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(72) Feltaláló(k):
WU, Frank, Jinan Shandong 250101 (CN)
WANG, Aichen, Jinan Shandong 250101 (CN)

(73) Jogosult(ak):
Xuanzhu Pharma Co., Ltd., Jinan Shandong 250101 (CN)

(74) Képviselő:
SBGK Szabadalmi Ügyvivői Iroda, Budapest

(54) **Tirozin-kináz inhibitor kinazolin származék, előállítási eljárása és alkalmazása**

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(54) **QUINAZOLINE DERIVATIVE AS TYROSINE-KINASE INHIBITOR, PREPARATION METHOD THEREFOR AND APPLICATION THEREOF**

CHINAZOLINDERIVAT ALS TYROSINKINASEHEMMER, VERFAHREN ZU SEINER HERSTELLUNG UND SEINE ANWENDUNG

DÉRIVÉ DE QUINAZOLINE EN TANT QU'INHIBITEUR DE TYROSINE-KINASE, SON PROCÉDÉ DE PRÉPARATION ET SON APPLICATION

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(73) Proprietor: **Xuanzhu Pharma Co., Ltd.**
Jinan Shandong 250101 (CN)

(72) Inventors:
- **WU, Frank**
  Jinan
  Shandong 250101 (CN)
- **WANG, Aichen**
  Jinan
  Shandong 250101 (CN)

(74) Representative: **Croce, Valeria et al**
Jacobacci & Partners S.p.A.
Via Senato, 8
20121 Milano (IT)

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EP 2 716 633 B1

Description

Technical Field

[0001] The present invention belongs to the field of pharmaceutical technology, more specifically relates to a quinazoline derivative as tyrosine kinase inhibitor, a pharmaceutically acceptable salt thereof and a stereoisomer thereof, a preparation method thereof, a pharmaceutical composition containing said derivative and a pharmaceutical formulation containing said derivative, a use of said compound in treating an excessive proliferative disease and a chronic obstructive pulmonary disease, and a use of said compound in the manufacture of a medicament for treating an excessive proliferative disease and a chronic obstructive pulmonary disease.

Background Art

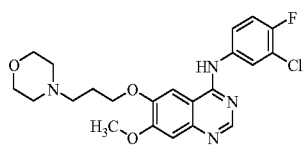
[0002] The protein tyrosine kinase is an enzyme that catalytically transfers the phosphate group from ATP to the tyrosine residue located at the protein substrate, and has a play in the normal cell growth. Many growth factor receptor proteins operate via the tyrosine kinase, and influence the conduction of signal passage and further regulate the cell growth by this process. However, in some circumstances, these receptors become abnormally due to either the mutation or the overexpression, which cause the uncontrolled cell multipliction, cause the tumor growth, and finally initiate the well-known disease, i.e., cancer. The growth factor receptor protein tyrosine kinase inhibitor, via the inhibition of the above phosphorylation process, may treat cancers and other diseases characterized by the uncontrolled or abnormal cell growth.

[0003] An epidermal growth factor receptor (EGFR) is a multifunction glycoprotein that is widely distributed on the cell membranes of the tissues of the human body, and is an oncogene analog of avian erythroblastic leukemia viral (v-erb-b). Human EGFR/HER1/ErbB-1 and HER2 (human epidermal growth factor receptor-2) /ErbB-2/Teu/p185, HER3/ErbB-3, HER4/ErbB-4 and the like are grouped into the HER/ErbB family, and belong to protein tyrosine kinases (PTKs). It is indicated in the clinical study that EGFR and the like are expressed in the epithelia-derived tumors such as squamous cell carcinoma of head and neck, mammary cancer, rectal cancer, ovarian cancer, prostate carcinoma, non-small cell lung cancer, and the like. Pan-HER tyrosine kinase inhibitor, via the competitive binding the kinase catalytic sites in the intracellular region against ATP, blocks the autophosphorylation of intramolecular tyrosine, blocks the tyrosine kinase activation, inhibits HER family activation, and therefore inhibits cell cycle progression, accelerates cell apoptosis, and exerts the therapeutic action.

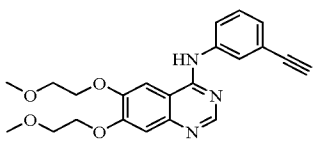
[0004] EGFR, after binding the ligand, forms a dimer with a subgroup of HER family, and then combines with ATP to activate the tyrosine kinase activity of the EGFR itself. Therefore, the autophosphorylation occurs in several tyrosine sites of the intracellular kinase region. Pan-HER tyrosine kinase inhibitor, via simultaneity acting on EGFR, and HER2/4, inhibits the activation of HER family, and play a good role in the tumor growth inhibition.

[0005] It is indicated in the study that Pan-HER tyrosine kinase irreversible inhibitor has an inhibition effect on HER2/4, besides it effectively inhibits EGFR. The pharmaceutical drugs of this kind, having an irreversible inhibition to both of HER/ErbB families, not only increase the drug activity, but also reduce the drug resistance, and have a substantial inhibition effect on H1975 cell lines which are resistant to Erlotinib.

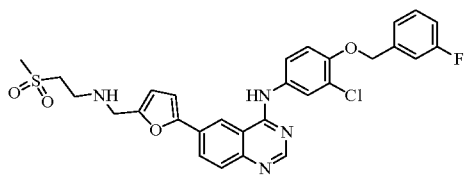
[0006] The pharmaceutical drugs that are now commercially available include selective EGFR tyrosine kinase inhibitor Gefitinb (Iressa, ZD1839), Erlotinib (Tarceva, OSI-774) and double EGFR/HER2 inhibitor Lapatinib (Tykerb, GW572016), and their structures are shown below. The above three drugs are all reversible EGF receptor tyrosine phosphorylation kinase inhibitor. It is found in the study that they have good therapeutic response to some tumors initially. However, several months after the treatment, the disease progression appears again and therefore a natural or secondary drug resistance forms.



Gefitinb



Erlotinib



Lapatinib

[0007] It is reported in the literature (Bioorganic & Medicinal Chemistry (2008) 16 pages 3482-3488) that the commercially available drugs such as gefitinb and erlotinib have been widely used clinically. The long-term treatment of the late

NSCLC (non-small cell lung cancer) may create an acquired drug-resistance, which has a negative effect on the therapeutical effect.

[0008] It is believed that the reversible EFG receptor tyrosine kinase inhibitor competes with ATP for the combination with EFG receptor tyrosine kinase. Due to the relative high concentration of the intracellular ATP (in order of mM), the reversible EGF receptor tyrosine kinase inhibitor, which shows a high acitivity in an in-vitro assay, is difficult to show the effect in the animal pathologic model. The irreversible EGF receptor tyrosine kinase inhibitor does not compete with ATP, and therefore it is expected that the non-reversible EGF receptor tyrosine kinase inhibitor may have a better in-vivo activity.

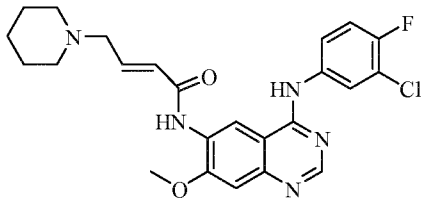
[0009] WO97/38983 discloses irreversible EGF receptor tyrosine kinase inhibitors. For these inhibitors, one Michael receptor is introduced at 6-position of quinazoline, and therefore a Michael addition reaction can be conducted between this receptor and -SH of the cysteine on the pouch wall of the EGF receptor tyrosine kinase activity center (Cys773). Moreover, the activities of these inhibitors and the complexity of the Michael addition reaction between these inhibitors and -SH of the cysteine are in a positive structure-function correlation.

[0010] US20010044435 A1 discloses a quinazoline derivative which has a lactone structure at 6-position of quinazoline. It is believed that it has an inhibition activity for the signal transduction mediated by the tyrosine kinase.

[0011] US20040044014 A1 discloses a quinazoline derivative which has a bridged ring structure at 6-position of quinazoline. It is believed that it has an inhibition activity for the signal transduction mediated by the tyrosine kinase.

[0012] It is reported in the reference (Adv Ther (2011) 28(2) p. 1-8) that PF-299 (Pfizer) and Afatinib (BIBW2992) (Boehringer Ingelheim) are in the clinical stage III, and Neratinib (HKI292) is in the clinical stage II. It is believed that these compounds are inreversible tyrosine kinase inhibitor, and can solve the EGFR resistance.

[0013] It is reported in the references (Cancer Res (2007); 67: (24) p. 11924-11932 and Mol Cancer Ther (2008); 7(7) p.1880-1889) that PF-00299804 has an acitivity for some types of tumour. PF-00299804 has a structure of:

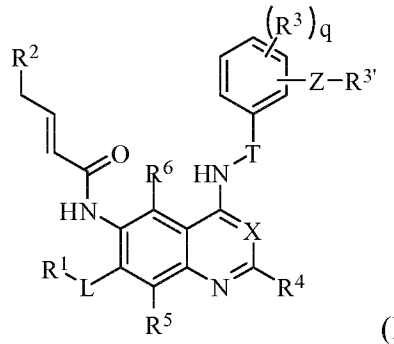


PF-00299804

[0014] Upon developing the drug having a good antineoplastic effect, being able to reduce the drug resistance and having a good tolerance, the present inventors discover a quinazoline derivative as tyrosine kinase inhibitor having a Pan-HER irreversible inhibition function.

Summary of the Invention

[0015] The invention is according to the content of the claims, the present description provides a compound represented by the general formula (I), a pharmaceutically acceptable salt thereof and a stereoisomer thereof:



(I),

wherein:

R^1 is selected from the group consisting of the following groups that are unsubstituted or substituted by 1-3 same or different Q^1: C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-8}cycloalkyl-C_{0-6}alkyl, 6-10-membered fused ring-C_{0-6}alkyl, 7-10-membered spiro ring-C_{0-6} alkyl and 7-10-membered bridged ring-C_{0-6}alkyl, and the carbon atom in said cycloalkyl, said fused ring, said spiro ring and said bridged ring may be optionally replaced by 1-3 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O);
Q^1 is selected from the group consisting of halogen, hydroxy, amino, carboxyl, cyano, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonyloxy, C_{1-4}alkoxylcarbonyl, C_{1-6}alkylacylamino, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonylamino and C_{3-8}cycloalkyl;
R^2 is selected from the group consisting of the following groups that are unsubstituted or substituted by 1-3 same or different Q^2: C_{3-4}cycloalkyl-C_{0-6}alkyl, 6-10-membered fused ring-C_{0-6}alkyl, 7-10-membered spiro ring-C_{0-6} alkyl and 7-10-membered bridged ring-C_{0-6}alkyl, and the carbon atom in said cycloalkyl, said fused ring, said spiro ring and said bridged ring may be optionally replaced by 1-3 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), provided that an ester structure "-O-C(O)-" is not present in the replaced ring, and when R^2 is 7-10-membered bridged ring-C_{0-6}alkyl, R^1 is not C_{3-4}cycloalkyl-C_{0-6}alkyl or C_{1-6}alkyl;
Q^2 is selected from the group consisting of halogen, hydroxy, amino, carboxyl, cyano, nitro, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonyloxy, C_{1-6}alkoxylcarbonyl, C_{1-6}alkylacylamino, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl and C_{1-6}alkylsulfonylamino;
R^3 is selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxyl, C_{1-6}alkyl substituted with halogen, C_{1-6}alkoxyl substituted with halogen, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, C_{1-6}alkylthio, C_{1-6}alkylcarbamoyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxylcarbonyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkylacylamino, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl and C_{1-6}alkylsulfonylamino;
$R^{3'}$ is absent;
R^4, R^5 and R^6 are each independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl substituted with halogen, C_{1-6}alkoxyl substituted with halogen, C_{1-6}alkylamino and di(C_{1-6}alkyl)amino;
X is selected from the group consisting of cyano-substituted methenyl or a nitrogen atom;
L is selected from the group consisting of O, $S(O)_m$, N(H), $N(CH_3)$ or C(O);
T is selected from the group consisting of a covalent bond, C(O) or CH(R'), R' is selected from the group consisting of hydrogen or C_{1-6}alkyl;
Z is hydrogen;
q is 2, and R^3 may be identical or different;
m is selected from the group consisting of 0, 1 or 2; and
n is selected from the group consisting of 0 or 1.

[0016] The present invention also describes a pharmaceutical composition containing a compound represented by the general formula (I), a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

[0017] The present invention also describes a pharmaceutical formulation containing a compound represented by the general formula (I), a pharmaceutically acceptable salt thereof or a stereoisomer thereof and a pharmaceutically acceptable carrier.

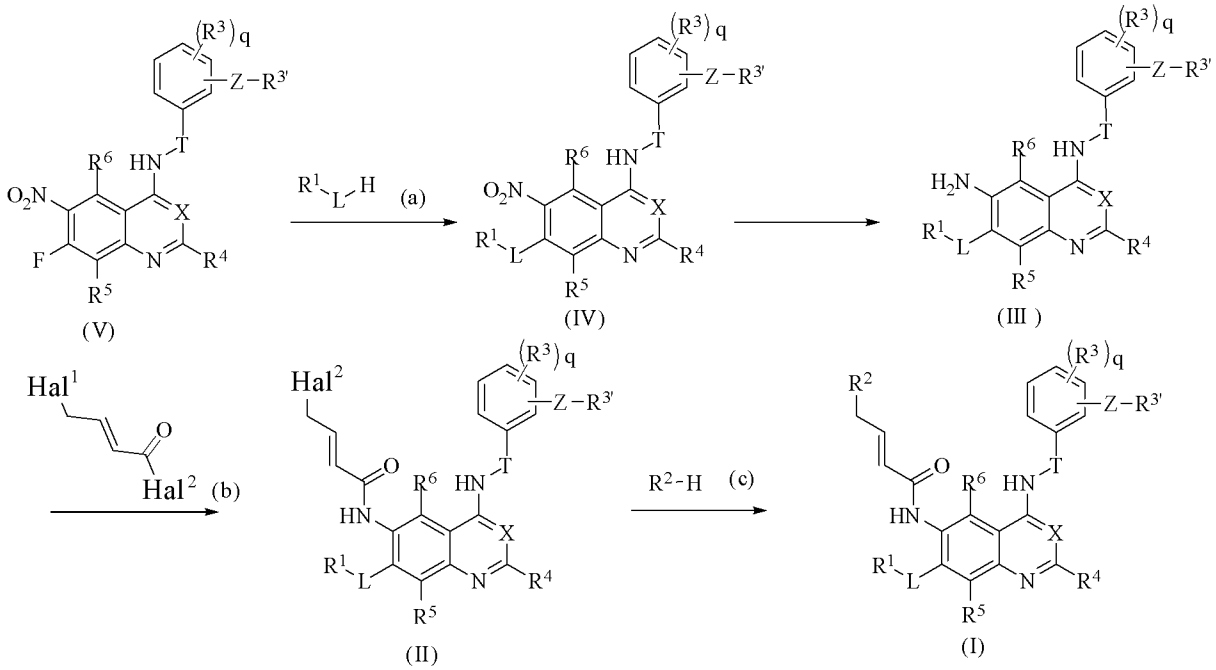
[0018] The present invention also describes a compound represented by the general formula (I), a pharmaceutically acceptable salt thereof or a stereoisomer thereof, or a pharmaceutical composition containing a compound represented by the general formula (I), a pharmaceutically acceptable salt thereof or a stereoisomer thereof as a medicament for treating an excessive proliferative disease and a chronic obstructive pulmonary disease.

[0019] The present invention also describes use of a compound represented by the general formula (I), a pharmaceutically acceptable salt thereof or a stereoisomer thereof, or a pharmaceutical composition containing a compound represented by the general formula (I), a pharmaceutically acceptable salt thereof or a stereoisomer thereof in the manufacture of a medicament for treating an excessive proliferative disease and a chronic obstructive pulmonary disease.

[0020] The present invention also describes a process for preparing a compound of the general formula (I), comprising the steps of:

Reaction Procedure:

[0021]



wherein R^1, R^2, R^3, $R^{3'}$, R^4, R^5, R^6, X, L, T, Z and q are as defined hereinbefore, Hal^1 is selected from the group consisting of Cl, Br and I, Hal^2 is selected from the group consisting of Cl and Br, and Hal^1 and Hal^2 may be identical or different;

1) Dissolving a compound of the starting material (a) in an organic solvent (such as dimethyl formamide (DMF), acetonitrile, tetrahydrofuran (THF), methanol or ethanol), and reacting it with a compound of the formula (V) in the presence of an inorganic base (such as NaH, NaOH or KOH) to produce a compound of the formula (IV);

2) Reacting the compound of the formula (IV) and a reducing agent (such as Fe powder, Zn powder, Pd/C or Raney Ni) to produce a compound of the formula (III);

3) Dissolving the compound of the formula (III) in an organic solvent (such as tetrahydrofuran, dichlormethane (DCM) or ethyl acetate (EA)), and reacting it with a compound of the formula (b) to produce a compound of the formula (II); and

4) Reacting the compound of the formula (II) and a compound of the formula (c) in the presence of a base (such as *N,N*-diisopropyl ethylamine (DIPEA), triethylamine (TEA), pyridine, K_2CO_3 or Na_2CO_3) to produce a compound of the formula (I);

where if necessary, a functional group that needs to be protected may be protected, and then deprotected according to the conventional method.

[0022] According to the present invention, the term "C_{0-6}alkyl" means a straight or branched alkyl group having a carbon atom number of 0-6 such as 0, 1, 2, 3, 4, 5 or 6. When the carbon atom number is zero, the alkyl is absent. The alkyl includes, for example, "C_{0-4}alkyl", "C_{1-6}alkyl", "C_{2-5}alkyl", and "C_{1-4}alkyl". Its example includes but is not limited to, e.g., methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, 2-methylbutyl, neopentyl, 1-ethylpropyl, n-hexyl, iso-hexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, 1-methyl-2-methylpropyl and the like.

[0023] According to the present invention, the term "C_{2-6}alkenyl" means a straight or branched or cyclic hydrocarbyl group having a double bond and a carbon atom number of 2-6, and includes, for example, "C_{3-6}alkenyl", "C_{3-5}alkenyl", "C_{2-4}alkenyl" and the like. Its example includes but is not limited to, e.g., ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-1-butenyl, 2-methyl-1-butenyl, 3-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-1-pentenyl, 2-methyl-1-pentenyl, 3-methyl-1-pentenyl, 4-methyl-1-pentenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 1-methyl-3-pentenyl, 2-methyl-3-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-1-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-1-butenyl, 1,3-dimethyl-2-butenyl, 1,3-dimethyl-2-butenyl, 2,2-dimethyl-3-

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[0024] According to the present invention, the term "C_{2-6}alkynyl" means a straight or branched hydrocarbyl group containing a triple bond and having a carbon atom number of 2-6, including, for example, "C_{3-6}alkynyl", "C_{3-5}alkynyl", "C_{2-4}alkynyl" and the like. Its example includes but is not limited to, e.g., ethynyl, 2-propynyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-methyl-2-butynyl, 1-methyl-3-butynyl, 2-methyl-3-butynyl, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 1-methyl-4-pentynyl, 2-methyl-3-pentynyl, 2-methyl-4-pentynyl, 3-methyl-4-pentynyl, 4-methyl-2-pentynyl, 1,1-dimethyl-2-butynyl, 1,1-dimethyl-3-butynyl, 1,2-dimethyl-3-butynyl, 2,2-dimethyl-3-butynyl, 1-ethyl-2-butynyl, 1-ethyl-3-butynyl, 2-ethyl-3-butynyl, 1-ethyl-1-methyl-2-propynyl and the like.

[0025] According to the present invention, the term "C_{1-6}alkoxyl" means "C_{1-6}alkyl-O-", wherein C_{1-6}alkyl is defined as above; including, for example, "C_{2-5}alkoxyl", "C_{1-4}alkoxyl" and the like. Its example includes but is not limited to, e.g., methoxy, ethoxy, propoxy, iso-propoxy, butoxy, iso-butoxy, tert-butoxy, sec-butoxy, pentoxy, neo-pentoxy, hexyloxy and the like.

[0026] According to the present invention, the term "C_{1-6}alkylthio" means "C_{1-6}alkyl-S-", wherein C_{1-6}alkyl is defined as above, including, for example, "C_{2-5}alkylthio", "C_{1-4}alkylthio" and the like. Its example includes but is not limited to, e.g., methylthio, ethylthio, propylthio, iso-propylthio, butylthio, iso-butylthio, tert-butylthio, sec-butylthio, pentylthio, neo-pentylthio, hexylthio and the like.

[0027] According to the present invention, the term "C_{1-6}alkylamino" means "C_{1-6}alkyl-NH-", wherein C_{1-6}alkyl is defined as above; including, for example, "C_{2-5}alkylamino", "C_{1-4}alkylamino" and the like. Its example includes but is not limited to, e.g., methylamino, ethylamino, propylamino, iso-propylamino, butylamino, iso-butylamino, tert-butylamino, sec-butylamino, pentylamino, neo-pentylamino, hexylamino and the like.

[0028] According to the present invention, the term "di(C_{1-6}alkyl)amino" means "(C_{1-6}alkyl)$_2$-N-", wherein two C_{1-6}alkyls may be identical or different, and are respectively defined as above.

[0029] According to the present invention, the term "C_{1-6}alkylcarbonyloxy", "C_{1-6}alkoxylcarbonyl", "C_{1-6}alkylcarbonyl", "C_{1-6}alkylsulfonyl", "C_{1-6}alkylsulfinyl", "C_{1-6}alkylsulfonylamino", "C_{1-6}alkylacylamino" and "C_{1-6}alkylcarbamoyl" respectively mean "C_{1-6}alkyl-C(O)-O-", "C_{1-6}alkyl-O-C(O)-", "C_{1-6}alkyl-C(O)-", "C_{1-6}alkyl-SO_2-", "C_{1-6}alkyl-SO-", "C_{1-6}alkyl-SO_2-NH-", "C_{1-6}alkyl-C(O)-NH-" and "C_{1-6}alkyl-NH-C(O)-", wherein "C_{1-6}alkyl" is defined as above.

[0030] According to the present invention, the term "halogen" means fluoro, chloro, bromo, iodo and the like.

[0031] According to the present invention, the term "C_{3-8}cycloalkyl" means a cycloalkyl, which is derived from an alkane containing 3-8, such as 3, 4, 5, 6, 7 or 8 carbon atoms by removing one hydrogen atom, including, for example, "C_{3-7}cycloalkyl", "C_{3-5}cycloalkyl", "C_{5-6}cycloalkyl", "C_{3-4}cycloalkyl" and the like, preferably "C_{3-6}cycloalkyl". Its example includes but is not limited to, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, cyclooctanyl, methylcyclopropyl, dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl, methylcyclopentyl, dimethylcyclopentyl, methylcyclohexanyl, dimethylcyclohexanyl and the like.

[0032] According to the present invention, the term "6-10-membered fused ring" group means a saturated or unsaturated fused ring group containing 6-10 carbon atoms and formed by the linking of at least two cyclic structures sharing two adjacent atoms with each other, wherein the cyclocarbon atom(s) may be optionally replaced with 1-3 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_m$, NCH_3 and C(O). Its example includes but is not limited to 5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl, 5,6-dihydro-1,7-naphthyridin-7(8*H*)-yl, 5H-pyrrolo[3,4-*b*]pyridin-6(7*H*)-yl, 7,8-dihydropyridino[4,3-*d*]pyrimidin-6(5*H*)-yl, 2,3,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridin-5(4*H*)-yl, 6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl, 3-methyl-6,7-dihydro-3*H*-pyrazolo[4,5-*c*]pyridin-5(4*H*)-yl, 2-methylhexahydrocyclopenta[*c*]pyrrol-5-yl and the like.

[0033] According to the present invention, the term "7-10-membered spiro ring" group means a saturated or unsaturated fused ring group containing 7-10 carbon atoms and formed by at least two rings sharing the same atom, wherein the cyclocarbon atom(s) may be replaced with 1-3 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_m$, NCH_3 and C(O). Its example includes but is not limited to 6-azaspiro[2.5]octan-6-yl, 7-azaspiro[3.5]nonan-7-yl, 8-azaspiro[4.5]decan-8-yl, 1-methyl-1,7-diazaspiro[4.4]nonan-7-yl, 2-methyl-2,6-diazaspiro[3.4]octan-6-yl, 6-azaspiro[3.4]octan-6-yl, 2-oxa-7-azaspiro[4.5]decan-7-yl, 2-oxa-8-azaspiro[4.5]decan-8-yl, 2-methyl-2,7-diazaspiro[4.5]decane and the like.

[0034] According to the present invention, the term "7-10-membered bridged ring" group means a saturated or unsaturated fused ring group containing 7-10 carbon atoms and formed by any two rings sharing two atoms which are not directly linked, wherein the cyclocarbon atom(s) may be replaced with 1-3 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_m$, NCH_3 and C(O). Its example includes but is not limited to (1*S*,4*S*)-2-methyl-2-azabicyclo[2.2.1]hexanyl, 2-azabicyclo[2.2.1]heptanyl, 8-methylbicyclo[3.2.1]oc-

tanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 2-azabicyclo[2.2.2]octanyl, 7-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.2.1]octanyl, 3-azabicyclo[3.3.2]decanyl, 7-oxabicyclo[2.2.1]heptanyl, 8-oxabicyclo[3.2.1]octanyl and the like.

[0035] According to the present invention, the term "a covalent bond" means a single bond for attaching two atoms or groups.

[0036] In a preferable embodiment according to the compound of the general formula (I), R^1 is selected from the group consisting of the following groups that are unsubstituted or substituted by 1-2 same or different Q^1: C_{1-4}alkyl, C_{3-8}cycloalkyl-C_{0-4}alkyl, 6-10-membered fused ring-C_{0-4}alkyl, 7-10-membered spiro ring-C_{0-4} alkyl and 7-10-membered bridged ring-C_{0-4}alkyl, and the carbon atom in said cycloalkyl, said fused ring, said spiro ring and said bridged ring may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O); wherein m is selected from the group consisting of 0, 1 or 2, n is selected from the group consisting of 0 or 1, and Q^1 is selected from the group consisting of halogen, hydroxy, amino, carboxyl, cyano, C_{1-4}alkyl, C_{1-4}alkoxyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylcarbonyloxy, C_{1-4}alkoxylcarbonyl, C_{1-4}alkylacylamino, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfinyl, C_{1-4}alkylsulfonylamino and C_{3-8}cycloalkyl.

[0037] In a further preferable embodiment according to the compound of the general formula (I), R^1 is selected from the group consisting of the following groups that are unsubstituted or substituted by 1-2 same or different Q^1:

(1)C_{1-4}alkyl, cyclopropyl-C_{0-4}alkyl, cyclobutyl-C_{0-4}alkyl, cyclopentyl-C_{0-4}alkyl, cyclohexyl-C_{0-4} alkyl and cycloheptyl-C_{0-4}alkyl, the carbon atom in said cyclopropyl, said cyclobutyl, said cyclopentyl, said cyclohexyl and said cycloheptyl may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), wherein, m is selected from the group consisting of 0, 1 or 2, and n is selected from the group consisting of 0 or 1; and

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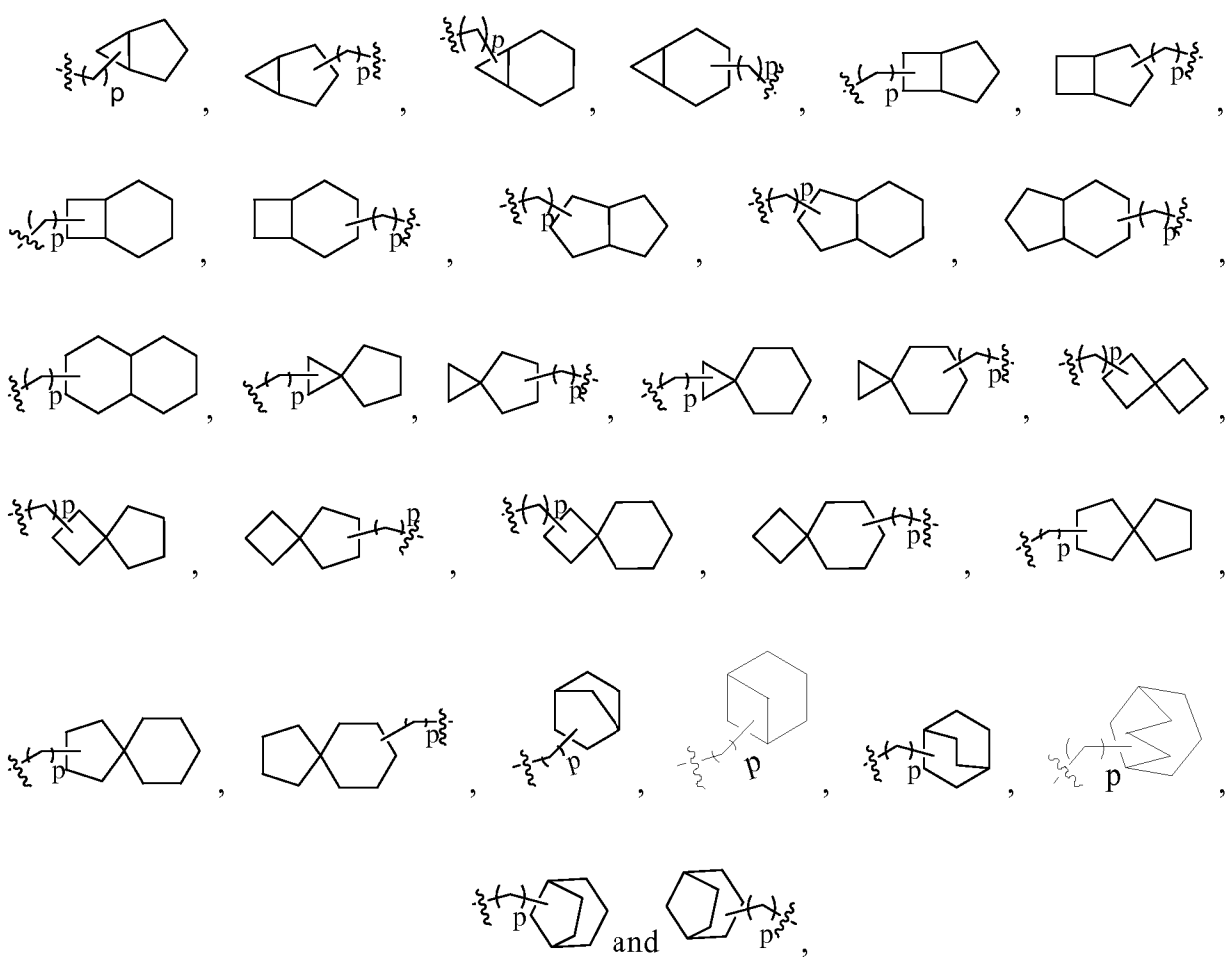

the carbon atom in said ring may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), wherein p is selected from

the group consisting of 0, 1 or 2, m is selected from the group consisting of 0, 1 or 2, and n is selected from the group consisting of 0 or 1; and
Q^1 is selected from the group consisting of halogen, hydroxy, amino, carboxyl, cyano, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetoxy, acetylamino, methylsulfonyl, ethylsulfonyl, methylsulfinyl, methylsulfonylamino, ethylsulfonylamino, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0038] In a further preferable embodiment according to the compound of the general formula (I), R^1 is selected from the group consisting of the following groups that are unsubstituted or substituted by Q^1:

(1)methyl, ethyl, propyl, cyclopropyl-C_{0-3}alkyl, cyclobutyl-C_{0-3}alkyl, cyclopentyl-C_{0-3}alkyl, cyclohexyl-C_{0-3}alkyl, azetidinyl-C_{0-3}alkyl, tetrahydrofuryl-C_{0-3}alkyl, pyrrolidinyl-C_{0-3}alkyl, piperidinyl-C_{0-3}alkyl, morpholinyl-C_{0-3} alkyl and piperazinyl-C_{0-3}alkyl; and

