4	ESI+: 506
75	Ex4	ESI+: 518
76	Ex4	ESI+: 492
77	Ex4	ESI+: 464
78	Ex4	ESI+: 502
79	Ex4	ESI+: 476
80	Ex4	ESI+: 482
81	Ex4	ESI+: 456
82	Ex4	ESI+: 428
83	Ex4	ESI+: 469, 471
84	Ex84	ESI+: 447
85	Ex84	ESI+: 433
86	Ex84	ESI+: 434
87	Ex4	ESI+: 434
88	Ex4	ESI+: 392
89	Ex84	ESI+: 400
90	Ex4	ESI+: 372

(continued)

Ex	Syn	Data
91	Ex4	ESI+: 520
92	Ex4	ESI+: 508
93	Ex4	ESI+: 488
94	Ex4	ESI+: 434
95	Ex4	ESI+: 462
96	Ex4	ESI+: 446
97	Ex4	ESI+: 472
98	Ex4	ESI+: 474
99	Ex4	ESI+: 460
100	Ex4	ESI+: 392
101	Ex84	FAB+: 419
102	Ex84	FAB+: 475
103	Ex84	FAB+: 448
104	Ex4	ESI+: 426
105	Ex4	ESI+: 426
106	Ex4	ESI+: 434
107	Ex4	ESI+: 422
108	Ex84	ESI+: 433
109	Ex84	ESI+: 448
110	Ex84	ESI+: 448
111	Ex84	FAB+: 406
112	Ex146	ESI+: 420
113	Ex4	ESI+: 436
114	Ex4	ESI+: 358
115	Ex4	ESI+: 392
116	Ex4	ESI+: 392
117	Ex84	ESI+: 423
118	Ex4	ESI+: 494
119	Ex4	ESI+: 508
120	Ex4	ESI+: 482
121	Ex4	ESI+: 428
122	Ex4	ESI+: 484
123	Ex4	ESI+: 468
124	Ex4	ESI+: 414
125	Ex4	ESI+: 468
126	Ex4	ESI+: 18
127	Ex4	ESI+: 486
128	Ex4	ESI+: 482

(continued)

Ex	Syn	Data
129	Ex4	ESI+: 522
130	Ex4	ESI+: 480
131	Ex4	FAB+: 508
132	Ex4	ESI+: 468

[Table 167]

Ex	Syn	Data
133	Ex4	FAB+: 414
134	Ex4	ESI+: 522
135	Ex4	FAB+: 534
136	Ex4	FAB+: 444
137	Ex4	ESI+: 498
138	Ex4	ESI+: 482
139	Ex4	FAB+: 428
140	Ex4	ESI+: 536
141	Ex4	ESI+: 460
142	Ex4	ESI+: 432
143	Ex4	ESI+: 488
144	Ex4	ESI+: 474
145	Ex4	ESI+: 460
146	Ex146	ESI+: 468
147	Ex84	ESI+: 486
148	Ex84	ESI+: 448
149	Ex84	ESI+: 434
150	Ex84	ESI+: 427
151	Ex84	ESI+: 535
152	Ex84	ESI+: 427
153	Ex84	ESI+: 427
154	Ex4	ESI+: 448
155	Ex84	ESI+: 447
156	Ex84	ESI+: 443
157	Ex84	ESI+: 433
158	Ex84	ESI+: 433
159	Ex159	ESI+: 440
160	Ex84	ESI+: 427
161	Ex84	ESI+: 481
162	Ex84	ESI+: 427

(continued)

Ex	Syn	Data
163	Ex84	ESI+: 447
164	Ex84	ESI+: 406
165	Ex146	ESI+: 448
166	Ex84	ESI+: 434
167	Ex84	ESI+: 461
168	Ex84	ESI+: 497
169	Ex84	ESI+: 461
170	Ex84	ESI+: 448
171	Ex84	FAB+: 431
172	Ex84	FAB+: 447
173	Ex4	FAB-: 405
174	Ex84	FAB-: 404
175	Ex84	FAB+: 479
176	Ex84	FAB+: 413
177	Ex84	ESI+: 454
178	Ex146	ESI+: 407
179	Ex84	ESI+: 454
180	Ex159	ESI+: 488
181	Ex181	ESI+: 484, 486
182	Ex84	ESI+: 357
183	Ex84	ESI+: 441
184	Ex84	ESI+: 469
185	Ex84	ESI+: 469
186	Ex84	ESI+: 441
187	Ex84	ESI+: 427
188	Ex84	ESI+: 346
189	Ex84	ESI+: 431
190	Ex190	ESI+: 532
191	Ex84	ESI+: 371
192	Ex146	APCI/ESI+: 371
193	Ex84	ESI+: 434
194	Ex84	ESI+: 434
195	Ex196	ESI+: 419
196	Ex196	ESI+: 433
197	Ex196	ESI+: 447
198	Ex196	ESI+: 447

[Table 168]

Ex	Syn	Data
199	Ex196	ESI+: 461
200	Ex196	ESI+: 515
201	Ex196	ESI+: 523
202	Ex196	ESI+: 447
203	Ex196	ESI+: 475
204	Ex196	ESI+: 491
205	Ex196	ESI+: 433
206	Ex196	ESI+: 433
207	Ex196	ESI+: 418
208	Ex196	ESI+: 448
209	Ex196	ESI+: 448
210	Ex196	ESI+: 496
211	Ex196	ESI+: 405
212	Ex196	ESI+: 405
213	Ex196	ESI+: 419
214	Ex196	ESI+: 495
215	Ex196	ESI+: 495
216	Ex196	ESI+: 419
217	Ex196	ESI+: 447
218	Ex196	ESI+: 420
219	Ex196	ESI+: 434
220	Ex196	ESI+: 438
221	Ex196	ESI+: 391
222	Ex196	ESI+: 405
223	Ex196	ESI+: 473
224	Ex196	ESI+: 447
225	Ex196	ESI+: 447
226	Ex196	ESI+: 449
227	Ex196	ESI+: 463
228	Ex196	ESI+: 515
229	Ex196	ESI+: 523
230	Ex196	ESI+: 433
231	Ex196	ESI+: 433
232	Ex196	ESI+: 433
233	Ex196	ESI+: 433
234	Ex196	ESI+: 433
235	Ex196	ESI+: 434

(continued)

Ex	Syn	Data
236	Ex196	ESI+: 434
237	Ex196	ESI+: 436
238	Ex196	ESI+: 448
239	Ex196	ESI+: 448
240	Ex196	ESI+: 447
241	Ex196	ESI+: 447
242	Ex196	ESI+: 420
243	Ex196	ESI+: 420
244	Ex196	ESI+: 405
245	Ex196	ESI+: 406
246	Ex196	ESI+: 462
247	Ex196	ESI+: 476
248	Ex196	ESI+: 447
249	Ex196	ESI+: 462
250	Ex196	ESI+: 463
251	Ex196	ESI+: 448
252	Ex196	ESI+: 433
253	Ex196	ESI+: 447
254	Ex196	ESI+: 434
255	Ex196	ESI+: 379
256	Ex196	ESI+: 393
257	Ex196	ESI+: 407
258	Ex196	ESI+: 421
259	Ex196	ESI+: 421
260	Ex196	ESI+: 421
261	Ex196	ESI+: 407
262	Ex196	ESI+: 380
263	Ex196	ESI+: 394
264	Ex196	ESI+: 408

[Table 169]

Ex	Syn	Data
265	Ex196	ESI+: 394
266	Ex196	ESI+: 410
267	Ex196	ESI+: 394
268	Ex196	ESI+: 438
269	Ex196	ESI+: 419

(continued)

Ex	Syn	Data
270	Ex196	ESI+: 481
271	Ex196	ESI+: 406
272	Ex196	ESI+: 434
273	Ex196	ESI+: 421
274	Ex196	ESI+: 394
275	Ex196	ESI+: 442
276	Ex196	ESI+: 413
277	Ex196	ESI+: 426
278	Ex196	ESI+: 456
279	Ex196	ESI+: 427
280	Ex196	ESI+: 528
281	Ex84	ESI+: 427
282	Ex84	ESI+: 455
283	Ex84	ESI+: 370
284	Ex84	ESI+: 567
285	Ex84	ESI+: 463
286	Ex84	ESI+: 483
287	Ex84	ESI+: 447
288	Ex84	ESI+: 443
289	Ex84	ESI+: 463
290	Ex84	ESI+: 535
291	Ex84	ESI+: 427
292	Ex84	ESI+: 396
293	Ex84	ESI+: 414
294	Ex84	ESI+: 525
295	Ex84	ESI+: 549
296	Ex146	ESI+: 448
297	Ex84	ESI+: 433
298	Ex84	ESI+: 407
299	Ex84	ESI+: 378
300	Ex84	ESI+: 404
301	Ex84	ESI+: 461
302	Ex302	ESI+: 489
303	Ex84	ESI+: 424
304	Ex84	ESI+: 396
305	Ex84	ESI+: 412
306	Ex84	ESI+: 407
307	Ex84	ESI+: 547

(continued)

Ex	Syn	Data
308	Ex84	ESI+: 429
309	Ex309	ESI+: 399
310	Ex310	ESI+: 453
311	Ex84	ESI+: 549
312	Ex84	ESI+: 428
313	Ex84	ESI+: 496
314	Ex84	ESI+: 494
315	Ex84	ESI+: 427
316	Ex84	ESI+: 480
317	Ex84	ESI+: 466
318	Ex84	ESI+: 494
319	Ex84	ESI+: 401
320	Ex84	ESI+: 447
321	Ex84	ESI+: 440
322	Ex302	ESI+: 468
323	Ex146	ESI+: 502
324	Ex84	ESI+: 440
325	Ex84	ESI+: 454
326	Ex84	ESI+: 526
327	Ex84	ESI+: 414
328	Ex84	ESI+: 410
329	Ex84	ESI+: 441
330	Ex84	ESI+: 414

[Table 170]

Ex	Syn	Data
331	Ex84	ESI+: 409
332	Ex84	ESI+: 508
333	Ex84	ESI+: 385
334	Ex84	ESI+: 482
335	Ex84	ESI+: 480
336	Ex84	ESI+: 468
337	Ex84	ESI+: 453
338	Ex84	ESI+: 512
339	Ex84	ESI+: 484
340	Ex84	ESI+: 567
341	Ex84	ESI+: 537

(continued)

Ex	Syn	Data
342	Ex84	ESI+: 466
343	Ex343	ESI+: 468
344	Ex84	ESI+: 512
345	Ex159	ESI+: 546
346	Ex381	ESI+: 446
347	Ex84	ESI+: 454
348	Ex84	ESI+: 581
349	Ex84	ESI+: 581
350	Ex84	ESI+: 570
351	Ex146	ESI+: 549
352	Ex84	ESI+: 449
353	Ex84	ESI+: 463
354	Ex84	ESI+: 522
355	Ex84	ESI+: 484
356	Ex84	ESI+: 539
357	Ex84	ESI+: 441
358	Ex381	ESI+: 439
359	Ex84	ESI+: 439
360	Ex84	ESI+: 636
361	Ex84	ESI+: 469
362	Ex84	ESI+: 468
363	Ex84	ESI+: 538
364	Ex84	ESI+: 560
365	Ex84	ESI+: 455
366	Ex84	ESI+: 476
367	Ex84	ESI+: 455
368	Ex84	ESI+: 442
369	Ex84	ESI+: 477
370	Ex146	ESI+: 605
371	Ex84	ESI+: 538
372	Ex84	ESI+: 560
373	Ex84	ESI+: 631
374	Ex84	ESI+: 456
375	Ex84	ESI+: 455
376	Ex84	ESI+: 552
377	Ex84	ESI+: 468
378	Ex84	ESI+: 551
379	Ex84	ESI+: 464

(continued)

Ex	Syn	Data
380	Ex84	ESI+: 442
381	Ex381	ESI+: 469
382	Ex84	ESI+: 569
383	Ex84	ESI+: 484
384	Ex84	ESI+: 522
385	Ex84	ESI+: 617
386	Ex84	ESI+: 644
387	Ex84	ESI+: 453
388	Ex343	ESI+: 619
389	Ex343	ESI+: 646
390	Ex84	ESI-: 488
391	Ex84	ESI+: 482
392	Ex84	ESI+: 565
393	Ex84	ESI+: 540
394	Ex381	ESI+: 440
395	Ex302	ESI+: 522
396	Ex302	ESI+: 524

[Table 171]

Ex	Syn	Data
397	Ex84	ESI+: 543
398	Ex84	ESI-: 479
399	Ex84	ESI+: 562
400	Ex84	ESI+: 434, 436
401	Ex84	ESI+: 484
402	Ex84	ESI+: 536
403	Ex84	ESI+: 537
404	Ex84	ESI+: 522
405	Ex405	ESI+: 481
406	Ex84	ESI+: 536
407	Ex84	ESI+: 536
408	Ex84	ESI+: 536
409	Ex84	ESI+: 550
410	Ex84	ESI+: 484
411	Ex84	ESI+: 441
412	Ex84	ESI+: 456
413	Ex84	ESI+: 468

(continued)

Ex	Syn	Data
414	Ex84	ESI+: 482
415	Ex31	ESI+: 518
416	Ex302	ESI+: 482
417	Ex302	ESI+: 540
418	Ex84	ESI+: 607
419	Ex381	ESI+: 508
420	Ex84	ESI+: 554
421	Ex381	ESI+: 454
422	Ex146	ESI+: 535
423	Ex302	ESI+: 590
424	Ex302	ESI+: 536
425	Ex302	ESI+: 550
426	Ex302	ESI+: 496
427	Ex84	ESI+: 496
428	Ex84	ESI+: 555
429	Ex84	ESI+: 576
430	Ex84	ESI+: 518
431	Ex302	ESI+: 521
432	Ex84	ESI+: 553
433	Ex381	ESI+: 453
434	Ex31	ESI+: 531
435	Ex84	ESI+: 564
436	Ex436	ESI+: 550
437	Ex436	ESI+: 550
438	Ex438	ESI+: 655
439	Ex438	ESI+: 655
440	Ex84	ESI+: 453
441	Ex84	ESI+: 483
442	Ex84	ESI+: 4488
443	Ex84	ESI+: 483
444	Ex84	ESI+: 566
445	Ex84	ESI+: 544
446	Ex84	ESI+: 597
447	Ex302	ESI+: 602
448	Ex84	ESI+: 550
449	Ex302	ESI+: 642
450	Ex302	ESI-: 636
451	Ex302	ESI+: 467

(continued)

Ex	Syn	Data
452	Ex84	ESI+: 482
453	Ex84	ESI+: 609
454	Ex84	ESI+: 482
455	Ex84	ESI+: 607
456	Ex84	ESI+: 536
457	Ex84	ESI+: 566
458	Ex84	APCI/ESI+: 511
459	Ex84	ESI+: 581
460	Ex534	ESI+: 507
461	Ex84	ESI+: 522
462	Ex405	ESI+: 549

[Table 172]

Ex	Syn	Data
463	Ex405	ESI+: 641
464	Ex302	ESI+: 644
465	Ex84	ESI+: 561
466	Ex84	ESI+: 565
467	Ex84	ESI+: 570
468	Ex381	ESI+: 470
469	Ex302	ESI+: 495
1470	Ex302	ESI+: 535
471	Ex302	ESI+: 449
472	Ex84	ESI+: 449
473	Ex84	ESI+: 607
474	Ex381	ESI+: 507
475	Ex84	ESI+: 482
476	Ex84	ESI+: 471
477	Ex84	ESI+: 469
478	Ex84	ESI+: 567
479	Ex84	ESI+: 554
480	Ex84	ESI+: 469
481	Ex84	ESI+: 499
482	Ex159	ESI+: 533
483	Ex84	ESI+: 565
484	Ex84	ESI+: 511
485	Ex84	ESI+: 547

(continued)

Ex	Syn	Data
486	Ex84	ESI+: 530
487	Ex84	ESI+: 525
488	Ex302	ESI+: 512
489	Ex302	ESI+: 552
490	Ex84	ESI+: 579
491	Ex84	ESI+: 579
492	Ex302	ESI+: 608
493	Ex84	ESI+: 593
494	Ex84	ESI+: 593
495	Ex495	ESI+: 489
496	Ex84	FAB+. 553
497	Ex84	ESI+: 553
498	Ex84	ESI+: 540
499	Ex499	ESI+: 573
500	Ex84	FAB+: 540
501	Ex84	ESI+: 485
502	Ex84	ESI+: 499
503	Ex84	ESI+: 512
504	Ex84	ESI+: 498
505	Ex84	ESI+: 567
506	Ex84	ESI+: 551
507	Ex84	APCI/ESI+: 626
508	Ex508	APCI/ESI+: 446
509	Ex84	ESI+: 539
510	Ex84	ESI+: 567
511	Ex84	ESI+: 554
512	Ex84	ESI+: 537
513	Ex84	ESI+: 611
514	Ex302	ESI+: 521
515	Ex84	ESI+: 532
516	Ex84	ESI+: 568
517	Ex146	ESI+: 651
518	Ex381	ESI+: 551
519	Ex84	ESI+: 572
520	Ex84	ESI+: 663
521	Ex84	ESI+: 594
522	Ex84	ESI+: 608
523	Ex84	ESI+: 494

(continued)

Ex	Syn	Data
524	Ex84	ESI+: 514
525	Ex84	ESI+: 561
526	Ex84	ESI+: 511
527	Ex84	ESI+: 644
528	Ex84	ESI+: 547

[Table 173]

Ex	Syn	Data
529	Ex84	ESI+: 525
530	Ex84	ESI+: 483
531	Ex84	ESI+: 499
532	Ex159	ESI+: 517
533	Ex159	ESI+: 533
534	Ex534	ESI+: 536
535	Ex84	ESI+: 564
536	Ex495	ESI+: 473
537	Ex495	ESI+: 489
538	Ex499	ESI+: 557
539	Ex499	ESI+: 573
540	Ex84	ESI+: 573
541	Ex84	ESI+: 559
542	Ex84	APCI/ESI+: 613
543	Ex84	ESI+: 613
544	Ex84	ESI+: 550
545	Ex84	ESI+: 440
546	Ex84	ESI+: 523
547	Ex84	ESI+: 553
548	Ex84	ESI+: 470
549	Ex343	ESI+: 537
550	Ex84	ESI+: 458
551	Ex302	ESI+: 553
552	Ex302	ESI+: 523
553	Ex84	ESI+: 484
554	Ex84	ESI+: 454
555	Ex84	ESI+: 472
556	Ex84	ESI+: 567
557	Ex84	ESI+: 541

(continued)

Ex	Syn	Data
558	Ex84	ESI+: 537
559	Ex84	ESI+: 555
560	Ex84	APCI/ESI+: 535
561	Ex84	ESI+: 556
562	Ex381	ESI+: 456
563	Ex84	ESI+: 524
564	Ex381	ESI+: 426
565	Ex84	ESI+: 454
566	Ex84	ESI+: 537
567	Ex343	ESI+: 468
568	Ex146	ESI+: 605
569	Ex84	ESI+: 551
570	Ex343	ESI+: 619
571	Ex84	ESI+: 565
572	Ex302	ESI+: 496
573	Ex84	ESI+: 565
574	Ex84	ESI+: 537
575	Ex499	ESI+: 557
576	Ex84	ESI+: 523
577	Ex84	ESI+: 553
578	Ex343	ESI+: 537
579	Ex84	ESI+: 441
580	Ex84	ESI+: 484
581	Ex84	ESI+: 454
582	Ex84	ESI+: 537

[Table 174]

Ex	Data
86	^{1}H-NMR (DMSO-d6): 1.19 (3H, t, J = 7.8 Hz), 1.33-1.50 (4H, m), 1.79-1.95 (4H, m), 2.60 (2H, q, J = 7.8 Hz), 3.21 (3H, s), 3.37-3.49 (1H, m), 3.89-4.01 (1H, m), 4.54 (1H, d, J = 4.4 Hz), 6.76 (1H, d, J = 7.9 Hz), 7.33-7.42 (1H, m), 7.44-7.57 (2H, m), 7.58-7.65 (1H, m), 7.96-8.03 (1H, m), 8.15-8.21 (1H, m), 11.59 (1H, s).
110	^{1}H-NMR (DMSO-d6): 1.13-1.25 (6H, m), 1.46-1.64 (6H, m), 1.79-1.91 (2H, m), 2.61 (2H, q, J = 7.4 Hz), 3.21 (3H, s), 3.94-4.09 (1H, m), 4.26 (1H, s), 6.72 (1H, d, J = 7.9 Hz), 7.33-7.42 (1H, m), 7.44-7.58 (2H, m), 7.59-7.66 (1H, m), 7.98-8.04 (1H, m), 8.16-8.20 (1H, m), 11.58 (1H, s).
284	^{1}H-NMR (CDCl3): 1.26-1.36 (5H, m), 1.48-1.56 (2H, m), 1.68-1.76 (2H, m), 1.95 (2H, d, J = 11.6 Hz), 2.08 (2H, d, J = 10.4 Hz), 2.26 (2H, d, J = 11.6 Hz), 2.30 (3H, s), 2.30-2.73 (13H, m), 3.64-3.74 (4H, m), 3.93-3.97 (4H, m), 4.52 (1H, d, J = 7.2 Hz), 5.13 (1H, br-s), 6.50 (1 H, dd, J = 2.4 Hz, 9.2 Hz), 6.58 (1 H, d, J = 2.4 Hz), 7.46 (1 H, br-s), 8.39 (1H, d, J = 8.8 Hz), 10.98 (1H, s).

(continued)

Ex	Data
325	^{1}H-NMR (DMSO-d6): 1.17 (3H, t, J = 7.4 Hz), 1.22-1.48 (4H, m), 1.84-2.00 (4H, m), 2.25 (3H, s), 2.44-2.59 (6H, m), 3.00-3.12 (4H, m), 3.43 (1H, m), 3.80 (1H, m), 4.56 (1H, d, J = 4.7 Hz), 6.63 (1H, d, J = 8.0 Hz), 6.87 (2H, d, J = 9.2 Hz), 7.13 (1H, br), 7.47 (1H, br), 7.51 (2H, d, J = 9.2 Hz), 10.9 (1H, s).
328	^{1}H-NMR (CDCl3): 1.25-1.67 (7H, m), 2.04 (2H, m), 2.17-2.22 (2H, m), 2.48-2.55 (2H, m), 3.72 (1H, m), 4.03 (3H, s), 4.05 (1H, m), 4.60 (1H, m), 5.19 (1H, m), 7.44 (1H, m), 7.51 (1H, m), 7.62 (1H, m), 7.78 (1H, s), 7.88 (1H, s), 11.14 (1H, br-s).
340	^{1}H-NMR (CDCl3): 1.22-1.54 (7H, m), 1.74-1.94 (4H, m), 2.01-2.10 (2H, m), 2.16-2.26 (2H, m), 2.30 (3H, s), 2.32-2.74 (13H, m), 3.50 (2H, d, J = 11.4 Hz), 3.65-3.76 (1H, m), 3.87 (3H, s), 3.92-4.03 (1H, m), 4.52 (1H, d, J = 7.3 Hz), 5.12 (1H, br-s), 6.71 (1H, s), 6.84-6.90 (2H, m), 7.45-7.55 (2H, m), 10.74 (1H, s).

[Table 175]

Ex	Data
341	^{1}H-NMR (DMSO-d6): 1.17 (3H, t, J = 7.4 Hz), 1.21-1.60 (6H, m), 1.75-2.00 (6H, m), 2.14 (3H, s), 2.20-2.72 (13H, m), 3.43 (1H, m), 3.58 (2H, m), 3.80 (1H, m), 4.57 (1H, d, J = 4.4 Hz), 6.63 (1H, d, J = 7.3 Hz), 6.86 (2H, d, J = 8.7 Hz), 7.13 (1H, br-s), 7.40-7.60 (3H, m), 10.92 (1H, s).
343	^{1}H-NMR (DMSO-d6): 1.14 (6H, d, J =6.6 Hz), 1.21-1.48 (4H, m), 1.85-1.98 (4H, m), 2.22 (3H, s), 2.41-2.48 (4H, m), 2.99-3.18 (5H, m), 3.37-3.48 (1H, m), 3.74-3.87 (1H, m), 4.56 (1H, d, J = 4.7 Hz), 6.67 (1H, d, J = 7.6 Hz), 6.86 (2H, d, J = 9.0 Hz), 7.11-7.18 (1H, m), 7.40-7.47 (1H, m), 7.50 (2H, d, J = 9.0 Hz), 10.91 (1H, s)
347	^{1}H-NMR (DMSO-d6): 1.10-1.49 (7H, m), 1.80-1.96 (4H, m), 2.22 (3H, s), 2.40-2.61 (6H, m), 3.06-3.18 (4H, m), 3.43 (1H, m), 3.86 (1H, m), 4.56 (1H, d, J = 4.3 Hz), 6.57 (1H, m), 6.63 (1H, d, J = 7.6 Hz), 6.91 (1H, m), 7.10 (1H, m), 7.18 (1H, br), 7.29 (1H, m), 7.51 (1H, br-s), 11.09 (1H, s).
354	^{1}H-NMR (DMSO-d6): 1.12-1.32 (5H, m), 1.36-1.50 (2H, m), 1.78-1.96 (4H, m), 2.22 (3H, s), 2.35-2.63 (6H, m), 2.78-2.88 (4H, m), 3.41 (1H, m), 3.87 (1H, m), 4.55 (1H, d, J = 3.9 Hz), 6.68 (1H, d, J = 7.9 Hz), 7.27 (1H, br-s), 7.46 (1H, d, J = 8.7 Hz), 7.56 (1H, br-s), 7.61 (1H, m), 8.18 (1H, m), 11.37 (1H, s)
355	^{1}H-NMR (DMSO-d6): 1.10-1.32 (5H, m), 1.32-1.50 (2H, m), 1.82-1.96 (4H, m), 2.21 (3H, s), 2.35-2.60 (6H, m), 2.84-2.99 (4H, m), 3.42 (1H, m), 3.81 (3H, s), 3.87 (1H, m), 4.56 (1H, d, J = 4.6 Hz), 6.61 (1H, d, J = 7.8 Hz), 6.79 (1H, d, J = 8.6 Hz), 7.09 (1H, d, J = 2.2 Hz), 7.16 (1 H, br-s), 7.24 (1H, dd, J = 8.6, 2.2 Hz), 7.49 (1H, br-s), 11.03 (1 H, s)
357	^{1}H-NMR (DMSO-d6): 1.17 (3H, t, J = 7.4 Hz), 1.21-1.48 (4H, m), 1.84-2.00 (4H, m), 2.55 (2H, q, J = 7.4 Hz), 3.00-3.06 (4H, m), 3.42 (1H, m), 3.69-3.86 (5H, m), 4.58 (1H, d, J = 4.8 Hz), 6.65 (1H, d, J = 7.4 Hz), 6.84-6.90 (2H, m), 7.16 (1H, m), 7.44-7.56 (3H, m), 10.95 (1H, s)

[Table 176]

Ex	Data
370	^{1}H-NMR (DMSO-d6): 1.10-1.32 (5H, m), 1.36-1.58 (4H, m), 1.75-1.93 (6H, m), 2.14 (3H, s), 2.22-2.38 (4H, m), 2.40-2.62 (5H, m), 2.65-2.78 (2H, m), 2.87-2.97 (2H, m), 3.20-3.48 (3H, m), 3.87 (1H, m), 4.56 (1H, d, J = 3.9 Hz), 6.67 (1H, d, J = 7.9 Hz), 7.27 (1H, br-s), 7.42 (1H, d, J = 8.7 Hz), 7.55 (1H, br-s), 7.62 (1H, m), 8.15 (1H, m), 11.37 (1H, s)
377	^{1}H-NMR (CDCl3): 1.24-1.35 (5H, m), 1.43-1.50 (2H, m), 2.04-2.07 (2H, m), 2.17-2.24 (2H, m), 2.32 (3H, s), 2.36 (3H, s), 2.47 (2H, q, J = 7.1 Hz), 2.58 (4H, br-s), 2.92-2.94 (4H, m), 3.70 (1H, m), 3.95-3.99 (1H, m), 4.51 (1H, d, J = 7.1 Hz), 5.11 (1H, br-s), 6.98 (1H, d, J = 8.3 Hz), 7.48-7.52 (3H, m), 10.70 (1H, br-s).
378	^{1}H-NMR (CDCl3): 1.23-1.32 (5H, m), 1.45-1.72 (4H, m), 1.92-2.08 (4H, m), 2.17-2.30 (8H, m), 2.45-2.67 (13H, m), 3.15 (2H, m), 3.71-3.73 (1H, m), 3.98 (1H, m), 4.51 (1H, d, J = 7.1 Hz), 5.11 (1H, m), 6.93 (1H, d, J = 8.5 Hz), 7.46-7.52 (3H, m), 10.70 (1H, br-s).

(continued)

Ex	Data
383	^{1}H-NMR (DMSO-d6): 1.17 (3H, t, J = 7.4 Hz), 1.20-1.32 (2H, m), 1.35-1.48 (2H, m), 1.81-1.93 (4H, m), 2.22 (3H, s), 2.40-2.60 (6H, m), 2.94-3.04 (4H, m), 3.36-3.47 (1H, m), 3.76 (3H, s), 3.80-3.93 (1H, m), 4.53 (1H, d, J = 4.3 Hz), 6.58 (1H, d, J = 7.7 Hz), 6.82 (1H, d, J = 8.6 Hz), 6.86 (1H, d, J = 2.0 Hz), 7.10-7.17 (1H, m), 7.37 (1H, dd, J = 2.0, 8.6 Hz), 7.44-7.51 (1H, m), 10.93 (1H, s)
387	^{1}H-NMR (DMSO-d6): 1.17 (3H, t, J = 7.3 Hz), 1.22-1.52 (4H, m), 1.54-1.78 (4H, m), 1.85-2.03 (6H, m), 2.18 (3H, s), 2.40 (1H, m), 2.56 (2H, q, J = 7.3 Hz), 2.80-2.90 (2H, m), 3.43 (1H, m), 3.82 (1H, m), 4.58 (1H, d, J = 4.7 Hz), 6.70 (1H, d, J = 7.3 H), 7.13 (2H, d, J = 8.5 Hz), 7.19 (1H, br), 7.50 (1H, br), 7.59 (2H, d, J = 8.5 Hz), 11.11 (1H, s)

[Table 177]

Ex	Data
388	1H-NMR (DMSO-d6): 1.15 (6H, d, J = 6.7 Hz), 1,18-1.33 (2H, m), 1.36-1.59 (4H, m), 1.75-1.91 (6H, m), 2.14 (3H, s), 2.21-2.56 (9H, m), 2.64-2.79 (2H, m), 2.87-2.98 (2H, m), 3.09-3.21 (1H, m), 3.36-3.48 (1H, m), 3.79-3.96 (1H, m), 4.56 (1H, d, J = 3.9 Hz), 6.72 (1H, d, J = 7.3 Hz), 7.22-7.33 (1H, m), 7.42 (1H, d, J = 9.0 Hz), 7.48-7.56 (1H, m), 7.58-7.66 (1H, m), 8.14 (1H, d, J = 2.3 Hz), 11.35 (1H, s).
391	1H-NMR (CDCl3): 1.26-1.30 (6H, m), 1.49-1.76 (6H, m), 1.97-2.01 (2H, m), 2.30 (3H, s), 2.36 (3H, s), 2.48 (2H, q, J = 7.3 Hz), 2.59 (4H, br-s), 2.91-2.94 (4H, m), 3.73-3.97 (1H, m), 4.61 (1H, d, J = 7.5 Hz), 5.10 (1H, br-s), 6.96 (1H, d, J = 8.5 Hz), 7.48-7.53 (3H, m), 10.69 (1H, br-s).
392	1H-NMR (CDCl3): 1.26-1.32 (6H, m), 1.54-1.76 (8H, m), 1.92-2.00 (4H, m), 2.28 (3H, s), 2.30 (3H, s), 2.47 (2H, q, J = 7.3 Hz), 2.60-2.66 (11H, m), 3.12-3.15 (2H, m), 3.94-3.97 (1H, m), 4.60 (1H, d, J = 7.3 Hz), 5.10 (1H, br-s), 6.91 (1H, d, J = 8.5 Hz), 7.41-7.71 (3H, m), 10.69 (1H, br-s).
399	1H-NMR (CDCl3): 0.13-0.16 (2H, m), 0.52-0.57 (2H, m), 0.92 (1H, m), 1.24-1.58 (7H, m), 2.03 (2H, m), 2.18 (2H, m), 2.33 (2H, m), 2.49 (2H, q, J = 7.6 Hz), 2.68 (4H, br-s), 2.98 (4H, m), 3.66 (1H, m), 4.00 (1H, m), 4.56 (1H, d, J = 7.6 Hz), 5.16 (1H, m), 7.34 (1H, d, J = 8.8 Hz), 7.51 (1H, m), 7.62 (1H, dd, J = 8.8, 2.4 Hz), 8.18 (1H, d, J = 2.4 Hz), 10.96 (1H, br-s).
406	1H-NMR (CDCl3): 1.29 (3H, t, J = 7.3 Hz), 1.43-1.52 (4H, m), 1.85-1.90 (1H, m), 2.01-2.04 (2H, m), 2.12-2.18 (3H, m), 2.29 (6H, s), 2.46 (2H, q, J = 7.3 Hz), 2.86-2.90 (1H, m), 3.16-3.37 (4H, m), 3.66 (1H, m), 3.97-4.00 (1H, m), 4.53 (1H, d, J = 7.6 Hz), 5.15 (1H, br-s), 7.11 (1H, d, J = 8.8 Hz), 7.48-7.55 (2H, m), 8.15 (1H, d, J = 2.4 Hz), 10.84 (1H, br-s).

[Table 178]

Ex	Data
426	1H-NMR (CDCl3): 1.11 (6H, d, J = 6.3 Hz), 1.24-1.32 (5H, m), 1.39-1.52 (2H, m), 2.05-2.07 (2H, m), 2.20-2.23 (2H, m), 2.32 (3H, s), 2.47 (2H, q, J = 7.3 Hz), 2.70-2.78 (5H, m), 2.94-2.96 (5H, m), 3.66-3.71 (1 H, m), 3.93-3.98 (1H, m), 4.54 (1H, d, J = 7.1 Hz), 5.19 (1H, br-s), 6.99 (1H, d, J = 8.5 Hz), 7.44-7.55 (3H, m), 10.68 (1H, br-s).
459	1H-NMR (CDCl3):1.20-1.54 (10H, m), 1.70-2.09 (6H, m), 2.21 (2H, d, J = 11.4 Hz), 2.29 (3H, s), 2.32-2.73 (13H, m), 3.54 (2H, d, J = 11.6 Hz), 3.63-3.75 (1H, m), 3.92-4.40 (1H, m), 4.07 (2H, q, J = 6.9 Hz), 4.52 (1H, d, J = 7.3 Hz), 5.12 (1H, br-s), 6.84 (1H, d, J = 8.7 Hz), 6.93 (1H, d, J = 2.1 Hz), 7.26 (1H, s), 7.47 (2H, dd, J = 8.5, 2,2 Hz), 10.72 (1H, s).
466	1H-NMR (CDCl3): 1.26-2.74 (38H, m), 3.12-3.15 (2H, m), 4.08 (1H, m), 4.63 (1H, d, J = 6.8 Hz), 5.14 (1H, br-s), 6.93 (1H, d, J = 8.1 Hz), 7.49-7.54 (3H, m), 10.71 (1H, br-s).
490	1H-NMR (CDCl3): 0.96 (3H, t, J = 7.6 Hz), 1.25-2.71 (36H, m), 3.11 - 3.15 (2H, m), 3.95-3.97 (1H, m), 4.61 (1H, d, J = 7.3 Hz), 5.09 (1H, br-s), 6.91 (1H, d, J = 8.8 Hz), 7.40-7.56 (3H, m), 10.68 (1H, br-s).
491	1 H-NMR (CDCl3): 0.92 (3H, t, J = 7.3 Hz), 1.26-2.71 (36H, m), 3.12-3.15 (2H, m), 4.11-4.17 (1H, m), 4.64 (1H, d, J = 6.8 Hz), 5.13 (1H, br-s), 6.93 (1H, d, J = 8.1 Hz), 7.49-7.54 (3H, m), 10.71 (1H, br-s).

(continued)

Ex	Data
493	1H-NMR (CDCl3): 0.96 (6H, d, J = 7.1 Hz), 1.26-1.30 (5H, m), 1.56-2.69 (30H, m), 3.13 (2H, d, J = 10.5 Hz), 3.94 (1H, m), 4.61 (1H, d, J = 7.8 Hz), 5.09 (1H, br-s), 6.91 (1H, d, J = 8.5 Hz), 7.40 (1H, d, J = 6.6 Hz), 7.48 (1H, br-s), 7.56 (1H, d, J = 2.7 Hz), 10.67 (1H, br-s).
494	1 H-NMR (CDCl3): 0.95 (6H, d, J = 6.8 Hz), 1.25-3.18 (37H, m), 3.64-3.67 (1H, m), 4.72 (1H, d, J = 7.1 Hz), 5.12 (1H, br-s), 6.92 (1H, d, J = 8.5 Hz), 7.48-7.54 (3H, m), 10.73 (1H, br-s).