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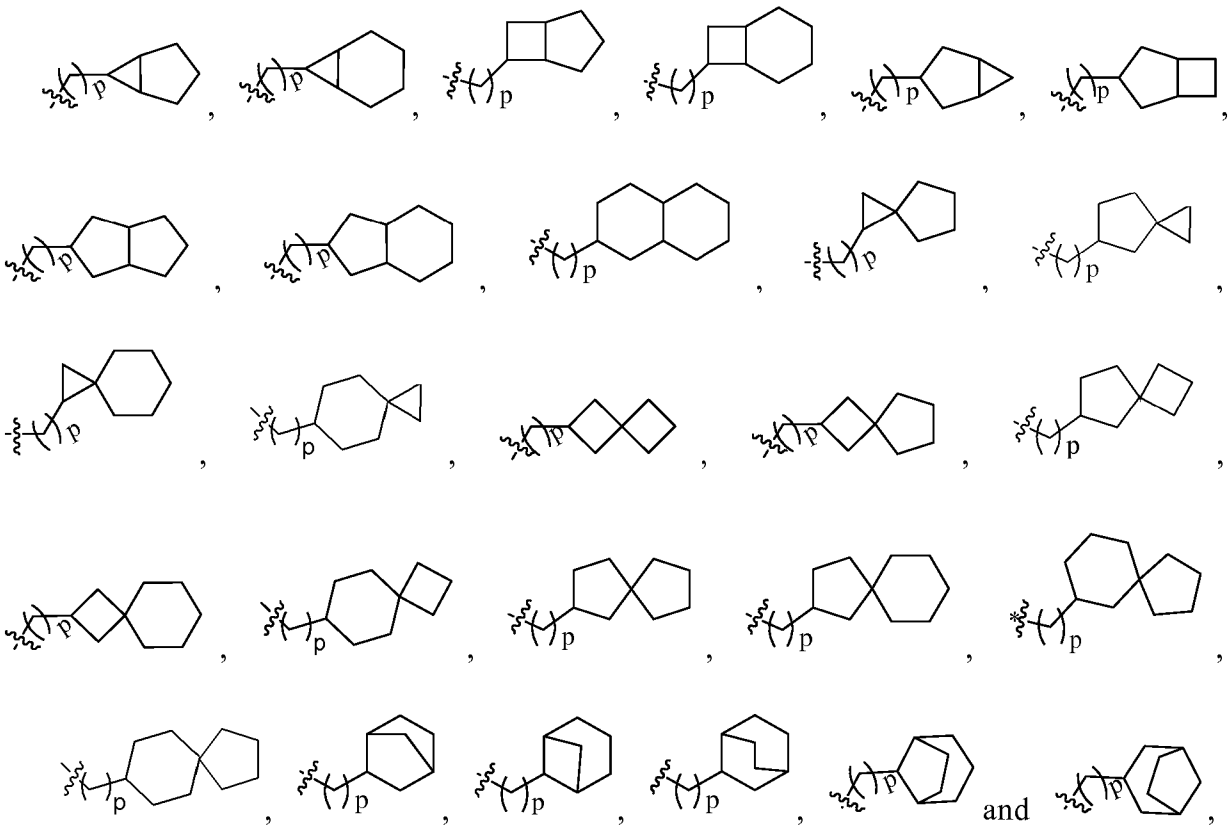
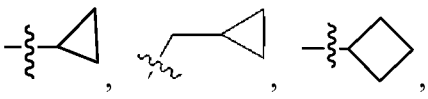
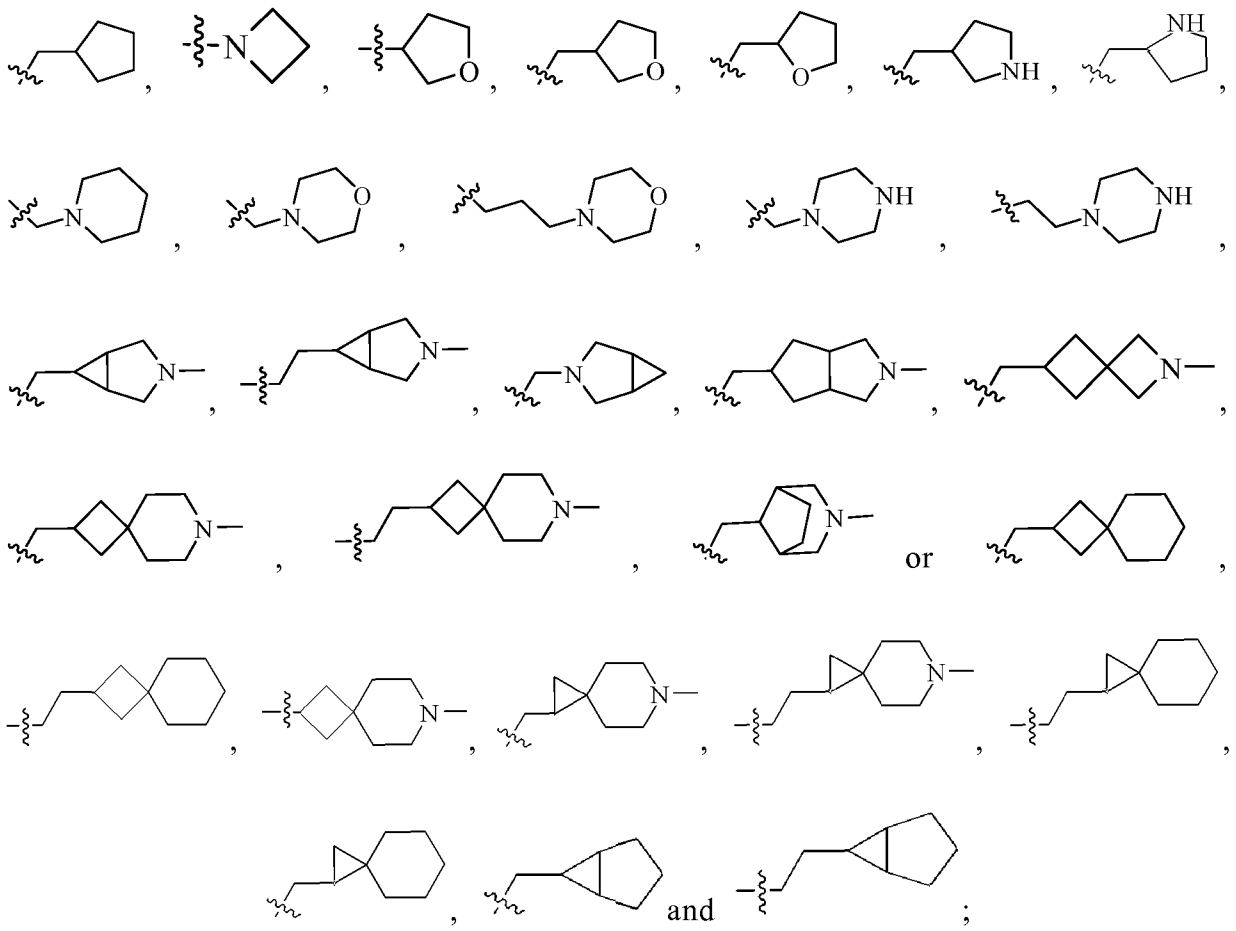


the carbon atom in said ring may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), wherein p is selected from the group consisting of 0, 1 or 2, m is selected from the group consisting of 0, 1 or 2, and n is selected from the group consisting of 0 or 1;
and
Q^1 is selected from the group consisting of halogen, hydroxy, amino, carboxyl, cyano, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino and diethylamino.

[0039] In a further preferable embodiment according to the compound of the general formula (I), R^1 is selected from the group consisting of the following groups that are unsubstituted or substituted by 1-2 same or different Q^1: methyl, ethyl,



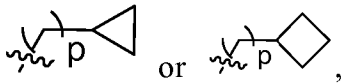


and Q^1 is selected from the group consisting of halogen, hydroxy, amino, carboxyl, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino and diethylamino.

[0040] In a preferable embodiment according to the compound of the general formula (I), R^2 is selected from the group consisting of the following groups that are unsubstituted or substituted by 1-2 same or different Q^2: cyclopropyl-C_{0-4}alkyl, cyclobutyl-C_{0-4}alkyl, 6-10-membered fused ring-C_{0-4}alkyl, 7-10-membered spiro ring-C_{0-4}alkyl or 7-10-membered bridged ring-C_{0-4}alkyl, and the carbon atom in said cyclopropyl, said cyclobutyl, said fused ring, said spiro ring and said bridged ring may be replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), provided that an ester structure "-O-C(O)-" is not present in the replaced ring, wherein m is selected from the group consisting of 0, 1 or 2, and n is selected from the group consisting of 0 or 1; Q^2 is selected from the group consisting of halogen, hydroxy, amino, cyano, C_{1-4}alkyl, C_{1-4}alkoxyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylcarbonyloxy, C_{1-4}alkoxylcarbonyl, C_{1-4}alkylacylamino, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfinyl and C_{1-4}alkylsulfonylamino.

[0041] In a further preferable embodiment according to the compound of the general formula (I), R^2 is selected from the group consisting of

(1)the following groups that are unsubstituted or substituted by 1-2 same or different Q^2:



the carbon atom in said ring may be replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), provided that an ester structure "-O-C(O)-" is not present in the replaced ring; wherein p is selected from the group consisting of 0, 1 or 2, m is selected from the group consisting of 0, 1 or 2, and n is selected from the group consisting of 0 or 1; and

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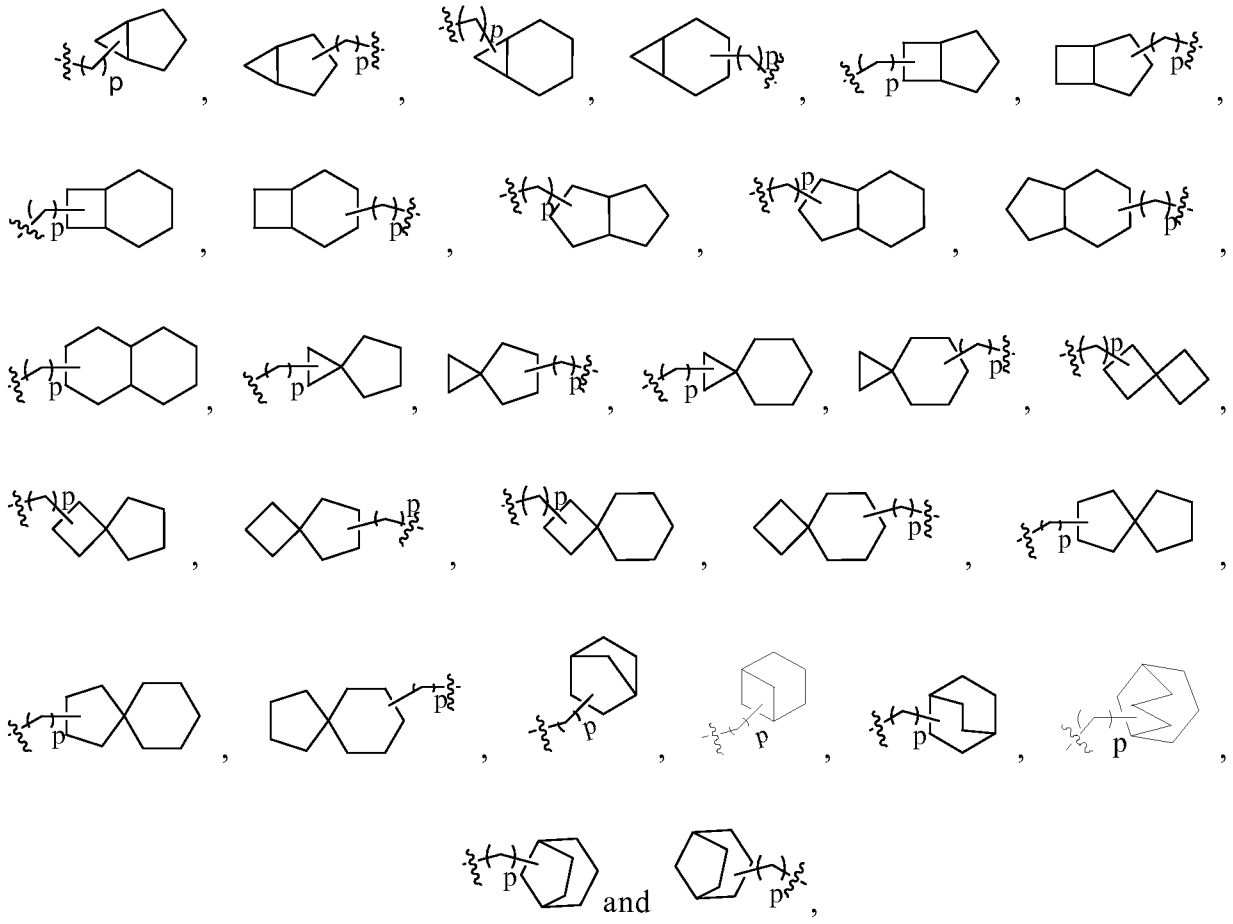

the carbon atom in said ring may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), provided that an ester structure "-O-C(O)-" is not present in the replaced ring, wherein p is selected from the group consisting of 0, 1 or 2, m is selected from the group consisting of 0, 1 or 2, and n is selected from the group consisting of 0 or 1;
and
Q^2 is selected from the group consisting of halogen, hydroxy, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetoxy, acetylamino, methylsulfonyl and methylsulfonylamino.

[0042] In a further preferable embodiment according to the compound of the general formula (I), R^2 is selected from the group consisting of

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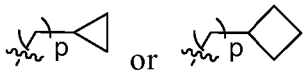

that is unsubstituted or substituted by Q^2, the carbon atom in said ring may be replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), provided that an ester structure "-O-C(O)-" is not present in the replaced ring; wherein p is selected from the group consisting of 0, 1 or 2, m is selected from the group consisting of 0, 1 or 2, and n is selected from the group consisting of 0 or 1; and

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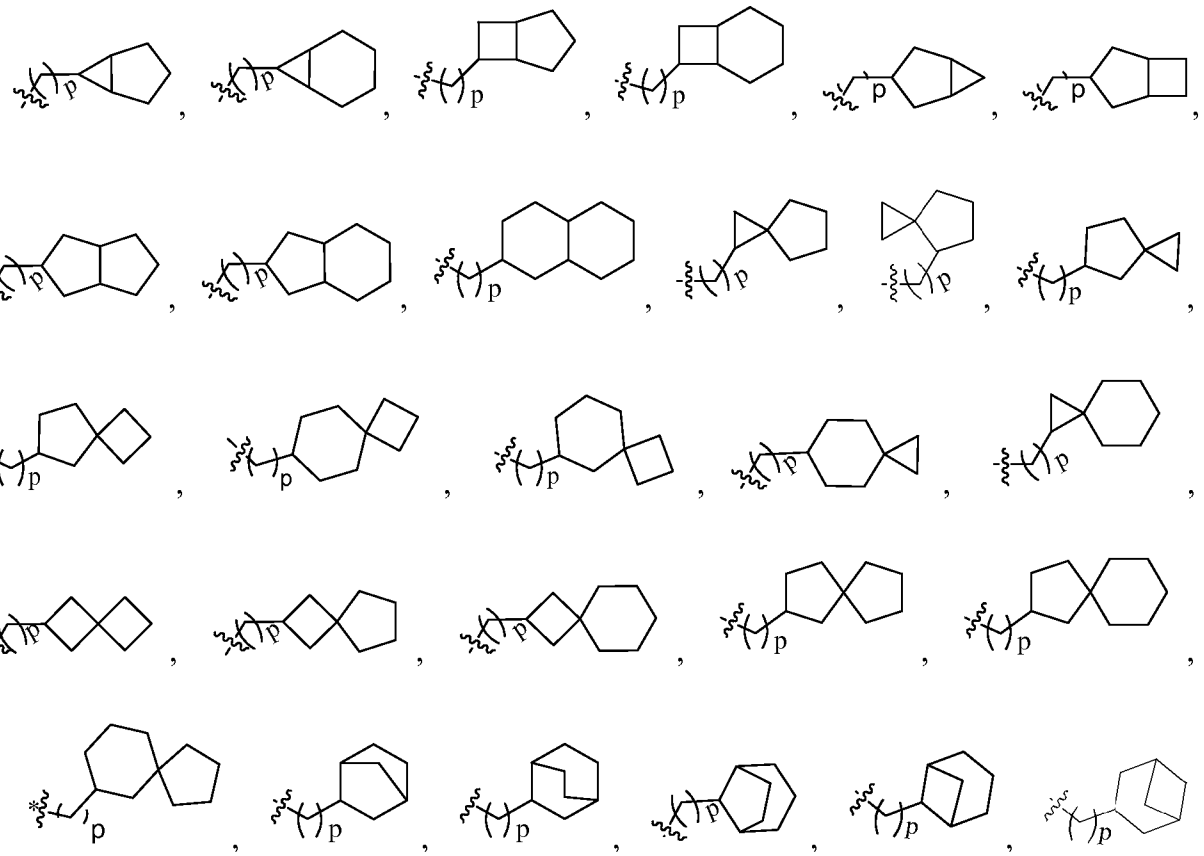
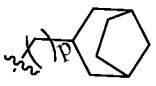
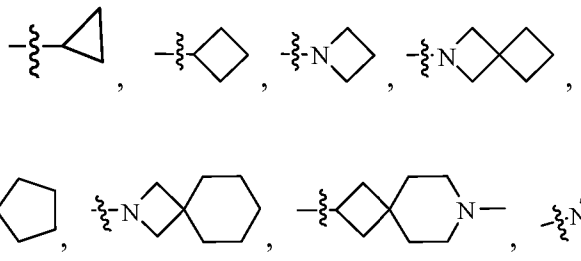


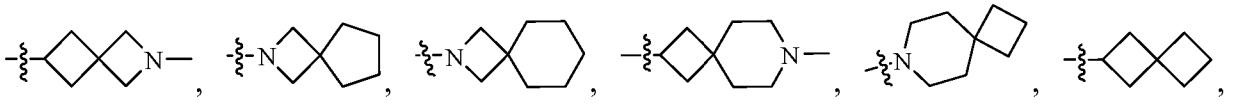
and

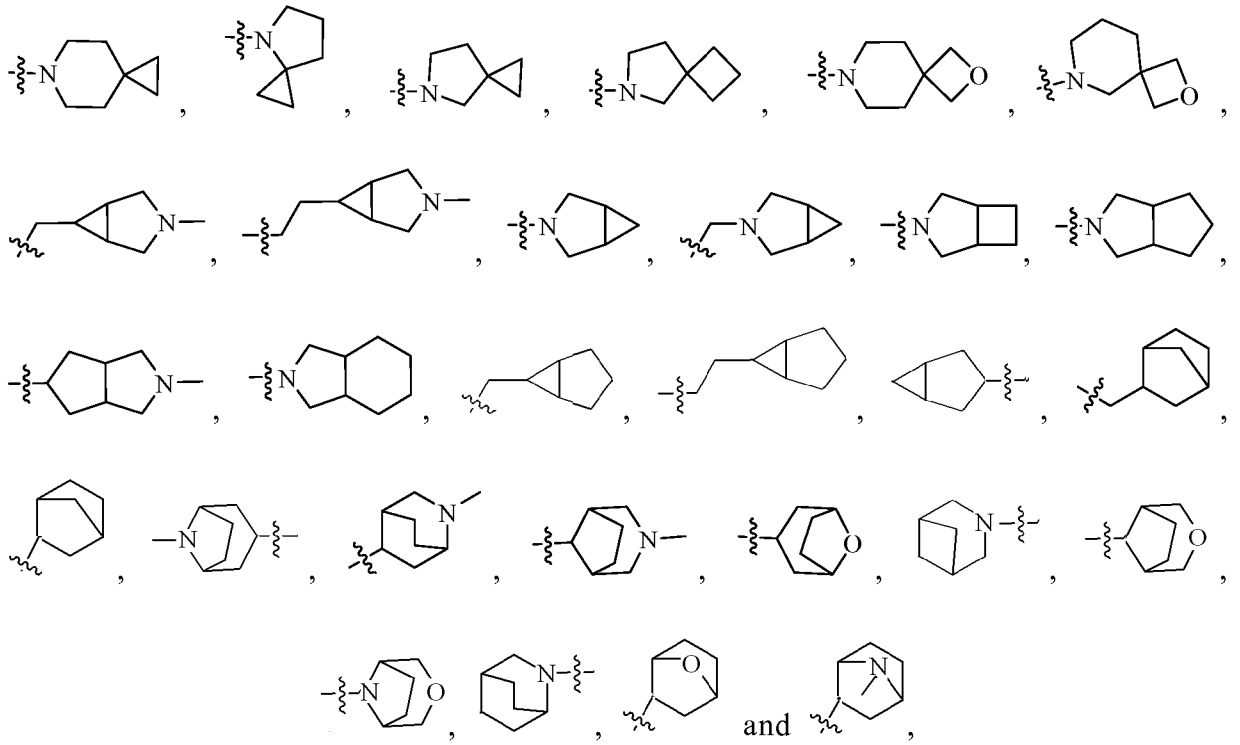


the carbon atom in said ring may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), provided that an ester structure "-O-C(O)-" is not present in the replaced ring, wherein p is selected from the group consisting of 0, 1 or 2, m is selected from the group consisting of 0, 1 or 2, and n is selected from the group consisting of 0 or 1;
and
Q^2 is selected from the group consisting of halogen, hydroxy, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetoxy, acetylamino, methylsulfonyl and methylsulfonylamino.

[0043] In a further preferable embodiment according to the compound of the general formula (I), R^2 is selected from the group consisting of the following groups that are unsubstituted or substituted by 1-2 same or different Q^2:







and Q^2 is selected from the group consisting of halogen, hydroxy, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetoxy, acetylamino, methylsulfonyl and methylsulfonylamino.

[0044] In a preferable embodiment according to the compound of the general formula (I), R^3 is selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, carbamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxyl, C_{1-4}alkyl substituted with halogen, C_{1-4}alkoxyl substituted with halogen, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylthio, C_{1-4}alkylcarbamoyl, C_{1-4}alkylcarbonyl, C_{1-4}alkoxylcarbonyl, C_{1-4}alkylcarbonyloxy, C_{1-4}alkylacylamino, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfinyl and C_{1-4}alkylsulfonylamino.

[0045] In a further preferable embodiment according to the compound of the general formula (I), R^3 is selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, carbamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, methyl substituted with halogen, methoxy substituted with halogen, methylamino, ethylamino, dimethylamino, methylthio, methylcarbamoyl, acetyl, methoxycarbonyl, acetoxy, acetylamino and methylsulfonylamino.

[0046] In a further preferable embodiment according to the compound of the general formula (I), R^3 is halogen, which is selected from the group consisting of fluoro, chloro, bromo, or iodo.

[0047] In a preferable embodiment according to the compound of the general formula (I), R^4, R^5 and R^6 are each independently selected from the group consisting of hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxyl, C_{1-4}alkyl substituted with halogen, C_{1-4}alkoxyl substituted with halogen, C_{1-4}alkylamino and di(C_{1-4}alkyl)amino.

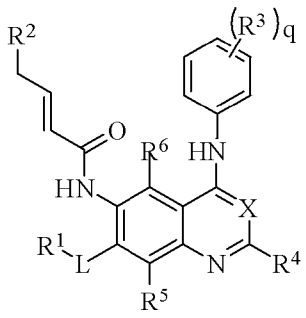
[0048] In a further preferable embodiment according to the compound of the general formula (I), R^4, R^5 and R^6 are each independently selected from the group consisting of hydrogen, halogen, methyl, methoxy, methyl substituted with halogen, methoxy substituted with halogen, methylamino and dimethylamino.

[0049] In a preferable embodiment according to the compound of the general formula (I), X is a nitrogen atom.

[0050] In a preferable embodiment according to the compound of the general formula (I), L is selected from the group consisting of O, $S(O)_m$ or $N(H)_n$; particularly preferably O.

[0051] In a preferable embodiment according to the compound of the general formula (I), T is selected from the group consisting of a covalent bond or CH(R'), R' is selected from the group consisting of hydrogen or C_{1-4}alkyl, such as methyl.

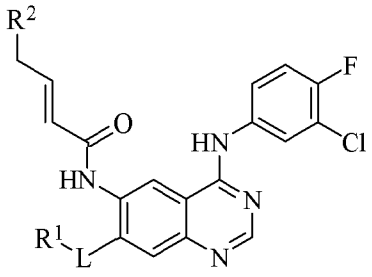
[0052] In a further preferable embodiment according to the compound of the general formula (I), T is a covalent bond, accordingly said compound has a structure of the following formula (I-1):



(I-1),

wherein R^1, R^2, R^3, R^4, R^5, R^6, X, L and q are defined as above.

[0053] In a preferable embodiment according to the compound of the general formula (I-1), R^3 is halogen, which is selected from the group consisting of chloro or fluoro, X is a nitrogen atom, and said compound has a structure of the following formula (I-2):



(I-2),

wherein R^1, R^2 and L are defined as above.

[0054] In another preferable embodiment according to the compound of the general formula (I),

R^1 is selected from the group consisting of the following groups that are unsubstituted or substituted by 1-3 same or different Q^1: C_{1-4}alkyl, C_{3-8}cycloalkyl-C_{0-4}alkyl, 6-10-membered fused ring-C_{0-4}alkyl, 7-10-membered spiro ring-C_{0-4} alkyl and 7-10-membered bridged ring-C_{0-4}alkyl, the carbon atom in said cycloalkyl, said fused ring, said spiro ring or said bridged ring may be optionally replaced by 1-3 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), Q^1 is selected from the group consisting of halogen, hydroxy, amino, carboxyl, cyano, C_{1-4}alkyl, C_{1-4}alkoxyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylcarbonyloxy, C_{1-4}alkoxylcarbonyl, C_{1-4}alkylacylamino, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfinyl, C_{1-4}alkylsulfonylamino and C_{3-8}cycloalkyl;

R^2 is selected from the group consisting of the following groups that are unsubstituted or substituted by 1-2 same or different Q^2: cyclopropyl-C_{0-4}alkyl, cyclobutyl-C_{0-4}alkyl, 6-10-membered fused ring-C_{0-4}alkyl, 7-10-membered spiro ring-C_{0-4}alkyl or 7-10-membered bridged ring-C_{0-4}alkyl, the carbon atom in said cyclopropyl, said cyclobutyl, said fused ring, said spiro ring or said bridged ring may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), provided that an ester structure "-O-C(O)-" is not present in the replaced ring, and when R^2 is 7-10-membered bridged ring-C_{0-4}alkyl, R^1 is not C_{3-4}cycloalkyl-C_{0-4}alkyl or C_{1-4}alkyl; Q^2 is selected from the group consisting of halogen, hydroxy, amino, cyano, C_{1-4}alkyl, C_{1-4}alkoxyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylcarbonyloxy, C_{1-4}alkoxylcarbonyl, C_{1-4}alkylacylamino, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfinyl and C_{1-4}alkylsulfonylamino;

R^3 is selected from the group consisting of hydrogen, halogen, hydroxy, cyano, nitro, carbamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxyl, C_{1-4}alkyl substituted with halogen, C_{1-4}alkoxyl substituted with halogen, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylthio, C_{1-4}alkylcarbamoyl, C_{1-4}alkylcarbonyl, C_{1-4}alkoxylcarbonyl, C_{1-4}alkylcarbonyloxy, C_{1-4}alkylacylamino, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfinyl and C_{1-4}alkylsulfonylamino;

R^3 is absent;

R^4, R^5 and R^6 are each independently selected from the group consisting of hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxyl, C_{1-4}alkyl substituted with halogen, C_{1-4}alkoxyl substituted with halogen, C_{1-4}alkylamino and di(C_{1-4}alkyl)amino;

X is selected from the group consisting of cyano-substituted methenyl or a nitrogen atom;

L is selected from the group consisting of O, $S(O)_m$ or N(H);

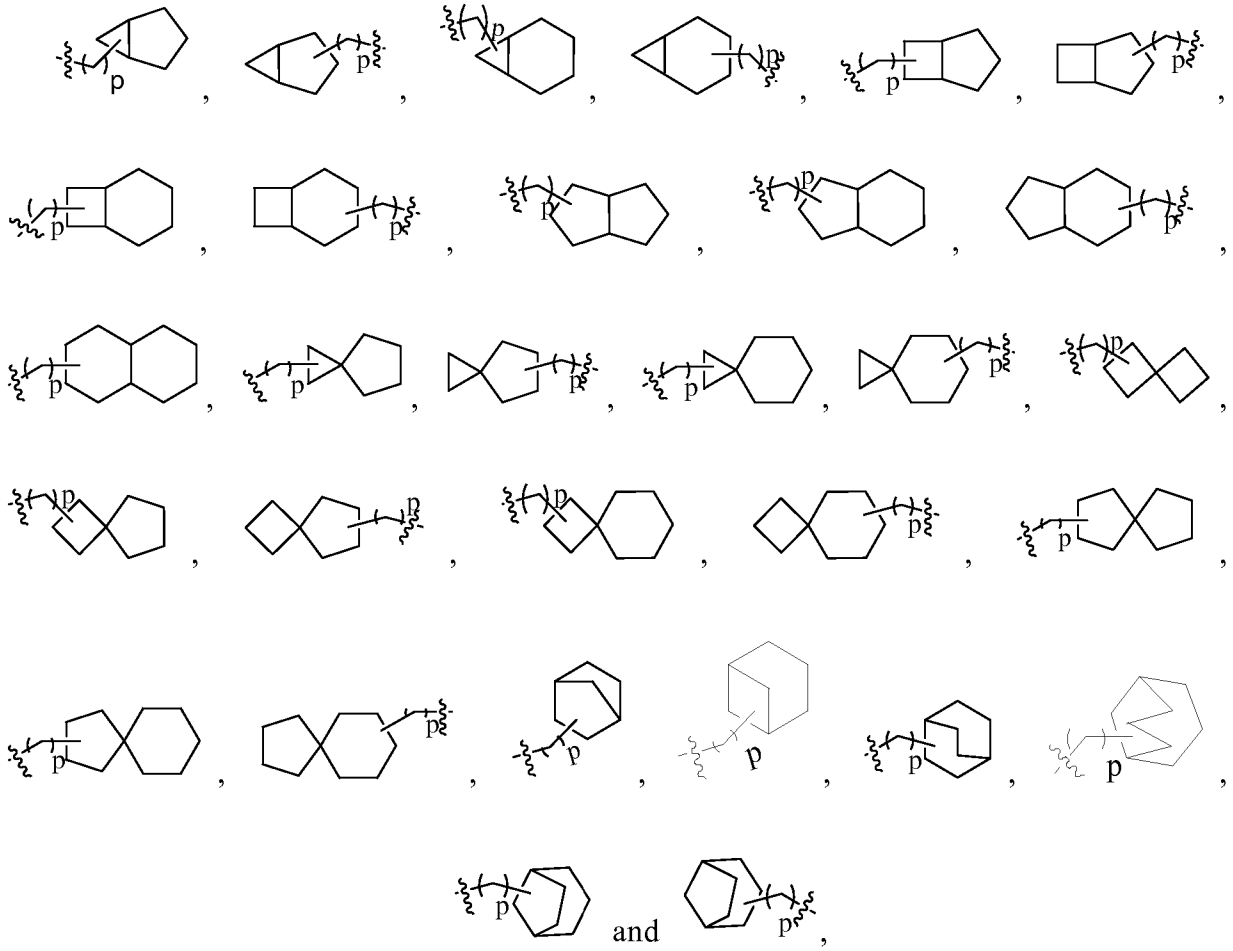
T is selected from the group consisting of a covalent bond or CH(R'), R' is selected from the group consisting of hydrogen or methyl;

Z is hydrogen;
q is 2, and R^3 may be identical or different;
m is selected from the group consisting of 0, 1 or 2; and
n is selected from the group consisting of 0 or 1.

[0055] In another preferable embodiment according to the compound of the general formula (I),
R^1 is selected from the group consisting of the following groups that are unsubstituted or substituted by 1-2 same or different Q^1:

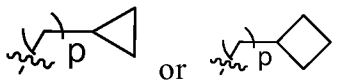
(1)C_{1-4}alkyl, cyclopropyl-C_{0-4}alkyl, cyclobutyl-C_{0-4}alkyl, cyclopentyl-C_{0-4}alkyl, cyclohexyl-C_{0-4} alkyl and cycloheptyl-C_{0-4}alkyl, the carbon atom in said cyclopropyl, said cyclobutyl, said cyclopentyl, said cyclohexyl and said cycloheptyl may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O); and

(2)



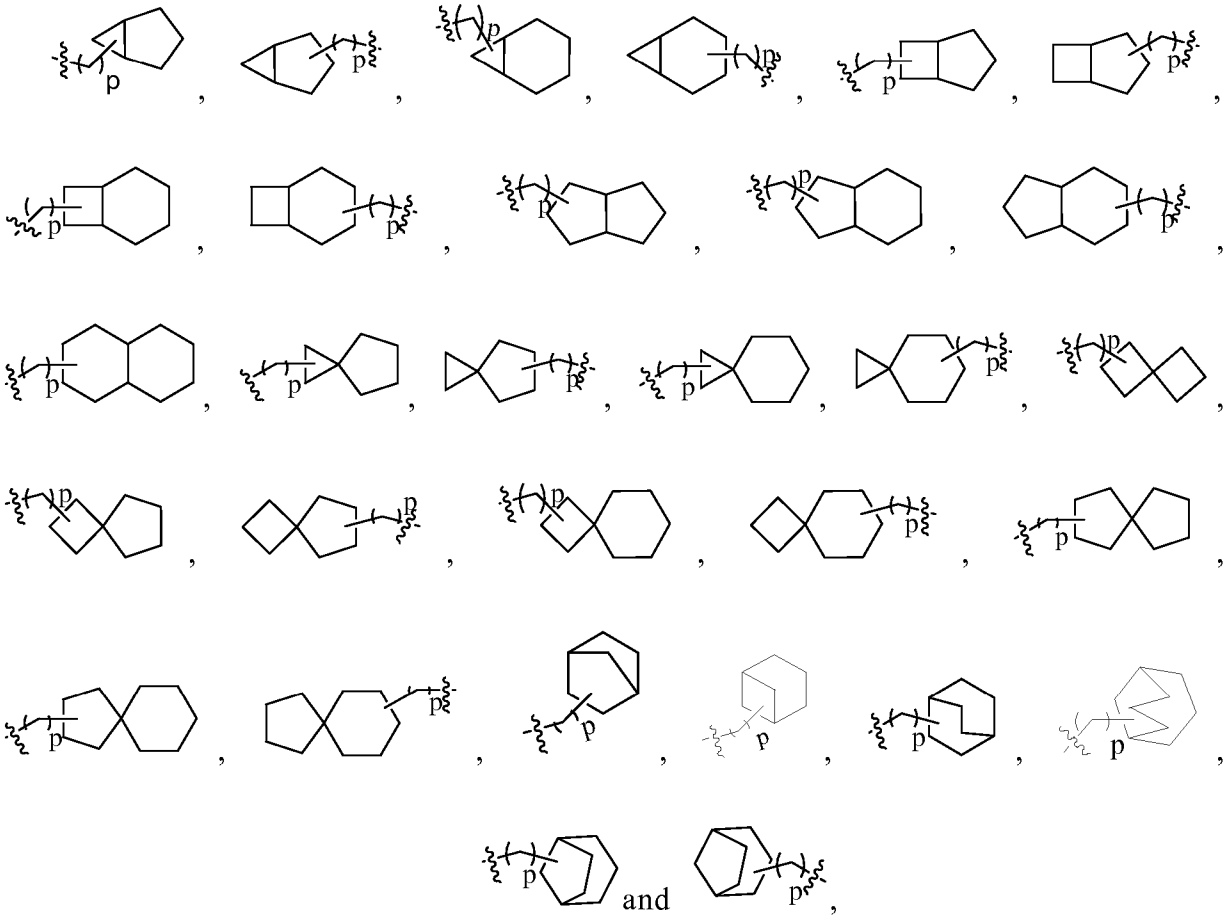
the carbon atom in said ring may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), wherein p is selected from the group consisting of 0, 1 or 2; and
Q^1 is selected from the group consisting of halogen, hydroxy, amino, carboxyl, cyano, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetoxy, acetylamino, methylsulfonyl, ethylsulfonyl, methylsulfinyl, methylsulfonylamino, ethylsulfonylamino, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;
R^2 is selected from the group consisting of

(1)the following groups that are unsubstituted or substituted by 1-2 same or different Q^2:

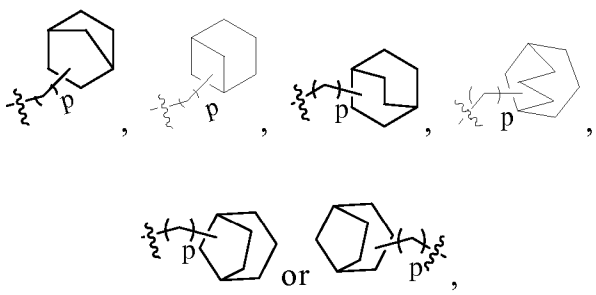


the carbon atom in said ring may be replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), provided that an ester structure "-O-C(O)-" is not present in the replaced ring; p is selected from the group consisting of 0, 1 or 2; and

(2)



the carbon atom in said ring may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), provided that an ester structure "-O-C(O)-" is not present in the replaced ring, wherein p is selected from the group consisting of 0, 1 or 2, and when R^2 is

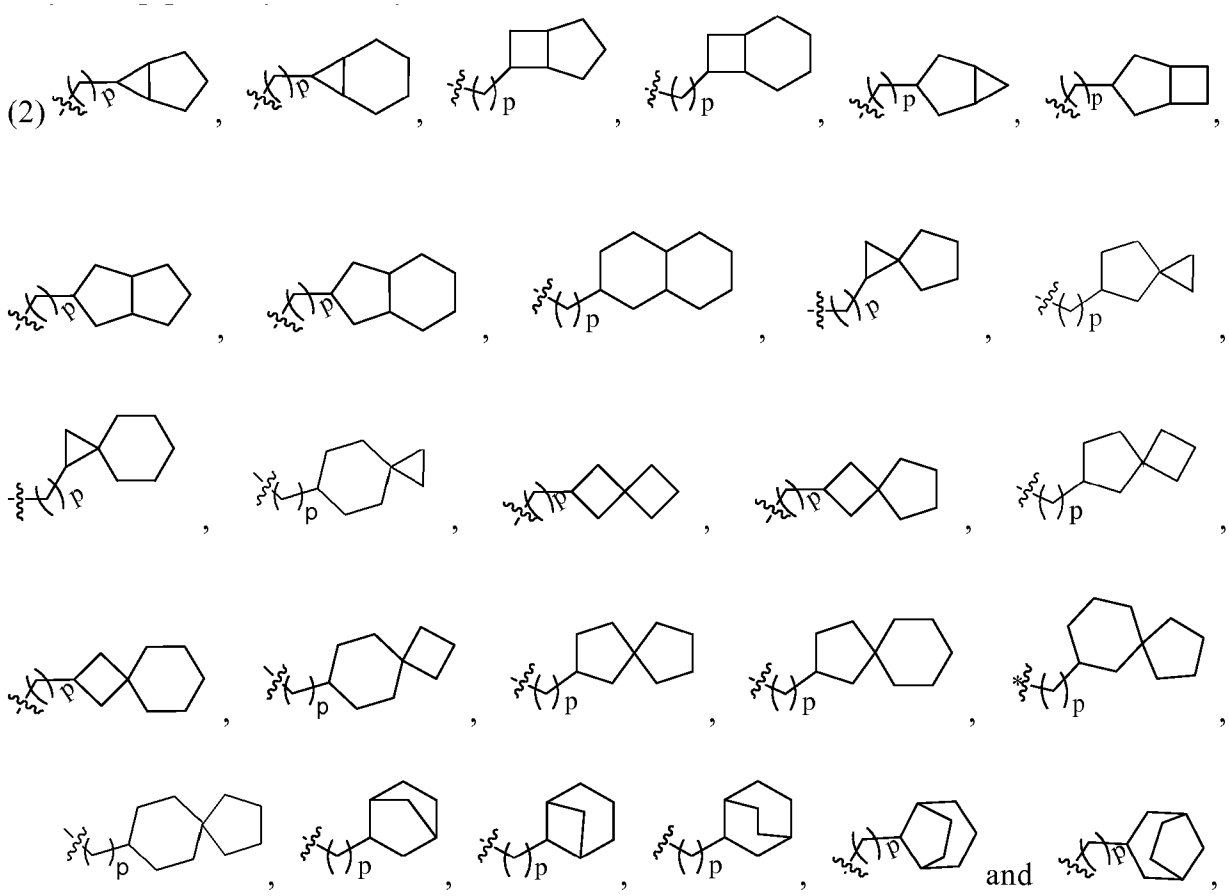


R^1 is not C_{1-4}alkyl, cyclopropyl-C_{0-4}alkyl or cyclobutyl-C_{0-4}alkyl; and

Q^2 is selected from the group consisting of halogen, hydroxy, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetoxy, acetylamino, methylsulfonyl and methylsulfonylamino;
R^3 is selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, carbamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, methyl substituted with halogen, methoxy substituted with halogen, methylamino, ethylamino, dimethylamino, methylthio, methylcarbamoyl, acetyl, methoxycarbonyl, acetoxy, acetylamino and methylsulfonylamino;
R^3 is absent;
R^4, R^5 and R^6 are each independently selected from the group consisting of hydrogen, halogen, methyl, methoxy, methyl substituted with halogen, methoxy substituted with halogen, methylamino and dimethylamino;
X is selected from the group consisting of cyano-substituted methenyl or a nitrogen atom;
L is O;
T is selected from the group consisting of a covalent bond or CH(R'), R' is selected from the group consisting of hydrogen or methyl;
Z is hydrogen;
q is 2, R^3 may be identical or different;
m is selected from the group consisting of 0, 1 or 2; and
n is selected from the group consisting of 0 or 1.

[0056] In a further preferable embodiment according to the compound of the general formula (I),
R^1 is selected from the group consisting of the following groups that are unsubstituted or substituted by Q^1:

(1)methyl, ethyl, propyl, cyclopropyl-C_{0-3}alkyl, cyclobutyl-C_{0-3}alkyl, cyclopentyl-C_{0-3}alkyl, cyclohexyl-C_{0-3}alkyl, azetidinyl-C_{0-3}alkyl, tetrahydrofury-lC_{0-3}alkyl, pyrrolidinyl-C_{0-3}alkyl, piperidinyl-C_{0-3}alkyl, morpholinyl-C_{0-3} alkyl and piperazinyl-C_{0-3}alkyl; and

(2) 

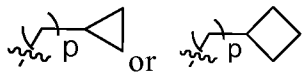
the carbon atom in said ring may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), wherein p is selected from the group consisting of 0, 1 or 2;

and

Q^1 is selected from the group consisting of halogen, hydroxy, amino, carboxyl, cyano, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino and diethylamino;

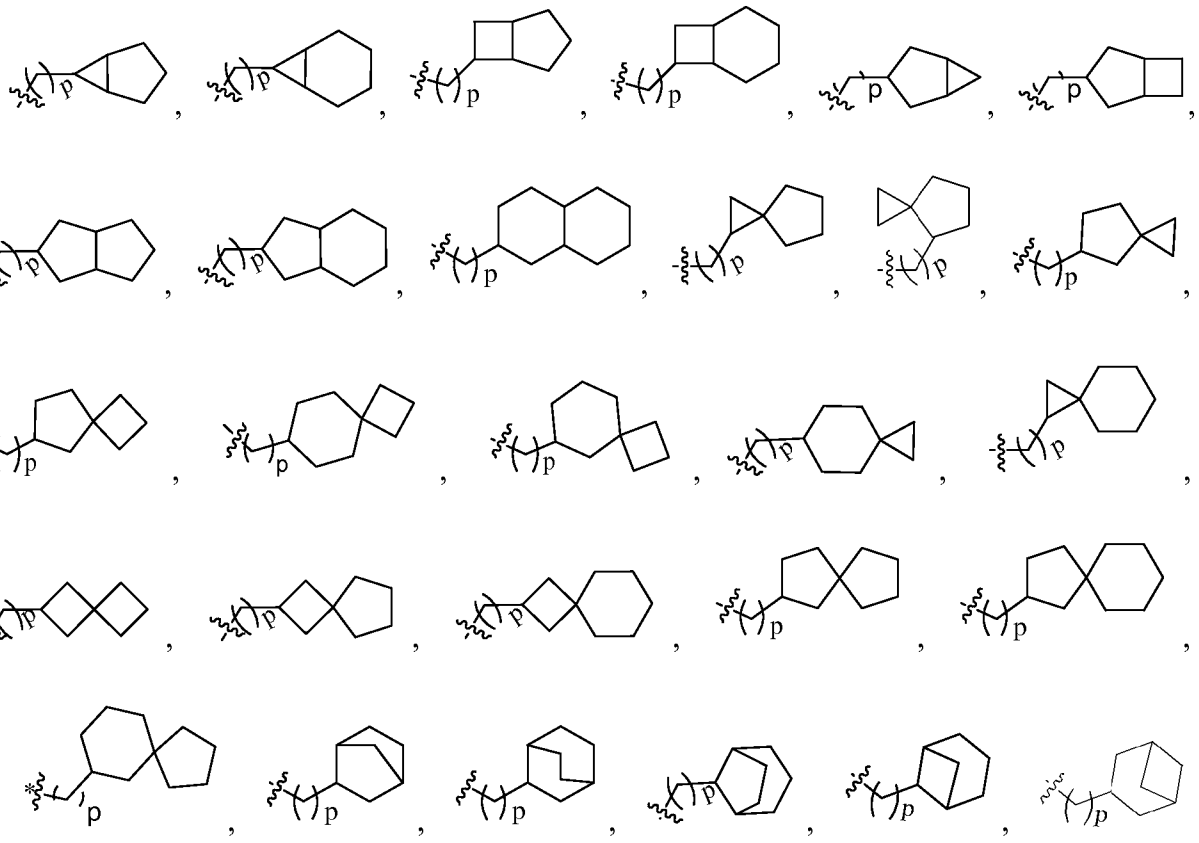
R^2 is selected from the group consisting of

(1)

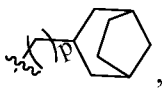


that is unsubstituted or substituted by Q^2, the carbon atom in said ring may be replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), provided that an ester structure "-O-C(O)-" is not present in the replaced ring; wherein p is selected from the group consisting of 0, 1 or 2; and

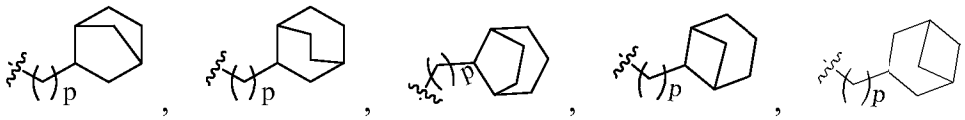
(2)



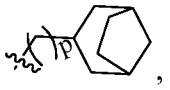
and



the carbon atom in said ring may be optionally replaced by 1-2 hetero atoms and/or groups that may be identical or different and are selected from the group consisting of O, $S(O)_m$, $N(H)_n$ and/or C(O), provided that an ester structure "-O-C(O)-" is not present in the replaced ring, wherein p is selected from the group consisting of 0, 1 or 2; and when R^2 is

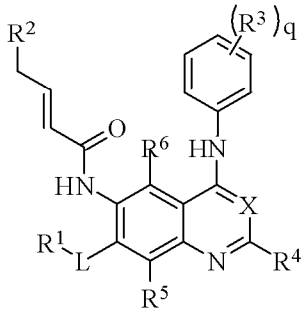


or



R^1 is not methyl, ethyl, propyl, cyclopropyl-C_{0-3}alkyl or cyclobutyl-C_{0-3}alkyl; and
Q^2 is selected from the group consisting of halogen, hydroxy, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetoxy, acetylamino, methylsulfonyl and methylsulfonylamino;
R^3 is selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, carbamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, methyl substituted with halogen, methoxy substituted with halogen, methylamino, ethylamino, dimethylamino, methylthio, methylcarbamoyl, acetyl, methoxycarbonyl, acetoxy, acetylamino and methylsulfonylamino;
R^4, R^5 and R^6 are each independently selected from the group consisting of hydrogen, halogen, methyl, methoxy, methyl substituted with halogen, methoxy substituted with halogen, methylamino and dimethylamino;
X is a nitrogen atom;
L is O;
T is selected from the group consisting of a covalent bond or CH(R'), R' is hydrogen;
Z is hydrogen;
q is 2, R^3 may be identical or different;
m is selected from the group consisting of 0, 1 or 2; and
n is selected from the group consisting of 0 or 1.

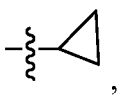
[0057] In a further preferable embodiment, the compound of the general formula (I) according to the present invention has a structure of the following formula (I-1):

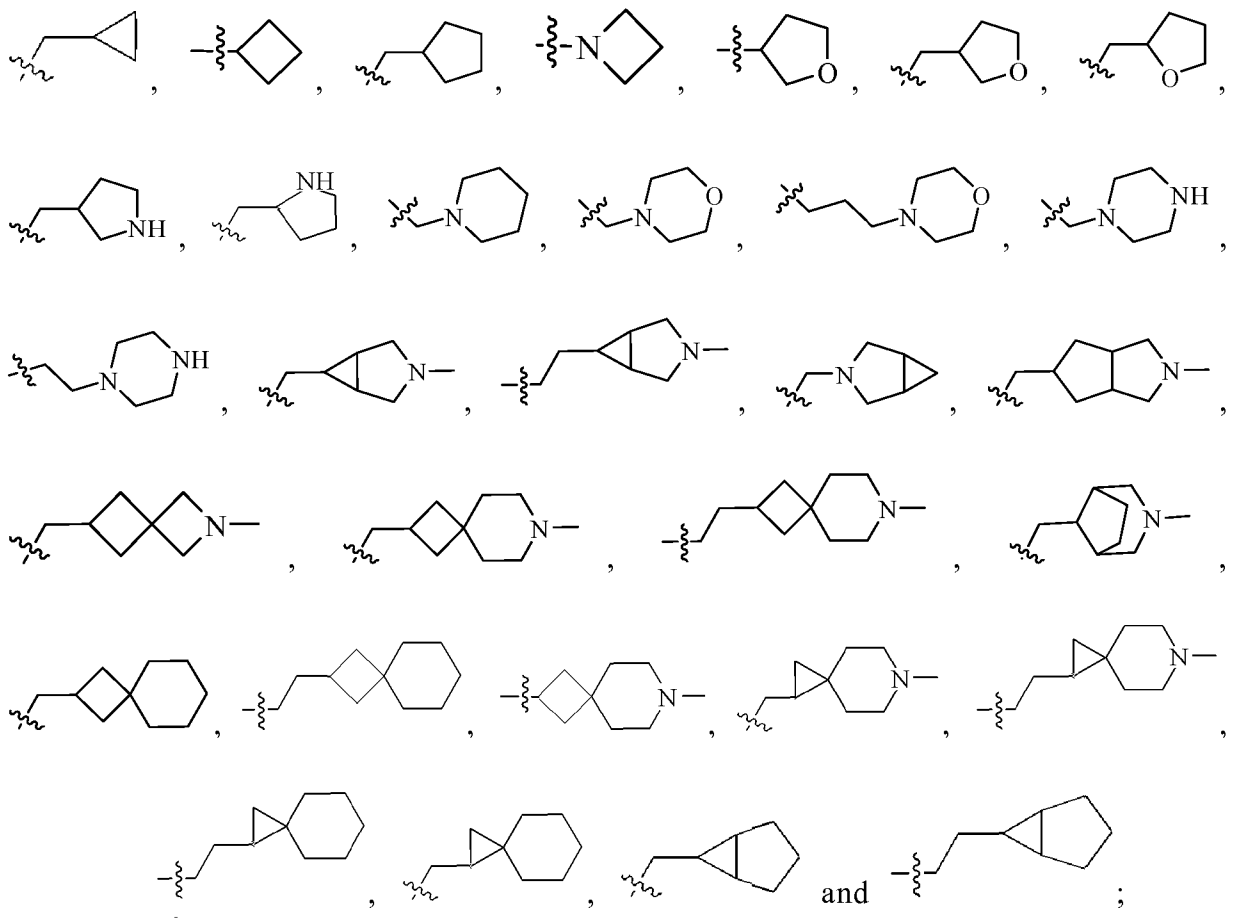


(I-1)

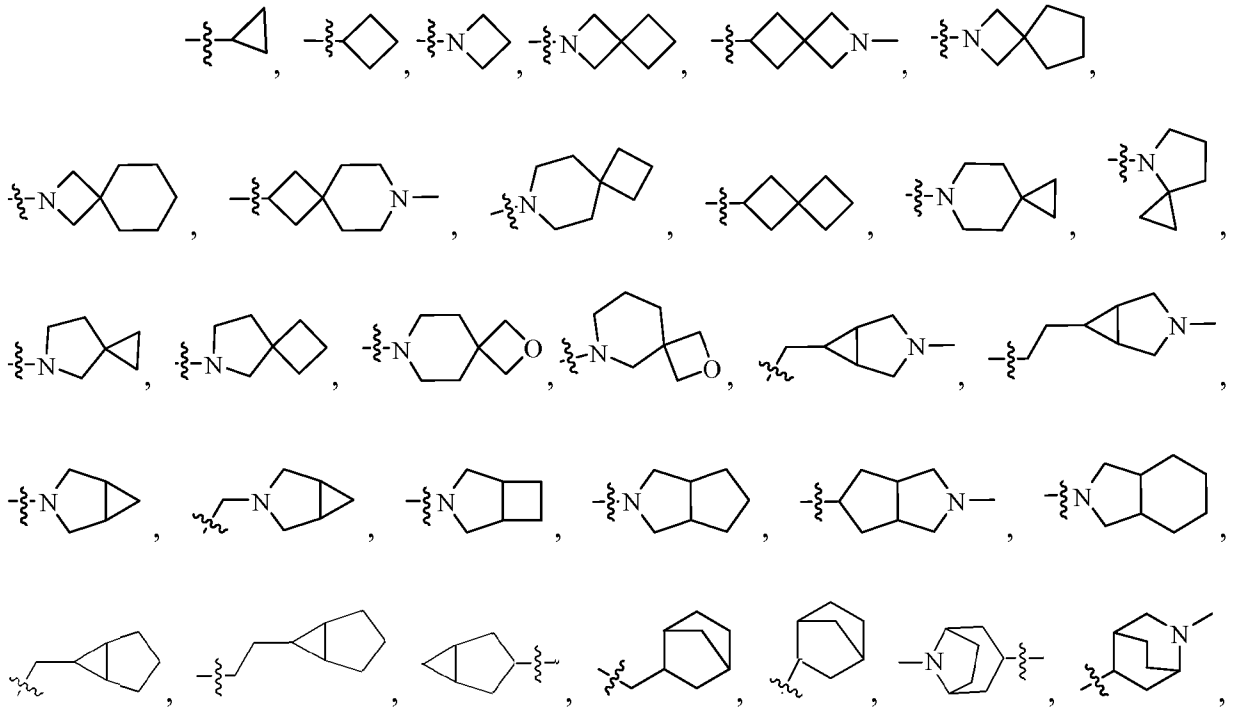
wherein:

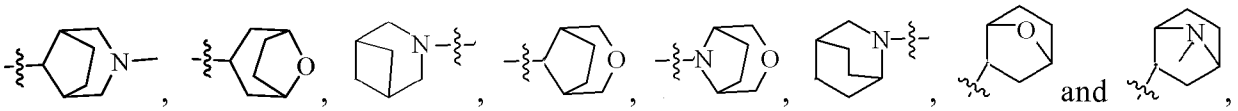
R^1 is selected from the group consisting of the following groups that are unsubstituted or substituted by halogen, hydroxy, amino, carboxyl, cyano, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, or diethylamino: methyl, ethyl,



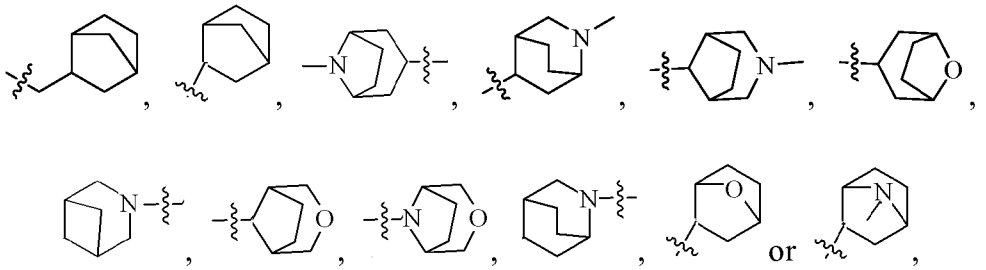


R^2 is selected from the group consisting of the following groups that are unsubstituted or substituted by halogen, hydroxy, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetoxy, acetylamino, methylsulfonyl, or methylsulfonylamino:

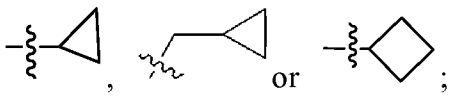




and when R^2 is

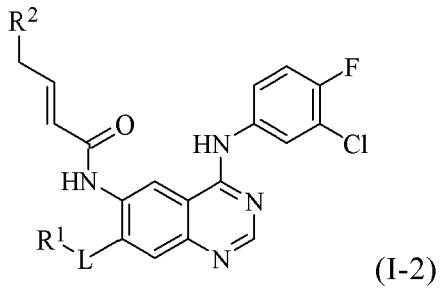


R^1 is not methyl, ethyl,



R^3 is halogen, which is selected from the group consisting of fluoro, chloro, bromo, or iodo;
R^4, R^5 and R^6 are each independently hydrogen;
X is a nitrogen atom;
L is O; and
q is 2.

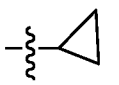
[0058] In a further preferable embodiment, the compound of the general formula (I-1) according to the present invention has a structure of the following formula (I-2):

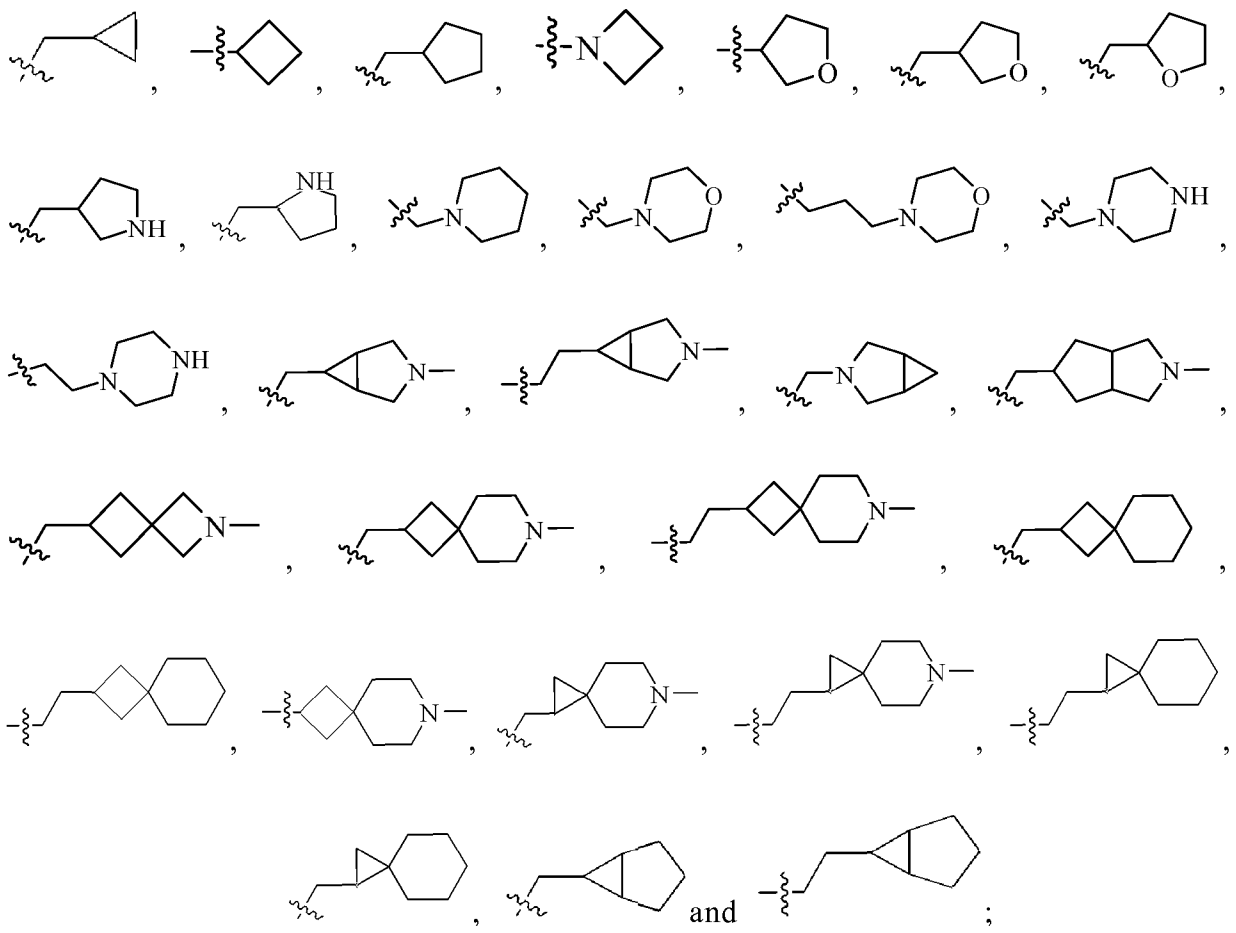


(I-2)

wherein

R^1 is selected from the group consisting of the following groups that are unsubstituted or substituted by halogen, hydroxy, amino, carboxyl, cyano, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, or diethylamino: methyl, ethyl,

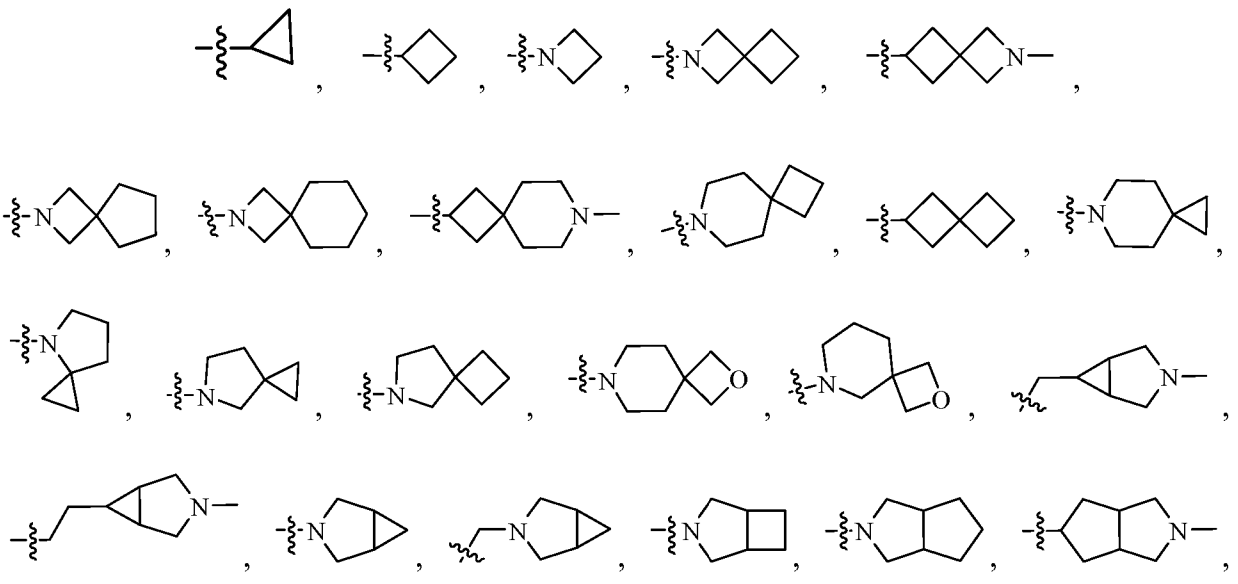


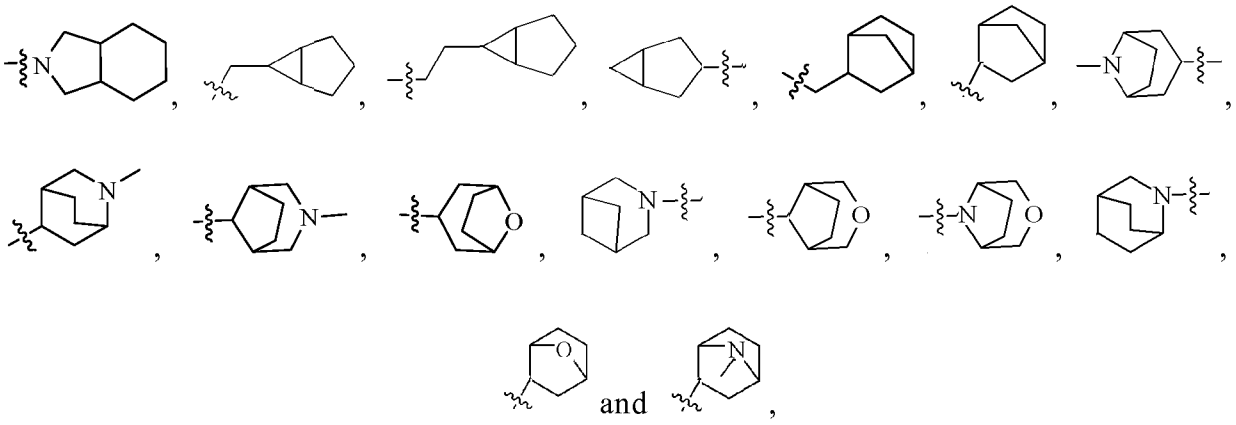


and

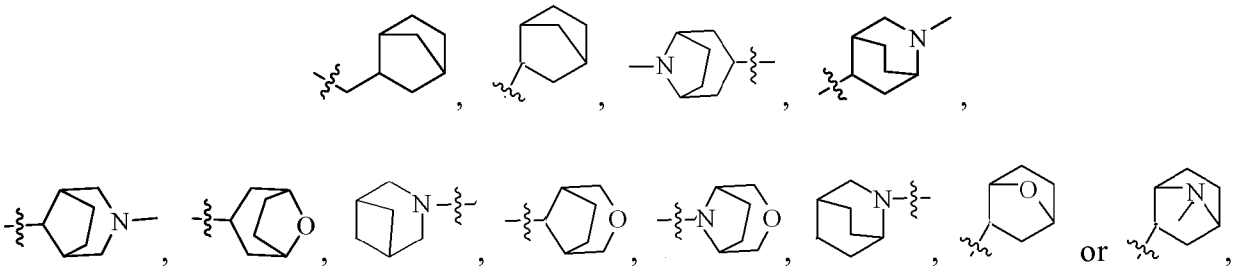
;

R^2 is selected from the group consisting of the following groups that are unsubstituted or substituted by halogen, hydroxy, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetoxy, acetylamino, methylsulfonyl, or methylsulfonylamino:

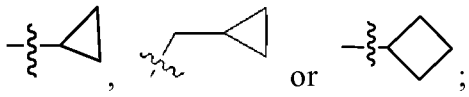




and when R^2 is

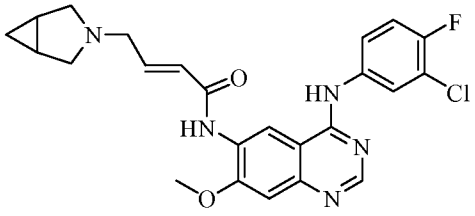
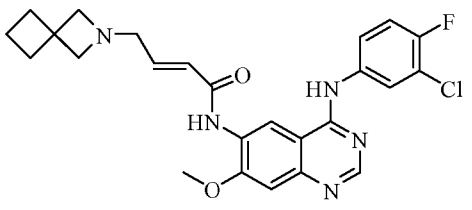


R^1 is not methyl, ethyl,

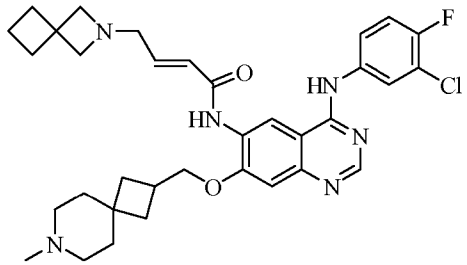
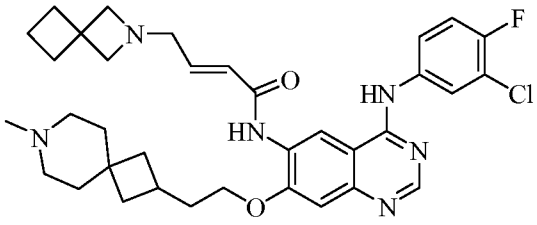
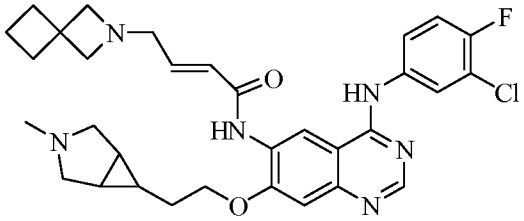
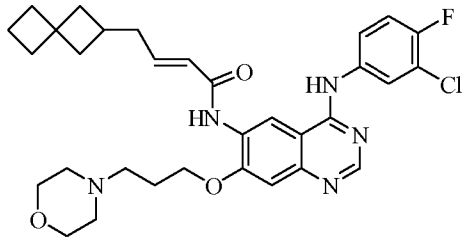
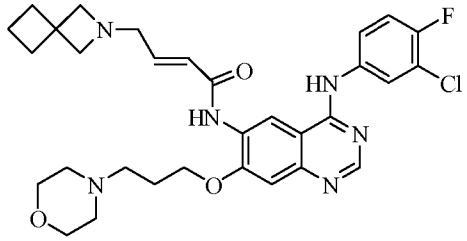
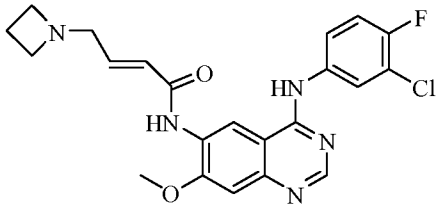


and
LisO.