[Table 179]

Ex	Data
512	1H-NMR (DMSO-d6): 1.19 (3H, t, J = 7.4 Hz), 1.46-1.72 (4H, m), 1.77-1.93 (4H, m), 2.15 (3H, s), 2.20-2.40 (8H, m), 2.44-2.63 (8H, m), 2.97-3.08 (2H, m), 3,34-3.46 (2H, m), 3.88-4.00 (2H, m), 4.11 (1H, m), 6.76 (1H, d, J = 7.5 Hz), 6.94 (1H, d, J = 8.6 Hz), 7.18 (1H, br-s), 7.34 (1H, m), 7.46 (1H, m), 7.51 (1H, br-s), 11.00 (1H, s).
534	1H-NMR (DMSO-d6): 1.18(3H, t, J = 7.4Hz), 1.39-1.61 (4H, m), 1.78-1.88 (4H, m), 2.14 (3H, s), 2.20-2.39 (8H, m), 2.44-2.62 (10H, m), 2.95-3.06 (4H, m), 3.95 (1H, m), 6.70 (1H, d, J = 7.6 Hz), 6.92 (1H, d, J = 8.6 Hz), 7.15 (1H, br-s), 7.36 (1H, m), 7.43-7.54 (2H, m), 11.01 (1H, s).
544	1H-NMR (DMSO-d6): 1.18 (3H, t, J = 7.4 Hz), 1,48-1.72 (4H, m), 1.77-1.90 (4H, m), 1.90-2.01 (2H, m), 2.14 (3H, s), 2.18 (3H, s), 2.21-2.62 (16H, m), 2.77-2.87 (2H, m), 2.97-3.07 (2H, m), 3.87 (1H, m), 6.72 (1H, m), 6.92 (1H, m), 7.19 (1H, m), 7.28 (1H, m), 7.46-7.56 (2H, m), 11.02 (1H, s)
545	1H-NMR (DMSO-d6): 1.18 (3H, t, J = 7.4 Hz), 1.55-1.69 (2H, m), 1.83-1.92 (2H, m), 2.22 (3H, s), 2.40-2.50 (4H, m), 2.57 (2H, q, J = 7.4 Hz), 2.98-3.14 (4H, m), 3.36-4.48 (2H, m), 3.88-3.98 (2H, m), 4.06 (1H, m), 6.78 (1H, m), 6.84-6.94 (2H, m), 7.18 (1H, m), 7.40-7.54 (3H, m), 10.91 (1H, s)
546	1H-NMR (DMSO-d6): 1.18 (3H, t, J = 7,4 Hz), 1.42-1.68 (4H, m), 1.78-1.92 (4H, m), 2.13 (3H, s), 2.20-2.64 (13H, m), 3.26-3.46 (2H, m), 3.57-3.67 (2H, m), 3.89-3.97 (2H, m), 4.05 (1H, m), 6.78 (1H, m), 6.85-6.93 (2H, m), 7.17 (1H, m), 7.42-7.53 (3H, m), 10.89 (1H, s)
547	1 H-NMR (DMSO-d6): 1.19 (3H, t, J = 7.4 Hz), 1.44-1.72 (4H, m), 1.74-1.90 (4H, m), 2.14 (3H, s), 2.18-2.64 (13H, m), 3.18-3.44 (4H, m), 3.81 (3H, s), 3.86-3.96 (2H, m), 4.10 (1H, m), 6.77 (1H, m), 6.82 (1H, m), 7.03 (1H, m), 7.20 (1H, m), 7.25 (1H, m), 7.52 (1H, m), 11.01 (1H, m)

[Table 180]

Ex	Data
565	1H-NMR (DMSO-d_6): 1.17 (3H, t, J = 7.2 Hz), 1.22-1.48 (4H, m), 1.86-1.98 (4H, m), 2.26 (3H, s), 2.47-2.58 (6H, m), 3.01-3.14 (4H, m), 3.14-3.60 (1H, m), 3.82-3.87 (1H, m), 4.59 (1H, br-s), 6.60 (1H, s), 6.65 (1H, d, J = 7.6 Hz), 6.83-6.90 (2H, m), 7.12-7.19 (1H, m), 7.44-7.54 (3H, m), 10.95 (1H, s) XRD: 12.6, 17.6, 22.2, 23.5, 24.2
566	1H-NMR (DMSO-d6): 1.17(3H,t,J=7.6Hz), 1.22-1.62(6H,m), 1.78-2.02 (6H, m), 2.20 (3H, s), 2.24-2.76 (14H, m), 3.10-3.88 (4H, m), 6.55 (1H, s), 6.66 (1H, d, J = 6.0 Hz), 6.83-6.90 (2H, m), 7.12-7.19 (1H, m), 7.44-7.54 (3H, m), 10.93 (1 H, s) XRD: 5.7, 18.0, 18.9, 20.1, 20.2
567	1H-NMR (DMSO-d6): 1.13 (6H, d, J = 6.8 Hz), 1.21-1.48 (4H, m), 1.84-1.98 (4H, m), 2.26 (3H, s), 2.48-2.56 (4H, m), 3.03-3.18 (5H, m), 3.37-3.47 (1H, m), 3.75-3.86 (1H, m), 4.58 (1H, br-s), 6.59 (1H, s), 6.70 (1H, d, J = 7.6 Hz), 6.84-6.90 (2H, m), 7.15-7.20 (1H, m), 7.42-7.47 (1H, m), 7.48-7.54 (2H, m), 10.92 (1H, s) XRD: 11.0, 11.2, 17.3, 17.5, 22.5
568	1H-NMR (DMSO-d6): 1.14-1.34 (5H, m), 1.36-1,61 (4H, m), 1.78-1.94 (6H, m), 2.22 (3H, s), 2.28-2.65 (12H, m), 2.68-2.80 (2H, m), 2.89-3.01 (2H, m), 3.36-3.47 (1H, m), 3.81-3.94 (1H, m), 6.55 (1H, s), 6.70 (1H, d, J = 7.6 Hz), 7.28-7.32 (1H, m), 7.43 (1H, d, J = 8.8 Hz), 7.54-7.64 (2H, m), 8.17 (1H, d, J = 2.4 Hz), 11.39 (1H, s) XRD: 8.4, 8.5, 20.2, 20.3, 20.4

(continued)

Ex	Data
569	1H-NMR (DMSO-d6): 1.17 (3H, t, J = 7.6 Hz), 1.21-1.35 (2H, m), 1.36-1.49 (2H, m), 1.50-1.63 (2H, m), 1.80-1.98 (6H, m), 2.24 (3H, s), 2.25 (3H, s), 2.30-2.70 (14H, m), 2.98-3.10 (2H, m), 3.37-3.48 (1H, m), 3.80-3.92 (1H, m), 6.57 (1H, s), 6.65 (1H, d, J = 7.6 Hz), 6.93 (1H, d, J = 8.8 Hz), 7.14-7.22 (1H, m), 7.37 (1H, dd, J = 2.4, 8,8 Hz), 7.46-7.53 (2H, m), 11.03 (1H, s) XRD: 9.5, 18.4, 19.0, 19.4, 23.9

[Table 181]

Ex	Data
570	1H-NMR (DMSO-d6): 1.15 (6H, d, J = 6.4 Hz), 1.18-1.32 (2H, m), 1.37-1.58 (4H, m), 1.78-1.91 (6H, m), 2.21 (3H, s), 2.28-2.80 (12H, m), 2.89-2.98 (2H, m), 3.10-3.60 (2H, m), 3.82-3.94 (1H, m), 6.55 (1H, s), 6.75 (1H, d, J = 8.0 Hz), 7.28-7.35 (1H, m), 7.43 (1H, d, J = 8.4 Hz), 7.50-7.57 (1H, m), 7.59-7.65 (1 H, m), 8.15 (1H, d, J = 2.8 Hz), 11.36 (1H, s) XRD: 17.9, 18.3, 18.4, 18.9, 19.0
571	1H-NMR (DMSO-d6): 1.12-1.20 (6H, m), 1.33-1.45 (2H, m), 1,59-1,89 (10H, m), 2.23 (3H, s), 2.26 (3H, s), 2.30-2.73 (13H, m), 2.97-3.07 (2H, m), 3.79-3.91 (1H, m), 4.03-4.14 (1H, m), 6.57 (1H, s), 6.72 (1H, d, J = 7.6 Hz), 6.92 (1H, d, J = 8.4 Hz), 7.14-7.19 (1H, m), 7.28 (1H, dd, J = 2.4, 8.4 Hz), 7.46-7.51 (1H, m), 7.56 (1H, d, J = 2.4 Hz), 11.01 (1H, s) XRD: 7.9, 15.1, 19.4, 19.9, 20.3
572	1H-NMR (DMSO-d6): 1.04 (6H, d, J = 6.8 Hz), 1.17 (3H, t, J = 7.2 Hz), 1.21-1.35 (2H, m), 1.36-1.50 (2H, m), 1.84-1.97 (4H, m), 2.27 (3H, s), 2.55 (2H, q, J = 7.2 Hz), 2.62-2.70 (4H, m), 2.72-2.86 (5H, m), 3.20-3.55 (2H, m), 3.80-3.91 (1H, m), 6.57 (1H, s), 6.66 (1H, d, J = 7.6 Hz), 6.94 (1H, d, J = 8.4 Hz), 7.15-7.21 (1H, m), 7.39 (1H, dd, J = 2.4, 8.4 Hz), 7.46-7.52 (2H, m), 11.02 (1H, s) XRD: 10.1, 14.5, 17.9, 22.1, 23.0
573	1H-NMR (DMSO-d6): 1.14-1.22 (6H, m), 1.43-1.65 (8H, m), 1.79-1.90 (4H, m), 2.25 (3H, s), 2.27 (3H, s), 2.30-2.70 (14H, m), 2.99-3.09 (2H, m), 3.86-3.98 (1H, m), 6.57 (2H, s), 6.62 (1H, d, J = 7.6 Hz), 6.93 (1H, d, J = 8.4 Hz), 7.15-7.21 (1H, m), 7.36 (1H, dd, J = 2.0, 8.4 Hz), 7.47-7.52 (2H, m), 11.03 (1H, s) XRD: 6.3, 13.7, 16.7, 17.7, 18.4

[Table 182]

Ex	Data
574	1H-NMR (DMSO-d6): 1.19 (3H, t, J = 7.6 Hz), 1.50-1.72 (4H, m), 1.80-1.93 (4H, m), 2.21 (3H, s), 2.24 (3H, s), 2.48-2.65 (13H, m), 2.99-3.08 (2H, m), 3.30-3.50 (2H, m), 3.90-4.00 (2H, m), 4.05-4.18 (1H, m), 6.56 (1H, s), 6.78 (1H, d, J = 7.6 Hz), 6.95 (1H, d, J = 8.4 Hz), 7.17-7.24 (1H, m), 7.34 (1H, dd, J = 2.4, 8.4 Hz), 7.46 (1H, d, J = 2.4 Hz), 7.49-7.55 (1H, m), 11.01 (1H, s) XRD: 11.5, 17.7, 19.1, 21.4, 22.3
575	1H-NMR (DMSO-d6): 1.17-1.33 (2H, m), 1.43-1.63 (4H, m), 1.79-1.94 (6H, m), 2.25 (3H, s), 2.26 (3H, s), 2.30-2.69 (11H, m), 2.99-3.89 (5H, m), 5.75 (2H, s), 6.95 (1H, d, J = 8.4 Hz), 7.07 (1H, d, J = 8.4 Hz), 7.31-7.35 (2H, m), 7.47-7.49 (1H, m), 7.54 (1H, s), 11.19 (1H, s) XRD: 5,6, 8.0, 17.8, 18.6, 24.0
576	1H-NMR (DMSO-d6): 1.18 (3H, t, J = 7.2 Hz), 1.44-1.72 (4H, m), 1.80-1.97 (4H, m), 2.21 (3H, s), 2.25-2.72 (13H, m), 3.30-3.70 (4H, m), 3.90-3.98 (2H, m), 3.99-4.11 (1H, m), 6.55 (1H, s), 6.78 (1H, d, J = 7.6 Hz), 6.85-6.93 (2H, m), 7.14-7.21 (1H, m), 7.43-7.52 (3H, m), 10.89 (1H, s) XRD: 8.9, 16.6, 13.1, 20.1, 22.4

(continued)

Ex	Data
577	1H-NMR (DMSO-d6): 1.19 (3H, t, J = 7.6 Hz), 1.49-1.70 (4H, m), 1.77-1.91 (4H, m), 2.21 (3H, s), 2.26-2.70 (13H, m), 3.29-3.43 (4H, m), 3.81 (3H, s), 3.88-3.97 (2H, m), 4.06-4.18 (1H, m), 6.55 (1H, s), 6.77 (1H, d, J = 7.6 Hz), 6.82 (1H, d, J = 8.4 Hz), 7.03 (1H, d, J = 2.0 Hz), 7.18-7.29 (2H, m), 7.49-7.55 (1H, m), 11.01 (1H, s) XRD: 11.6, 17.7, 19.2, 21.5, 22.4
578	1H-NMR (DMSO-d6): 1.15 (6H, d, J = 6.8 Hz), 1.42-1.70 (4H, m), 1.78-1.92 (4H, m), 2.21 (3H, s), 2.26-2.72 (11H, m), 3.08-3.21 (1H, m), 3.34-3.48 (2H, m), 3.56-3.69 (2H, m), 3.87-3.98 (2H, m), 4.00-4.13 (1H, m), 6.55 (1H, s), 6.83 (1H, d, J = 7.6 Hz), 6.85-6.93 (2H, m), 7.15-7.22 (1H, m), 7.41-7.51 (3H, m), 10.87 (1H, s) XRD: 10.3, 16.9, 19.3, 19.9, 21.1

[Table 183]

Ex	Data
579	1H-NMR (DMSO-d6): 1.19 (3H, t, J = 7.6 Hz), 1.58-1.72 (2H, m), 1.84-1.94 (2H, m), 2.26 (3H, s), 2.45-2.64 (6H, m), 2.91-3.02 (4H, m), 3.33-3.49 (2H, m), 3.91-3.99 (2H, m), 4.02-4.14 (1H, m), 6.59 (1H, s), 6.86-6.92 (1H, m), 6.93-7.04 (2H, m), 7.24-7.30 (1H, m), 7.52-7.59 (1H, m), 7.88 (1H, dd, J = 2.4, 16 Hz), 11.18 (1H, s) XRD: 5.7, 11.5, 18.2, 23.6, 23.9
580	1H-NMR (DMSO-d6): 1.16 (6H, d, J = 6,8 Hz), 1.57-1.70 (2H, m), 1.80-1.89 (2H, m), 2.29 (3H, s), 2.48-2.60 (4H, m), 2.89-3.00 (4H, m), 3.10-3.22 (1H, m), 3.30-3.42 (2H, m), 3.81 (3H, s), 3.87-3.96 (2H, m), 4.06-4.19 (1H, m), 6.58 (1H, s), 6.78-6.86 (2H, m), 7.04 (1H, d, J = 2.0 Hz), 7.19-7.30 (2H, m), 7.46-7.53 (1H, m), 11.00 (1H, s) XRD: 8.2, 11.8, 15.9, 18.0, 21.3
581	1H-NMR (DMSO-d6): 1.15 (6H, d, J = 6.4 Hz), 1.55-1.70 (2H, m), 1.81-1.91 (2H, m), 2.27 (3H, s), 2.47-2.55 (4H, m), 3.01-3.22 (5H, m), 3.34-3.50 (2H, m), 3.88-3.98 (2H, m), 4.00-4.13 (1H, m), 6.59 (1H, s), 6.83 (1H, d, J = 7.2 Hz), 6.86-6.92 (2H, m), 7.16-7.23 (1H, m), 7.43-7.51 (3H, m), 10.89 (1H, s) XRD: 11.1, 17.2, 19.5, 20.1, 20.5
582	1H-NMR (DMSO-d6): 1.19 (3H, t, J = 7.2 Hz), 1.43-1.57 (2H, m), 1.58-1.71 (2H, m), 1.74-1.91 (4H, m), 2.03-2.16 (2H, m), 2.20-2.30 (8H, m), 2.53-2.69 (5H, m), 2.74-2.84 (4H, m), 2.87-2.98 (2H, m), 3.34-3.45 (2H, m), 3.89-3.99 (2H, m), 4.04-4.17 (1H, m), 6.52 (1H, s), 6.79 (1H, d, J = 7.6 Hz), 6.96 (1H, d, J = 8.4 Hz), 7.18-7.23 (1H, m), 7.36 (1H, dd, J = 2.4, 8.4 Hz), 7.46 (1H, d, J = 2.4 Hz), 7.49-7.54 (1H, m), 11.01 (1H, s) XRD: 8.1, 13.1, 15.1, 17.5, 23.8

[0227] Tables 184 to 201 show the structures of other compounds of the present invention. These compounds were synthesized, or can be synthesized, using the above preparation processes, processes described in the Examples, processes obvious to those skilled in the art, or modified processes thereof.

[0228] The meanings of the symbols in the tables are as follows.

No: Compound No.

$-R^{11}$ and $-R^{12}$: substituents in the general formulas.

cBu: cyclobutyl, 2Py: 2-pyridyl, 3Py: 3-pyridyl, 4Py: 4-pyridyl.