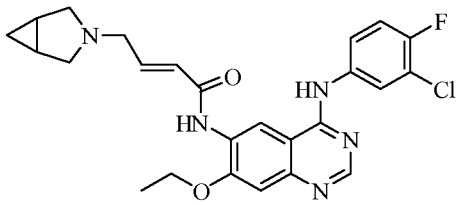
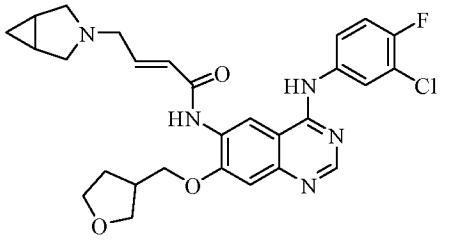
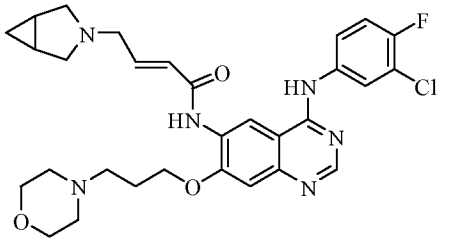
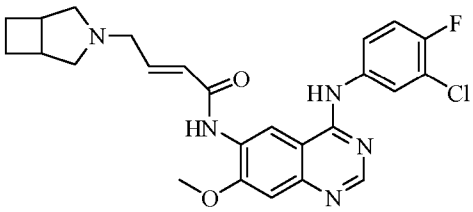
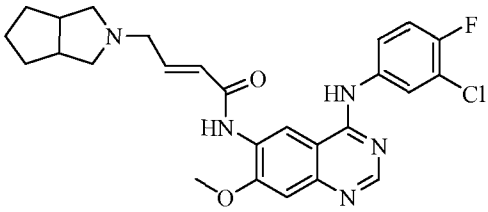
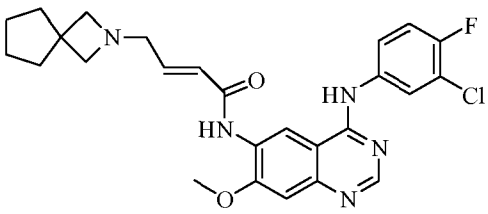
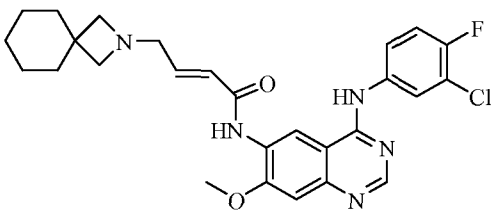
[0059] The specific preferable compounds according to the present invention include the following compounds and their pharmaceutically acceptable salts and stereoisomers:

No.	Structure	Name
1		(*E*)-4-[3-azabicyclo[3.1.0]hexan-3-yl]-*N*-[4-(3-chloro-4-fluorophenylamino)-7-meth oxyquinazolin-6-yl]-2-butenamide
2		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[azaspiro[3. 3]heptan-2-yl]-2-butenamide

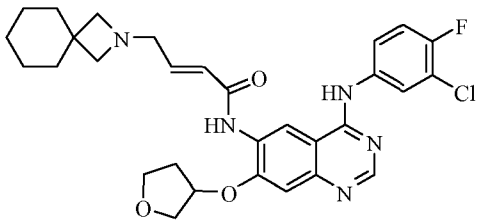
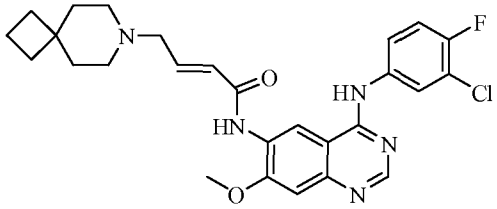
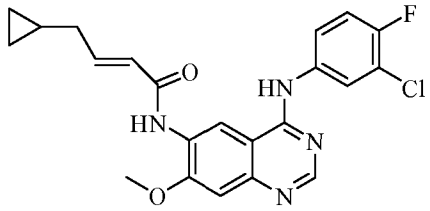
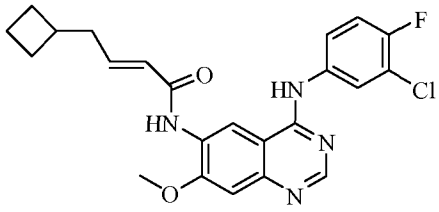
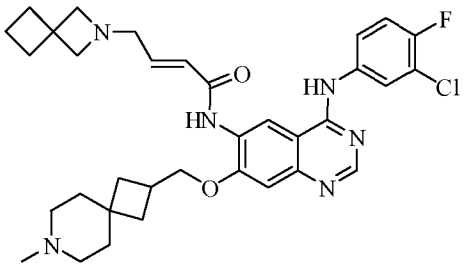
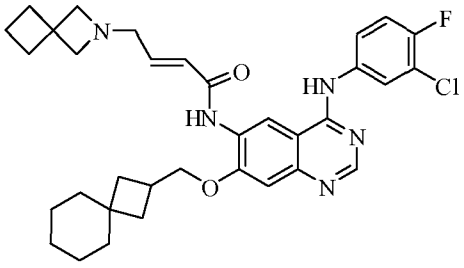
(continued)

No.	Structure	Name
3		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-[[7-methyl-7-azaspiro[3.5]nonan-2-yl]m ethoxy]quinazolin-6-yl]-4-[2-azaspiro[3.3]heptan-2-yl]-2-butenamide
4		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-[2-[7-methyl-7-azaspiro[3.5]nonan-2-yl]ethoxy]quinazolin-6-yl]-4-[2-azaspiro[3. 3]heptan-2-yl]-2-butenamide
5		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-[2-[3-methyl-3-azabicyclo[3.1.0]hexan-6-yl]ethoxy]quinazolin-6-yl]-4-[2-azaspir o[3.3]heptan-2-yl]-2-butenamide
6		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholinopropoxy)quinazolin-6-yl] -4-[spiro[3.3]heptan-2-yl]-2-butenamide
7		(E)-N-[4-(3-chloro-4-fluorophenylamino)-7-[3-morpholinopropoxy]quinazolin-6-yl] -4-[2-azaspiro[3.3]heptan-2-yl]-2-butena mide
8		(*E*)-4-(azetidin-1-yl)-*N*-[4-(3-chloro-4-flu orophenylamino)-7-methoxyquinazolin-6-yl]-2-butenamide

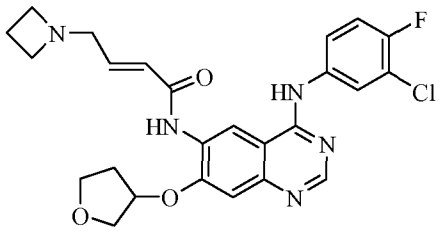
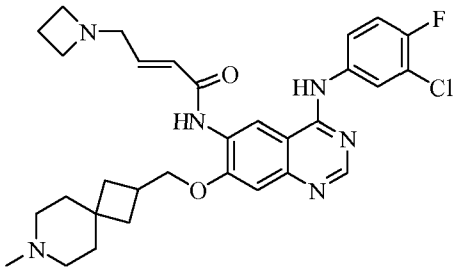
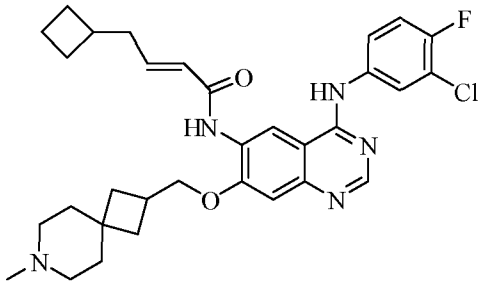
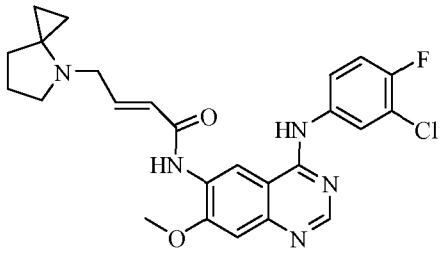
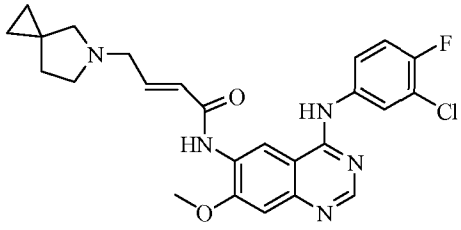
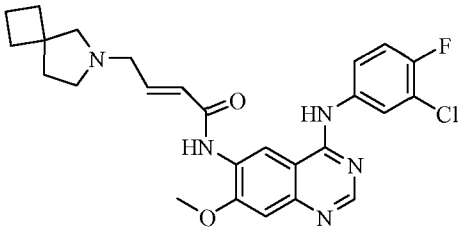
(continued)

No.	Structure	Name
9		(*E*)-4-[3-azabicyclo[3.1.0]hexan-3-yl]-*N*-[4-(3-chloro-4-fluorophenylamino)-7-etho xyquinazolin-6-yl]-2-butenamide
10		(*E*)-4-[3-azabicyclo[3.1.0]hexan-3-yl]-*N*-[4-(3-chloro-4-fluorophenylamino)-7-[(tetr ahydrofuran-3-yl)methoxy]quinazolin-6-y 1]-2-butenamide
11		(*E*)-4-[3-azabicyclo[3.1.0]hexan-3-yl]-*N*-[4-(3-chloro-4-fluorophenylamino)-7-(3-m orpholinopropoxy)quinazolin-6-yl]-2-bute namide
12		(*E*)-4-(3-azabicyclo[3.2.0]heptan-3-yl)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-met hoxyquinazolin-6-yl]-2-butenamide
13		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[hexahydroc yclopenta[*c*]pyrrol-2(1*H*)-yl]-2-butenamid e
14		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[2-azaspiro[3.4]octan-2-yl]-2-butenamide
15		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[2-azaspiro[3.5]nonan-2-yl]-2-butenamide

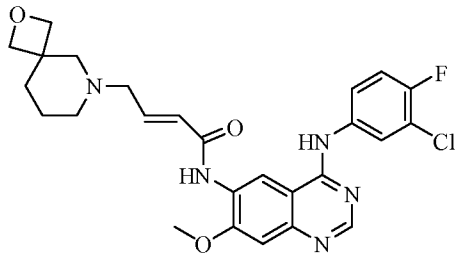
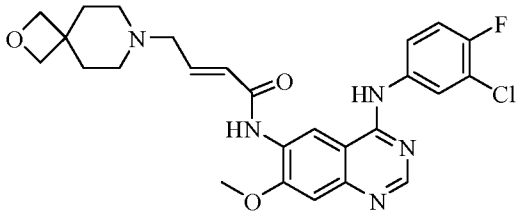
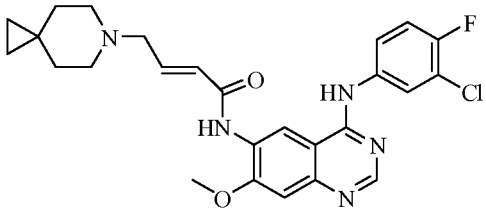
(continued)

No.	Structure	Name
16		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl]-4-[2-azaspiro[3.5]nonan-2-yl]-2-buten amide
17		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[7-azaspiro[3.5]nonan-7-yl]-2-butenamide
18		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-cyclopropyl -2-butenamide
19		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-cyclobutyl-2 -butenamide
20		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-[[7-methyl-7-azaspiro[3.5]nonan-2-yl]m ethoxy]quinazolin-6-yl]-4-[2-azaspiro[3.3]heptan-2-yl]-2-butenamide
21		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-[spiro[3.5]nonan-2-ylmethoxy]quinazoli n-6-yl]-4-[2-azaspiro[3.3]heptan-2-yl]-2-b utenamide

(continued)

No.	Structure	Name
22		(*E*)-4-(azetidin-1-yl)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl]-2-butenamide
23		(*E*)-4-(azetidin-1-yl)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-[[7-methyl-7-azaspiro[3.5]nonan-2-yl]methoxy)quinazolin-6-yl] -2-butenamide
24		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-[[7-methyl-7-azaspiro[3.5]nonan-2-yl]methoxy]quinazolin-6-yl]-4-cyclobutyl-2-b utenamide
25		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[4-azaspiro[2.4]heptan-4-yl]-2-butenamide
26		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[5-azaspiro[2.4]heptan-5-yl]-2-butenamide
27		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[6-azaspiro[3.4]octan-6-yl]-2-butenamide

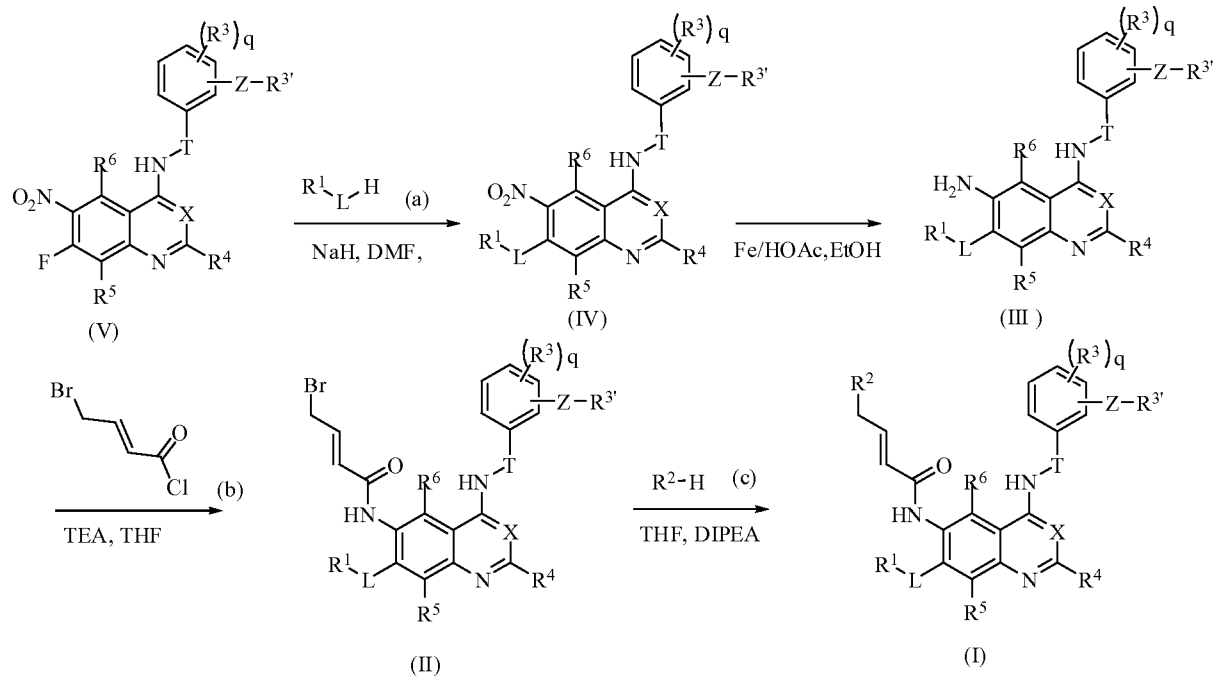
(continued)

No.	Structure	Name
28		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[2-oxa-6-az aspiro[3.5]nonan-6-yl]-2-butenamide
29		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[2-oxa-7-az aspiro[3.5]nonan-7-yl]-2-butenamide
30		(*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[6-azaspiro[2.5]octan-6-yl]-2-butenamide

[0060] In an embodiment of the preparation method for preparing the compound of the general formula (I) of the present invention, the compound of the general formula (I) of the present invention can be prepared through, for example, the following steps of:

Reaction Procedure:

[0061]



wherein R^1, R^2, R^3, R^3, R^4, R^5, R^6, X, L, T, Z and q are defined as above, and Br in formula (b) may be replaced with Cl or I, and Cl can also be replaced with Br;

Step 1: The preparation of a compound of the formula (IV)

[0062] A compound of the formula (V) is dissolved an organic solvent (such as DMF, THF, acetonitrile, methanol or ethanol). To the mixure is added an inorganic base (such as NaH, NaOH or KOH) in batch. The resulting mixture is reacted under stirring at room temperature. Then a compound of formula (a) is added to the reaction mixture. The resulting mixture is reacted under heating to reflux for hours to produce a compound of the formula (IV).

Step 2: The preparation of a compound of the formula (III)

[0063] A compound of the formula (IV) is added in batch to a mixed solution of a polar organic solvent (such as ethanol, methanol or THF) and an acid (such as acetic acid, formic acid, hydrochloric acid or dilute sulfuric acid). To the resulting mixture is then added a reducing agent (such as Fe powder, Zn powder, Pd/C or Raney Ni). The mixture is reacted under heating to produce a compound of the formula (III).

Step 3: The preparation of a compound of the formula (II)

[0064] A compound of the formula (III) is dissolved in an organic solvent (such as THF, DCM or EA). To the resulting mixture is added a compound of the formula (b) under cooling in an ice-water bath, and then is added dropwise an organic base (such as triethylamine or DIPEA). The mixture is reacted under stirring to produce a compound of the formula (II).

Step 4: The preparation of a compound of the formula (I)

[0065] A compound of the formula (II) is dissolved in an organic solvent (such as THF, DCM, DMF or acetonitrile). To the resulting mixture is successively added a base (such as DIPEA, TEA, pyridine, K_2CO_3 or Na_2CO_3) and a compound of the formula (c). The mixture is reacted under stirring at room temperature to produce a compound of the formula (I).

[0066] Where if necessary, a functional group that needs to be protected, e.g. hydroxy, amino and the like, may be protected, and then deprotected according to the conventional method.

[0067] The present invention also comprises "a pharmaceutically acceptable salt" of the compound of the formula (I). The pharmaceutically acceptable salt of the compound of the formula (I) of the present invention comprises alkali metal salts, such as Na salt, K salt, Li salt and the like; alkaline-earth metal salts, such as Ca salt, Mg salt and the like; other metal salts, such as A1 salt, Fe salt, Zn salt, Cu salt, Ni salt, Co salt and the like; inorganic base salts, such as ammonium

salt; organic base salts, such as tert-octylamine salt, dibenzylamine salt, morpholine salt, glucosamine salt, alkyl phenylglycinate salt, ethylene diamine salt, *N*-methylglucosamine salt, guanidine salt, diethylamine salt, triethylamine salt, dicyclohexyl amine salt, *N*,*N*'-dibenzylethylene diamine salt, chloroprocaine salt, procaine salt, diethanol amine salt, *N*-benzyl-phenylethyl amine salt, piperazine salt, tetramethyl amine salt, tris(hydroxymethyl)aminomethane salt and the like; inorganic acid salts, such as halogen acid salt, such as hydrofluoric acid salt, hydrochloride, hydrobromide, hydriodate and the like, nitrate, perchlorate, sulfate, phosphate and the like; organic acid salts, such as lower alkanesulfonate, e.g. mesylate, trifluoromesylate, ethanesulfonate and the like, arylsulfonate, such as benzenesulfonate, para-benzenesulfonate and the like, carboxylate, such as acetate, malate, fumarate, succinate, citrate, tartrate, oxalate, maleate and the like, amino acid salts, such as glycine salt, trimethylglycinate salt, arginine salt, ornithine salt, glutamate salt, asprtate salt and the like.

[0068] The present invention also describes all of possible isomers of the compound of the formula (I). The enantiomorph can be present in case that one or more asymmetric carbon atoms are present in the compound structure; the cis/trans-isomer can be present in case that the compound contains an alkenyl group or a cyclic structure; and the tautomer can be present in case that the compound contains a keto group or a nitrosyl group. All of these isomers and the mixtures thereof are in the scope of the present invention.

[0069] The compound of the general formula (I) of the present description and a pharmaceutically acceptable salt and a stereoisomer thereof can be administered to a mammal, e.g. human orally, parenterally (intravenously, intramuscularly, subcutaneously or rectally and the like), pulmonarily, and locally. The daily dosage of the present compound can be about 1 to about 1000 mg.

[0070] The compound of the general formula (I) of the present description or a pharmaceutically acceptable salt or a stereoisomer thereof can be administered alone or in combination with other therapeutical agents, in particular a second therapeutical agent selected from the group consisting of an antineoplastic agent and an immunosuppressive agent. Said second therapeutical agent is selected from the group consisting of antimetabolite, including but not limited to e.g. capecitabine, gemcitabine and the like; a growth factor inhibitor, including but not limited to e.g. pazopanib, imatinib and the like; an antibody, including but not limited to e.g. herceptin, bevacizumab and the like; a mitotic inhibitor, including but not limited to e.g. paclitaxel, vinorelbine, docetaxel, doxorubicin and the like; antineoplastic hormone, including but not limited to e.g. letrozole, tamoxifen, fulvestrant and the like; alkylating agent, including but not limited to e.g. cyclophosphamide, carmustine and the like; a metal platinum, including but not limited to e.g. carboplatin, cisplatin, oxaliplatin and the like; a topoisomerase inhibitor, including but not limited to e.g. topotecan and the like; an immunosuppressant, including but not limited to e.g. everolimus and the like. All of components to be administered can be administered at the same time or successively and separately in a form of the single formulation or in a combination of the divided formulations.

[0071] The present compound of formula (I), a pharmaceutically acceptable salt thereof or a stereoisomer thereof can be used to treat an excessive proliferative disease and a chronic obstructive pulmonary disease. The excessive proliferative disease includes cancerous disease and non-cancerous disease. The cancerous disease is selected from the group consisting of cerebroma, lung cancer, non-small cell lung cancer, squamous cell, bladder carcinoma, gastric cancer, ovarian cancer, peritoneal cancer, pancreatic cancer, mammary cancer, head and neck cancer, cervical cancer, endometrial cancer, colorectal cancer, liver cancer, renal carcinoma, adenocarcinoma of esophagus, esophageal squamous cell cancer, solid tumor, non-Hodgkin lymphoma, central nervous system tumor (glioma, gliobastona multiforme, glioma sarcomatosis), prostate carcinoma or thyroid carcinoma; the non-cancerous disease includes for example benign proliferative diseases of skin or prostate.

[0072] The present invention also describes a pharmaceutical composition, containing the compound of the general formula (I) of the present invention, a pharmaceutically acceptable salt, or a stereoisomer thereof as described above and one or more pharmaceutically acceptable carriers. Said composition can be prepared by mixing the compound of the general formula (I) of the present description or a pharmaceutically acceptable salt, or a stereoisomer thereof and one or more conventional pharmaceutically acceptable carrier. Said composition can be prepared into a conventional clinically or pharmaceutically acceptable dosage form to administer orally, parenterally, pulmonarily or locally to the patient in need thereof.

[0073] For the oral administration, The compound of the general formula (I) of the present description or a pharmaceutically acceptable salt, or a stereoisomer thereof can be formulated into a conventional solid preparation, such as tablet, granule, capsule, powder and the like; or the oral liquid preparation, such as an oral solution, an oral suspension, a syrup and the like. For preparing the oral preparation, suitable filler, binder, disintegrant, lubricant, diluent and the like can be added. Conventional filler includes starch, sugar powder, calcium phosphate, calcium sulfate dihydrate, dextrin, microcrystalline cellulose, lactose, pregelatinized starch, mannitol and the like. Conventional binder includes sodium carboxymethylcellulose, PVP-K30, hydroxypropyl cellulose, starch paste, methyl cellulose, ethyl cellulose, hypromellose, gelatinized starch and the like. Conventional disintegrant includes dry starch, polyvinylpolypyrrolidone (cPVP), croscarmellose sodium, sodium carboxymethyl starch, low-substituted hydroxypropyl cellulose and the like. Conventional lubricant includes magnesium stearate, talc powder, sodium dodecylsulfate, Silica powder and the like. Conventional

diluent includes water, ethanol, glycerin and the like.

[0074] For the parenteral administration, according to the conventional method, The compound of the general formula (I) of the present description or a pharmaceutically acceptable salt, or a stereoisomer thereof can be formulated into an injectable preparation, including an injection solution, a sterile injection powder and a concentrated injection solution. For preparing the injectable preparation, a conventional method in the pharmaceutical production can be used, and an aqueous solvent or a nonaqueous solvent can be used. The most commonly used aqueous solvent is water for injection. 0.9% aqueous NaCl solution or other suitable aqeous solution can also be used. The most commonly used nonaqueous solvent is vegetable oil, such as soy oil for injection. The aqueous solution of ethanol, propylene glycol, polyethylene glycol or the like can also be used. For preparing the injectable preparation, an additive can be optionally added, depending on the nature of drug. The additive includes an osmotic regulator, a pH-value regulator, a solubilizer, a filler, an antioxidant, a bacteriostatic agent, an emulsifier, a suspending agent or the like.

[0075] For the rectal, pulmonary or local administration, The compound of the general formula (I) of the present description or a pharmaceutically acceptable salt, or a stereoisomer thereof can be formulated into an inhalant, a sublingual formulation, a gel, an ointment, a suppository, a lotion, a nasal drop, a spraying agent, a transdermal patch and the like according to the conventional method.

[0076] It is demonstrated that the compound of the present invention is a tyrosine kinase inhibitor and has an excellent antineoplastic effect. The compound of the present invention therefore has a good therapeutic effect on an excessive proliferative disease and a chronic obstructive pulmonary disease and reduces the formation of drug resistance. In addition, it is easy to prepare the compound of the present invention; the compound of the present invention has a stable quality, and therefore the compound of the present invention is apt to be produced on the industrial scale.

Best Mode of Carrying Out the Invention

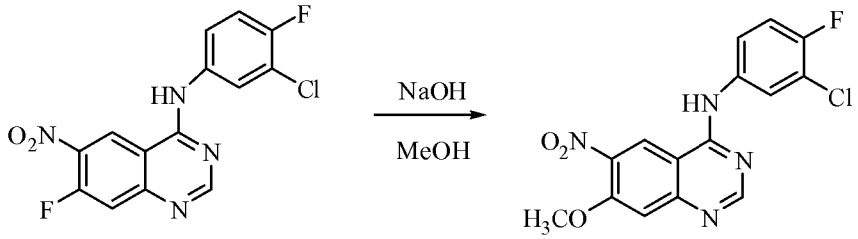
[0077] The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. All of the technical solutions that can be accomplished based on the above disclosure fall in the scope of the present invention.

I. The preparation example for the compound of the present invention

Example 1: The preparation of (*E*)-4-[3-azabicyclo[3.1.0]hexan-3-yl]-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-2-butenamide (Compound 1) hydrochloride

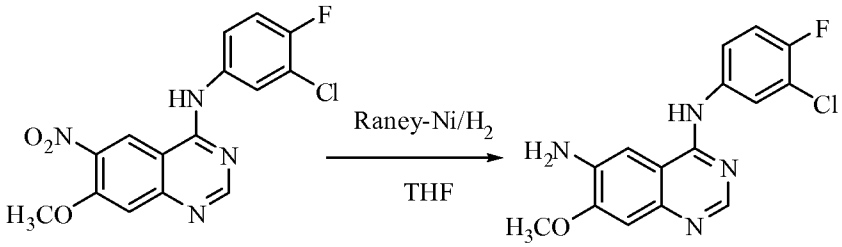
[0078]

(1) The preparation of 4-(3-chloro-4-fluorophenylamino)-6-nitro-7-methoxyquinazoline



4-(3-chloro-4-fluorophenyl)amino-6-nitro-7-fluoroquinazoline (25.4 g, 75.4 mmol) and a 50% NaOH solution (7.85 mL, 98.125 mmol) were added to 500 mL methanol. The resulting mixture was reacted at 70°C under reflux for 2h. The reaction liquor was poured into ice-water. A large amount of solid separated. After filtering, the filter cake was dried to produce 25.3 g of the target product as yellow solid in a yield of 96.4%.