[Table 184]

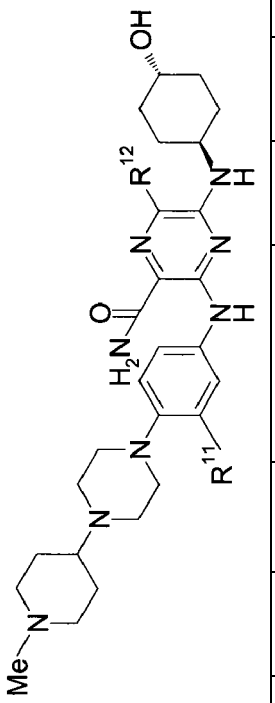
No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
A1#	-H	-H	A31#	-H	-Me	A61	-H	-Et
A2#	-Me	-H	A32#	-Me	-Me	A62	-Me	-Et
A3#	-Et	-H	A33#	-Et	-Me	A63	-Et	-Et
A4#	-nPr	-H	A34#	-nPr	-Me	A64	-nPr	-Et
A5#	-iPr	-H	A35#	-iPr	-Me	A65	-iPr	-Et
A6#	-cPr	-H	A36#	-cPr	-Me	A66#	-cPr	-Et
A7#	-cBu	-H	A37#	-cBu	-Me	A67#	-cBu	-Et
A8#		-H	A38#		-Me	A68#		-Et
A9#		-H	A39#		-Me	A69#		-Et
A10#		-H	A40#		-Me	A70#		-Et
All#	$-CF_3$	-H	A41#	$-CF_3$	-Me	A71	$-CF_3$	-Et
A12#	-CN	-H	A42#	-CN	-Me	A72#	-CN	-Et
A13#	-Ph	-H	A43#	-Ph	-Me	A73#	-Ph	-Et
A14#	-OMe	-H	A44#	-OMe	-Me	A74	-OMe	-Et

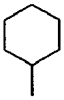
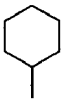
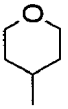
(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
A15#	-OEt	-H	A45#	-OEt	-Me	A75	-OEt	-Et
A16#	-OnPr	-H	A46#	-OnPr	-Me	A76	-OnPr	-Et
A17#	-OiPr	-H	A47#	-OiPr	-Me	A77	-OiPr	-Et
A18#	-OcPr	-H	A48#	-OcPr	-Me	A78#	-OcPr	-Et
A19#	$-OCH_2cPr$	-H	A49#	$-OCH_2cPr$	-Me	A79#	$-OCH_2cPr$	-Et
A20#	$-OCHCF_2$	-H	A50#	$-OCHCF_2$	-Me	A80	$-OCHCF_2$	-Et
A21#	$-OCF_3$	-H	A51#	$-OCF_3$	-Me	A81	$-OCF_3$	-Et
A22#	$-OCH_2CF_3$	-H	A52#	$-OCH_2CF_3$	-Me	A82	$-OCH_2CF_3$	-Et
A23#	$-OCH_2CH_2F$	-H	A53#	$-OCH_2CH_2F$	-Me	A83	$-OCH_2CH_2F$	-Et
A24#	$-OCH_2CH_2OMe$	-H	A54#	$-OCH_2CH_2OMe$	-Me	A84#	$-OCH_2CH_2OMe$	-Et
A25#	$-OCH_2CH_2NMe_2$	-H	A55#	$-OCH_2CH_2NMe_2$	-Me	A85#	$-OCH_2CH_2NMe_2$	-Et
A26#	-F	-H	A56#	-F	-Me	A86	-F	-Et
A27#	-Cl	-H	A57#	-Cl	-Me	A87	-Cl	-Et
A28#	-Br	-H	A58#	-Br	-Me	A88	-Br	-Et
A29#	-I	-H	A59#	-I	-Me	A89	-I	-Et
A30a#	-2Py	-H	A60a#	-2Py	-Me	A90a#	-2Py	-Et
A30b#	-3Py	-H	A60b#	-3Py	-Me	A90b#	-3Py	-Et
A30c#	-4Py	-H	A60c#	-4Py	-Me	A90c#	-4Py	-Et

(# not part of the invention)

[Table 185]



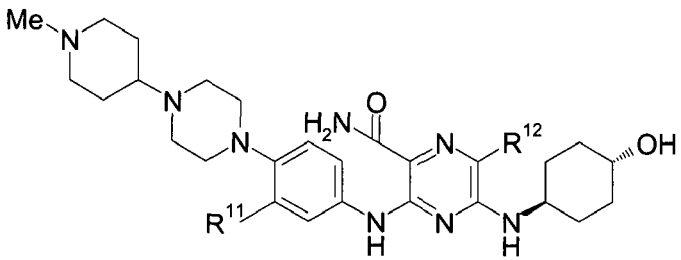
No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
B1#	-H	-nPr	B31	-H	-iPr	B61#	-H	-cPr
B2#	-Me	-nPr	B32	-Me	-iPr	B62#	-Me	-cPr
B3#	-Et	-nPr	B33	-Et	-iPr	B63#	-Et	-cPr
B4#	-nPr	-nPr	B34	-nPr	-iPr	B64#	-nPr	-cPr
B5#	-iPr	-nPr	B35	-iPr	-iPr	B65#	-iPr	-cPr
B6#	-cPr	-nPr	B36#	-cPr	-iPr	B66#	-cPr	-cPr
B7#	-cBu	-nPr	B37#	-cBu	-iPr	B67#	-cBu	-cPr
B8#		-nPr	B38#		-iPr	B68#		-cPr
B9#		-nPr	B39#		-iPr	B69#		-cPr
B10#		-nPr	B40#		-iPr	B70#		-cPr
B11#	$-CF_3$	-nPr	B41	$-CF_3$	-iPr	B71#	$-CF_3$	-cPr
B12#	-CN	-nPr	B42#	-CN	-iPr	B72#	-CN	-cPr
B13#	-Ph	-nPr	B43#	-Ph	-iPr	B73#	-Ph	-cPr
B14#	-OMe	-nPr	B44	-OMe	-iPr	B74#	-OMe	-cPr

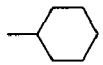
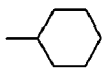
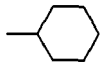
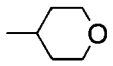
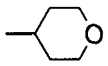
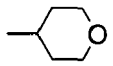
(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
B15#	-OEt	-nPr	B45	-OEt	-iPr	B75#	-OEt	-cPr
B16#	-OnPr	-nPr	B46	-OnPr	-iPr	B76#	-OnPr	-cPr
B17#	-OiPr	-nPr	B47	-OiPr	-iPr	B77#	-OiPr	-cPr
B18#	-OcPr	-nPr	B48#	-OcPr	-iPr	B78#	-OcPr	-cPr
B19#	$-OCH_2cPr$	-nPr	B49#	$-OCH_2cPr$	-iPr	B79#	$-OCH_2cPr$	-cPr
B20#	$-OCHCF_2$	-nPr	B50	$-OCHCF_2$	-iPr	B80#	$-OCHCF_2$	-cPr
B21#	$-OCF_3$	-nPr	B51	$-OCF_3$	-iPr	B81#	$-OCF_3$	-cPr
B22#	$-OCH_2CF_3$	-nPr	B52	$-OCH_2CF_3$	-iPr	B82#	$-OCH_2CF_3$	-cPr
B23#	$-OCH_2CH_2F$	-nPr	B53	$-OCH_2CH_2F$	-iPr	B83#	$-OCH_2CH_2F$	-cPr
B24#	$-OCH_2CH_2OMe$	-nPr	B54#	$-OCH_2CH_2OMe$	-iPr	B84#	$-OCH_2CH_2OMe$	-cPr
B25#	$-OCH_2CH_2NMe_2$	-nPr	B55#	$-OCH_2CH_2NMe_2$	-iPr	B85#	$-OCH_2CH_2NMe_2$	-cPr
B26#	-F	-nPr	B56	-F	-iPr	B86#	-F	-cPr
B27#	-Cl	-nPr	B57	-Cl	-iPr	B87#	-Cl	-cPr
B28#	-Br	-nPr	B58	-Br	-iPr	B88#	-Br	-cPr
B29#	-I	-nPr	B59	-I	-iPr	B89#	-I	-cPr
B30a#	-2Py	-nPr	B60a#	-2Py	-iPr	B90a#	-2Py	-cPr
B30b#	-3Py	-nPr	B60b#	-3Py	-iPr	B90b#	-3Py	-cPr
B30c#	-4Py	-nPr	B60c#	-4Py	-iPr	B90c#	-4Py	-cPr

(# not part of the invention)

[Table 186]



No	-R^{11}	-R^{12}	No	-R^{11}	-R^{12}	No	-R^{11}	-R^{12}
C1	-H	-Cl	C31#	-H	-Br	C61#	-H	-I
C2	-Me	-Cl	C32#	-Me	-Br	C62#	-Me	-I
C3	-Et	-Cl	C33#	-Et	-Br	C63#	-Et	-I
C4	-nPr	-Cl	C34#	-nPr	-Br	C64#	-nPr	-I
C5	-iPr	-Cl	C35#	-iPr	-Br	C65#	-iPr	-I
C6#	-cPr	-Cl	C36#	-cPr	-Br	C66#	-cPr	-I
C7#	-cBu	-Cl	C37#	-cBu	-Br	C67#	-cBu	-I
C8#		-Cl	C38#		-Br	C68#		-I
C9#		-Cl	C39#		-Br	C69#		-I
C10#		-Cl	C40#		-Br	C70#		-I
C11	-CF_3	-Cl	C41#	-CF_3	-Br	C71#	-CF_3	-I
C12#	-CN	-Cl	C42#	-CN	-Br	C72#	-CN	-I
C13#	-Ph	-Cl	C43#	-Ph	-Br	C73#	-Ph	-I
C14	-OMe	-Cl	C44#	-OMe	-Br	C74#	-OMe	-I

(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
C15	-OEt	-Cl	C45#	-OEt	-Br	C75#	-OEt	-I
C16	-OnPr	-Cl	C46#	-OnPr	-Br	C76#	-OnPr	-I
C17	-OiPr	-Cl	C47#	-OiPr	-Br	C77#	-OiPr	-I
C18#	-OcPr	-Cl	C48#	-OcPr	-Br	C78#	-OcPr	-I
C19#	$-OCH_2cPr$	-Cl	C49#	$-OCH_2cPr$	-Br	C79#	$-OCH_2cPr$	-I
C20	$-OCHCF_2$	-Cl	C50#	$-OCHCF_2$	-Br	C80#	$-OCHCF_2$	-I
C21	$-OCF_3$	-Cl	C51#	$-OCF_3$	-Br	C81#	$-OCF_3$	-I
C22	$-OCH_2CF_3$	-Cl	C52#	$-OCH_2CF_3$	-Br	C82#	$-OCH_2CF_3$	-I
C23	$-OCH_2CH_2F$	-Cl	C53#	$-OCH_2CH_2F$	-Br	C83#	$-OCH_2CH_2F$	-I
C24#	$-OCH_2CH_2OMe$	-Cl	C54#	$-OCH_2CH_2OMe$	-Br	C84#	$-OCH_2CH_2OMe$	-I
C25#	$-OCH_2CH_2NMe_2$	-Cl	C55#	$-OCH_2CH_2NMe_2$	-Br	C85#	$-OCH_2CH_2NMe_2$	-I
C26	-F	-Cl	C56#	-F	-Br	C86#	-F	-I
C27	-Cl	-Cl	C57#	-Cl	-Br	C87#	-Cl	-I
C28	-Br	-Cl	C58#	-Br	-Br	C88#	-Br	-I
C29	-I	-Cl	C59#	-I	-Br	C89#	-I	-I
C30a#	-2Py	-Cl	C60a#	-2Py	-Br	C90a#	-2Py	-I
C30b#	-3Py	-Cl	C60b#	-3Py	-Br	C90b#	-3Py	-I
C30c#	-4Py	-Cl	C60c#	-4Py	-Br	C90c#	-4Py	-I

(# not part of the invention)

[Table 187]

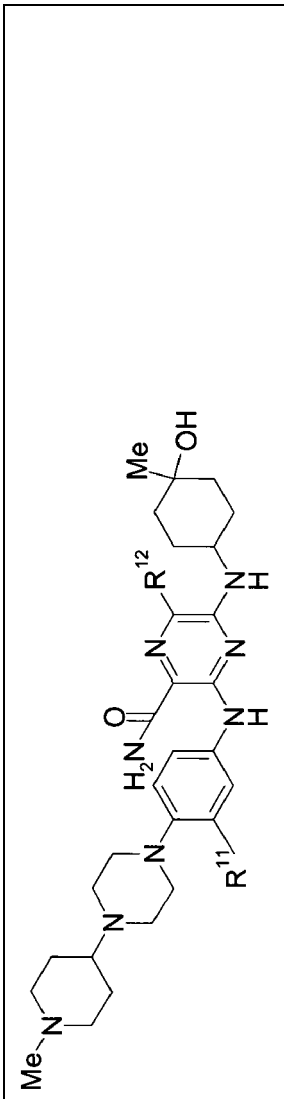
No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
D1#	-H	-H	D31#	-H	-Me	D61	-H	-Et
D2#	-Me	-H	D32#	-Me	-Me	D62	-Me	-Et
D3#	-Et	-H	D33#	-Et	-Me	D63	-Et	-Et
D4#	-nPr	-H	D34#	-nPr	-Me	D64	-nPr	-Et
D5#	-iPr	-H	D35#	-iPr	-Me	D65	-iPr	-Et
D6#	-cPr	-H	D36#	-cPr	-Me	D66#	-cPr	-Et
D7#	-cBu	-H	D37#	-cBu	-Me	D67#	-cBu	-Et
D8#		-H	D38#		-Me	D68#		-Et
D9#		-H	D39#		-Me	D69#		-Et
D10#		-H	D40#		-Me	D70#		-Et
D11#	$-CF_3$	-H	D41#	$-CF_3$	-Me	D71	$-CF_3$	-Et
D12#	-CN	-H	D42#	-CN	-Me	D72#	-CN	-Et
D13#	-Ph	-H	D43#	-Ph	-Me	D73#	-Ph	-Et
D14#	-OMe	-H	D44#	-OMe	-Me	D74	-OMe	-Et
D15#	-OEt	-H	D45#	-OEt	-Me	D75	-OEt	-Et

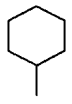
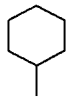
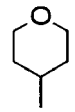
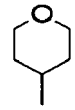
(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
D16#	-OnPr	-H	D46#	-OnPr	-Me	D76	-OnPr	-Et
D17#	-OiPr	-H	D47#	-OiPr	-Me	D77	-OiPr	-Et
D18#	-OcPr	-H	D48#	-OcPr	-Me	D78#	-OcPr	-Et
D19#	$-OCH_2cPr$	-H	D49#	$-OCH_2cPr$	-Me	D79#	$-OCH_2cPr$	-Et
D20#	$-OCHCF_2$	-H	D50#	$-OCHCF_2$	-Me	D80	$-OCHCF_2$	-Et
D21#	$-OCF_3$	-H	D51#	$-OCF_3$	-Me	D81	$-OCF_3$	-Et
D22#	$-OCH_2CF_3$	-H	D52#	$-OCH_2CF_3$	-Me	D82	$-OCH_2CF_3$	-Et
D23#	$-OCH_2CH_2F$	-H	D53#	$-OCH_2CH_2F$	-Me	D83	$-OCH_2CH_2F$	-Et
D24#	$-OCH_2CH_2OMe$	-H	D54#	$-OCH_2CH_2OMe$	-Me	D84#	$-OCH_2CH_2OMe$	-Et
D25#	$-OCH_2CH_2NMe_2$	-H	D55#	$-OCH_2CH_2NMe_2$	-Me	D85#	$-OCH_2CH_2NMe_2$	-Et
D26#	-F	-H	D56#	-F	-Me	D86	-F	-Et
D27#	-Cl	-H	D57#	-Cl	-Me	D87	-Cl	-Et
D28#	-Br	-H	D58#	-Br	-Me	D88	-Br	-Et
D29#	-I	-H	D59#	-I	-Me	D89	-I	-Et
D30a#	-2Py	-H	D60a#	-2Py	-Me	D90a#	-2Py	-Et
D30b#	-3Py	-H	D60b#	-3Py	-Me	D90b#	-3Py	-Et
D30c#	-4Py	-H	D60c#	-4Py	-Me	D90c#	-4Py	-Et

(# not part of the invention)

[Table 188]



No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
E1#	-H	-nPr	E31	-H	-iPr	E61#	-H	-cPr
E2#	-Me	-nPr	E32	-Me	-iPr	E62#	-Me	-cPr
E3#	-Et	-nPr	E33	-Et	-iPr	E63#	-Et	-cPr
E4#	-nPr	-nPr	E34	-nPr	-iPr	E64#	-nPr	-cPr
E5#	-iPr	-nPr	E35	-iPr	-iPr	E65#	-iPr	-cPr
E6#	-cPr	-nPr	E36#	-cPr	-iPr	E66#	-cPr	-cPr
E7#	-cBu	-nPr	E37#	-cBu	-iPr	E67#	-cBu	-cPr
E8#		-nPr	E38#		-iPr	E68#		-cPr
E9#		-nPr	E39#		-iPr	E69#		-cPr
E10#		-nPr	E40#		-iPr	E70#		-cPr
E11#	$-CF_3$	-nPr	E41	$-CF_3$	-iPr	E71#	$-CF_3$	-cPr
E12#	-CN	-nPr	E42#	-CN	-iPr	E72#	-CN	-cPr
E13#	-Ph	-nPr	E43#	-Ph	-iPr	E73#	-Ph	-cPr
E14#	-OMe	-nPr	E44	-OMe	-iPr	E74#	-OMe	-cPr
E15#	-OEt	-nPr	E45	-OEt	-iPr	E75#	-OEt	-cPr

(continued)

No	$-R^{11}$	$-R^{12}$		No	$-R^{11}$	$-R^{12}$		No	$-R^{11}$	$-R^{12}$
E16#	-OnPr	-nPr		E46	-OnPr	-iPr		E76#	-OnPr	-cPr
E17#	-OiPr	-nPr		E47	-OiPr	-iPr		E77#	-OiPr	-cPr
E18#	-OcPr	-nPr		E48#	-OcPr	-iPr		E78#	-OcPr	-cPr
E19#	$-OCH_2cPr$	-nPr		E49#	$-OCH_2cPr$	-iPr		E79#	$-OCH_2cPr$	-cPr
E20#	$-OCHCF_2$	-nPr		E50	$-OCHCF_2$	-iPr		E80#	$-OCHCF_2$	-cPr
E21#	$-OCF_3$	-nPr		E51	$-OCF_3$	-iPr		E81#	$-OCF_3$	-cPr
E22#	$-OCH_2CF_3$	-nPr		E52	$-OCH_2CF_3$	-iPr		E82#	$-OCH_2CF_3$	-cPr
E23#	$-OCH_2CH_2F$	-nPr		E53	$-OCH_2CH_2F$	-iPr		E83#	$-OCH_2CH_2F$	-cPr
E24#	$-OCH_2CH_2OMe$	-nPr		E54#	$-OCH_2CH_2OMe$	-iPr		E84#	$-OCH_2CH_2OMe$	-cPr
E25#	$-OCH_2CH_2NMe_2$	-nPr		E55#	$-OCH_2CH_2NMe_2$	-iPr		E85#	$-OCH_2CH_2NMe_2$	-cPr
E26#	-F	-nPr		E56	-F	-iPr		E86#	-F	-cPr
E27#	-Cl	-nPr		E57	-Cl	-iPr		E87#	-Cl	-cPr
E28#	-Br	-nPr		E58	-Br	-iPr		E88#	-Br	-cPr
E29#	-I	-nPr		E59	-I	-iPr		E89#	-I	-cPr
E30a#	-2Py	-nPr		E60a#	-2Py	-iPr		E90a#	-2Py	-cPr
E30b#	-3Py	-nPr		E60b#	-3Py	-iPr		E90b#	-3Py	-cPr
E30c#	-4Py	-nPr		E60c#	-4Py	-iPr		E90c#	-4Py	-cPr

(# not part of the invention)

[Table 189]

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
F1	-H	-Cl	F31#	-H	-Br	F61#	-H	-I
F2	-Me	-Cl	F32#	-Me	-Br	F62#	-Me	-I
F3	-Et	-Cl	F33#	-Et	-Br	F63#	-Et	-I
F4	-nPr	-Cl	F34#	-nPr	-Br	F64#	-nPr	-I
F5	-iPr	-Cl	F35#	-iPr	-Br	F65#	-iPr	-I
F6#	-cPr	-Cl	F36#	-cPr	-Br	F66#	-cPr	-I
F7#	-cBu	-Cl	F37#	-cBu	-Br	F67#	-cBu	-I
F8#		-Cl	F38#		-Br	F68#		-I
F9#		-Cl	F39#		-Br	F69#		-I
F10#		-Cl	F40#		-Br	F70#		-I
F11	$-CF_3$	-Cl	F41#	$-CF_3$	-Br	F71#	$-CF_3$	-I
F12#	-CN	-Cl	F42#	-CN	-Br	F72#	-CN	-I
F13#	-Ph	-Cl	F43#	-Ph	-Br	F73#	-Ph	-I
F14	-OMe	-Cl	F44#	-OMe	-Br	F74#	-OMe	-I
F15	-OEt	-Cl	F45#	-OEt	-Br	F75#	-OEt	-I