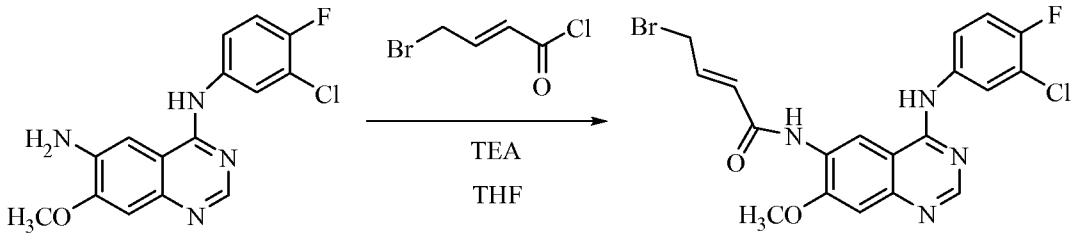
(2) The preparation of 4-(3-chloro-4-fluorophenyl)amino-6-amino-7-methoxyquinazoline



4-(3-chloro-4-fluorophenylamino)-6-nitro-7-methoxyquinazoline (25.3 g, 72.7 mmol) was dissolved in 500 mL tetrahydrofuran. To the solution was added 7.6 g Raney-Ni. To the resulting mixture was added hydrogen gas. The mixture was stirred at room temperature for 24h, filtered and rotary-evaporated to remove the solvent. The resulting residue was washed with ethyl acetate to produce 13.345 g 4-(3-chloro-4-fluorophenyl)amino-6-amino-7-methoxyquinazoline as yellow solid in a yield of 57.7%.

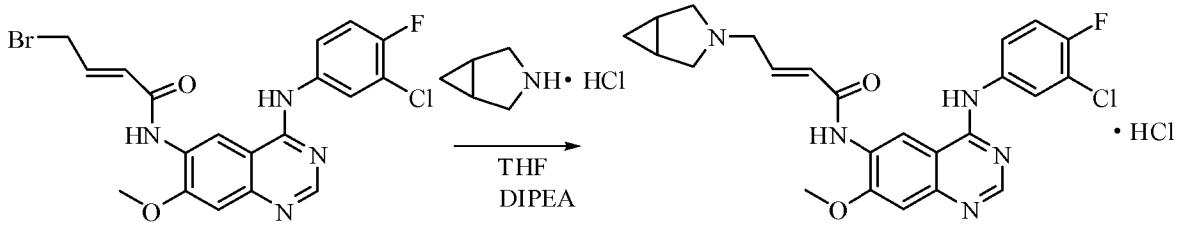
^{1}H-NMR (DMSO-d_6, 400 MHz): δ10.17 (s, 1H), 9.22 (s, 1H), 8.68 (s, 1H), 8.15 (d, J = 4.8 Hz, 1H), 7.78 (br. s., 1H), 7.35 - 7.55 (m, 2H), 4.05 (s, 3H).

(3) The preparation of (*E*)-4-bromo-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-2-butena mide



In a dried reaction bottle, 4-(3-chloro-4-fluorophenyl)amino-6-amino-7-methoxyquinazoline (0.567g, 1.778 mmol) and triethylamine (0.61 mL, 4.387 mmol) were dissolved indissolved in 20 mL tetrahydrofuran. To the reaction bottom was added dropwise at 0°C (*E*)-4-bromo-2-crotonyl chloride(0.555 g, 3.023 mmol). The resulting mixture was stirred for 1h with maintaining the temperature. To the reaction liquor was added an appropriate amount of water. The mixture was extracted with dichlormethane. The organic phases were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to produce (*E*)-4-bromo-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-2-butena mide (0.742 g in a yield of 89.6%) as yellow solid.

(4) The preparation of (*E*)-4-[3-azabicyclo[3.1.0]hexan-3-yl]-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyq uinazolin-6-yl]-2-butenamide (Compound 1) hydrochloride



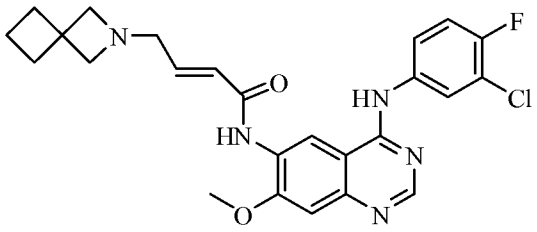
(*E*)-4-bromo-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-2-butena mide (600mg, 1.29mmol) was dissolved in 20mL THF. To the resulting mixture was added 3-azabicyclo[3.1.0]hexane hydrochloride (200mg, 1.69mmol), and then added dropwise 1mL DIPEA slowly. The mixture was reacted under heating to reflux for 12h. The reaction mixture was concentrated. To the resulting condensate was added an appropriate amount of water. The resulting mixture was extracted with dichlormethane. The organic phase was dried over anhydrous sodium sulfate, and then separated with a silica-gel column (dichlormethane: methanol=5:1) to produce a white solid. The white solid was dissolved in 20mL absolute alcohol. The resulting mixture was reacted with the introduction of hydrogen chloride gas under cooling in an ice-water bath for 0.5h, and then rotary-evaporated to dryness in vaccum to produce 42mg target product of (*E*)-4-[3-azabicyclo[3.1.0]hexan-3-yl]-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyq uinazolin-6-yl]-2-butenamide hydrochloride in a yield of 6%.

Formula: $C_{24}H_{24}Cl_2FN_5O_2$ molecular weight: 504.4 mass spectrum (m/e): 468.5(M+1) ^{1}H-NMR (DMSO-d_6, 400

MHz): 811.58(br, 1H), 11.43(s, 1H), 10.21(s, 1H), 9.18(s, 1H), 8.89(s, 1H), 7.98(d, 1H), 7.69(br, 1H), 7.58(s, 1H), 7.54(t,1H), 6.97(m, 1H), 6.77(d, 1H), 4.07(s, 3H), 3.98(s, 2H), 3.16(t, 2H), 1.75(br, 2H), 1.20(m, 2H), 1.16(m, 1H), 0.61(m, 1H).

Example 2: The preparation of (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[azaspiro[3.3]heptan-2-yl]-2-butenamide (Compound 2) hydrochloride

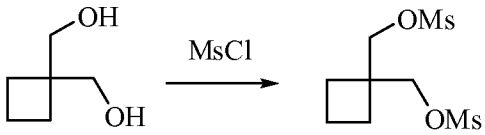
[0079]



(1) The preparation of cyclobutane-1,1-diyldimethanol

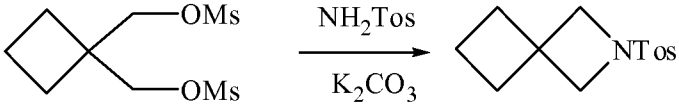
Cyclobutane-1,1-dicarboxylic acid (28.8g, 0.2mol) was dissolved in 100mL THF. To the resulting mixture was added in batch lithium aluminum hydride (22g, 0.58mol) under cooling in an ice-water bath. The mixture was reacted at room temperature for 10h. The reaction was quenched with ethyl acetate and water. The resulting reaction mixture was dried over anhydrous sodium sulfate, filtered, and rotary-evaporated to remove the solvent to produce 21.3g target product as yellow oil in a yield of 92%. The crude product was directly used in the next step without purification.

(2) The preparation of cyclobutane-1,1-diylbis(methylene) dimethanesulfonate



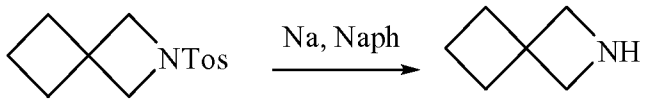
The crude product obtained in the previous step was dissolved in 1000mL dichlormethane and 15mL triethylamine. To the resulting mixture was added dropwise MsCl (61.56g, 0.55mol) under cooling in an ice-water bath. The reaction was continued for 3h. After filtering, the filtrate was concentrated to dryness to produce 52.6g target product as yellow solid. The crude product was directly used in the next step without purification.

(3) The preparation of 2-tosyl-2-azaspiro[3.3]heptane



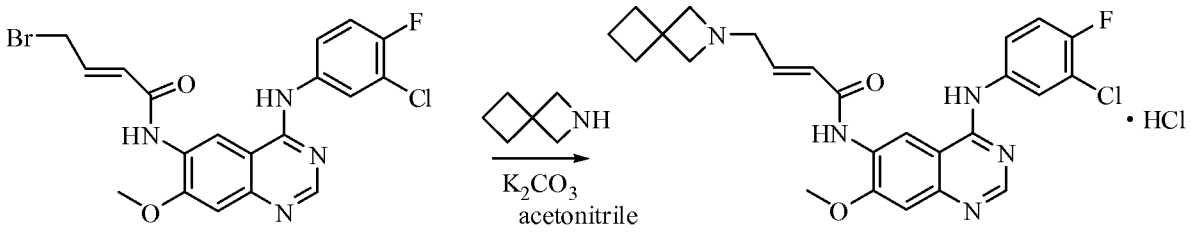
The crude cyclobutane-1,1-diylbis(methylene) dimethanesulfonate (25.3g, 0.09mmol) and potassium carbonate (27.6g, 0.2mol) were dissolved in 200mL DMSO. To the resulting mixture was added p-toluenesulfonamide (34.2g, 0.2mol) at room temperature. The mixture was reacted for 12h under heating to 110°C. The reaction system was cooled. To the mixture was added 1000mL ethyl acetate. The mixture was washed with water. The organic layer was dried over anhydrous sodium sulfate, and rotary-evaporated to dryness. The resulting residue was separated with a silica-gel column (petroleum ether: ethyl acetate=7:1) to produce 14.74g target product as colorless oil in a yield of 65%.

(4) The preparation of 2-azaspiro[3.3]heptane



2-tosyl-2-azaspiro[3.3]heptanes (7.3g, 0.03mol) was dissolved in 30mL 1,2-dimethoxyethane. To the resulting mixture was added dropwise 50mL of a fresh-made sodium naphthalene solution under cooling in ice-water. The resulting mixture was reacted at room temperature for 1h. The reaction was quenched with water. The reaction liquor was concentrated and then purified with a silica-gel column (dichlormethane:methanol=20: 0-1: 0) to produce 2.41g 2-azaspiro[3.3]heptane in a yield of 83%.

(5) The preparation of (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[2-azaspiro[3.3]heptan-2-yl]-2-butenamide hydrochloride

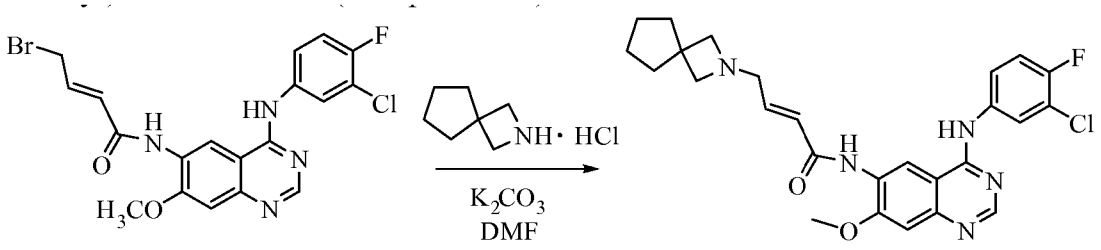


(*E*)-4-bromo-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-2-butena mide (595mg, 1.28mmol), 2-azaspiro[3.3]heptane(415mg, 4.25mmol) and potassium carbonate (781mg, 5.66mmol) were dissolved in 50mL acetonitrile. The resulting mixture was reacted at 60°C for 10h. The mixture was cooled to room temperature. To the mixture was added 100mL water. The mixture was extracted with dichlormethane. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was separated with a silica-gel column (dichlormethane: methanol=20:1) to produce 72.5mg yellow solid in a yield of 12%. The yellow solid (150mg, 0.31mmol) was dissolved in 10mLhydrogen chloride/ethanol. The resulting mixture was reacted at room temperature for 2h. The reaction liquor was rotary-evaporated to dryness to produce the target product (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-[azaspiro[3.3]hep tan-2-yl]-2-butenamide hydrochloride.

Formula: $C_{25}H_{26}Cl_2FN_5O_2$ molecular weight: 518.4 mass spectrum (m/e): 482.2 (M+1) ^{1}H-NMR($CDCl_3$, 400 MHz): 89.09(s, 1H), 8.63(s, 1H), 8.10(s, 1H), 7.88(d, 1H), 7.71(br, 1H), 7.50(br, 1H), 7.23(s, 1H), 7.10(br, 1H), 6.90(m, 1H), 6.13(d,1H), 4.04(s,3H), 3.24(br, 6H), 2.13(t, 4H), 1.82(t, 2H).

Example 3: The preparation of (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(2-azaspiro[3.4]octan-2-yl) -2-butenamide (Compound 14)

[0080]

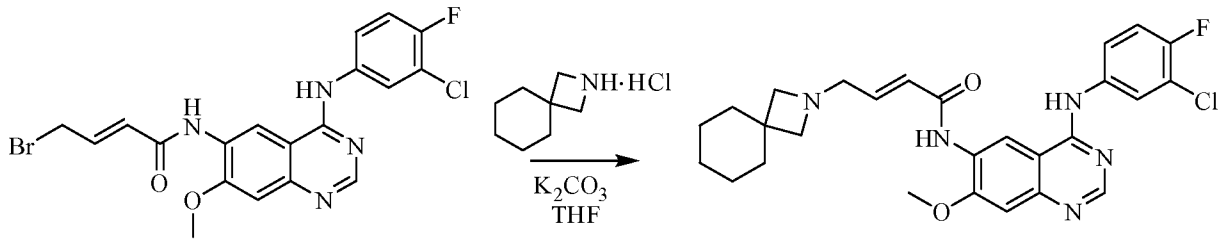


[0081] In a dried reaction vessel, (*E*)-4-bromo-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-2-butena mide (0.742 g, 1.59 mmol), 2-azaspiro[3,4]octane hydrochloride (0.307 g, 2.082 mmol) and anhydrous potassium carbonate (0.663 g, 4.797 mmol) were dissolved in 25 mL DMF. The resulting mixture was stirred at room temperature for 24h. To the resulting reaction liquor was added an appropriate amount of water. The resulting mixture was extracted ethyl acetate. The organic phases were combined. The combined mixture was successively washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified with a silica-gel column chromatography (dichlormethane: methanol=20:1), and then treated with acetonitrile, to produce 110 mg of *N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(2-azaspiro[3.4]octan -2-yl)-2-butenamide as pale yellow solid in a yield of 13.9%.

Formula: $C_{26}H_{27}ClFN_5O_2$ molecular weight: 496.0 mass spectrum (m/e): 496.2(M+1) ^{1}H-NMR (DMSO-d_6, 400 MHz): δ9.79 (s, 1H), 9.69 (s, 1H), 8.90 (s, 1H), 8.51 (s, 1H), 8.06 - 8.18 (m, 1H), 7.71 - 7.84 (m, 1H), 7.41 (t, J = 9.0 Hz, 1H), 7.27 (s, 1H), 6.71 (dt, J = 15.3, 4.8 Hz, 1H), 6.51 (d, J = 15.3 Hz, 1H), 4.00 (s, 3H), 3.19 (d, J = 3.3 Hz, 2H), 3.06 (s, 4H), 1.69 (br. s., 4H), 1.49 (br. s., 4H).

Example 4: The preparation of (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(2-azaspiro[3.5]n onan-2-yl)-2-butenamide (Compound 15)

[0082]

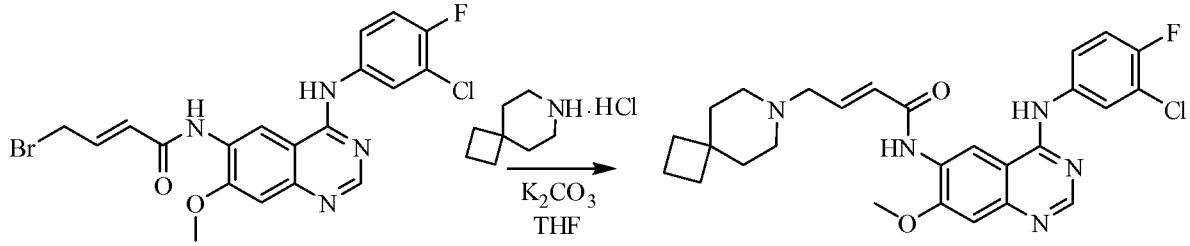


[0083] (*E*)-4-bromo-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-2-butena mide (3.06g, 6.6mmol) and 2-azaspiro[3.5]nonane hydrochloride (2.13g, 13.2mmol) were dissolved in 10mL DMF. To the resulting mixture was added K_2CO_3 (2.73g, 19.8mmol). The mixture was stirred at room temperature for 30min. After the completion of reaction, 50mL water was added. The resulting mixture was extracted with ethyl acetate. The organic phase was rotary-evaporated to dryness. The resulting solid was purified with a silica-gel column (dichlormethane: methanol=15:1) to produce 1.21g (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(2-azaspiro[3.5]n onan-2-yl)-2-butenamide in a yield of 36%.

Formula: $C_{27}H_{29}ClFN_5O_2$ molecular weight: 510.0 mass spectrum (m/e): 510.2 (M+1) ^{1}H-NMR(MeOD-d_6, 400 MHz): δ9.26(s 1H), 8.76(s, 1H), 7.93(d, 1H), 7.67-7.63(m, 1H), 7.40(t, 1H), 7.38 (s, 1H), 7.00-6.89 (m, 1H), 6.81 (d, 1H), 4.19(s, 3H), 4.02(d, 2H), 3.49-3.45 (d, 2H), 3.04-3.00 (t, 2H), 2.08-1.60(m, 10H).

Example 5: The preparation of (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(7-azaspiro[3.5]n onan-7-yl)-2-butenamide (Compound 17)

[0084]

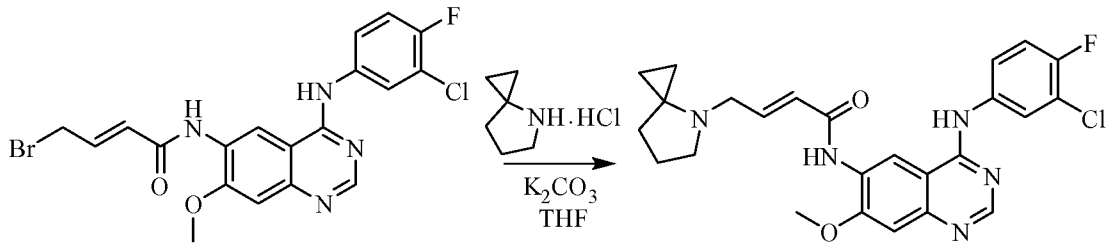


[0085] According to the method of Example 3, 2-azaspiro[3,4]octane hydrochloride was replaced with 7-aza-spiro[3.5]nonane hydrochloride to produce 1.21g (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(7-azaspiro[3.5]n onan-7-yl)-2-butenamide in a yield of 36%.

Formula: $C_{27}H_{29}ClFN_5O_2$ molecular weight: 510.0 mass spectrum (m/e): 510.2 (M+1) ^{1}H-NMR(MeOD-d_6, 400 MHz): δ9.26(s,1H), 8.76(s, 1H), 7.93(d, 1H), 7.67-7.63(m, 1H), 7.38(t, 1H), 7.32(s, 1H), 6.93-6.89 (m, 1H), 6.77(d, 1.0H), 4.37(d, 2H), 4.19-4.05(m, 5H), 3.49-3.48(d, 2H), 2.04-1.78(m, 5H), 1.56-1.29(m, 5H).

Example 6: The preparation of (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(4-azaspiro[2.4]h eptan-4-yl)-2-butenamide (Compound 25)

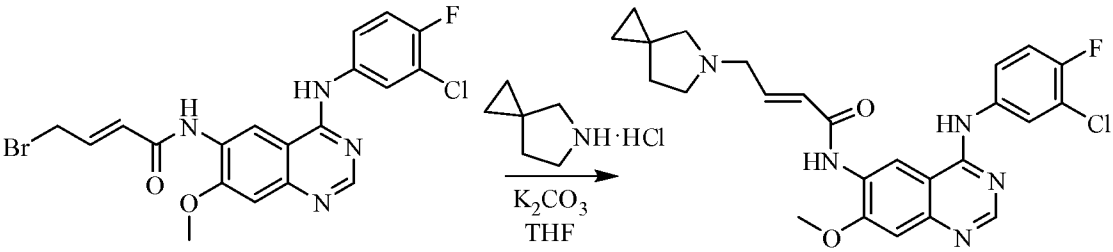
[0086]



[0087] According to the method of Example 3, 2-azaspiro[3,4]octane hydrochloride was replaced with 4-azaspiro[2.4]heptane hydrochloride to produce 0.825g (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(4-azaspiro[2.4]h eptan-4-yl)-2-butenamide in a yield of 26%.
Formula: $C_{25}H_{25}ClFN_5O_2$ molecular weight: 482.0 mass spectrum (m/e): 482.2 (M+1) ^{1}H-NMR(MeOD-d_6, 400 MHz): δ9.26(s,1H), 8.76(s, 1H), 7.93 (d, 1H), 7.67-7.63 (m, 1H), 7.40 (t, 1H), 7.34 (s, 1H), 6.89-6.88 (m, 1H), 6.77 (d, 1.0H), 4.19 (s, 3H), 4.05-3.92 (m, 2H), 3.49-3.46 (d, 2H), 2.42-1.99 (m, 4H), 1.56-1.29 (m, 4H).

Example 7: The preparation of (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(5-azaspiro[2.4]h eptan-5-yl) -2-butenamide (Compound 26)

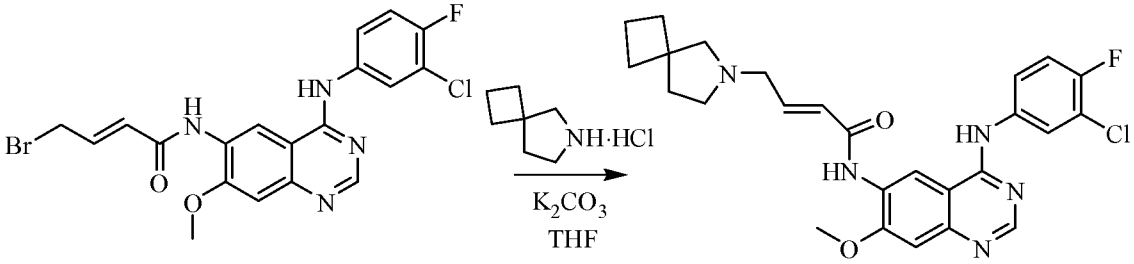
[0088]



[0089] According to the method of Example 3, 2-azaspiro[3.4]octane hydrochloride was replaced with 5-azaspiro[2.4]heptane hydrochloride to produce the target compound.
Formula: $C_{25}H_{25}ClFN_5O_2$ molecular weight: 482.0 mass spectrum (m/e): 482.2(M+1) ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.80 (s, 1H), 9.69 (s, 1H), 8.86 - 8.99 (m, 1H), 8.52 (s, 1H), 8.06 - 8.18 (m, 1H), 7.75 - 7.87 (m, 1H), 7.41 (t, J = 9.0 Hz, 1H), 7.27 (s, 1H), 6.76 - 6.91 (m, 1H), 6.59 (d, J = 15.6 Hz, 1H), 4.00 (s, 3H), 3.24 (m, 2H), 2.60 - 2.77 (m, 2H), 1.74 (m, 2H), 0.51 (m, 4H).

Example 8: The preparation of (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(6-azaspiro[3.4]n onan-6-yl) -2-butenamide (Compound 27)

[0090]

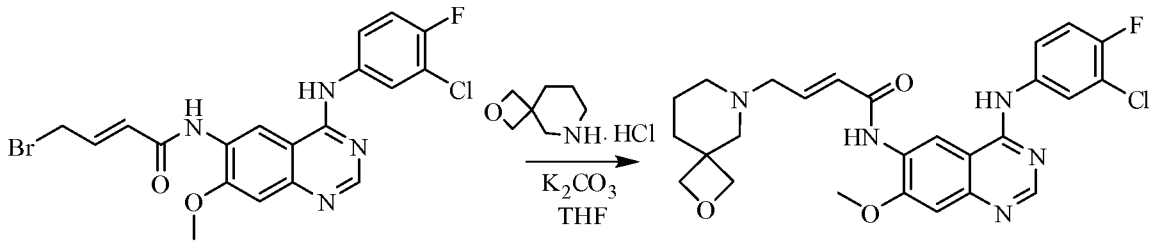


[0091] According to the method of Example 3, 2-azaspiro[3,4]octane hydrochloride was replaced with 6-azaspiro[3.4]octane hydrochloride to produce the target compound.
Formula: $C_{26}H_{27}ClFN_5O_2$ molecular weight: 496.0 mass spectrum (m/e): 496.2(M+1) ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.80 (s, 1H), 9.71 (br. s., 1H), 8.91 (s, 1H), 8.52 (s, 1H), 8.09 - 8.15 (m, 1H), 7.75 - 7.82 (m, 1H), 7.41 (t, J = 9.0 Hz, 1H), 7.27 (s, 1H), 6.80 (dt, J = 15.2, 5.8 Hz, 1H), 6.58 (d, J = 15.3 Hz, 1H), 4.00 (s, 3H), 3.27 (br. s., 2H), 2.59 (s, 4H), 1.71

- 2.02 (m, 8H).

Example 9: The preparation of (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(2-oxa-6-azaspiro [3.5]nonane)-6-yl)-2-butenamide (Compound 28)

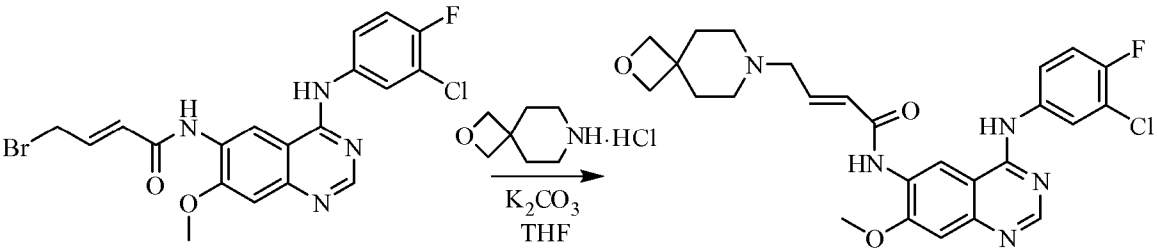
[0092]



[0093] According to the method of Example 3, 2-azaspiro[3.4]octane hydrochloride was replaced with 2-oxa-6-aza-spiro[3.5]nonane hydrochloride to produce 0.71g of the target compound (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(2-oxa-6-azaspiro [3.5]nonane)-6-yl)-2-butenamide in a yield of 21%.
Formula: $C_{26}H_{27}ClFN_5O_3$ molecular weight: 512.0 mass spectrum (m/e): 512.2 (M+1) ^{1}H-NMR($CDCl_3$-d_6, 400 MHz): δ9.11(s,1H), 8.63(s, 1H), 7.96(d, 1H), 7.68-7.60 (m, 2H), 7.34(s, 1H), 7.04(t, 1H), 6.22(d, 1H), 4.42(d, 4H), 4.08(d, 3H), 3.25 (d, 2H), 2.40 (s, 2H), 2.22-2.20 (m, 2H),2.02 (m, 2H), 1.59-1.56(m, 2H).

Example 10: The preparation of (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(2-oxa-7-azaspiro [3.5]nonan-7-yl) -2-butenamide (Compound 29)

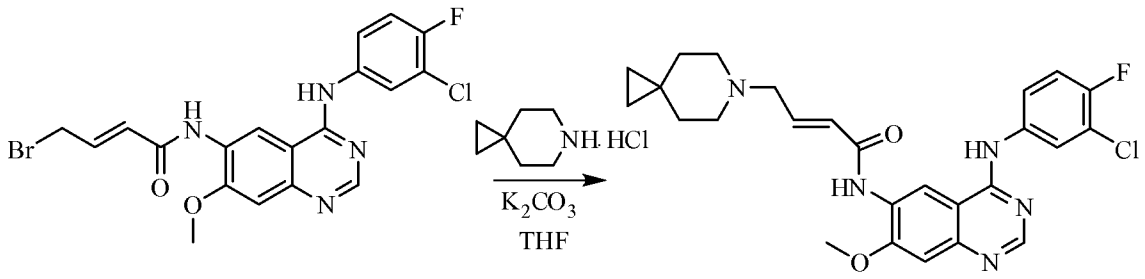
[0094]



[0095] According to the method of Example 4, 2-azaspiro[3.4]octane hydrochloride was replaced with 2-oxa-7-aza-spiro[3.5]nonane hydrochloride to produce the target compound. Formula: $C_{26}H_{27}ClFN_5O_3$ molecular weight: 512.0 mass spectrum (m/e): 512.2(M+1)
^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.79 (s, 1H), 9.69 (s, 1H), 8.91 (s, 1H), 8.52 (s, 1H), 8.12 (dd, J = 6.8, 2.3 Hz, 1H), 7.79 (dt, J = 8.5, 3.5 Hz, 1H), 7.41 (t, J = 9.2 Hz, 1H), 7.27 (s, 1H), 6.77 (dt, J = 15.3, 6.0 Hz, 1H), 6.55 (d, J = 15.3 Hz, 1H), 4.26 (s, 4H), 4.00 (s, 3H), 3.07 (d, J = 5.8 Hz, 2H), 2.27 (br. s., 4H), 1.78 (br. s., 4H).

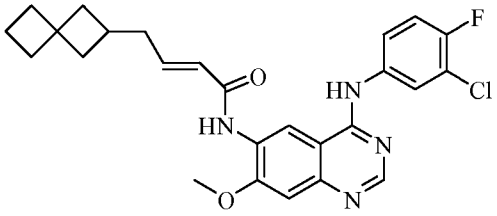
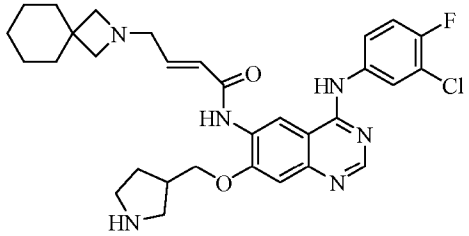
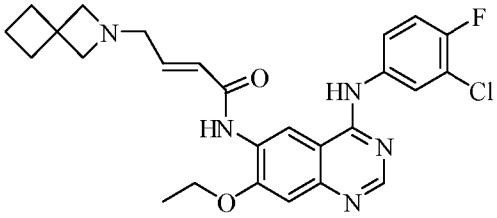
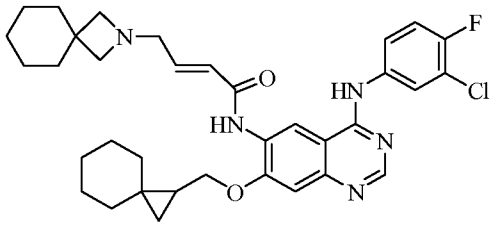
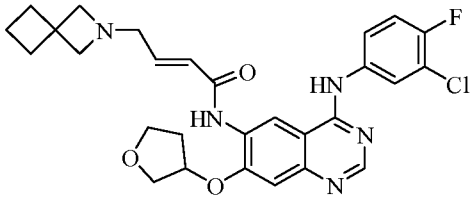
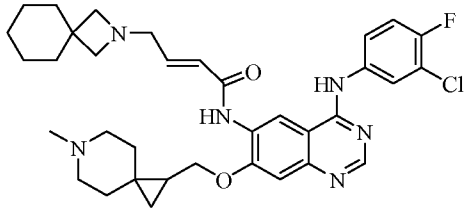
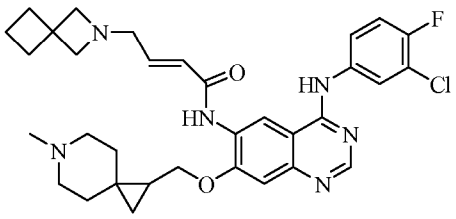
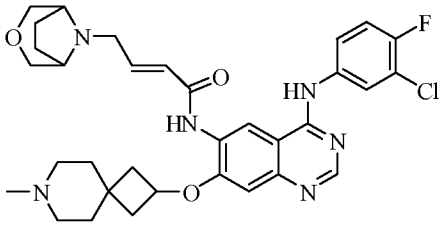
Example 11: The preparation of (*E*)-*N*-[4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]-4-(6-azaspiro[2.5]octan-6-yl)-2-butenamide (Compound 30)

[0096]



[0097] According to the method of Example 4,2-azaspiro[3.4]octane hydrochloride was replaced with 6-azaspiro[2.5]octane hydrochloride to produce the target compound.
Formula: $C_{26}H_{27}ClFN_5O_2$ molecular weight: 496.0 mass spectrum (m/e): 496.2(M+1) ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.79 (s, 1H), 9.69 (s, 1H), 8.91 (s, 1H), 8.52 (s, 1H), 8.12 (dd, J = 6.8, 2.3 Hz, 1H), 7.79 (dt, J = 8.3, 3.5 Hz, 1H), 7.41 (t, J = 9.2, 1H), 7.27(s, 1H), 6.82 (dt, J = 15.2, 6.1 Hz, 1H), 6.57 (d, J = 15.6 Hz, 1H), 4.00 (s, 3H), 3.16 (d, J = 4.8 Hz, 2H), 2.42 (br. s., 4H), 1.35 (br. s., 4H), 0.24 (s, 4H).