(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
F16	-OnPr	-Cl	F46#	-OnPr	-Br	F76#	-OnPr	-I
F17	-OiPr	-Cl	F47#	-OiPr	-Br	F77#	-OiPr	-I
F18#	-OcPr	-Cl	F48#	-OcPr	-Br	F78#	-OcPr	-I
F19#	$-OCH_2cPr$	-Cl	F49#	$-OCH_2cPr$	-Br	F79#	$-OCH_2cPr$	-I
F20	$-OCHCF_2$	-Cl	F50#	$-OCHCF_2$	-Br	F80#	$-OCHCF_2$	-I
F21	$-OCF_3$	-Cl	F51#	$-OCF_3$	-Br	F81#	$-OCF_3$	-I
F22	$-OCH_2CF_3$	-Cl	F52#	$-OCH_2CF_3$	-Br	F82#	$-OCH_2CF_3$	-I
F23	$-OCH_2CH_2F$	-Cl	F53#	$-OCH_2CH_2F$	-Br	F83#	$-OCH_2CH_2F$	-I
F24#	$-OCH_2CH_2OMe$	-Cl	F54#	$-OCH_2CH_2OMe$	-Br	F84#	$-OCH_2CH_2OMe$	-I
F25#	$-OCH_2CH_2NMe_2$	-Cl	F55#	$-OCH_2CH_2NMe_2$	-Br	F85#	$-OCH_2CH_2NMe_2$	-I
F26	-F	-Cl	F56#	-F	-Br	F86#	-F	-I
F27	-Cl	-Cl	F57#	-Cl	-Br	F87#	-Cl	-I
F28	-Br	-Cl	F58#	-Br	-Br	F88#	-Br	-I
F29	-I	-Cl	F59#	-I	-Br	F89#	-I	-I
F30a#	-2Py	-Cl	F60a#	-2Py	-Br	F90a#	-2Py	-I
F30b#	-3Py	-Cl	F60b#	-3Py	-Br	F90b#	-3Py	-I
F30c#	-4Py	-Cl	F60c#	-4Py	-Br	F90c#	-4Py	-I

(# not part of the invention)

[Table 190]

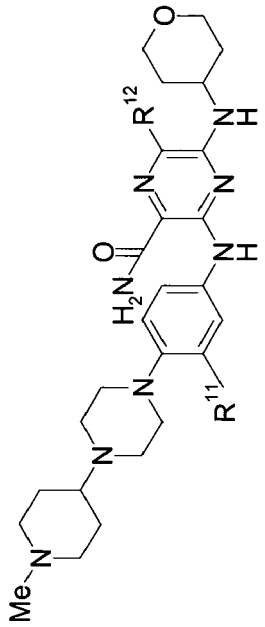
No	R^{11}	R^{12}	No	R^{11}	R^{12}	No	R^{11}	R^{12}
G1#	-H	-H	G31#	-H	-Me	G61	-H	-Et
G2#	-Me	-H	G32#	-Me	-Me	G62	-Me	-Et
G3#	-Et	-H	G33#	-Et	-Me	G63	-Et	-Et
G4#	-nPr	-H	G34#	-nPr	-Me	G64	-nPr	-Et
G5#	-iPr	-H	G35#	-iPr	-Me	G65	-iPr	-Et
G6#	-cPr	-H	G36#	-cPr	-Me	G66#	-cPr	-Et
G7#	-cBu	-H	G37#	-cBu	-Me	G67#	-cBu	-Et
G8#		-H	G38#		-Me	G68#		-Et
G9#		-H	G39#		-Me	G69#		-Et
G10#		-H	G40#		-Me	G70#		-Et
G11#	$-CF_3$	-H	G41#	$-CF_3$	-Me	G71	$-CF_3$	-Et
G12#	-CN	-H	G42#	-CN	-Me	G72#	-CN	-Et
G13#	-Ph	-H	G43#	-Ph	-Me	G73#	-Ph	-Et
G14#	-OMe	-H	G44#	-OMe	-Me	G74	-OMe	-Et
G15#	-OEt	-H	G45#	-OEt	-Me	G75	-OEt	-Et

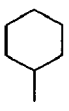
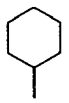
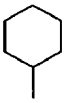
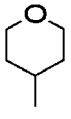
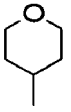
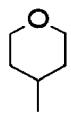
(continued)

No	R^{11}	R^{12}	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
G16#	-OnPr	-H	G46#	-OnPr	-Me	G76	-OnPr	-Et
G17#	-OiPr	-H	G47#	-OiPr	-Me	G77	-OiPr	-Et
G18#	-OcPr	-H	G48#	-OcPr	-Me	G78#	-OcPr	-Et
G19#	$-OCH_2cPr$	-H	G49#	$-OCH_2cPr$	-Me	G79#	$-OCH_2cPr$	-Et
G20#	$-OCHCF_2$	-H	G50#	$-OCHCF_2$	-Me	G80	$-OCHCF_2$	-Et
G21#	$-OCF_3$	-H	G51#	$-OCF_3$	-Me	G81	$-OCF_3$	-Et
G22#	$-OCH_2CF_3$	-H	G52#	$-OCH_2CF_3$	-Me	G82	$-OCH_2CF_3$	-Et
G23#	$-OCH_2CH_2F$	-H	G53#	$-OCH_2CH_2F$	-Me	G83	$-OCH_2CH_2F$	-Et
G24#	$-OCH_2CH_2OMe$	-H	G54#	$-OCH_2CH_2OMe$	-Me	G84#	$-OCH_2CH_2OMe$	-Et
G25#	$-OCH_2CH_2NMe_2$	-H	G55#	$-OCH_2CH_2NMe_2$	-Me	G85#	$-OCH_2CH_2NMe_2$	-Et
G26#	-F	-H	G56#	-F	-Me	G86	-F	-Et
G27#	-Cl	-H	G57#	-Cl	-Me	G87	-Cl	-Et
G28#	-Br	-H	G58#	-Br	-Me	G88	-Br	-Et
G29#	-I	-H	G59#	-I	-Me	G89	-I	-Et
G30a#	-2Py	-H	G60a#	-2Py	-Me	G90a#	-2Py	-Et
G30b#	-3Py	-H	G60b#	-3Py	-Me	G90b#	-3Py	-Et
G30c#	-4Py	-H	G60c#	-4Py	-Me	G90c#	-4Py	-Et

(# not part of the invention)

[Table 191]



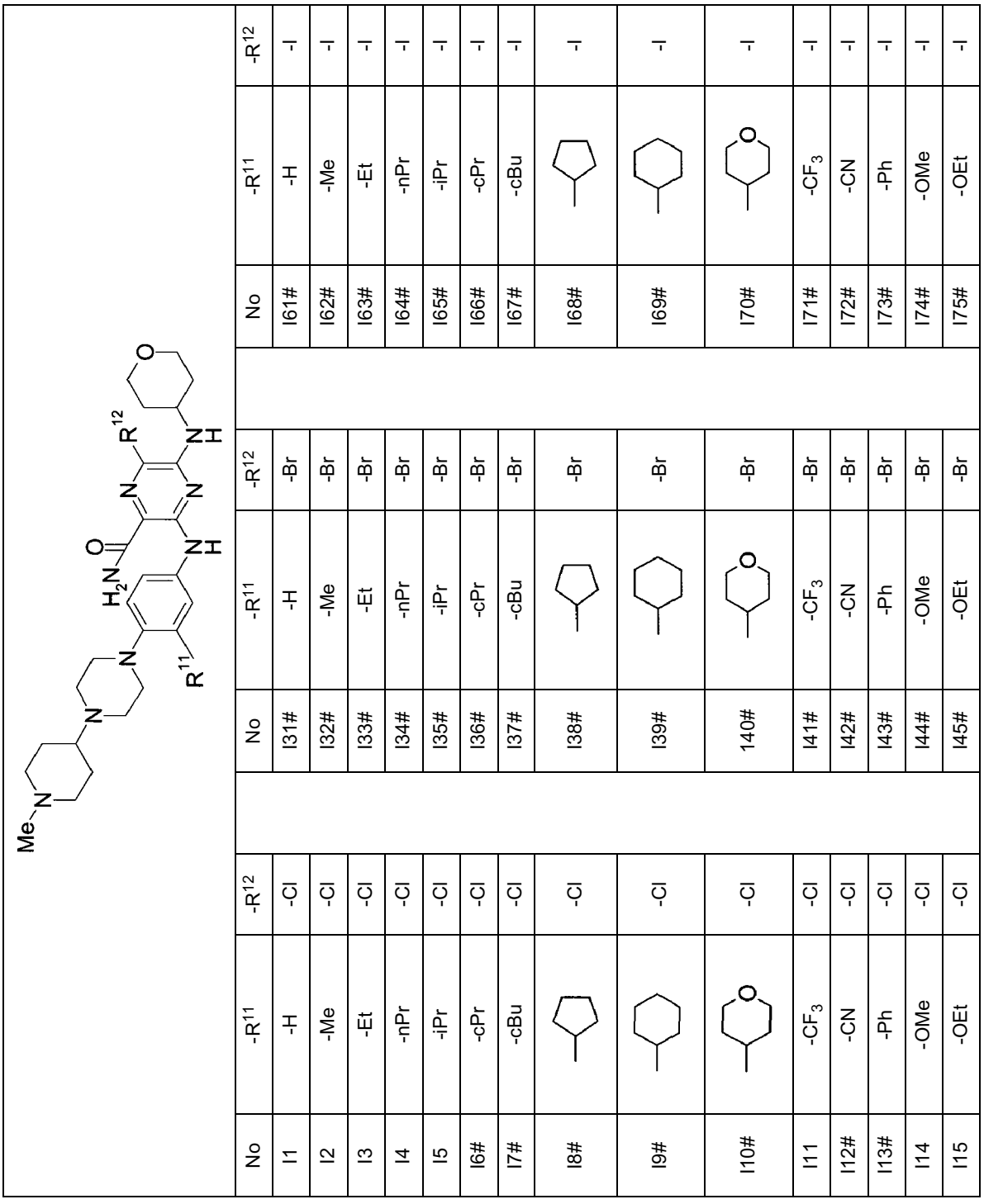
No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
H1#	-H	-nPr	H31	-H	-iPr	H61#	-H	-cPr
H2#	-Me	-nPr	H32	-Me	-iPr	H62#	-Me	-cPr
H3#	-Et	-nPr	H33	-Et	-iPr	H63#	-Et	-cPr
H4#	-nPr	-nPr	H34	-nPr	-iPr	H64#	-nPr	-cPr
H5#	-iPr	-nPr	H35	-iPr	-iPr	H65#	-iPr	-cPr
H6#	-cPr	-nPr	H36#	-cPr	-iPr	H66#	-cPr	-cPr
H7#	-cBu	-nPr	H37#	-cBu	-iPr	H67#	-cBu	-cPr
H8#		-nPr	H38#		-iPr	H68#		-cPr
H9#		-nPr	H39#		-iPr	H69#		-cPr
H10#		-nPr	H40#		-iPr	H70#		-cPr
H11#	$-CF_3$	-nPr	H41	$-CF_3$	-iPr	H71#	$-CF_3$	-cPr
H12#	-CN	-nPr	H42#	-CN	-iPr	H72#	-CN	-cPr
H13#	-Ph	-nPr	H43#	-Ph	-iPr	H73#	-Ph	-cPr
H14#	-OMe	-nPr	H44	-OMe	-iPr	H74#	-OMe	-cPr
H15#	-OEt	-nPr	H45	-OEt	-iPr	H75#	-OEt	-cPr

(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
H16#	-OnPr	-nPr	H46	-OnPr	-iPr	H76#	-OnPr	-cPr
H17#	-OiPr	-nPr	H47	-OiPr	-iPr	H77#	-OiPr	-cPr
H18#	-OcPr	-nPr	H48#	-OcPr	-iPr	H78#	-OcPr	-cPr
H19#	$-OCH_2cPr$	-nPr	H49#	$-OCH_2cPr$	-iPr	H79#	$-OCH_2cPr$	-cPr
H20#	$-OCHCF_2$	-nPr	H50	$-OCHCF_2$	-iPr	H80#	$-OCHCF_2$	-cPr
H21#	$-OCF_3$	-nPr	H51	$-OCF_3$	-iPr	H81#	$-OCF_3$	-cPr
H22#	$-OCH_2CF_3$	-nPr	H52	$-OCH_2CF_3$	-iPr	H82#	$-OCH_2CF_3$	-cPr
H23#	$-OCH_2CH_2F$	-nPr	H53	$-OCH_2CH_2F$	-iPr	H83#	$-OCH_2CH_2F$	-cPr
H24#	$-OCH_2CH_2OMe$	-nPr	H54#	$-OCH_2CH_2OMe$	-iPr	H84#	$-OCH_2CH_2OMe$	-cPr
H25#	$-OCH_2CH_2NMe_2$	-nPr	H55#	$-OCH_2CH_2NMe_2$	-iPr	H85#	$-OCH_2CH_2NMe_2$	-cPr
H26#	-F	-nPr	H56	-F	-iPr	H86#	-F	-cPr
H27#	-Cl	-nPr	H57	-Cl	-iPr	H87#	-Cl	-cPr
H28#	-Br	-nPr	H58	-Br	-iPr	H88#	-Br	-cPr
H29#	-I	-nPr	H59	-I	-iPr	H89#	-I	-cPr
H30a#	-2Py	-nPr	H60a#	-2Py	-iPr	H90a#	-2Py	-cPr
H30b#	-3Py	-nPr	H60b#	-3Py	-iPr	H90b#	-3Py	-cPr
H30c#	-4Py	-nPr	H60c#	-4Py	-iPr	H90c#	-4Py	-cPr

(# not part of the invention)

[Table 192]



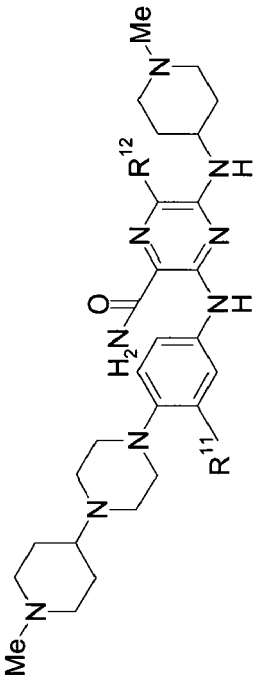
No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
I1	-H	-Cl	I31#	-H	-Br	I61#	-H	-I
I2	-Me	-Cl	I32#	-Me	-Br	I62#	-Me	-I
I3	-Et	-Cl	I33#	-Et	-Br	I63#	-Et	-I
I4	-nPr	-Cl	I34#	-nPr	-Br	I64#	-nPr	-I
I5	-iPr	-Cl	I35#	-iPr	-Br	I65#	-iPr	-I
I6#	-cPr	-Cl	I36#	-cPr	-Br	I66#	-cPr	-I
I7#	-cBu	-Cl	I37#	-cBu	-Br	I67#	-cBu	-I
I8#		-Cl	I38#		-Br	I68#		-I
I9#		-Cl	I39#		-Br	I69#		-I
I10#		-Cl	140#		-Br	I70#		-I
I11	$-CF_3$	-Cl	I41#	$-CF_3$	-Br	I71#	$-CF_3$	-I
I12#	-CN	-Cl	I42#	-CN	-Br	I72#	-CN	-I
I13#	-Ph	-Cl	I43#	-Ph	-Br	I73#	-Ph	-I
I14	-OMe	-Cl	I44#	-OMe	-Br	I74#	-OMe	-I
I15	-OEt	-Cl	I45#	-OEt	-Br	I75#	-OEt	-I

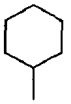
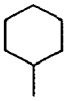
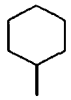
(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
I16	-OnPr	-Cl	I46#	-OnPr	-Br	I76#	-OnPr	-I
I17	-OiPr	-Cl	I47#	-OiPr	-Br	I77#	-OiPr	-I
I18#	-OcPr	-Cl	I48#	-OcPr	-Br	I78#	-OcPr	-I
I19#	$-OCH_2cPr$	-Cl	I49#	$-OCH_2cPr$	-Br	I79#	$-OCH_2cPr$	-I
I20	$-OCHCF_2$	-Cl	I50#	$-OCHCF_2$	-Br	I80#	$-OCHCF_2$	-I
I21	$-OCF_3$	-Cl	I51#	$-OCF_3$	-Br	I81#	$-OCF_3$	-I
I22	$-OCH_2CF_3$	-Cl	I52#	$-OCH_2CF_3$	-Br	I82#	$-OCH_2CF_3$	-I
I23	$-OCH_2CH_2F$	-Cl	I53#	$-OCH_2CH_2F$	-Br	I83#	$-OCH_2CH_2F$	-I
I24#	$-OCH_2CH_2OMe$	-Cl	I54#	$-OCH_2CH_2OMe$	-Br	I84#	$-OCH_2CH_2OMe$	-I
I25#	$-OCH_2CH_2NMe_2$	-Cl	I55#	$-OCH_2CH_2NMe_2$	-Br	I85#	$-OCH_2CH_2NMe_2$	-I
I26	-F	-Cl	I56#	-F	-Br	I86#	-F	-I
I27	-Cl	-Cl	I57#	-Cl	-Br	I87#	-Cl	-I
I28	-Br	-Cl	I58#	-Br	-Br	I88#	-Br	-I
I29	-I	-Cl	I59#	-I	-Br	I89#	-I	-I
I30a#	-2Py	-Cl	I60a#	-2Py	-Br	I90a#	-2Py	-I
I30b#	-3Py	-Cl	I60b#	-3Py	-Br	I90b#	-3Py	-I
I30c#	-4Py	-Cl	I60c#	-4Py	-Br	I90c#	-4Py	-I

(# not part of the invention)

[Table 193]



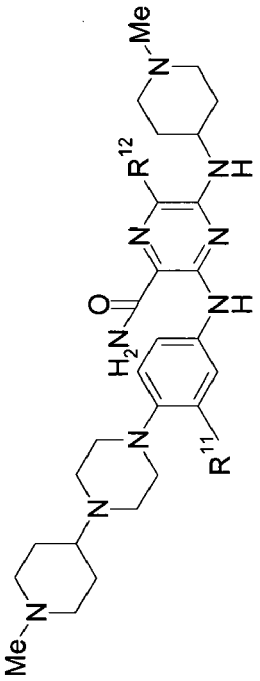
No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
J1#	-H	-H	J31#	-H	-Me	J61	-H	-Et
J2#	-Me	-H	J32#	-Me	-Me	J62	-Me	-Et
J3#	-Et	-H	J33#	-Et	-Me	J63	-Et	-Et
J4#	-nPr	-H	J34#	-nPr	-Me	J64	-nPr	-Et
J5#	-iPr	-H	J35#	-iPr	-Me	J65	-iPr	-Et
J6#	-cPr	-H	J36#	-cPr	-Me	J66#	-cPr	-Et
J7#	-cBu	-H	J37#	-cBu	-Me	J67#	-cBu	-Et
J8#		-H	J38#		-Me	J68#		-Et
J9#		-H	J39#		-Me	J69#		-Et
J10#		-H	J40#		-Me	J70#		-Et
J11#	$-CF_3$	-H	J41#	$-CF_3$	-Me	J71	$-CF_3$	-Et
J12#	-CN	-H	J42#	-CN	-Me	J72#	-CN	-Et
J13#	-Ph	-H	J43#	-Ph	-Me	J73#	-Ph	-Et
J14#	-OMe	-H	J44#	-OMe	-Me	J74	-OMe	-Et
J15#	-OEt	-H	J45#	-OEt	-Me	J75	-OEt	-Et

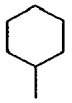
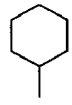
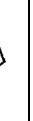
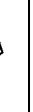
(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
J16#	-OnPr	-H	J46#	-OnPr	-Me	J76	-OnPr	-Et
J17#	-OiPr	-H	J47#	-OiPr	-Me	J77	-OiPr	-Et
J18#	-OcPr	-H	J48#	-OcPr	-Me	J78#	-OcPr	-Et
J19#	$-OCH_2cPr$	-H	J49#	$-OCH_2cPr$	-Me	J79#	$-OCH_2cPr$	-Et
J20#	$-OCHCF_2$	-H	J50#	$-OCHCF_2$	-Me	J80	$-OCHCF_2$	-Et
J21#	$-OCF_3$	-H	J51#	$-OCF_3$	-Me	J81	$-OCF_3$	-Et
J22#	$-OCH_2CF_3$	-H	J52#	$-OCH_2CF_3$	-Me	J82	$-OCH_2CF_3$	-Et
J23#	$-OCH_2CH_2F$	-H	J53#	$-OCH_2CH_2F$	-Me	J83	$-OCH_2CH_2F$	-Et
J24#	$-OCH_2CH_2OMe$	-H	J54#	$-OCH_2CH_2OMe$	-Me	J84#	$-OCH_2CH_2OMe$	-Et
J25#	$-OCH_2CH_2NMe_2$	-H	J55#	$-OCH_2CH_2NMe_2$	-Me	J85#	$-OCH_2CH_2NMe_2$	-Et
J26#	-F	-H	J56#	-F	-Me	J86	-F	-Et
J27#	-Cl	-H	J57#	-Cl	-Me	J87	-Cl	-Et
J28#	-Br	-H	J58#	-Br	-Me	J88	-Br	-Et
J29#	-I	-H	J59#	-I	-Me	J89	-I	-Et
J30a#	-2Py	-H	J60a#	-2Py	-Me	J90a#	-2Py	-Et
J30b#	-3Py	-H	J60b#	-3Py	-Me	J90b#	-3Py	-Et
J30c#	-4Py	-H	J60c#	-4Py	-Me	J90c#	-4Py	-Et

(# not part of the invention)

[Table 194]



No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
K1#	-H	-nPr	K31	-H	-iPr	K61#	-H	-cPr
K2#	-Me	-nPr	K32	-Me	-iPr	K62#	-Me	-cPr
K3#	-Et	-nPr	K33	-Et	-iPr	K63#	-Et	-cPr
K4#	-nPr	-nPr	K34	-nPr	-iPr	K64#	-nPr	-cPr
K5#	-iPr	-nPr	K35	-iPr	-iPr	K65#	-iPr	-cPr
K6#	-cPr	-nPr	K36#	-cPr	-iPr	K66#	-cPr	-cPr
K7#	-cBu	-nPr	K37#	-cBu	-iPr	K67#	-cBu	-cPr
K8#		-nPr	K38#		-iPr	K68#		-cPr
K9#		-nPr	K39#		-iPr	K69#		-cPr
K10#		-nPr	K40#		-iPr	K70#		-cPr
K11#	$-CF_3$	-nPr	K41	$-CF_3$	-iPr	K71#	$-CF_3$	-cPr
K12#	-CN	-nPr	K42#	-CN	-iPr	K72#	-CN	-cPr
K13#	-Ph	-nPr	K43#	-Ph	-iPr	K73#	-Ph	-cPr
K14#	-OMe	-nPr	K44	-OMe	-iPr	K74#	-OMe	-cPr
K15#	-OEt	-nPr	K45	-OEt	-iPr	K75#	-OEt	-cPr

(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
K16#	-OnPr	-nPr	K46	-OnPr	-iPr	K76#	-OnPr	-cPr
K17#	-OiPr	-nPr	K47	-OiPr	-iPr	K77#	-OiPr	-cPr
K18#	-OcPr	-nPr	K48#	-OcPr	-iPr	K78#	-OcPr	-cPr
K19#	$-OCH_2cPr$	-nPr	K49#	$-OCH_2cPr$	-iPr	K79#	$-OCH_2cPr$	-cPr
K20#	$-OCHCF_2$	-nPr	K50	$-OCHCF_2$	-iPr	K80#	$-OCHCF_2$	-cPr
K21#	$-OCF_3$	-nPr	K51	$-OCF_3$	-iPr	K81#	$-OCF_3$	-cPr
K22#	$-OCH_2CF_3$	-nPr	K52	$-OCH_2CF_3$	-iPr	K82#	$-OCH_2CF_3$	-cPr
K23#	$-OCH_2CH_2F$	-nPr	K53	$-OCH_2CH_2F$	-iPr	K83#	$-OCH_2CH_2F$	-cPr
K24#	$-OCH_2CH_2OMe$	-nPr	K54#	$-OCH_2CH_2OMe$	-iPr	K84#	$-OCH_2CH_2OMe$	-cPr
K25#	$-OCH_2CH_2NMe_2$	-nPr	K55#	$-OCH_2CH_2NMe_2$	-iPr	K85#	$-OCH_2CH_2NMe_2$	-cPr
K26#	-F	-nPr	K56	-F	-iPr	K86#	-F	-cPr
K27#	-Cl	-nPr	K57	-Cl	-iPr	K87#	-Cl	-cPr
K28#	-Br	-nPr	K58	-Br	-iPr	K88#	-Br	-cPr
K29#	-I	-nPr	K59	-I	-iPr	K89#	-I	-cPr
K30a#	-2Py	-nPr	K60a#	-2Py	-iPr	K90a#	-2Py	-cPr
K30b#	-3Py	-nPr	K60b#	-3Py	-iPr	K90b#	-3Py	-cPr
K30c#	-4Py	-nPr	K60c#	-4Py	-iPr	K90c#	-4Py	-cPr

(# not part of the invention)

[Table 195]

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
L1	-H	-Cl	L31#	-H	-Br	L61#	-H	-I
L2	-Me	-Cl	L32#	-Me	-Br	L62#	-Me	-I
L3	-Et	-Cl	L33#	-Et	-Br	L63#	-Et	-I
L4	-nPr	-Cl	L34#	-nPr	-Br	L64#	-nPr	-I
L5	-iPr	-Cl	L35#	-iPr	-Br	L65#	-iPr	-I
L6#	-cPr	-Cl	L36#	-cPr	-Br	L66#	-cPr	-I
L7#	-cBu	-Cl	L37#	-cBu	-Br	L67#	-cBu	-I
L8#		-Cl	L38#		-Br	L68#		-I
L9#		-Cl	L39#		-Br	L69#		-I
L10#		-Cl	L40#		-Br	L70#		-I
L11	$-CF_3$	-Cl	L41#	$-CF_3$	-Br	L71#	$-CF_3$	-I
L12#	-CN	-Cl	L42#	-CN	-Br	L72#	-CN	-I
L13#	-Ph	-Cl	L43#	-Ph	-Br	L73#	-Ph	-I
L14	-OMe	-Cl	L44#	-OMe	-Br	L74#	-OMe	-I
L15	-OEt	-Cl	L45#	-OEt	-Br	L75#	-OEt	-I

(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
L16	-OnPr	-Cl	L46#	-OnPr	-Br	L76#	-OnPr	-I
L17	-OiPr	-Cl	L47#	-OiPr	-Br	L77#	-OiPr	-I
L18#	-OcPr	-Cl	L48#	-OcPr	-Br	L78#	-OcPr	-I
L19#	$-OCH_2cPr$	-Cl	L49#	$-OCH_2cPr$	-Br	L79#	$-OCH_2cPr$	-I
L20	$-OCHCF_2$	-Cl	L50#	$-OCHCF_2$	-Br	L80#	$-OCHCF_2$	-I
L21	$-OCF_3$	-Cl	L51#	$-OCF_3$	-Br	L81#	$-OCF_3$	-I
L22	$-OCH_2CF_3$	-Cl	L52#	$-OCH_2CF_3$	-Br	L82#	$-OCH_2CF_3$	-I
L23	$-OCH_2CH_2F$	-Cl	L53#	$-OCH_2CH_2F$	-Br	L83#	$-OCH_2CH_2F$	-I
L24#	$-OCH_2CH_2OMe$	-Cl	L54#	$-OCH_2CH_2OMe$	-Br	L84#	$-OCH_2CH_2OMe$	-I
L25#	$-OCH_2CH_2NMe_2$	-Cl	L55#	$-OCH_2CH_2NMe_2$	-Br	L85#	$-OCH_2CH_2NMe_2$	-I
L26	-F	-Cl	L56#	-F	-Br	L86#	-F	-I
L27	-Cl	-Cl	L57#	-Cl	-Br	L87#	-Cl	-I
L28	-Br	-Cl	L58#	-Br	-Br	L88#	-Br	-I
L29	-I	-Cl	L59#	-I	-Br	L89#	-I	-I
L30a#	-2Py	-Cl	L60a#	-2Py	-Br	L90a#	-2Py	-I
L30b#	-3Py	-Cl	L60b#	-3Py	-Br	L90b#	-3Py	-I
L30c#	-4Py	-Cl	L60c#	-4Py	-Br	L90c#	-4Py	-I

(# not part of the invention)

[Table 196]

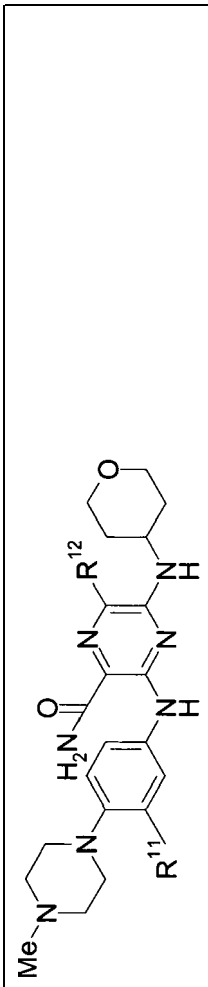
No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
M1#	-H	-H	M31#	-H	-Me	M61	-H	-Et
M2#	-Me	-H	M32#	-Me	-Me	M62	-Me	-Et
M3#	-Et	-H	M33#	-Et	-Me	M63	-Et	-Et
M4#	-nPr	-H	M34#	-nPr	-Me	M64	-nPr	-Et
M5#	-iPr	-H	M35#	-iPr	-Me	M65	-iPr	-Et
M6#	-cPr	-H	M36#	-cPr	-Me	M66	-cPr	-Et
M7#	-cBu	-H	M37#	-cBu	-Me	M67	-cBu	-Et
M8#		-H	M38#		-Me	M68		-Et
M9#		-H	M39#		-Me	M69		-Et
M10#		-H	M40#		-Me	M70		-Et
M11#	$-CF_3$	-H	M41#	$-CF_3$	-Me	M71	$-CF_3$	-Et
M12#	-CN	-H	M42#	-CN	-Me	M72	-CN	-Et
M13#	-Ph	-H	M43#	-Ph	-Me	M73	-Ph	-Et
M14#	-OMe	-H	M44#	-OMe	-Me	M74	-OMe	-Et
M15#	-OEt	-H	M45#	-OEt	-Me	M75	-OEt	-Et
M16#	-OnPr	-H	M46#	-OnPr	-Me	M76	-OnPr	-Et
M17#	-OiPr	-H	M47#	-OiPr	-Me	M77	-OiPr	-Et

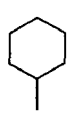
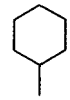
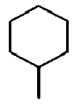
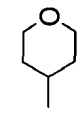
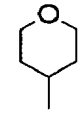
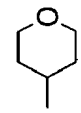
(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
M18#	-OcPr	-H	M48#	-OcPr	-Me	M78	-OcPr	-Et
M19#	$-OCH_2cPr$	-H	M49#	$-OCH_2cPr$	-Me	M79	$-OCH_2cPr$	-Et
M20#	$-OCHCF_2$	-H	M50#	$-OCHCF_2$	-Me	M80	$-OCHCF_2$	-Et
M21#	$-OCF_3$	-H	M51#	$-OCF_3$	-Me	M81	$-OCF_3$	-Et
M22#	$-OCH_2CF_3$	-H	M52#	$-OCH_2CF_3$	-Me	M82	$-OCH_2CF_3$	-Et
M23#	$-OCH_2CH_2F$	-H	M53#	$-OCH_2CH_2F$	-Me	M83	$-OCH_2CH_2F$	-Et
M24#	$-OCH_2CH_2OMe$	-H	M54#	$-OCH_2CH_2OMe$	-Me	M84	$-OCH_2CH_2OMe$	-Et
M25#	$-OCH_2CH_2NMe_2$	-H	M55#	$-OCH_2CH_2NMe_2$	-Me	M85	$-OCH_2CH_2NMe_2$	-Et
M26#	-F	-H	M56#	-F	-Me	M86	-F	-Et
M27#	-Cl	-H	M57#	-Cl	-Me	M87	-Cl	-Et
M28#	-Br	-H	M58#	-Br	-Me	M88	-Br	-Et
M29#	-I	-H	M59#	-I	-Me	M89	-I	-Et
M30a#	-2Py	-H	M60a#	-2Py	-Me	M90a	-2Py	-Et
M30b#	-3Py	-H	M60b#	-3Py	-Me	M90b	-3Py	-Et
M30c#	-4Py	-H	M60c#	-4Py	-Me	M90c	-4Py	-Et

(# not part of the invention)

[Table 197]



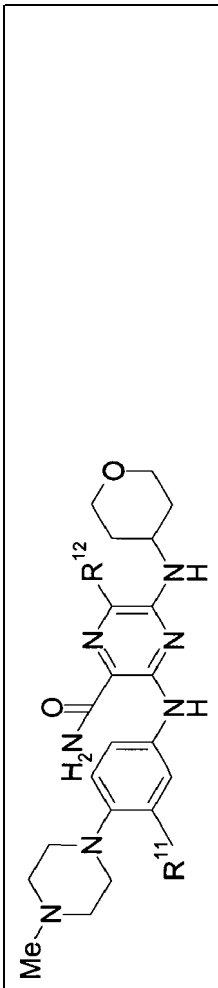
No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
N1#	-H	-nPr	N31	-H	-iPr	N61#	-H	-cPr
N2#	-Me	-nPr	N32	-Me	-iPr	N62#	-Me	-cPr
N3#	-Et	-nPr	N33	-Et	-iPr	N63#	-Et	-cPr
N4#	-nPr	-nPr	N34	-nPr	-iPr	N64#	-nPr	-cPr
N5#	-iPr	-nPr	N35	-iPr	-iPr	N65#	-iPr	-cPr
N6#	-cPr	-nPr	N36#	-cPr	-iPr	N66#	-cPr	-cPr
N7#	-cBu	-nPr	N37#	-cBu	-iPr	N67#	-cBu	-cPr
N8#		-nPr	N38#		-iPr	N68#		-cPr
N9#		-nPr	N39#		-iPr	N69#		-cPr
N10#		-nPr	N40#		-iPr	N70#		-cPr
N11#	$-CF_3$	-nPr	N41	$-CF_3$	-iPr	N71#	$-CF_3$	-cPr
N12#	-CN	-nPr	N42#	-CN	-iPr	N72#	-CN	-cPr
N13#	-Ph	-nPr	N43#	-Ph	-iPr	N73#	-Ph	-cPr
N14#	-OMe	-nPr	N44	-OMe	-iPr	N74#	-OMe	-cPr
N15#	-OEt	-nPr	N45	-OEt	-iPr	N75#	-OEt	-cPr
N16#	-OnPr	-nPr	N46	-OnPr	-iPr	N76#	-OnPr	-cPr
N17#	-OiPr	-nPr	N47	-OiPr	-iPr	N77#	-OiPr	-cPr

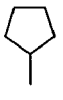
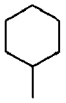
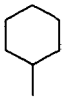
(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
N18#	-OcPr	-nPr	N48#	-OcPr	-iPr	N78#	-OcPr	-cPr
N19#	$-OCH_2cPr$	-nPr	N49#	$-OCH_2cPr$	-iPr	N79#	$-OCH_2cPr$	-cPr
N20#	$-OCHCF_2$	-nPr	N50	$-OCHCF_2$	-iPr	N80#	$-OCHCF_2$	-cPr
N21#	$-OCF_3$	-nPr	N51	$-OCF_3$	-iPr	N81#	$-OCF_3$	-cPr
N22#	$-OCH_2CF_3$	-nPr	N52	$-OCH_2CF_3$	-iPr	N82#	$-OCH_2CF_3$	-cPr
N23#	$-OCH_2CH_2F$	-nPr	N53	$-OCH_2CH_2F$	-iPr	N83#	$-OCH_2CH_2F$	-cPr
N24#	$-OCH_2CH_2OMe$	-nPr	N54#	$-OCH_2CH_2OMe$	-iPr	N84#	$-OCH_2CH_2OMe$	-cPr
N25#	$-OCH_2CH_2NMe_2$	-nPr	N55#	$-OCH_2CH_2NMe_2$	-iPr	N85#	$-OCH_2CH_2NMe_2$	-cPr
N26#	-F	-nPr	N56	-F	-iPr	N86#	-F	-cPr
N27#	-Cl	-nPr	N57	-Cl	-iPr	N87#	-Cl	-cPr
N28#	-Br	-nPr	N58	-Br	-iPr	N88#	-Br	-cPr
N29#	-I	-nPr	N59	-I	-iPr	N89#	-I	-cPr
N30a#	-2Py	-nPr	N60a#	-2Py	-iPr	N90a#	-2Py	-cPr
N30b#	-3Py	-nPr	N60b#	-3Py	-iPr	N90b#	-3Py	-cPr
N30c#	-4Py	-nPr	N60c#	-4Py	-iPr	N90c#	-4Py	-cPr

(# not part of the invention)

[Table 198]