[0098] The following compounds could also be prepared according to the above-mentioned methods:

No.	Compound	No.	Compound
31		51	
32		52	
33		53	
34		54	

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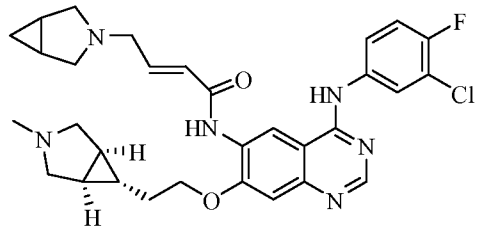
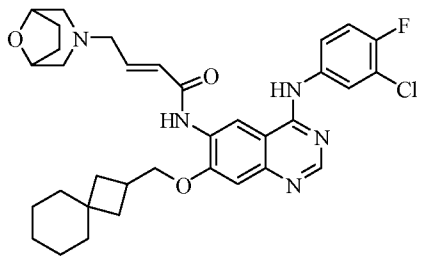
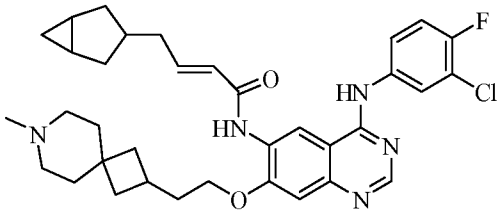
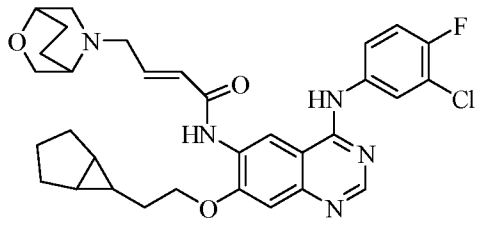
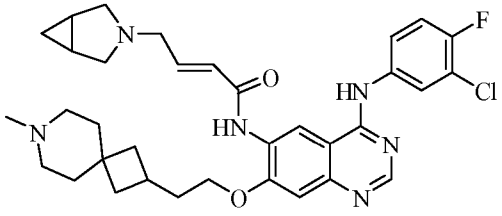
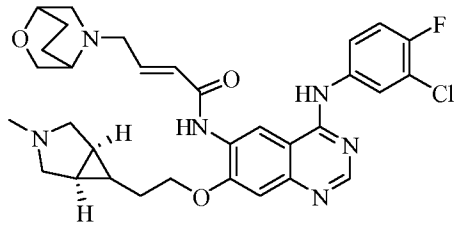
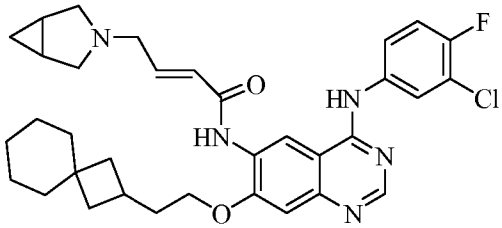
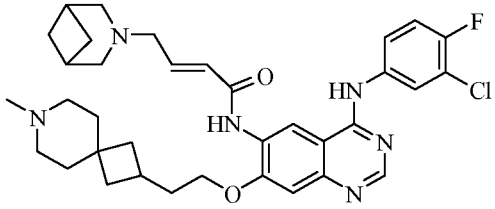
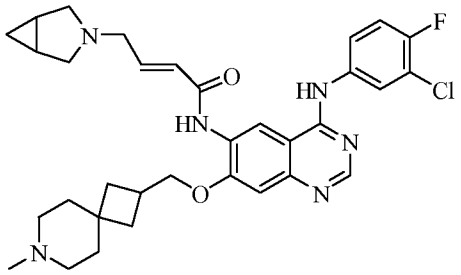
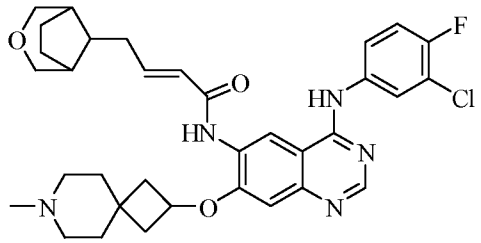
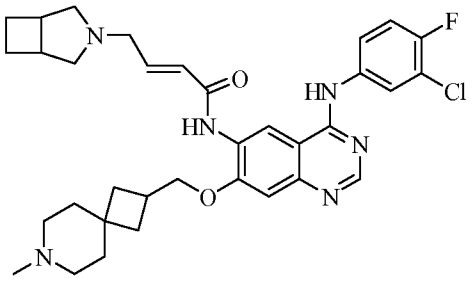
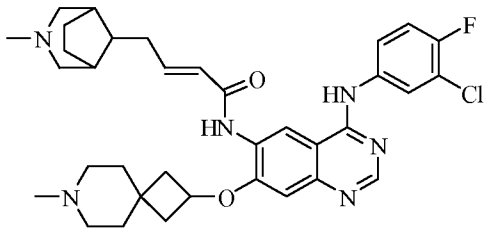
35		55	
36		56	
37		57	
38		58	
39		59	
40		60	

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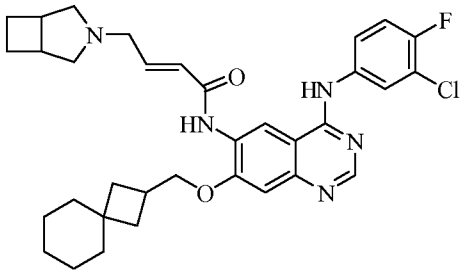
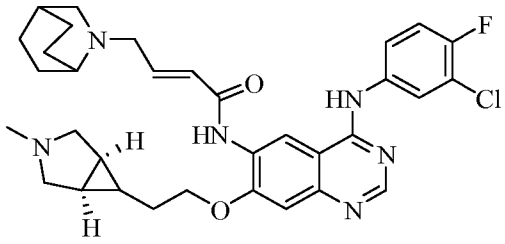
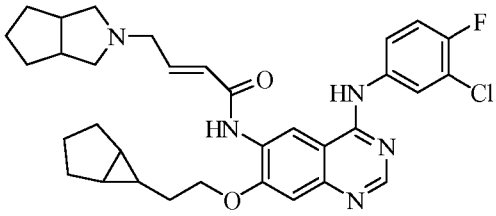
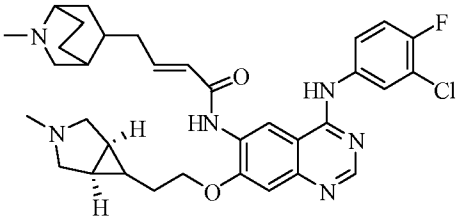
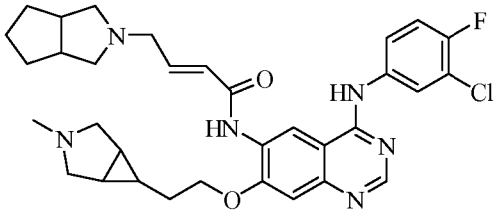
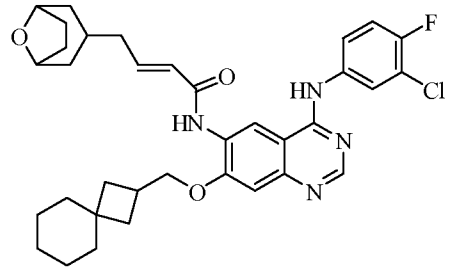
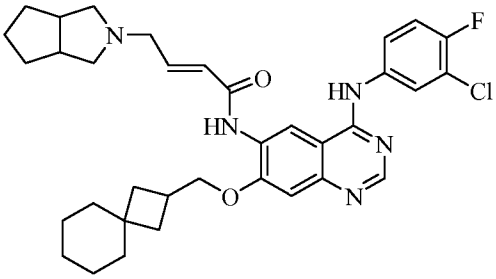
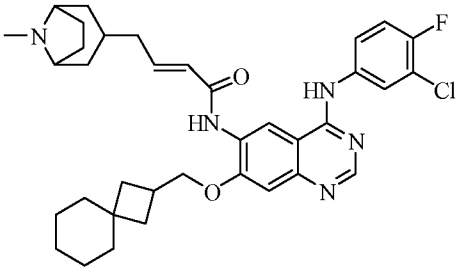
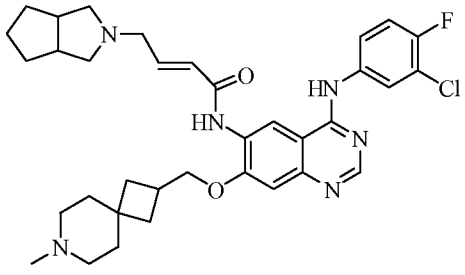
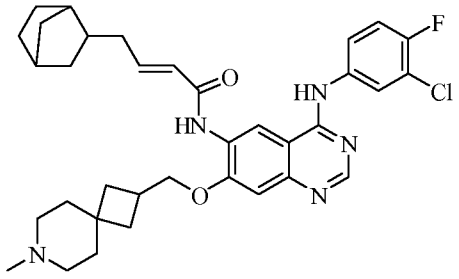
41		61	
42		62	
43		63	
44		64	
45		65	

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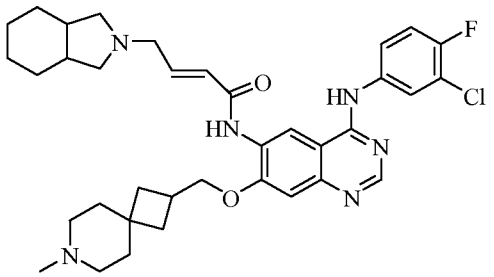
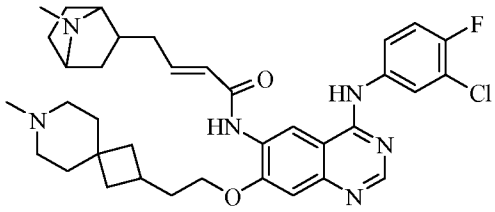
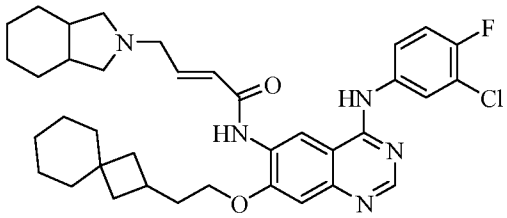
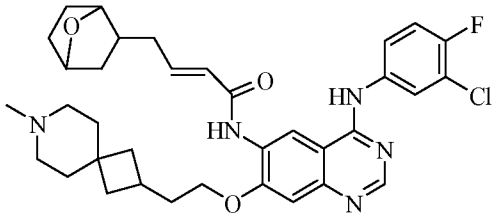
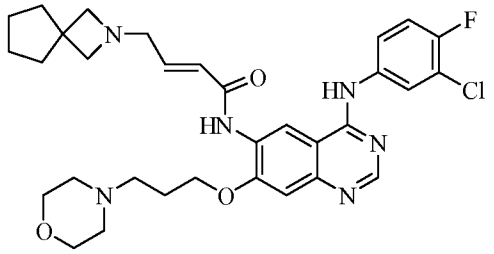
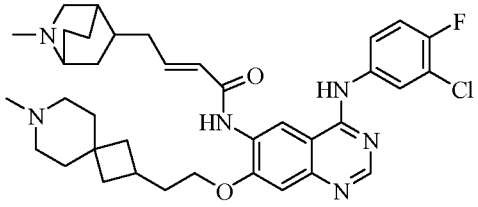
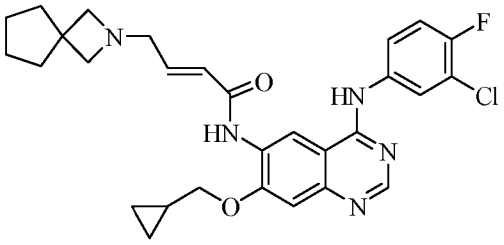
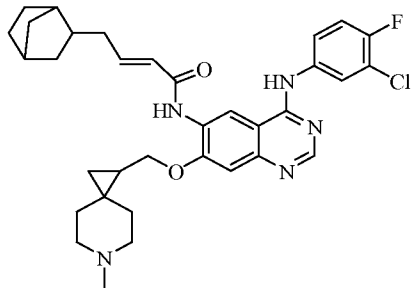
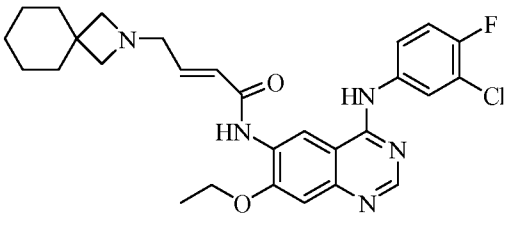
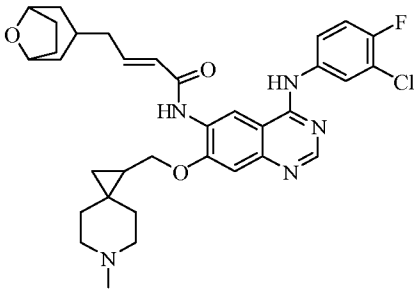
46		66	
47		67	
48		68	
49		69	
50		70	

II. In vitro assays for the antineoplastic activities of the present compounds

[0099] Hereinafter, the beneficial effects of the present compounds will be illustrated by in vitro enzyme inhibitory activity and in vitro cellular inhibitory activity. However, it should be noted that the beneficial effects of the present compounds are not limited to the effects as illustrated below.

Assay 1

In vitro enzyme inhibitory activity of the present compounds

Samples:

[0100] Controls: PF-00299804, lab-made; Gefitinib, purchased from Anqing worldchem Co., LTD.; Erlotinib hydrochloride, purchased from Anqing worldchem Co., LTD.; Lapatinib ditosylate, purchased from Taizhou Xingcheng Chempharm Co., Ltd.; referring to the section "Background Art" hereinabove for the structures of the above-mentioned four compounds; and
The present compounds: lab-made, their chemical names and structural formulae are shown in the preparation examples.

Assay procedures:

[0101] The abbreviations used in the following assay have the following meanings:

HEPES: hydroxyethyl piperazine ethanesulfonic acid;
Brij-35: polyethylene glycol lauryl ether;
DTT: dithiothreitol;
Coating Reagent #3: #3 coating agent;
EDTA: ethylene diamine tetraacetic acid, purchased from Sigma Co. Ltd.;
FAM labeled peptide: fluorescein labeled peptide 22 (GL Biochem);
ATP: adenosine triphosphate (Sigma);
DMSO: dimethyl sulfoxide;
EGFR: human epidermal growth factor receptor (Carna);
HER2: human epidermal growth factor receptor 2 (Carna);
HER4: human epidermal growth factor receptor 4 (Carna).

1. Formulating the agents to be used in the assay

(1) 1.25-fold $MnCl_2$-free kinase buffer (62.5 mM HEPES, PH 7.5, 0.001875% Brij-35, 12.5 mM $MgCl_2$, 2.5 mM DTT);
(2) 1.25-fold $MnCl_2$-containing kinase buffer (62.5 mM HEPES, pH 7.5, 0.001875% Brij-35, 12.5 mM $MgCl_2$, 12.5 mM $MnCl_2$, 2.5 mM DTT);
(3) Stop buffer (100 mM HEPES, pH 7.5, 0.015% Brij-35, 0.2% Coating Reagent #3, 50 mM EDTA);
(4) 2.5-fold kinase solutions (to the 1.25-fold kinase buffers were added the corresponding kinases to formulate 2.5-fold EGFR, HER2, HER4 kinase solutions);
(5) 2.5-fold peptide solutions (to the 1.25-fold kinase buffers were added FAM labeled peptide and ATP to formulate the peptide solutions);
(6) 5-fold compound solutions (using 100% DMSO to formulate 50-fold compound solutions having different concentration gradients, and diluting with water by 10 times to obtain 5-fold compound solutions having different concentration gradients);

2. Adding 5μL of a 5-fold compound solution to a 384-well plate;
3. Adding 10 μL of a 2.5-fold kinase solution to incubate for 10min;
4. Then adding 10μL of a 2.5-fold peptide solution, and reacting at 28°C for 1h; and
5. Finally, adding 25μL of stop buffer to terminate the reaction, and reading the data with Caliper.
6. Curve fitting to obtain an IC_{50} value.

The calculated inhibition ratio (%)=(the maximum conversion rate - the conversion rate)/(the maximum conversion rate - the minimum conversion rate)×100

[0102] The curve fitting was conducted with the Xlfit software to obtain IC_{50} values.

The results:

[0103] See Table 1 below.

Table 1 In vitro enzyme inhibitory activity

Compound	Enzyme inhibitory activity IC_{50}(nM)		
	EGFR	HER2	HER4
PF-00299804	0.89	11	1.7
Gefitinib	1.6	318	7.6
Erlotinib hydrochloride	1.3	454	49
Lapatinib ditosylate	16	4.0	250
Compound 1	0.55	14	3.1
Compound 2(hydrochloride)	0.65	19	8.9

Conclusion:

[0104] It can be seen from Table 1 that the present compounds have stronger inhibitory activities on EGFR, HER2 and HER4 kinases. The present compounds have a remarkably better inhibitory activity on the EGFR kinase than Lapatinib ditosylate; the present compounds have a remarkably better inhibitory activity on the HER2 kinase than Gefitinib and Erlotinib hydrochloride; the present compounds have a remarkably better inhibitory activity on the HER4 kinase than Erlotinib hydrochloride and Lapatinib ditosylate; and the present compounds are comparable with PF-00299804 in the inhibitory activities on EGFR, HER2 and HER4 kinases.

Assay 2

In vitro cellular inhibitory activity of the present compounds

Samples:

[0105] Controls: PF-00299804, lab-made; Gefitinib, purchased from Anqing worldchem Co., LTD.; Erlotinib hydrochloride, purchased from Anqing worldchem Co., LTD.; Lapatinib ditosylate, purchased from Taizhou Xingcheng Chempharm Co., Ltd.; and
The present compounds: lab-made, their chemical names and structural formulae are shown in the preparation examples.

Materials and Apparatuses in Assay:

Materials and Apparatuses	batch number / model number	Source
3,3'-Sodium [1-(phenylcarbamoyl)-3,4-tetrazolium]-di(4-met hoxy-6-nitro)benzene-sulfonate/2,3-Bis-(2-methoxy-4-nitro-5-sulfophe nyl]-2*H*-tetrazolium-5-carboxamide salt (XTT)	X4251	Sigma
RPMI1640 (a medium designed by Roswell Park	NWB0377	Hyclone
Memorial Institute)		
DMEM	NVH0300	Hyclone
MEM	NVK0322	Hyclone
F12K	30612100	M&G
McCoy's 5A	1814342	GIBCO
Fetal calf serum	GUH0069	Hyclone
Phosphate buffer (PBS)	Formulated on 2011-02-19	Homemade
96-well plate	3599	Corning
Microplate oscillator	QB-9002	QILINBEIER

(continued)

Materials and Apparatuses	batch number / model number	Source
Centrifuger	5810R	Eppendorf
CO_2 incubator	371	Thermo Scientific
Microplate reader	Infinite M200	TECAN

Cells	No.	Source
H1975	CRL-5908	Chinese Vendor
SKOV3	HTB-77	Chinese Vendor
A431	CRL-1555	Chinese Vendor

Assay procedures:

[0106]

1. Formulating the agents and the compounds

1) Formulating PBS: NaCl (8g), KCl (0.2g), Na_2HPO_4(1.44g), and KH_2PO_4 (0.24g) were added to ultrapure water (800mL). After adjusting the pH to 7.4, ultrapure water was further added until the volume reached 1L. The mixture was autoclaved for 20 min.
2) Formulating the XTT working liquor: XTT powder (100mg) was taken and, while being kept in darkness, dissolved into 300ml of the serum-free RPMI1640 culture medium that was warmed to 50°C and did not contain phenol red. The mixture was filtered, packaged separately, and used immediately or within one week. It is necessary for all of the processes to be kept in darkness.
3) Formulating test compounds

- Formulating a stock solution of test compound:

  The compound powder was dissolved into DMSO until a concentration of 10 mM reached.

- Formulating gradient dilute solutions of test compound:

  First, the 10mM stock solution of test compound was diluted with DMSO in a 4-fold successive gradient for 10 concentrations. 2 μL DMSO-diluted compound was added to 998μL of the culture medium containing 10% FBS. Therefore, the maximum concentration of the compound is 20μM, the concentration of DMSO is 0.2%, and there are 10 concentration gradients in total.

2. Culturing cells

1) Thawing cells:

- A cell-freezing tube was removed from liquid nitrogen, and placed in a water bath of 37°C-39°C to thaw the cells quickly.
- A freezing-preserving solution was transfered to 15 ml sterile centrifuge tube, to which was added a culture medium in a volume 10 times larger than that of the freezing-preserving solution. The mixture was centrifuged at 1000 rpm at 4°C for 5 min. The culture medium in the centrifuge tube was discarded, and then a culture medium containing 10% FBS was added. The cells were resuspended and transferred to the culture bottle. On the next day, the solution was changed.

2) Passing cells

- For the logarithmic growth phase cells, the culture medium was discarded and an appropriate volume of PBS was added to wash the cells once. Then an appropriate volume of a digestive juice containing 0.25% pancreatic enzyme and 0.02% EDTA was added. The solution was placed on stand at 37°C for 2-5 min, and then washed once with PBS after the digestive juice was discarded. An appropriate volume of a culture medium containing 10% FBS was added to terminate the digestion. The pipette was blown and hit slightly, and the cells were digested down to produce a cell suspension for cell passage and further experiment.

3) Freezing and preserving cells

- For the logarithmic growth phase cells, a digestive juice containg 0.25% pancreatic enzyme and 0.02% EDTA was used to digest cells to produce a cell suspension. The suspension was centrifuged at 1000 rpm at 4 °C for 5 min. The culture medium was discarded and a freezing-preserving solution containing 10% DMSO and 90% FBS was added to resuspend the cells. The cells were packaged separately in the cell-freezing tubes in 2×10^6 cells/tube. The cell-freezing tubes were placed in a programmed cooling cassette, kept at -80°C for 24 hours, and then transferred to liquid nitrogen for freezing and preserving.

3. Plating Cells

1) Praparing the cell suspension

- The culture medium was removed from the culture bottle. The cells were rinsed twice with PBS. The pancreatic enzyme was added to digest cells. The digested cells were collected by centrifuge. The cells were resuspended with a culture medium containing 10% fetal calf serum, counted and adjusted to an appropriate concentration (the cell viability should be over 90%). The cell concentration was 5×10^4/ml.

2) The cell suspension was added to the 96-well plate, 100 μL per well.
3) The plate was placed in the incubator and incubated at 37°C under 5% CO_2 overnight.

4. Treating with drugs
Drugs were added to the cell culture plate. The plate was placed in the incubator and incubated at 37°C under 5% CO_2 for 72 hours.
5. Testing the cell viability with the XTT method
The XTT working solution was added to the plate. The plate was placed in the incubator and incubated at 37°C under 5% CO_2 for 2 hr. Then the plate was placed in a microplate reader to read the absorbance at 450 nm.
6. Data processing

1) The percent inhibition was calculated by the following calculation.

$$\%\text{inhibition}=(\text{Absorbance(medium)} - \text{Absorbance(Compound)})/(\text{Absorbance(medium)} - \text{Absorbance(positive control)})\times100\%;$$

2) Data were input into GraphPad Prism 5.0 to plot a curve and obtain IC_{50}.

Result:

[0107] See the Tables 2-4 below.

Table 2 in vitro cellular inhibitory activities on H1975 (NSCLC, non-small cell lung cancer)

H1975 Cells	
Compound	IC_{50} (nM)
PF-00299804	356.5
Erlotinib hydrochloride	3985.0
Lapatinib ditosylate	4534.0
Compound 2	147.8

(continued)

H1975 Cells	
Compound	IC_{50} (nM)
Compound 14	133.5
Compound 15	179.4
Compound 26	85.6
Compound 27	91.9
Compound 28	39.01
Compound 29	57.1

Table 3 in vitro cellular inhibitory activities on SKOV3 (Ovarian carcinoma)

SKOV3 cells	
Compound	IC_{50} (nM)
PF-00299804	3959.0
Erlotinib hydrochloride	>10000
Lapatinib ditosylate	4329.0
Compound 2	3218.0
Compound 14	3711.0
Compound 15	3645.0
Compound 17	3063.0
Compound 26	3074.0
Compound 27	3186.0
Compound 30	3348.0

Table 4 in vitro cellular inhibitory activities on A431 (Epidermoid carcinoma)

A431 cells	
Compound	IC_{50} (nM)
PF-00299804	548.5
Erlotinib hydrochloride	1269.0
Lapatinib ditosylate	3282.0
Compound 2	33.3

Conclusions:

[0108] It can be seen from Table 2 that the cellular proliferation inhibition effect of the present compounds on H1975 (NSCLC, non-small cell lung cancer) is remarkably superior to Erlotinib hydrochloride, Lapatinib ditosylate and PF-00299804.

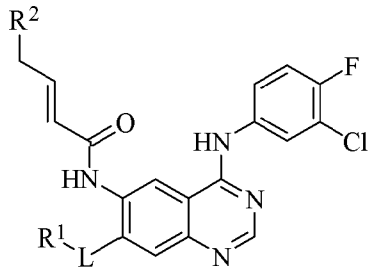
[0109] It can be seen from Table 3 that the cellular proliferation inhibition effect of the present compounds on SKOV3 (Ovarian carcinoma) is remarkably superior to Erlotinib hydrochloride, and is comparable with PF-00299804 and Lapatinib ditosylate.

[0110] It can be seen from Table 4 that the cellular proliferation inhibition effect of the present compounds on A431

(Epidermoid carcinoma) is remarkably superior to Erlotinib hydrochloride, Lapatinib ditosylate and PF-00299804.

Claims

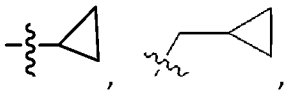
1. A compound represented by the general formula (I-2), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

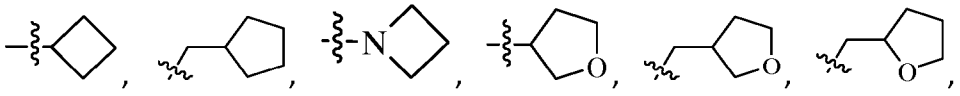


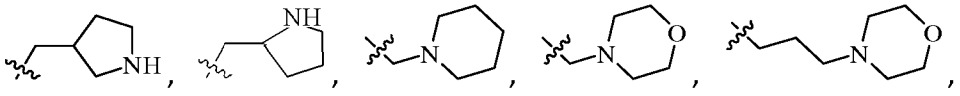
(I-2),

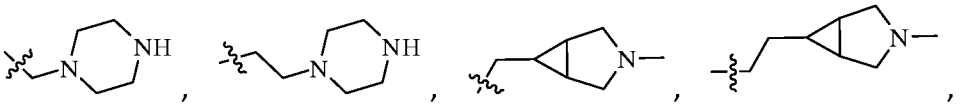
wherein

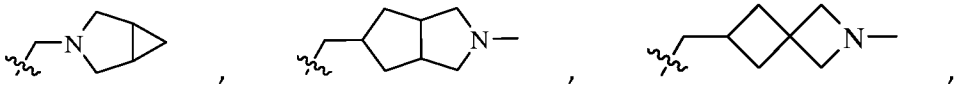
R^1 is selected from the group consisting of the following groups that are unsubstituted or substituted by halogen, hydroxy, amino, carboxyl, cyano, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, or diethylamino: methyl, ethyl,

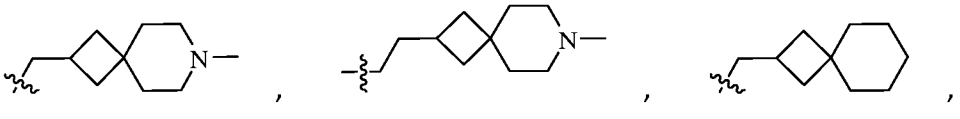


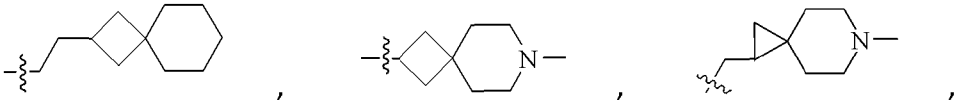


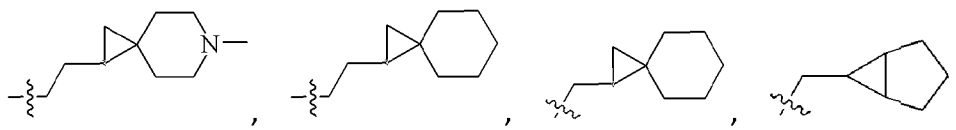












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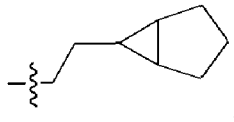
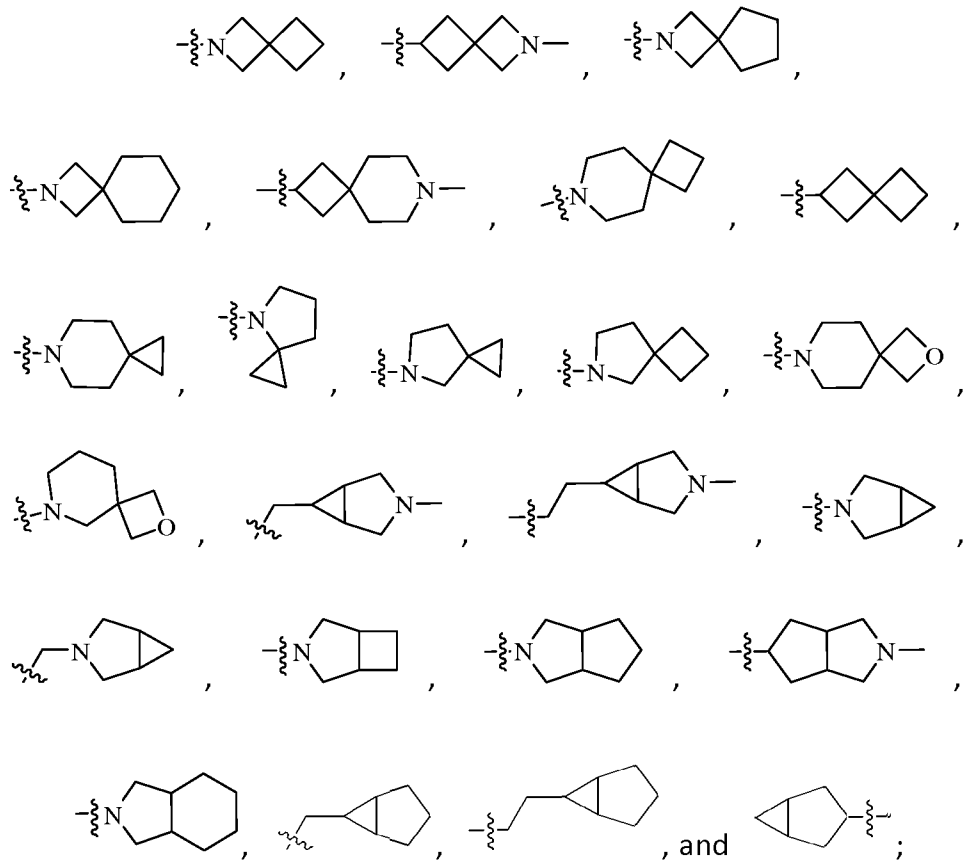


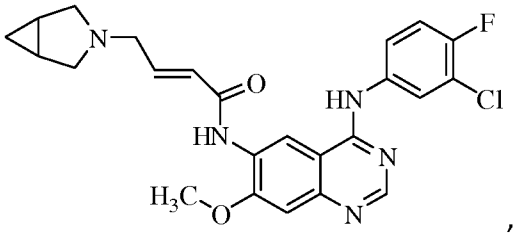
;

R^2 is selected from the group consisting of the following groups that are unsubstituted or substituted by halogen, hydroxy, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetoxy, acetylamino, methylsulfonyl, or methylsulfonylamino:



and
L is O.