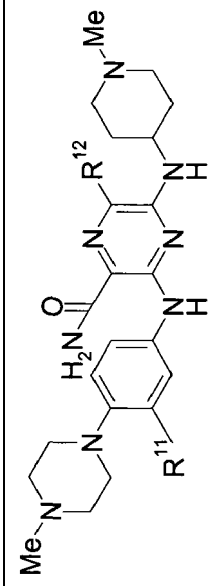
No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
O1	-H	-Cl	O31#	-H	-Br	O61#	-H	-I
O2	-Me	-Cl	O32#	-Me	-Br	O62#	-Me	-I
O3	-Et	-Cl	O33#	-Et	-Br	O63#	-Et	-I
O4	-nPr	-Cl	O34#	-nPr	-Br	O64#	-nPr	-I
O5	-iPr	-Cl	O35#	-iPr	-Br	O65#	-iPr	-I
O6#	-cPr	-Cl	O36#	-cPr	-Br	O66#	-cPr	-I
O7#	-cBu	-Cl	O37#	-cBu	-Br	O67#	-cBu	-I
O8#		-Cl	O38#		-Br	O68#		-I
O9#		-Cl	O39#		-Br	O69#		-I
O10#		-Cl	O40#		-Br	O70#		-I
O11	$-CF_3$	-Cl	O41#	$-CF_3$	-Br	O71#	$-CF_3$	-I
O12#	-CN	-Cl	O42#	-CN	-Br	O72#	-CN	-I
O13#	-Ph	-Cl	O43#	-Ph	-Br	O73#	-Ph	-I
O14	-OMe	-Cl	O44#	-OMe	-Br	O74#	-OMe	-I
O15	-OEt	-Cl	O45#	-OEt	-Br	O75#	-OEt	-I
O16	-OnPr	-Cl	O46#	-OnPr	-Br	O76#	-OnPr	-I

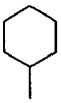
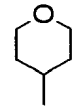
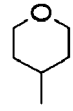
(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
O17	-OiPr	-Cl	O47#	-OiPr	-Br	O77#	-OiPr	-I
O18#	-OcPr	-Cl	O48#	-OcPr	-Br	O78#	-OcPr	-I
O19#	$-OCH_2cPr$	-Cl	O49#	$-OCH_2cPr$	-Br	O79#	$-OCH_2cPr$	-I
O20	$-OCHCF_2$	-Cl	O50#	$-OCHCF_2$	-Br	O80#	$-OCHCF_2$	-I
O21	$-OCF_3$	-Cl	O51#	$-OCF_3$	-Br	O81#	$-OCF_3$	-I
O22	$-OCH_2CF_3$	-Cl	O52#	$-OCH_2CF_3$	-Br	O82#	$-OCH_2CF_3$	-I
O23	$-OCH_2CH_2F$	-Cl	O53#	$-OCH_2CH_2F$	-Br	O83#	$-OCH_2CH_2F$	-I
O24#	$-OCH_2CH_2OMe$	-Cl	O54#	$-OCH_2CH_2OMe$	-Br	O84#	$-OCH_2CH_2OMe$	-I
O25#	$-OCH_2CH_2NMe_2$	-Cl	O55#	$-OCH_2CH_2NMe_2$	-Br	O85#	$-OCH_2CH_2NMe_2$	-I
O26	-F	-Cl	O56#	-F	-Br	O86#	-F	-I
O27	-Cl	-Cl	O57#	-Cl	-Br	O87#	-Cl	-I
O28	-Br	-Cl	O58#	-Br	-Br	O88#	-Br	-I
O29	-I	-Cl	O59#	-I	-Br	O89#	-I	-I
O30a#	-2Py	-Cl	O60a#	-2Py	-Br	O90a#	-2Py	-I
O30b#	-3Py	-Cl	O60b#	-3Py	-Br	O90b#	-3Py	-I
O30c#	-4Py	-Cl	O60c#	-4Py	-Br	O90c#	-4Py	-I

(# not part of the invention)

[Table 199]



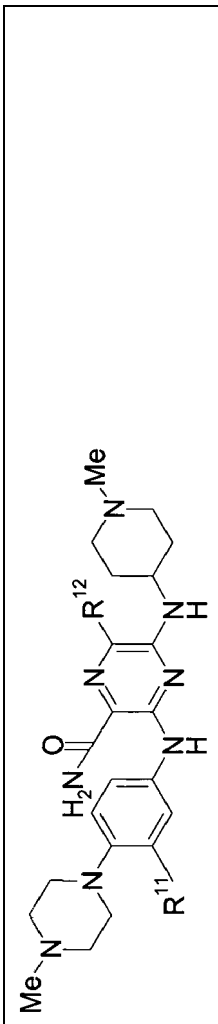
No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
P1#	-H	-H	P31#	-H	-Me	P61	-H	-Et
P2#	-Me	-H	P32#	-Me	-Me	P62	-Me	-Et
P3#	-Et	-H	P33#	-Et	-Me	P63	-Et	-Et
P4#	-nPr	-H	P34#	-nPr	-Me	P64	-nPr	-Et
P5#	-iPr	-H	P35#	-iPr	-Me	P65	-iPr	-Et
P6#	-cPr	-H	P36#	-cPr	-Me	P66#	-cPr	-Et
P7#	-cBu	-H	P37#	-cBu	-Me	P67#	-cBu	-Et
P8#		-H	P38#		-Me	P68#		-Et
P9#		-H	P39#		-Me	P69#		-Et
P10#		-H	P40#		-Me	P70#		-Et
P11#	$-CF_3$	-H	P41#	$-CF_3$	-Me	P71	$-CF_3$	-Et
P12#	-CN	-H	P42#	-CN	-Me	P72#	-CN	-Et
P13#	-Ph	-H	P43#	-Ph	-Me	P73#	-Ph	-Et
P14#	-OMe	-H	P44#	-OMe	-Me	P74	-OMe	-Et
P15#	-OEt	-H	P45#	-OEt	-Me	P75	-OEt	-Et
P16#	-OnPr	-H	P46#	-OnPr	-Me	P76	-OnPr	-Et

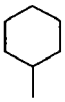
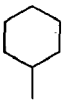
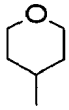
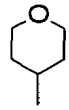
(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
P17#	-OiPr	-H	P47#	-OiPr	-Me	P77	-OiPr	-Et
P18#	-OcPr	-H	P48#	-OcPr	-Me	P78#	-OcPr	-Et
P19#	$-OCH_2cPr$	-H	P49#	$-OCH_2cPr$	-Me	P79#	$-OCH_2cPr$	-Et
P20#	$-OCHCF_2$	-H	P50#	$-OCHCF_2$	-Me	P80	$-OCHCF_2$	-Et
P21#	$-OCF_3$	-H	P51#	$-OCF_3$	-Me	P81	$-OCF_3$	-Et
P22#	$-OCH_2CF_3$	-H	P52#	$-OCH_2CF_3$	-Me	P82	$-OCH_2CF_3$	-Et
P23#	$-OCH_2CH_2F$	-H	P53#	$-OCH_2CH_2F$	-Me	P83	$-OCH_2CH_2F$	-Et
P24#	$-OCH_2CH_2OMe$	-H	P54#	$-OCH_2CH_2OMe$	-Me	P84#	$-OCH_2CH_2OMe$	-Et
P25#	$-OCH_2CH_2NMe_2$	-H	P55#	$-OCH_2CH_2NMe_2$	-Me	P85#	$-OCH_2CH_2NMe_2$	-Et
P26#	-F	-H	P56#	-F	-Me	P86	-F	-Et
P27#	-Cl	-H	P57#	-Cl	-Me	P87	-Cl	-Et
P28#	-Br	-H	P58#	-Br	-Me	P88	-Br	-Et
P29#	-I	-H	P59#	-I	-Me	P89	-I	-Et
P30a#	-2Py	-H	P60a#	-2Py	-Me	P90a#	-2Py	-Et
P30b#	-3Py	-H	P60b#	-3Py	-Me	P90b#	-3Py	-Et
P30c#	-4Py	-H	P60c#	-4Py	-Me	P90c#	-4Py	-Et

(# not part of the invention)

[Table 200]



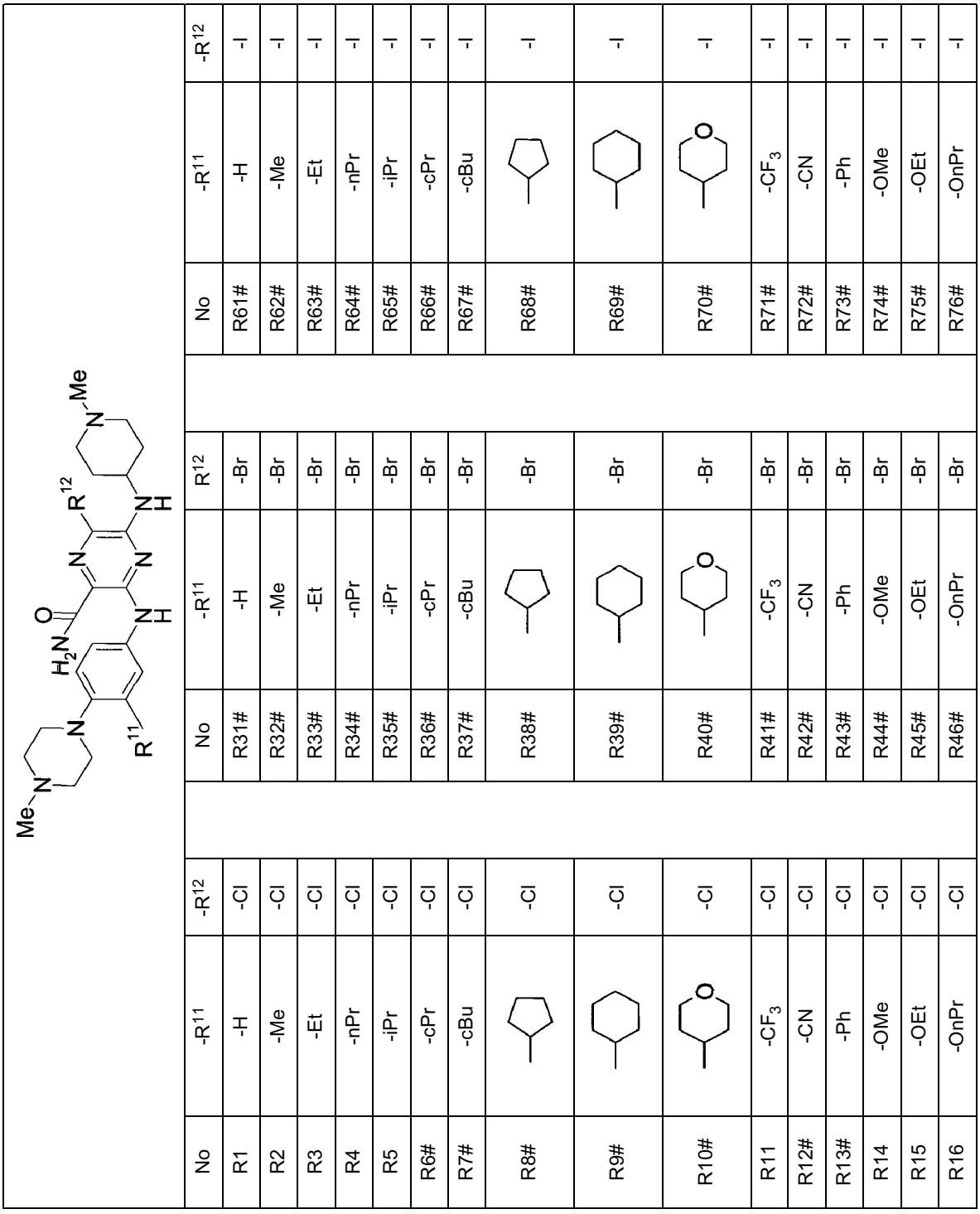
No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
Q1#	-H	-nPr	Q31	-H	-iPr	Q61#	-H	-cPr
Q2#	-Me	-nPr	Q32	-Me	-iPr	Q62#	-Me	-cPr
Q3#	-Et	-nPr	Q33	-Et	-iPr	Q63#	-Et	-cPr
Q4#	-nPr	-nPr	Q34	-nPr	-iPr	Q64#	-nPr	-cPr
Q5#	-iPr	-nPr	Q35	-iPr	-iPr	Q65#	-iPr	-cPr
Q6#	-cPr	-nPr	Q36#	-cPr	-iPr	Q66#	-cPr	-cPr
Q7#	-cBu	-nPr	Q37#	-cBu	-iPr	Q67#	-cBu	-cPr
Q8#		-nPr	Q38#		-iPr	Q68#		-cPr
Q9#		-nPr	Q39#		-iPr	Q69#		-cPr
Q10#		-nPr	Q40#		-iPr	Q70#		-cPr
Q11#	$-CF_3$	-nPr	Q41	$-CF_3$	-iPr	Q71#	$-CF_3$	-cPr
Q12#	-CN	-nPr	Q42#	-CN	-iPr	Q72#	-CN	-cPr
Q13#	-Ph	-nPr	Q43#	-Ph	-iPr	Q73#	-Ph	-cPr
Q14#	-OMe	-nPr	Q44	-OMe	-iPr	Q74#	-OMe	-cPr
Q15#	-OEt	-nPr	Q45	-OEt	-iPr	Q75#	-OEt	-cPr
Q16#	-OnPr	-nPr	Q46	-OnPr	-iPr	Q76#	-OnPr	-cPr

(continued)

No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	$-R^{12}$
Q17#	-OiPr	-nPr	Q47	-OiPr	-iPr	Q77#	-OiPr	-cPr
Q18#	-OcPr	-nPr	Q48#	-OcPr	-iPr	Q78#	-OcPr	-cPr
Q19#	$-OCH_2cPr$	-nPr	Q49#	$-OCH_2cPr$	-iPr	Q79#	$-OCH_2cPr$	-cPr
Q20#	$-OCHCF_2$	-nPr	Q50	$-OCHCF_2$	-iPr	Q80#	$-OCHCF_2$	-cPr
Q21#	$-OCF_3$	-nPr	Q51	$-OCF_3$	-iPr	Q81#	$-OCF_3$	-cPr
Q22#	$-OCH_2CF_3$	-nPr	Q52	$-OCH_2CF_3$	-iPr	Q82#	$-OCH_2CF_3$	-cPr
Q23#	$-OCH_2CH_2F$	-nPr	Q53	$-OCH_2CH_2F$	-iPr	Q83#	$-OCH_2CH_2F$	-cPr
Q24#	$-OCH_2CH_2OMe$	-nPr	Q54#	$-OCH_2CH_2OMe$	-iPr	Q84#	$-OCH_2CH_2OMe$	-cPr
Q25#	$-OCH_2CH_2NMe_2$	-nPr	Q55#	$-OCH_2CH_2NMe_2$	-iPr	Q85#	$-OCH_2CH_2NMe_2$	-cPr
Q26#	-F	-nPr	Q56	-F	-iPr	Q86#	-F	-cPr
Q27#	-Cl	-nPr	Q57	-Cl	-iPr	Q87#	-Cl	-cPr
Q28#	-Br	-nPr	Q58	-Br	-iPr	Q88#	-Br	-cPr
Q29#	-I	-nPr	Q59	-I	-iPr	Q89#	-I	-cPr
Q30a#	-2Py	-nPr	Q60a#	-2Py	-iPr	Q90a#	-2Py	-cPr
Q30b#	-3Py	-nPr	Q60b#	-3Py	-iPr	Q90b#	-3Py	-cPr
Q30c#	-4Py	-nPr	Q60c#	-4Py	-iPr	Q90c#	-4Py	-cPr

(# not part of the invention)

[Table 201]



No	$-R^{11}$	$-R^{12}$	No	$-R^{11}$	R^{12}	No	$-R^{11}$	$-R^{12}$
R1	-H	-Cl	R31#	-H	-Br	R61#	-H	-I
R2	-Me	-Cl	R32#	-Me	-Br	R62#	-Me	-I
R3	-Et	-Cl	R33#	-Et	-Br	R63#	-Et	-I
R4	-nPr	-Cl	R34#	-nPr	-Br	R64#	-nPr	-I
R5	-iPr	-Cl	R35#	-iPr	-Br	R65#	-iPr	-I
R6#	-cPr	-Cl	R36#	-cPr	-Br	R66#	-cPr	-I
R7#	-cBu	-Cl	R37#	-cBu	-Br	R67#	-cBu	-I
R8#		-Cl	R38#		-Br	R68#		-I
R9#		-Cl	R39#		-Br	R69#		-I
R10#		-Cl	R40#		-Br	R70#		-I
R11	$-CF_3$	-Cl	R41#	$-CF_3$	-Br	R71#	$-CF_3$	-I
R12#	-CN	-Cl	R42#	-CN	-Br	R72#	-CN	-I
R13#	-Ph	-Cl	R43#	-Ph	-Br	R73#	-Ph	-I
R14	-OMe	-Cl	R44#	-OMe	-Br	R74#	-OMe	-I
R15	-OEt	-Cl	R45#	-OEt	-Br	R75#	-OEt	-I
R16	-OnPr	-Cl	R46#	-OnPr	-Br	R76#	-OnPr	-I

(continued)

No	$-R^{11}$	$-R^{12}$		No	$-R^{11}$	R^{12}		No	$-R^{11}$	$-R^{12}$
R17	-OiPr	-Cl		R47#	-OiPr	-Br		R77#	-OiPr	-I
R18#	-OcPr	-Cl		R48#	-OcPr	-Br		R78#	-OcPr	-I
R19#	$-OCH_2cPr$	-Cl		R49#	$-OCH_2cPr$	-Br		R79#	$-OCH_2cPr$	-I
R20	$-OCHCF_2$	-Cl		R50#	$-OCHCF_2$	-Br		R80#	$-OCHCF_2$	-I
R21	$-OCF_3$	-Cl		R51#	$-OCF_3$	-Br		R81#	$-OCF_3$	-I
R22	$-OCH_2CF_3$	-Cl		R52#	$-OCH_2CF_3$	-Br		R82#	$-OCH_2CF_3$	-I
R23	$-OCH_2CH_2F$	-Cl		R53#	$-OCH_2CH_2F$	-Br		R83#	$-OCH_2CH_2F$	-I
R24#	$-OCH_2CH_2OMe$	-Cl		R54#	$-OCH_2CH_2OMe$	-Br		R84#	$-OCH_2CH_2OMe$	-I
R25#	$-OCH_2CH_2NMe_2$	-Cl		R55#	$-OCH_2CH_2NMe_2$	-Br		R85#	$-OCH_2CH_2NMe_2$	-I
R26	-F	-Cl		R56#	-F	-Br		R86#	-F	-I
R27	-Cl	-Cl		R57#	-Cl	-Br		R87#	-Cl	-I
R28	-Br	-Cl		R58#	-Br	-Br		R88#	-Br	-I
R29	-I	-Cl		R59#	-I	-Br		R89#	-I	-I
R30a#	-2Py	-Cl		R60a#	-2Py	-Br		R90a#	-2Py	-I
R30b#	-3Py	-Cl		R60b#	-3Py	-Br		R90b#	-3Py	-I
R30c#	-4Py	-Cl		R60c#	-4Py	-Br		R90c#	-4Py	-I

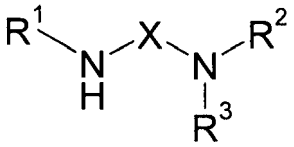
(# not part of the invention)

INDUSTRIAL APPLICABILITY

[0229] The compound of formula (I) or a salt thereof has inhibitory activity against the kinase activity of EML4-ALK fusion protein, as well as growth inhibitory activity against EML4-ALK fusion protein-dependent cells, and can be used as an active ingredient in pharmaceutical compositions for preventing and/or treating cancer, such as lung cancer in one embodiment, non-small cell lung cancer or small cell lung cancer in another embodiment, ALK fusion polynucleotide-positive cancer in yet another embodiment, ALK fusion polynucleotide-positive lung cancer in yet another embodiment, ALK fusion polynucleotide-positive non-small cell lung cancer in yet another embodiment, ALK fusion protein-positive cancer in yet another embodiment, ALK fusion protein-positive lung cancer in yet another embodiment, ALK fusion protein-positive non-small cell lung cancer in yet another embodiment, EML4-ALK fusion polynucleotide-positive cancer in yet another embodiment, EML4-ALK fusion polynucleotide-positive lung cancer in yet another embodiment, EML4-ALK fusion polynucleotide-positive non-small cell lung cancer in yet another embodiment, EML4-ALK fusion protein-positive cancer in yet another embodiment, EML4-ALK fusion protein-positive lung cancer in yet another embodiment, or EML4-ALK fusion protein-positive non-small cell lung cancer in yet another embodiment.