2. The compound according to claim 1 or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group consisting of:



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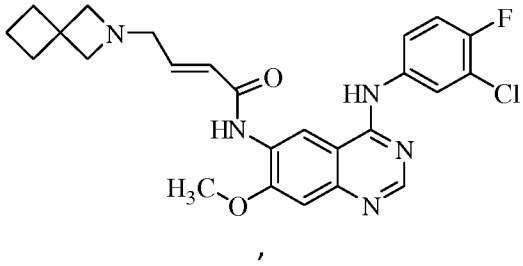

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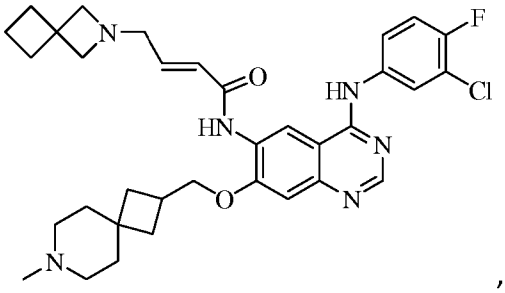

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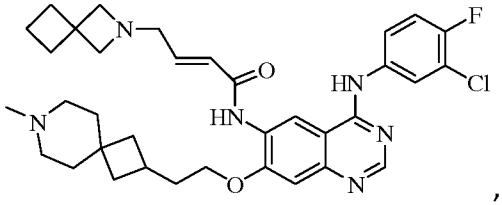

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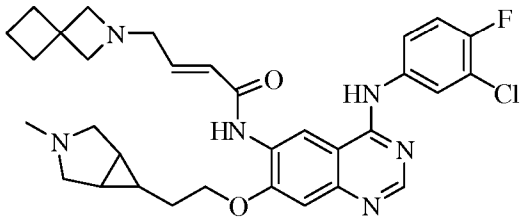

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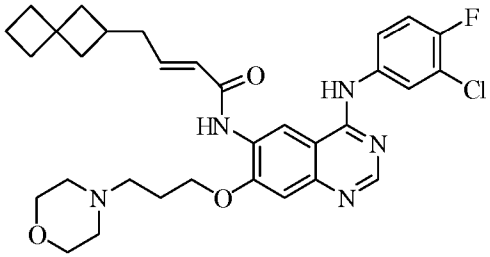

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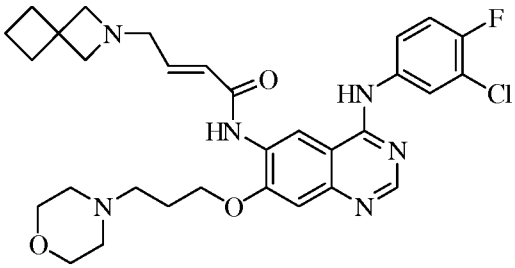

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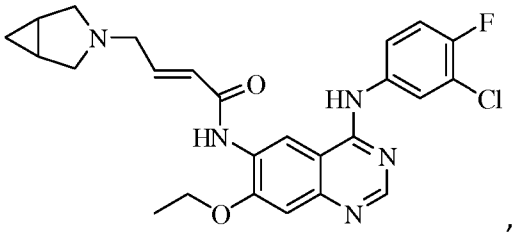

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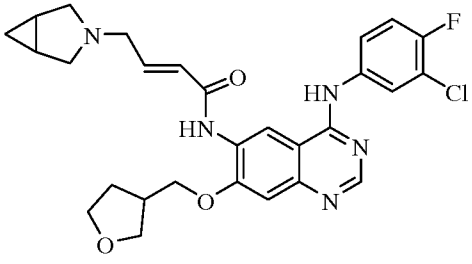

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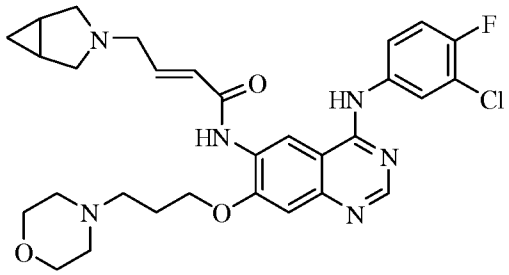
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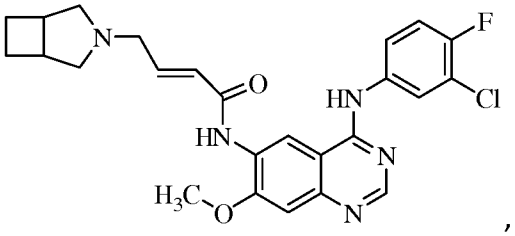
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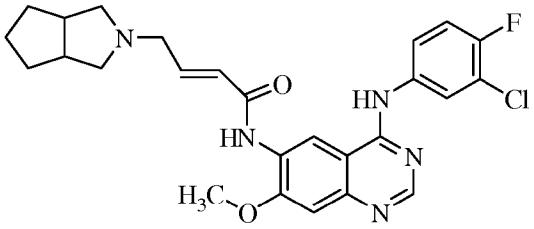
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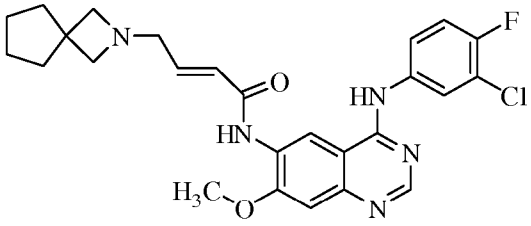
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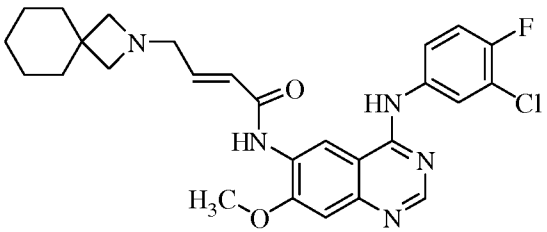
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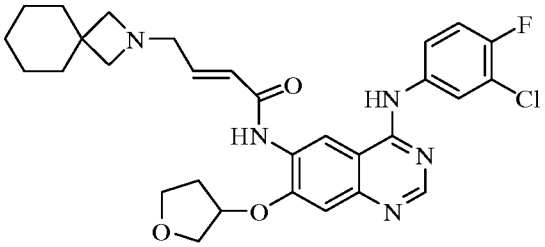
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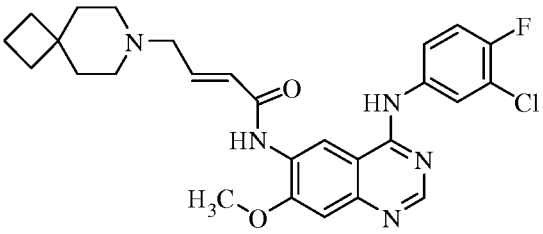
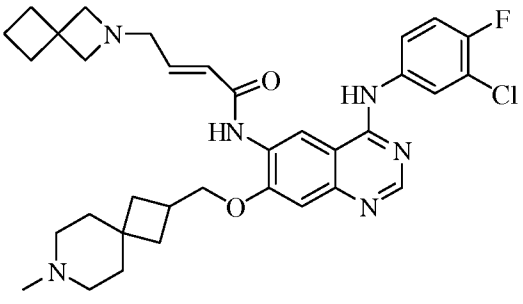

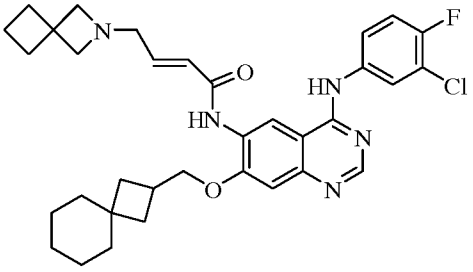

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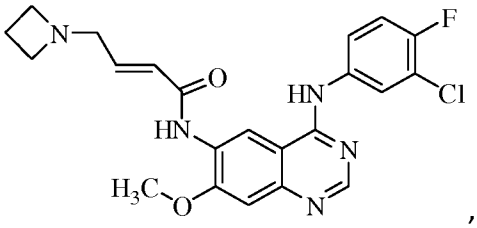
3. A compound, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group consisting of:



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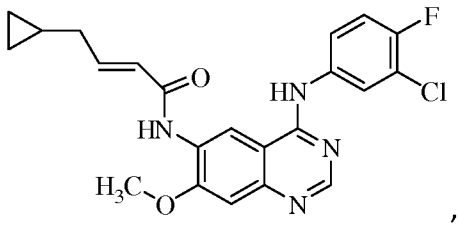

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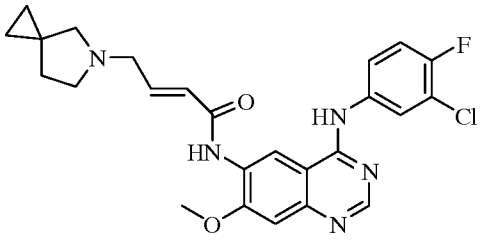

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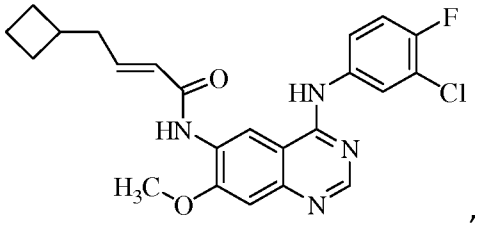

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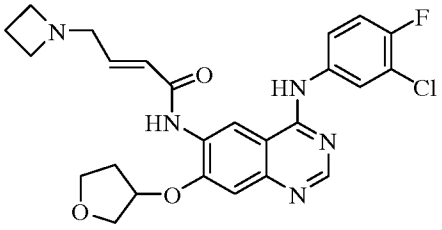

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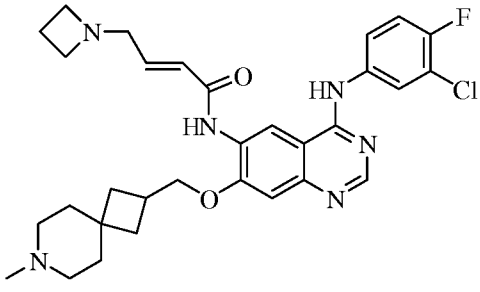

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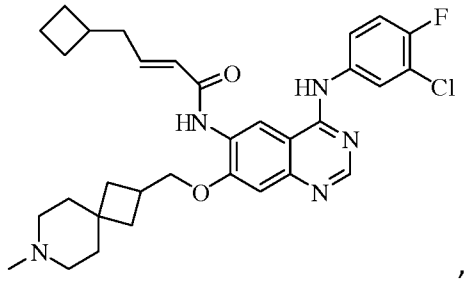

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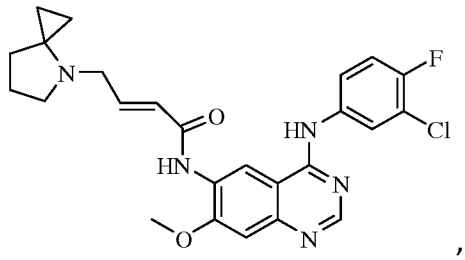

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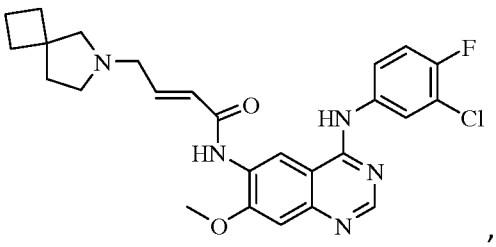

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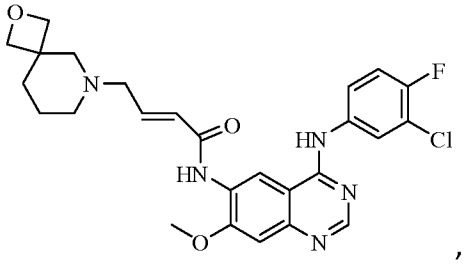

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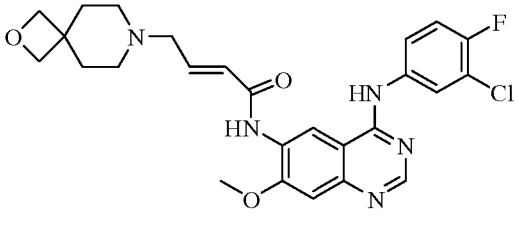

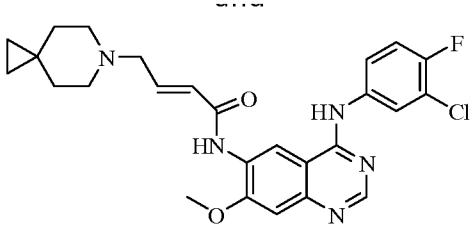

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4. A pharmaceutical composition, which contains the compound according to any one of claims 1-3, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

5. The pharmaceutical composition according to claim 4, which further contains a second therapeutical agent selected from the group consisting of an antineoplastic agent and an immunosuppressive agent, said second therapeutical agent is selected from the group consisting of an antimetabolite, including capecitabine and gemcitabine; a growth factor inhibitor, including pazopanib and imatinib; an antibody, including herceptin and bevacizumab; a mitotic inhibitor, including paclitaxel, vinorelbine, docetaxel, and doxorubicin; an antineoplastic hormone, including letrozole, tamoxifen, and fulvestrant; an alkylating agent, including cyclophosphamide and carmustine; a metal platinum, including carboplatin, cisplatin, and oxaliplatin; a topoisomerase inhibitor, including topotecan; and an immunosuppressant, including everolimus.

6. A pharmaceutical formulation containing a compound according to any one of claims 1-3, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

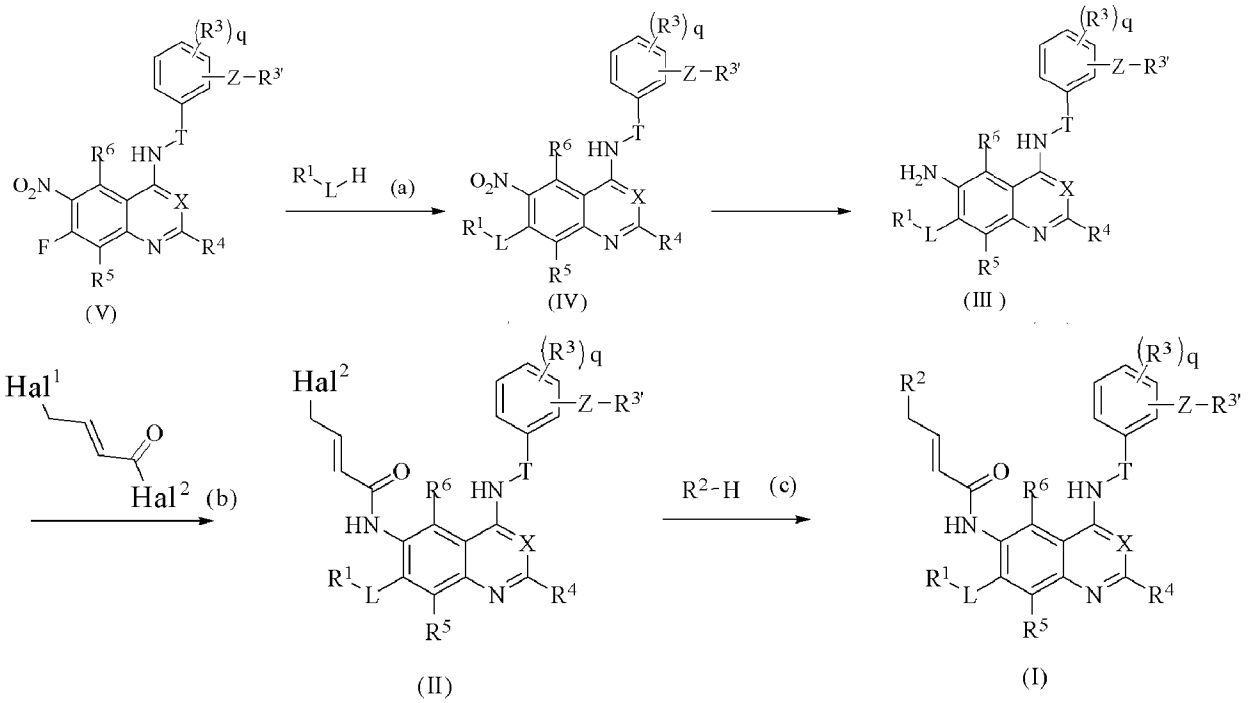
7. The compound according to any one of claims 1-3, or a stereoisomer thereof, or a pharmaceutically acceptable salt

thereof for use in treating an excessive proliferative disease or a chronic obstructive pulmonary disease.

8. The compound for use according to claim 7, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein said excessive proliferative disease includes a cancerous disease and a non-cancerous disease, the cancerous disease is selected from the group consisting of cerebroma, lung cancer, non-small cell lung cancer, squamous cell, bladder carcinoma, gastric cancer, ovarian cancer, peritoneal cancer, pancreatic cancer, mammary cancer, head and neck cancer, cervical cancer, endometrial cancer, colorectal cancer, liver cancer, renal carcinoma, adenocarcinoma of esophagus, esophageal squamous cell cancer, solid tumor, non-Hodgkin lymphoma, central nervous system tumor (glioma, gliobastona multiforme, glioma sarcomatosis), prostate carcinoma or thyroid carcinoma; and the non-cancerous disease is benign proliferative diseases of skin or prostate.

9. A process for preparing a compound according to claim 1, comprising the steps of:

Reaction Procedure:



wherein R^1, R^2, R^3, $R^{3'}$, R^4, R^5, R^6, X, L, T, Z and q are as defined in claim 1, Hal^1 is selected from the group consisting of Cl, Br and I, Hal^2 is selected from the group consisting of Cl and Br, and Hal^1 and Hal^2 may be identical or different;

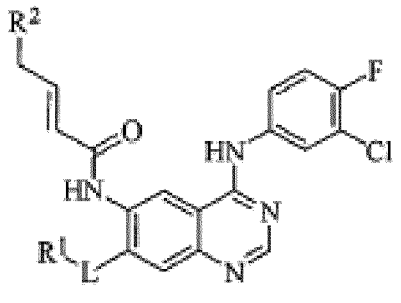
1) Dissolving a compound of the starting material (a) in an organic solvent, and reacting it with a compound of the formula (V) in the presence of an inorganic base to produce a compound of the formula (IV);
2) Reacting the compound of the formula (IV) and a reducing agent to produce a compound of the formula (III);
3) Dissolving the compound of the formula (III) in an organic solvent, and reacting it with a compound of the formula (b) to produce a compound of the formula (II); and
4) Reacting the compound of the formula (II) and a compound of the formula (c) in the presence of a base to produce a compound of the formula (I);

where if necessary, a functional group that needs to be protected may be protected, and then deprotected according to a conventional method.

Patentansprüche

1. Verbindung dargestellt durch die allgemeine Formel (I-2) oder ein Stereoisomer davon oder ein pharmazeutisch

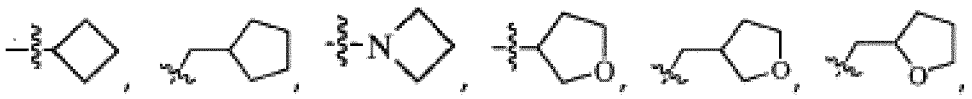
annehmbares Salz davon:

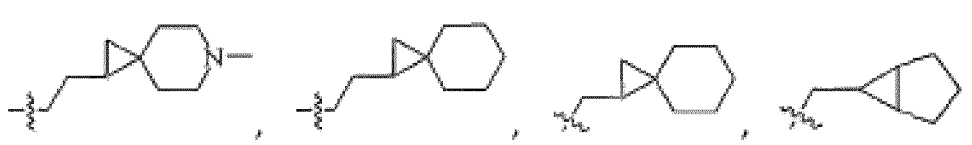


(I-2),

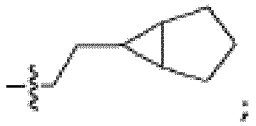
wobei

R^1 ausgewählt ist aus der Gruppe bestehend aus den folgenden Gruppen, die nicht substituiert oder durch Halogen, Hydroxy, Amino, Carboxyl, Cyano, Methyl, Ethyl, Methoxy, Ethoxy, Methylamino, Ethylamino, Dimethylamino oder Diethylamino substituiert sind: Methyl, Ethyl,



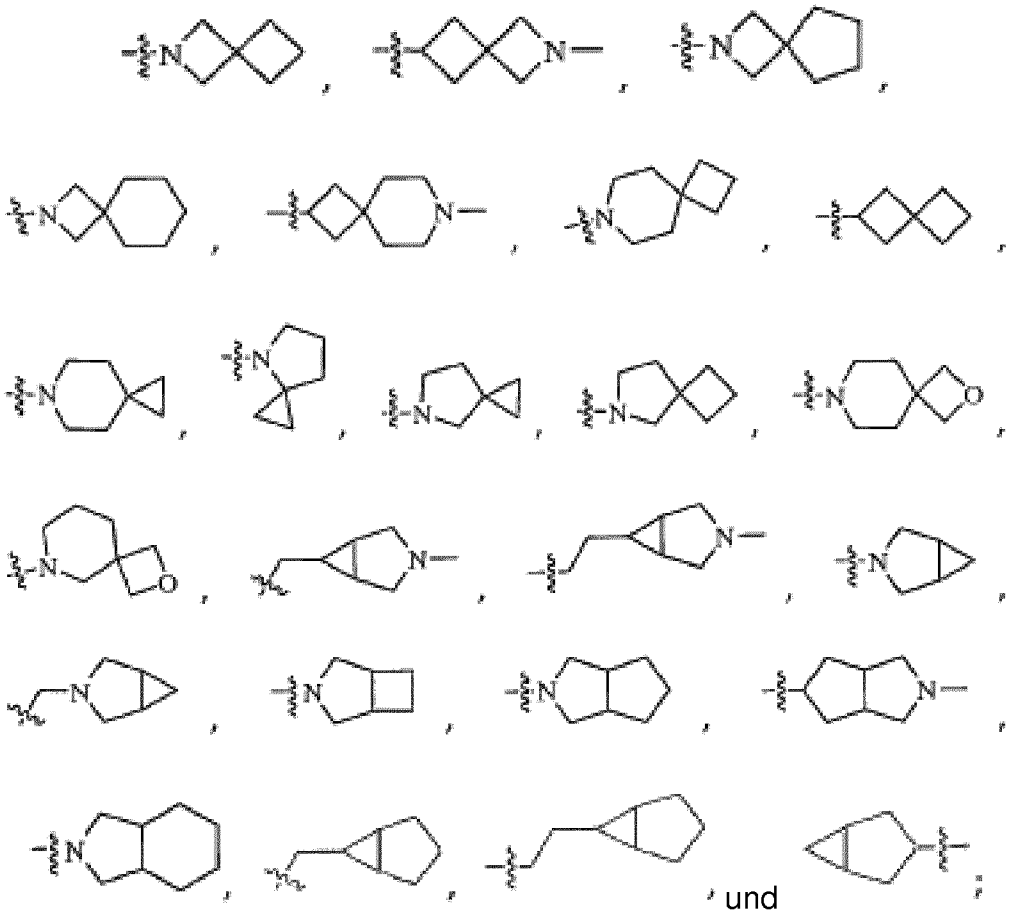


und



;

R^2 ausgewählt ist aus der Gruppe bestehend aus den folgenden Gruppen, die nicht substituiert oder durch Halogen, Hydroxy, Amino, Methyl, Ethyl, Methoxy, Ethoxy, Methylamino, Ethylamino, Dimethylamino, Diethylamino, Acetoxy, Acetylamino, Methylsulfonyl oder Methylsulfonylamino substituiert sind:

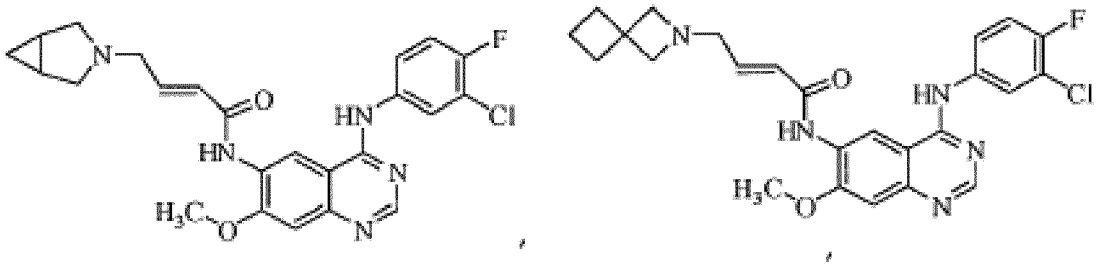


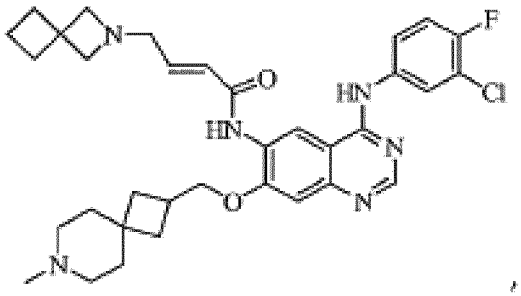
und

und

L O ist.

2. Verbindung gemäß Anspruch 1 oder ein Stereoisomer davon oder ein pharmazeutisch annehmbares Salz davon, wobei die Verbindung ausgewählt ist aus der Gruppe bestehend aus:





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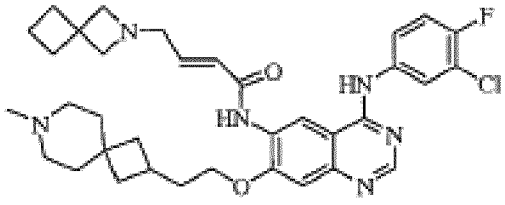

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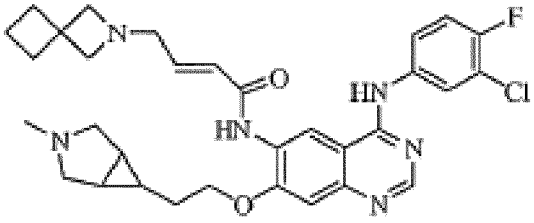

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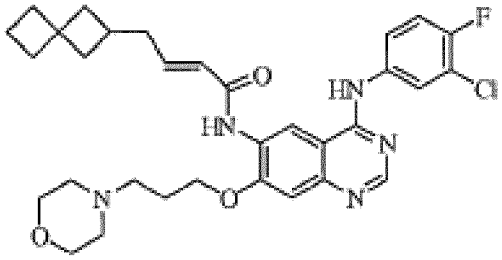

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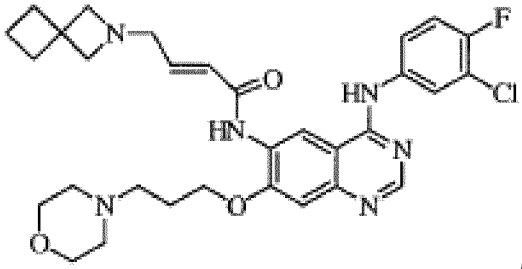

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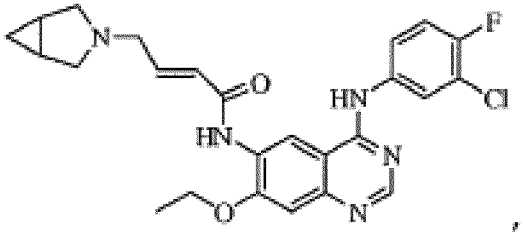

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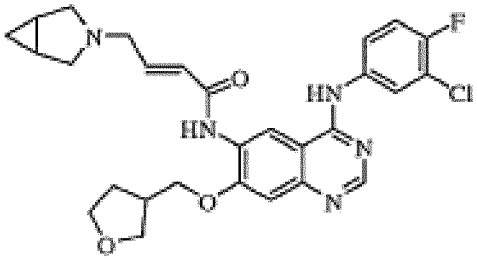

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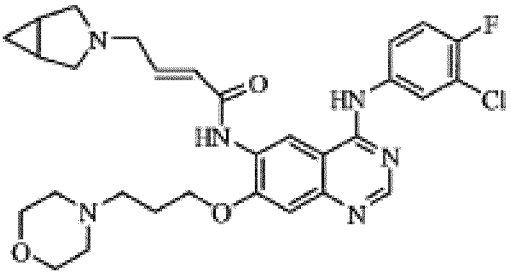

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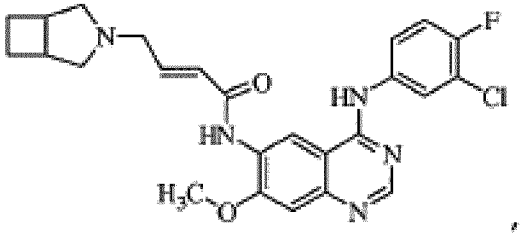
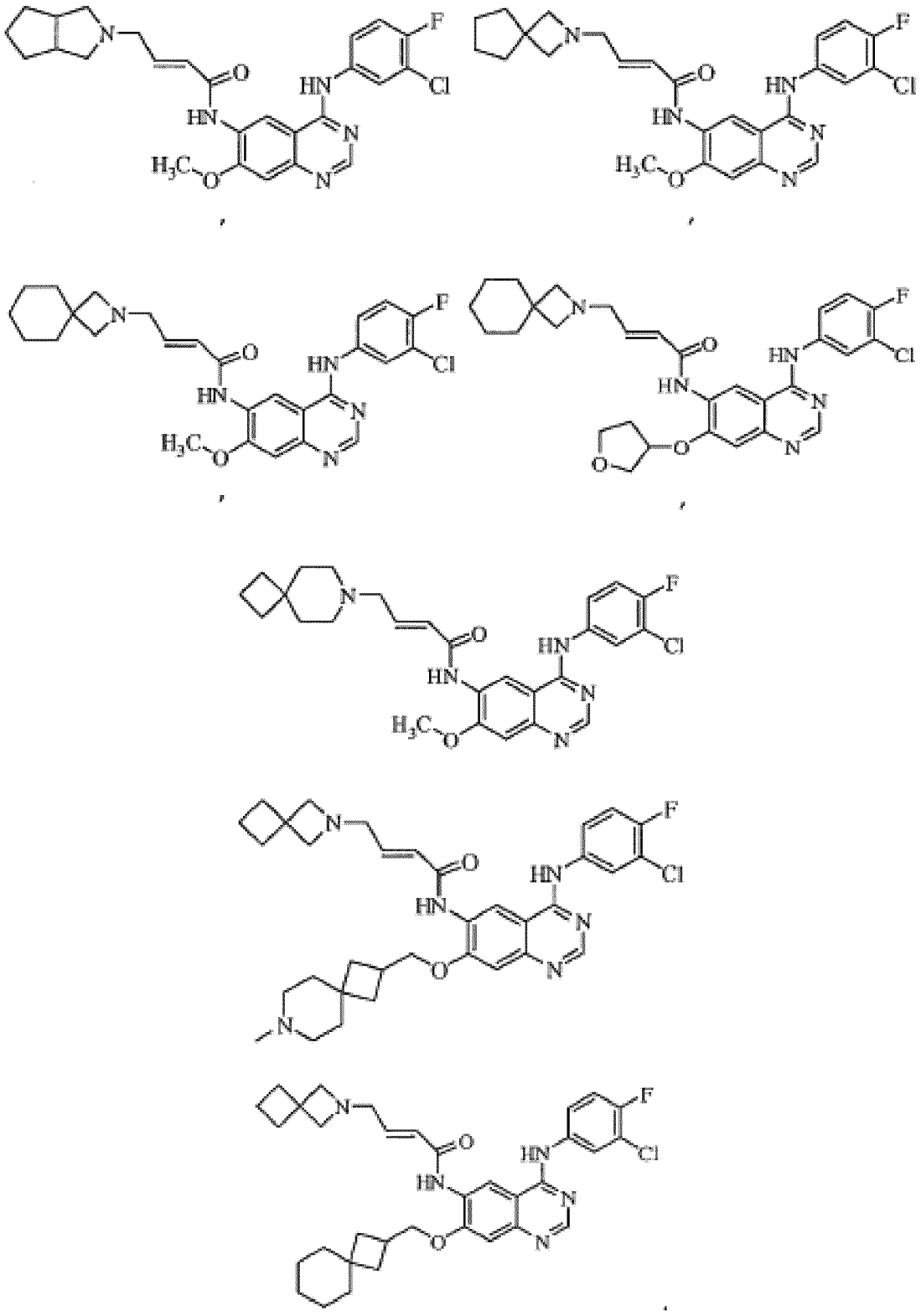
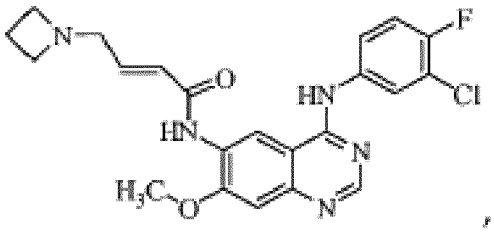
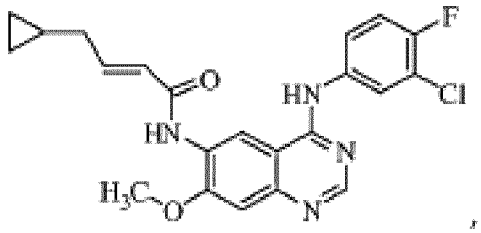
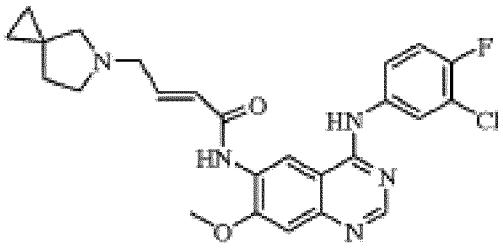