Claims

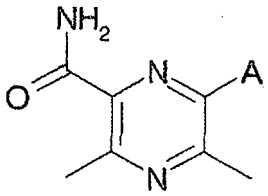
1. A compound of formula (I) or a salt thereof:



(I)

(wherein the symbols are as defined below:

-X-: a group of formula (II);



(II)

A: chloro, ethyl or isopropyl;
R^1:

(1) phenyl in which the carbon at the 4-position is substituted with -W-Y-Z and the carbon at the 3-position may be substituted with a group selected from the group consisting of halogen, R^{00} and -O-R^{00};
Z: a non-aromatic heterocyclic ring which may be substituted with one or more R^{00};
R^{00}: linear or branched C_{1-6} alkyl which may be substituted with one or more halogens;
-W-: a bond, piperidine-1,4-diyl, or piperazine-1,4-diyl;
-Y-: a bond;;
R^2:

(i) cycloalkyl which may be substituted with one or more groups selected from the group consisting of $N(C_{1-6}$ linear or branched alkyl$)_2$, C_{1-6} linear or branched alkyl, -COO-C_{1-6} linear or branched alkyl, -OH, -COOH, -CONH-R^{ZB} and morpholinyl, or,
(ii) a non-aromatic heterocyclic ring which may be substituted with one or more groups selected from the group consisting of C_{1-6} linear or branched alkyl, -CO- C_{1-6} linear or branched alkyl, oxo, -CO-R^{ZB} and benzyl;

R^{ZB}: phenyl which may be substituted with a group selected from the group consisting of halogen and -O-linear or branched C_{1-6} alkyl;
R^3: -H.

2. The compound according to Claim 1 or a salt thereof, wherein R^1 is phenyl in which the carbon at the 4-position is substituted with a group selected from the group consisting of 4-(4-methylpiperazin-1-yl)piperidin-1-yl, 4-(1-methylpiperidin-4-yl)piperazin-1-yl, 4-methylpiperazin-1-yl, and 4-isopropylpiperazin-1-yl, and the carbon at the 3-position may be substituted with a group selected from the group consisting of fluoro, methyl, trifluoromethyl, and methoxy.

3. The compound according to Claim 2 or a salt thereof, wherein R^2 is 4-hydroxycyclohexyl, 4-hydroxy-4-methylcyclohexyl, or tetrahydropyran-4-yl.

4. The compound according to Claim 1 or a salt thereof, wherein said compound is:

6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
5-[(trans-4-hydroxycyclohexyl)amino]-6-isopropyl-3- {[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-3-(trifluoromethyl)phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
5-[(trans-4-hydroxycyclohexyl)amino]-6-isopropyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-3-(trifluoromethyl)phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(cis-4-hydroxy-4-methylcyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(4-isopropylpiperazin-1-yl)-3-methylphenyl]amino}pyrazine-2-carboxamide,
6-ethyl-5-[(trans-4-hydroxy-4-methylcyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-chloro-5-[(trans-4-hydroxycyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)pyrazine-2-carboxamide,
6-ethyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-ethyl-3-({3-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-isopropyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-ethyl-3-{[3-fluoro-4-(4-methylpiperazin-1-yl)phenyl]amino}-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-isopropyl-3-{[3-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
6-isopropyl-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide, or
6-ethyl-3-({3-methyl-4-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide.

5. A pharmaceutical composition, which comprises the compound according to Claim 1 or a salt thereof and a pharmaceutically acceptable excipient.

6. Compound according to claim 1 or a salt thereof for use in a method for inhibiting the kinase activity of EML4-ALK fusion protein.

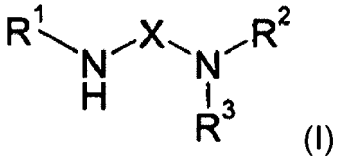
7. A pharmaceutical composition for use in a method for preventing or treating cancer, lung cancer, non-small cell lung

cancer, small cell lung cancer, EML4-ALK fusion polynucleotide-positive cancer, EML4-ALK fusion polynucleotide-positive lung cancer, or EML4-ALK fusion polynucleotide-positive non-small cell lung cancer, which comprises the compound according to Claim 1 or a salt thereof.

8. Compound according to Claim 1 or a salt thereof for use in a method for preventing or treating of cancer, lung cancer, non-small cell lung cancer, small cell lung cancer, EML4-ALK fusion polynucleotide-positive cancer, EML4-ALK fusion polynucleotide-positive lung cancer, or EML4-ALK fusion polynucleotide-positive non-small cell lung cancer.

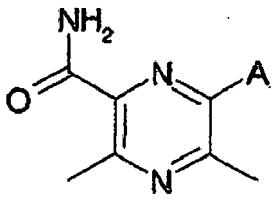
Patentansprüche

1. Verbindung der Formel (I) oder ein Salz davon:


(I)

worin die Symbole wie nachstehend definiert sind:

- X-: eine Gruppe der Formel (II);


(II)

A: Chlor, Ethyl oder Isopropyl;
R^1: (1) Phenyl, in dem der Kohlenstoff an der 4-Position mit -W-Y-Z substituiert ist und der Kohlenstoff an der 3-Position mit einer Gruppe, ausgewählt aus der Gruppe bestehend aus Halogen, R^{00} und -O-R^{00}, substituiert sein kann;
Z: ein nicht-aromatischer heterocyclischer Ring, der mit einem oder mehreren R^{00} substituiert sein kann;
R^{00}: geradkettiges oder verzweigtes C_{1-6}-Alkyl, das mit einer oder mehreren Halogenverbindung(en) substituiert sein kann;
-W-: eine Bindung, Piperidin-1,4-diyl oder Piperazin-1,4-diyl;
-Y-: eine Bindung;
R^2:

(i) Cycloalkyl, das mit einer oder mehreren Gruppe(n), ausgewählt aus der Gruppe bestehend aus -N(geradkettigem oder verzweigtem C_{1-6}-Alkyl)$_2$, geradkettigem oder verzweigtem C_{1-6}-Alkyl, -COOgeradkettigem oder verzweigtem C_{1-6}-Alkyl, -OH, -COOH, -CONH-R^{ZB} und Morpholinyl, substituiert sein kann oder,
(ii) ein nicht-aromatischer heterocyclischer Ring, der mit einer oder mehreren Gruppe(n), ausgewählt aus der Gruppe bestehend aus geradkettigem oder verzweigtem C_{1-6}-Alkyl, -CO-geradkettigem oder verzweigtem C_{1-6}-Alkyl, Oxo, -CO-R^{ZB} und Benzyl, substituiert sein kann;

R^{ZB}: Phenyl, das mit einer Gruppe, ausgewählt aus der Gruppe bestehend aus Halogen und -O-geradkettigem oder verzweigtem C_{1-6}-Alkyl, substituiert sein kann;
R^3: -H.

2. Verbindung gemäss Anspruch 1 oder ein Salz davon, worin R^1 Phenyl ist, in dem der Kohlenstoff an der 4-Position mit einer Gruppe, ausgewählt aus der Gruppe bestehend aus 4-(4-Methylpiperazin-1-yl)piperidin-1-yl, 4-(1-Methylpiperidin-4-yl)piperazin-1-yl, 4-Methylpiperazin-1-yl und 4-Isopropylpiperazin-1-yl, substituiert ist und der Kohlenstoff

an der 3-Position mit einer Gruppe, ausgewählt aus der Gruppe bestehend aus Fluor, Methyl, Trifluormethyl und Methoxy, substituiert sein kann.

3. Verbindung gemäss Anspruch 2 oder ein Salz davon, worin R^2 4-Hydroxycyclohexyl, 4-Hydroxy-4-methylcyclohexyl oder Tetrahydropyran-4-yl ist.

4. Verbindung gemäss Anspruch 1 oder ein Salz davon, worin die Verbindung ist:

6-Ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazin-2-carboxamid,
6-Ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-pyrazin-2-carboxamid,
5-[(trans-4-Hydroxycyclohexyl)amino]-6-isopropyl-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrazin-2-carboxamid,
6-Ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-3-(trifluormethyl)phenyl}amino)pyrazin-2-carboxamid,
6-Ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-phenyl}amino)pyrazin-2-carboxamid,
5-[(trans-4-Hydroxycyclohexyl)amino]-6-isopropyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-3-(trifluormethyl)phenyl}amino)pyrazin-2-carboxamid,
6-Ethyl-5-[(cis-4-hydroxy-4-methylcyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-phenyl}amino)pyrazin-2-carboxamid,
6-Ethyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(4-isopropylpiperazin-1-yl)-3-methylphenyl]amino}pyrazin-2-carboxamid,
6-Ethyl-5-[(trans-4-hydroxy-4-methylcyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-phenyl}amino)pyrazin-2-carboxamid,
6-Ethyl-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)-piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazin-2-carboxamid,
6-Chlor-5-[(trans-4-hydroxycyclohexyl)amino]-3-({3-methyl-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-phenyl}amino)pyrazin-2-carboxamid,
6-Ethyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)-pyrazin-2-carboxamid,
6-Ethyl-3-({3-methoxy-4-[4-(4-methylpiperazin-1-yl)-piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazin-2-carboxamid,
6-Isopropyl-3-({4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)-pyrazin-2-carboxamid,
6-Ethyl-3-{[3-fluor-4-(4-methylpiperazin-1-yl)phenyl]-amino}-5-(tetrahydro-2H-pyran-4-ylamino)pyrazin-2-carboxamid,
6-Isopropyl-3-{[3-methoxy-4-(4-methylpiperazin-1-yl)-phenyl]amino}-5-(tetrahydro-2H-pyran-4-ylamino)pyrazin-2-carboxamid,
6-Isopropyl-3-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-5-(tetrahydro-2H-pyran-4-ylamino)pyrazin-2-carboxamid oder
6-Ethyl-3-({3-methyl-4-[4-(1-methylpiperidin-4-yl)-piperazin-1-yl]phenyl}amino)-5-(tetrahydro-2H-pyran-4-ylamino)pyrazin-2-carboxamid.

5. Pharmazeutische Zusammensetzung, die eine Verbindung gemäss Anspruch 1 oder ein Salz davon und einen pharmazeutisch annehmbaren Hilfsstoff umfasst.

6. Verbindung gemäss Anspruch 1 oder ein Salz davon zur Verwendung in einem Verfahren zur Inhibierung der Kinaseaktivität eines EML4-ALK-Fusionsproteins.

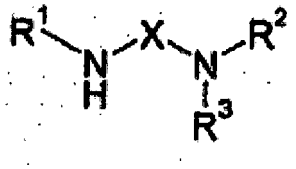
7. Pharmazeutische Zusammensetzung zur Verwendung in einem Verfahren zur Prävention oder Behandlung von Krebs, Lungenkrebs, nicht-kleinzelligem Lungenkrebs, kleinzelligem Lungenkrebs, EML4-ALK-Fusions-Polynukleotid-positivem Krebs, EML4-ALK-Fusions-Polynukleotid-positivem Lungenkrebs oder EML4-ALK-Fusions-Polynukleotid-positivem nicht-kleinzelligem Lungenkrebs, die eine Verbindung gemäss Anspruch 1 oder ein Salz davon umfasst.

8. Verbindung gemäss Anspruch 1 oder ein Salz davon zur Verwendung in einem Verfahren zur Prävention oder

Behandlung von Krebs, Lungenkrebs, nicht-kleinzelligem Lungenkrebs, kleinzelligem Lungenkrebs, EML4-ALK-Fusions-Polynukleotid-positivem Krebs, EML4-ALK-Fusions-Polynukleotid-positivem Lungenkrebs oder EML4-ALK-Fusions-Polynukleotid-positivem nicht-kleinzelligem Lungenkrebs.

Revendications

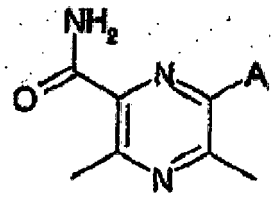
1. Composé de formule (I) ou sel de celui-ci :



(I)

(dans laquelle les symboles sont tels que définis ci-dessous :

-X- : un groupe de formule (II) ;



(II)

A : chloro, éthyle ou isopropyle ;
R^1 :

(1) un phényle dans lequel le carbone en position 4 est substitué par -W-Y-Z et le carbone en position 3 peut être substitué par un groupe choisi dans le groupe constitué par un halogène, R^{00} et -O-R^{00} ;
Z : un noyau hétérocyclique non aromatique qui peut être substitué par un ou plusieurs R^{00} ;
R^{00} : un alkyle linéaire ou ramifié en C_{1-6} qui peut être substitué par un ou plusieurs halogènes ;
-W- : une liaison, un pipéridine-1,4-diyle, ou un pipérazine-1,4-diyle ;
-Y- : une liaison ;

R^2 :

(i) un cycloalkyle qui peut être substitué par un ou plusieurs groupes choisis dans le groupe constitué par un - N(alkyle linéaire ou ramifié en $C_{1-6})_2$, alkyle linéaire ou ramifié en C_{1-6}, -COO-alkyle linéaire ou ramifié en C_{1-6}, - OH, -COOH, -CONH-R^{ZB} et morpholinyle, ou,
(ii) un noyau hétérocyclique non aromatique qui peut être substitué par un ou plusieurs groupes choisis dans le groupe constitué par un alkyle linéaire ou ramifié en C_{1-6}, -CO-alkyle linéaire ou ramifié en C_{1-6}, oxo, -CO-R^{ZB} et benzyle ;

R^{ZB} : un phényle qui peut être substitué par un groupe choisi dans le groupe constitué par un halogène et -O-alkyle linéaire ou ramifié en C_{1-6} ;
R^3 : -H.

2. Composé selon la revendication 1 ou sel de celui-ci, dans lequel R^1 est un phényle dans lequel le carbone en position 4 est substitué par un groupe choisi dans le groupe constitué par un 4-(4-méthylpipérazin-1-yl)pipéridin-1-yle, 4-(1-méthylpipéridin-4-yl)pipérazin-1-yle, 4-méthylpipérazin-1-yle, et 4-isopropylpipérazin-1-yle, et le carbone en position 3 peut être substitué par un groupe choisi dans le groupe constitué par un fluoro, méthyle, trifluorométhyle

et méthoxy.

3. Composé selon la revendication 2 ou sel de celui-ci, dans lequel R^2 est un 4-hydroxycyclohexyle, 4-hydroxy-4-méthylcyclohexyle, ou tétrahydropyran-4-yle.

4. Composé selon la revendication 1 ou sel de celui-ci, dans lequel ledit composé est :

le 6-éthyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(4-méthylpipérazin-1-yl)phényl]amino}pyrazine-2-carboxamide,
le 6-éthyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl]phényl}amino)pyrazine-2-carboxamide,
le 5-[(trans-4-hydroxycyclohexyl)amino]-6-isopropyl-3-{[4-(4-méthylpipérazin-1-yl)phényl]amino}pyrazine-2-carboxamide,
le 6-éthyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl]-3-(trifluorométhyl)phényl}amino)pyrazine-2-carboxamide,
le 6-éthyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-({3-méthyl-4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl]phényl}amino)pyrazine-2-carboxamide,
le 5-[(trans-4-hydroxycyclohexyl)amino]-6-isopropyl-3-({4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl]-3-(trifluorométhyl)phényl}amino)pyrazine-2-carboxamide,
le 6-éthyl-5-[(cis-4-hydroxy-4-méthylcyclohexyl)amino]-3-({3-méthyl-4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl]phényl}amino)pyrazine-2-carboxamide,
le 6-éthyl-5-[(trans-4-hydroxycyclohexyl)amino]-3-{[4-(4-isopropylpipérazin-1-yl)-3-méthylphényl]amino}pyrazine-2-carboxamide,
le 6-éthyl-5-[(trans-4-hydroxy-4-méthylcyclohexyl)amino]-3-({3-méthyl4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl]phényl}amino)pyrazine-2-carboxamide,
le 6-éthyl-3-({3-méthyl-4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl]phényl}amino)-5-(tétrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
le 6-chloro-5-[(trans-4-hydroxycyclohexyl)amino]-3-({3-méthyl-4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl]phényl}amino)pyrazine-2-carboxamide,
le 6-éthyl-3-({4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl]phényl}amino)-5-(tétrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
le 6-éthyl-3-({3-méthoxy-4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl]phényl}amino)-5-(tétrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
le 6-isopropyl-3-({4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl)phényl}amino)-5-(tétrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
le 6-éthyl-3-{[3-fluoro-4-(4-méthylpipérazin-1-yl)phényl]amino}-5-(tétrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
le 6-isopropyl-3-{[3-méthoxy-4-(4-méthylpipérazin-1-yl)phényl]amino}-5-(tétrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide,
le 6-isopropyl-3-{[4-(4-méthylpipérazin-1-yl)phényl]amino}-5-(tétrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide, ou
le 6-éthyl-3-({3-méthyl-4-[4-(1-méthylpipéridin-4-yl)pipérazin-1-yl]phényl}amino)-5-(tétrahydro-2H-pyran-4-ylamino)pyrazine-2-carboxamide.

5. Composition pharmaceutique, qui comprend le composé selon la revendication 1, ou un sel de celui-ci et un excipient pharmaceutiquement acceptable.

6. Composé selon la revendication 1, ou un sel de celui-ci destiné à être utilisé dans un procédé pour inhiber l'activité kinase de la protéine de fusion EML4-ALK.

7. Composition pharmaceutique destinée à être utilisée dans un procédé pour prévenir ou traiter un cancer, un cancer du poumon, un cancer du poumon non à petites cellules, un cancer du poumon à petites cellules, un cancer positif pour un polynucléotide de fusion EML4-ALK, un cancer du poumon positif pour un polynucléotide de fusion EML4-ALK ou un cancer du poumon non à petites cellules positif pour un polynucléotide de fusion EML4-ALK, qui comprend le composé selon la revendication 1 ou un sel de celui-ci.

8. Composé selon la revendication 1 ou sel de celui-ci destiné à être utilisé dans un procédé pour prévenir ou traiter un cancer, un cancer du poumon, un cancer du poumon non à petites cellules, un cancer du poumon à petites

cellules, un cancer positif pour un polynucléotide de fusion EML4-ALK, un cancer du poumon positif pour un polynucléotide de fusion EML4-ALK ou un cancer du poumon non à petites cellules positif pour un polynucléotide de fusion EML4-ALK.

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