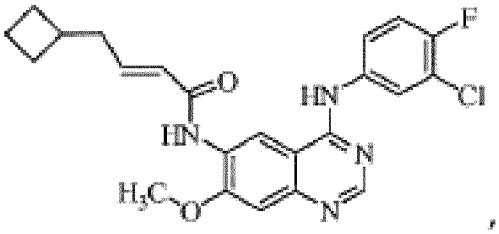


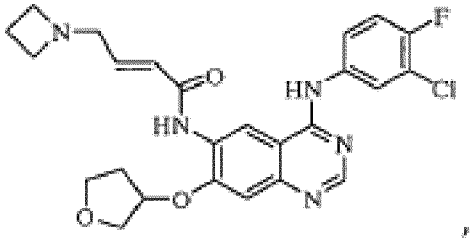
3. Verbindung oder ein Stereoisomer davon oder ein pharmazeutisch annehmbares Salz davon, wobei die Verbindung ausgewählt ist aus der Gruppe bestehend aus:

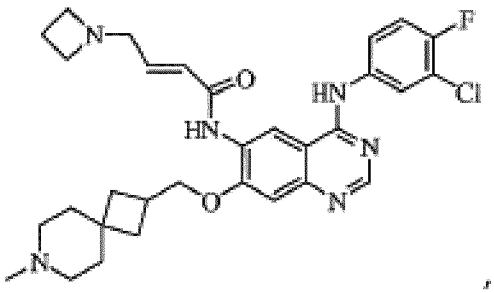


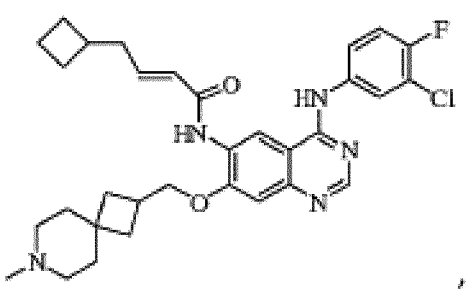


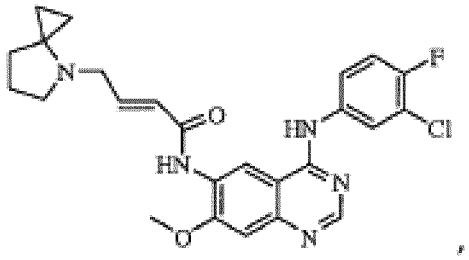


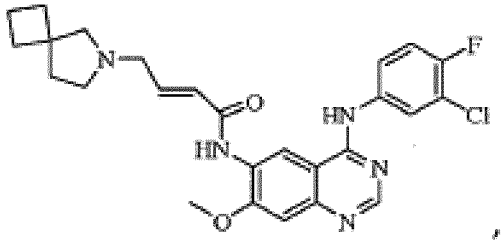


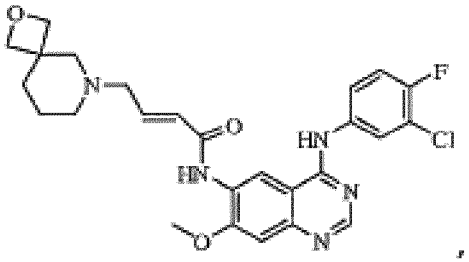












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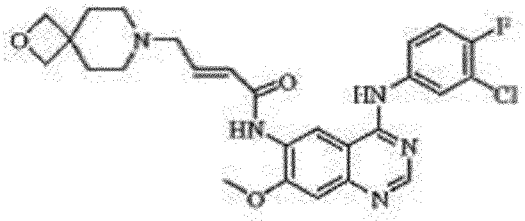
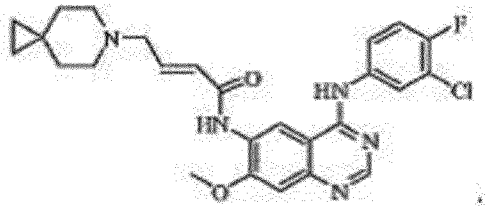




4. Pharmazeutische Zusammensetzung, die die Verbindung gemäß einem der Ansprüche 1-3 oder ein Stereoisomer davon oder ein pharmazeutisch annehmbares Salz davon enthält.

5. Pharmazeutische Zusammensetzung gemäß Anspruch 4, die ferner einen zweiten therapeutischen Wirkstoff ausgewählt aus der Gruppe bestehend aus einem antineoplastischen Wirkstoff und einem immunsuppressiven Wirkstoff enthält, wobei der zweite therapeutische Wirkstoff ausgewählt ist aus der Gruppe bestehend aus einem Antimetabolit, einschließlich Capecitabin und Gemcitabin; einem Wachstumsfaktor-Inhibitor, einschließlich Pazopanib und Imatinib; einem Antikörper, einschließlich Herceptin und Bevacizumab; einem mitotischen Inhibitor, einschließlich Paclitaxel, Vinorelbin, Docetaxel und Doxorubicin; einem antineoplastischen Hormon, einschließlich Letrozol, Tamoxifen und Fulvestrant; einem Alkylierungsmittel, einschließlich Cyclophosphamid und Carmustin; einem metallischen Platin, einschließlich Carboplatin, Cisplatin und Oxaliplatin; einem Topoisomerase-Inhibitor, einschließlich Topotecan; und einem Immunsuppressivum, einschließlich Everolimus.

6. Pharmazeutische Formulierung umfassend eine Verbindung gemäß einem der Ansprüche 1-3 oder ein Stereoisomer davon oder ein pharmazeutisch annehmbares Salz davon und einen oder mehrere pharmazeutisch annehmbare Träger.

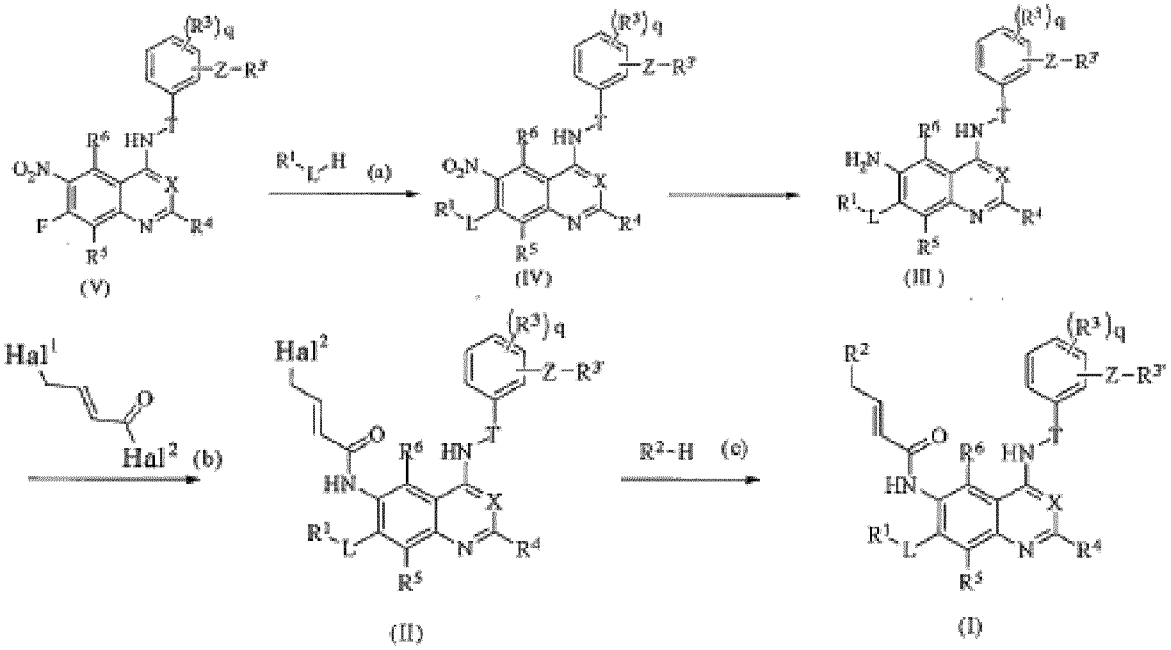
7. Verbindung gemäß einem der Ansprüche 1-3 oder ein Stereoisomer davon oder ein pharmazeutisch annehmbares Salz davon zur Verwendung zur Behandlung einer exzessiven proliferativen Erkrankung oder einer chronisch obstruktiven Lungenerkrankung.

8. Verbindung zur Verwendung gemäß Anspruch 7 oder ein Stereoisomer davon oder ein pharmazeutisch annehmbares Salz davon, wobei die exzessive proliferative Erkrankung eine krebsartige Erkrankung und eine nicht krebsartige Erkrankung einschließt, wobei die krebsartige Erkrankung ausgewählt ist aus der Gruppe bestehend aus Cerebroma, Lungenkrebs, nichtkleinzelligem Lungenkrebs, Plattenepithelkrebs, Blasenkarzinom, Magenkrebs, Eierstockkrebs, Bauchfellkrebs, Bauchspeicheldrüsenkrebs, Brustkrebs, Kopf- und Halskrebs, Gebärmutterhalskrebs, Endometriumkrebs, Dickdarmkrebs, Leberkrebs, Nierenkarzinom, Adenokarzinom des Ösophagus, Ösophagus-

plattenepithelkrebs, fester Tumor, Non-Hodgkin Lymphom, Tumor im zentralen Nervensystem (Gliom, Glioblastoma multiforme, Gliom Sarkomatose), Prostatakarzinom oder Schilddrüsenkarzinom und die nicht krebsartige Erkrankung gutartige proliferative Erkrankungen der Haut oder der Prostata ist.

9. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, umfassend die Schritte:

Reaktionsvorgang:



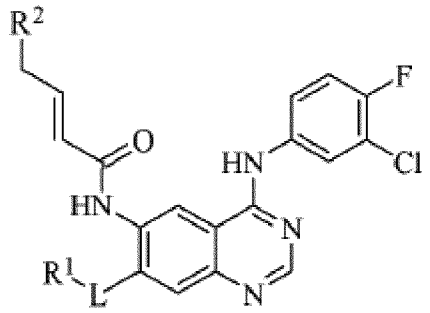
wobei R^1, R^2, R^3, $R^{3'}$, R^4, R^5, R^6, X, L, T, Z und q wie in Anspruch 1 definiert sind, Hal^1 ausgewählt ist aus der Gruppe bestehend aus Cl, Br und I, Hal^2 ausgewählt ist aus der Gruppe bestehend aus Cl und Br und Hal^1 und Hal^2 identisch oder unterschiedlich sein können;

1) Auflösen einer Verbindung des Ausgangsmaterials (a) in einem organischen Lösungsmittel und Reagieren mit einer Verbindung der Formel (V) in Anwesenheit einer anorganischen Base, um eine Verbindung der Formel (IV) herzustellen;
2) Reagieren der Verbindung der Formel (IV) und eines Reduktionsmittels, um eine Verbindung der Formel (III) herzustellen;
3) Auflösen der Verbindung der Formel (III) in einem organischen Lösungsmittel und Reagieren mit einer Verbindung der Formel (b), um eine Verbindung der Formel (II) herzustellen; und
4) Reagieren der Verbindung der Formel (II) und einer Verbindung der Formel (c) in Anwesenheit einer Base, um eine Verbindung der Formel (I) herzustellen;

wo falls nötig eine funktionelle Gruppe, die geschützt werden muss, geschützt und dann gemäß einer konventionellen Methode entschützt werden kann.

Revendications

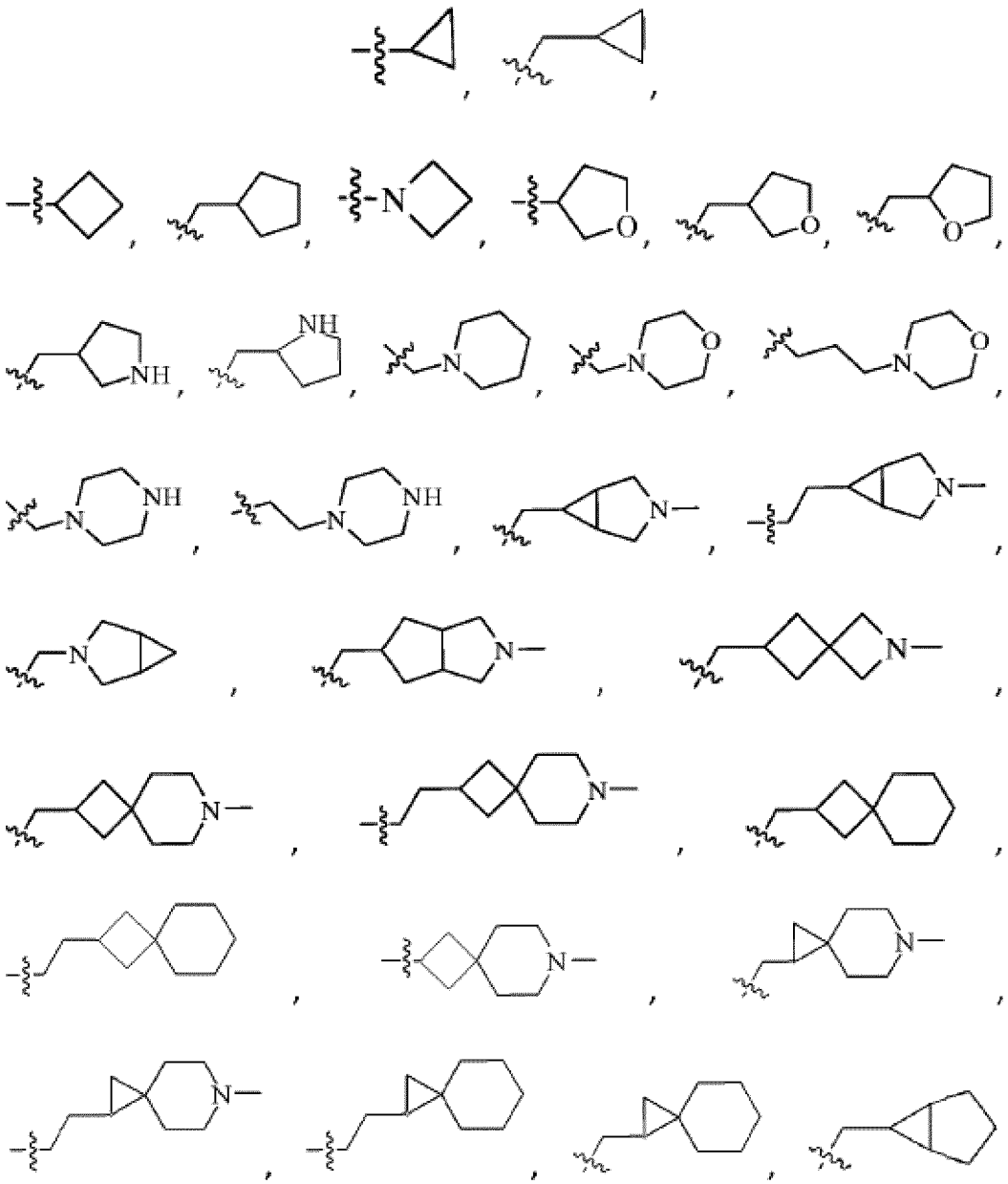
1. Composé représenté par la formule générale (1-2), ou un stéréoisomère de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci :



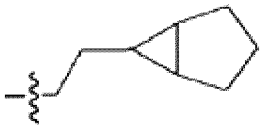
(I-2),

dans lequel

R^1 est choisi dans le groupe constitué des groupes suivants qui sont non substitués ou substitués avec un halogène, un hydroxy, un amino, un carboxyle, un cyano, un méthyle, un éthyle, un méthoxy, un éthoxy, un méthylamino, un éthylamino, un diméthylamino, ou un diéthylamino : un méthyle, un éthyle,

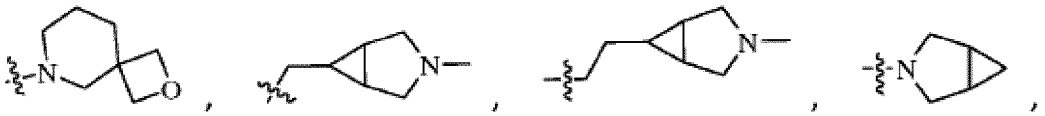


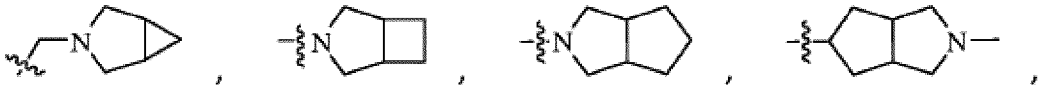
et

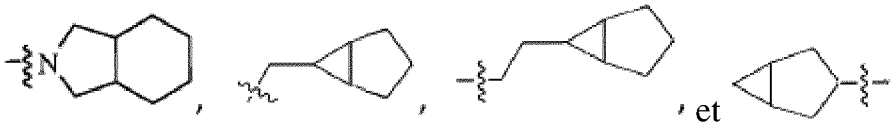


;

R^2 est choisi dans le groupe constitué des groupes suivants qui sont non substitués ou substitués avec un halogène, un hydroxy, un amino, un méthyle, un éthyle, un méthoxy, un éthoxy, un méthylamino, un éthylamino, un diméthylamino, un diéthylamino, un acétoxy, un acétylamino, un méthylsulfonyle, ou un méthylsulfonylamino :



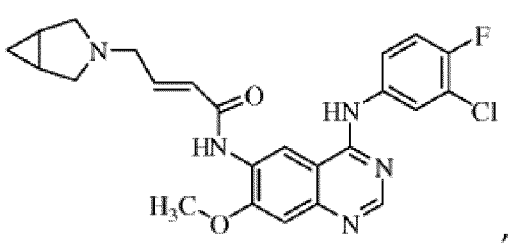




et

L est O.

2. Composé selon la revendication 1 ou un stéréoisomère de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel ledit composé est choisi dans le groupe constitué de :



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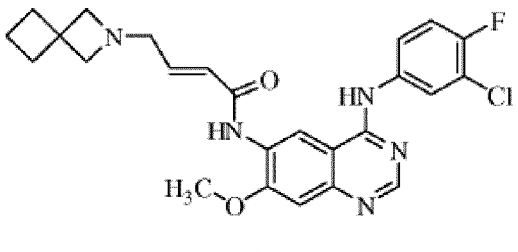

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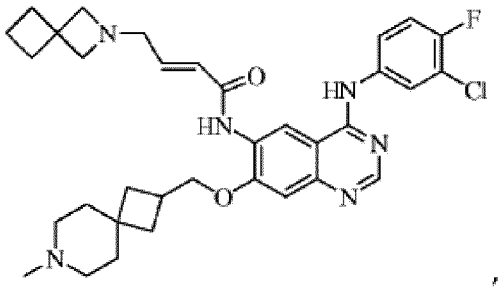

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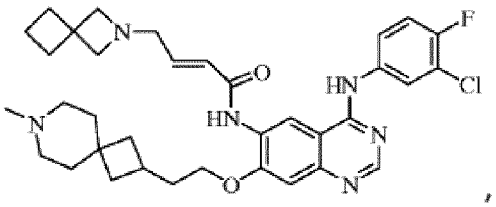

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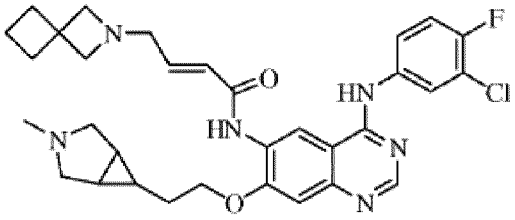

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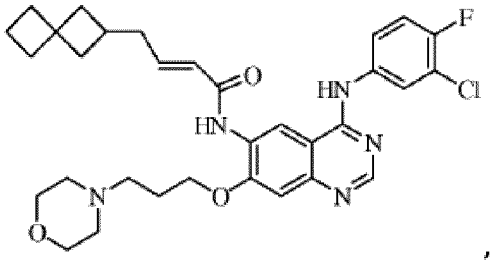

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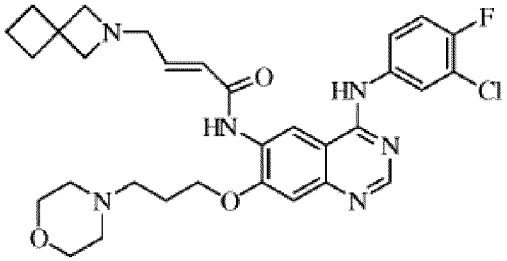

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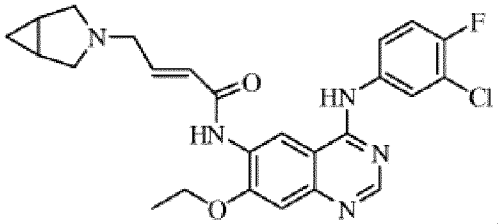

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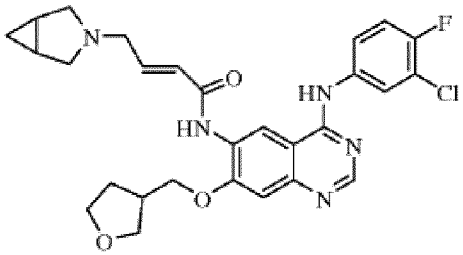

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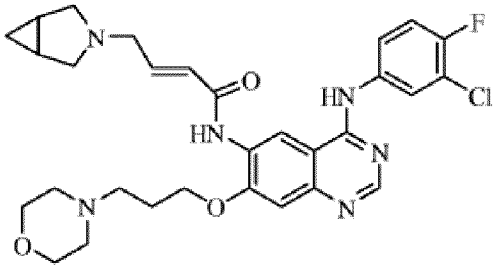

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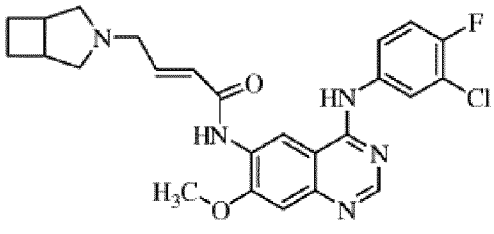

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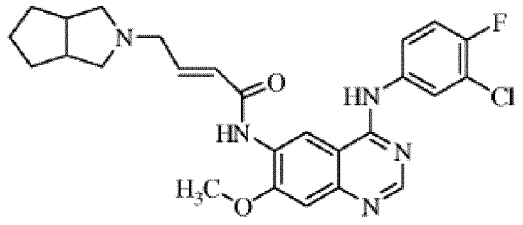

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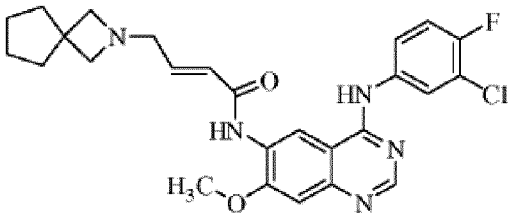

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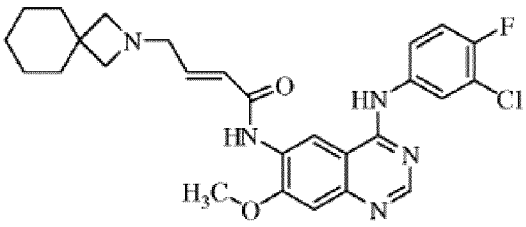

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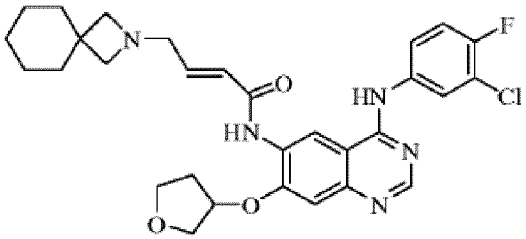

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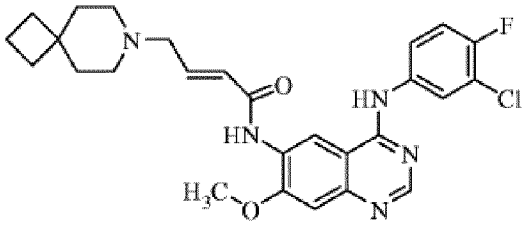
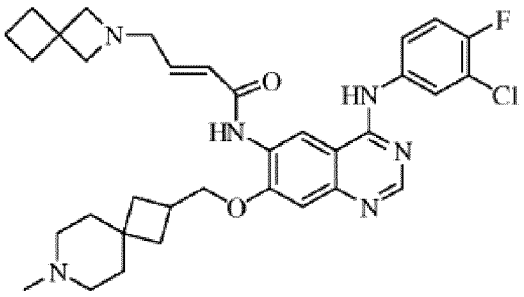
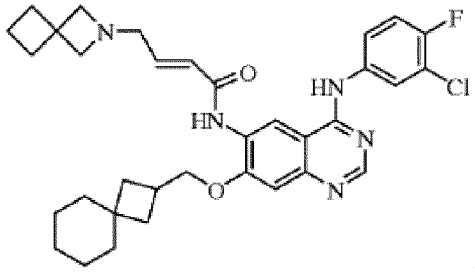
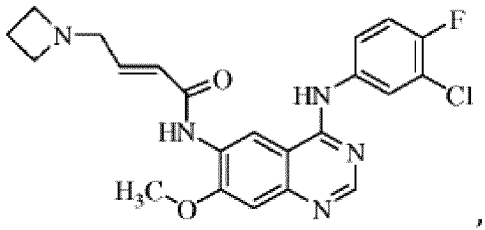






.

3. Composé, ou un stéréoisomère de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel ledit composé est choisi dans le groupe constitué de :



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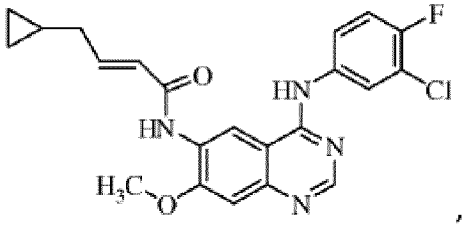

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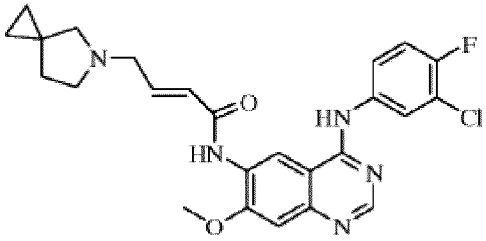

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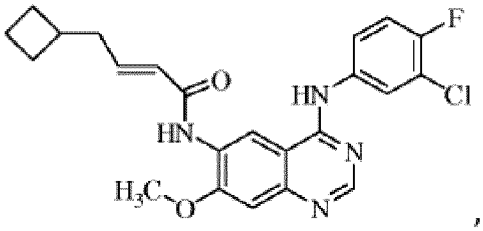

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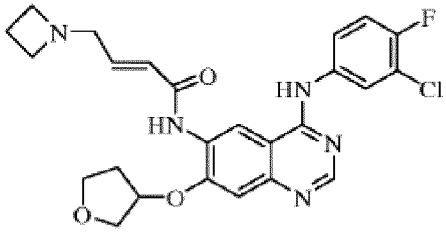

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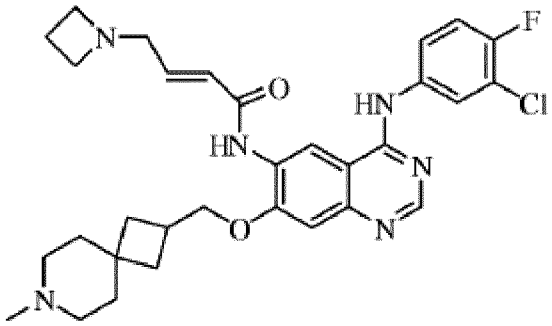

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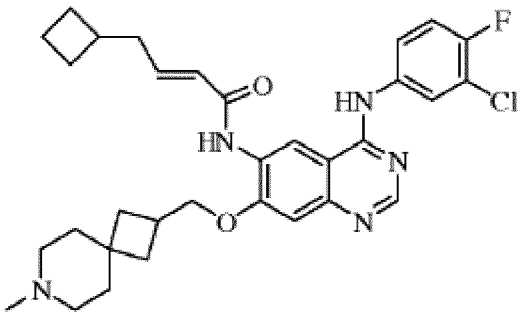

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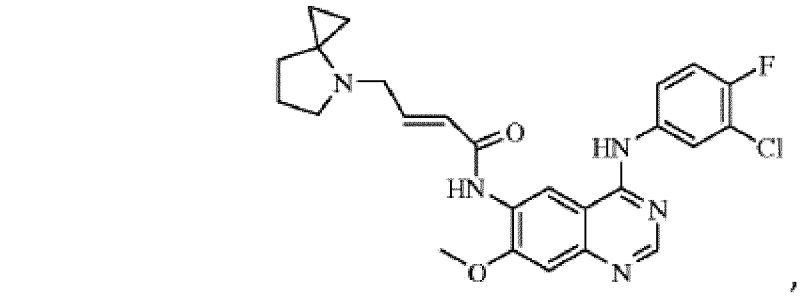

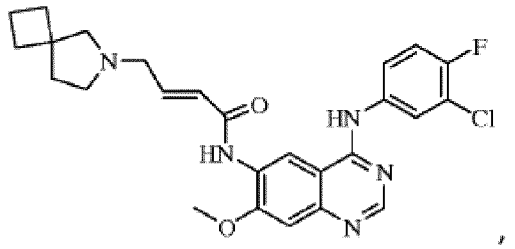

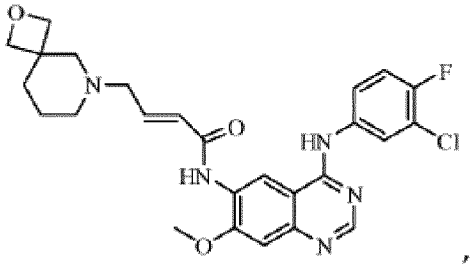

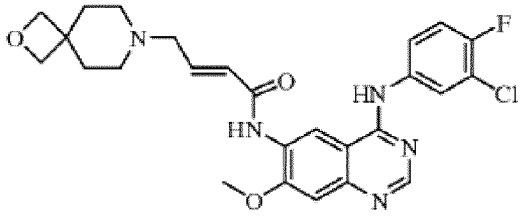

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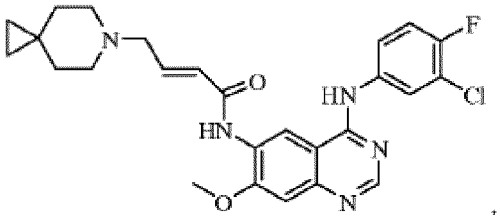


4. Composition pharmaceutique, qui contient le composé selon l'une quelconque des revendications 1 à 3, ou un stéréoisomère de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci.

5. Composition pharmaceutique selon la revendication 4, qui contient en outre un second agent thérapeutique choisi dans le groupe constitué d'un agent antinéoplasique et d'un agent immunosuppresseur, ledit second agent thérapeutique est choisi dans le groupe constitué d'un antimétabolite, notamment la capécitabine et la gemcitabine ; un inhibiteur de facteur de croissance, notamment le pazopanib et l'imatinib ; un anticorps, notamment l'herceptine et le bévacizumab ; un inhibiteur mitotique, notamment le paclitaxel, la vinorelbine, le docétaxel, et la doxorubicine ; une hormone antinéoplasique, notamment le létrozole, le tamoxifène, et le fulvestrant ; un agent alkylant, notamment le cyclophosphamide et la carmustine ; un platine métallique, notamment le carboplatine, le cisplatine, et l'oxaliplatine ; un inhibiteur de topoisomérase, notamment le topotécan ; et un immunosuppresseur, notamment l'évérolimus.

6. Formulation pharmaceutique contenant un composé selon l'une quelconque des revendications 1 à 3, ou un stéréoisomère de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci et un ou plusieurs supports pharmaceutiquement acceptables.

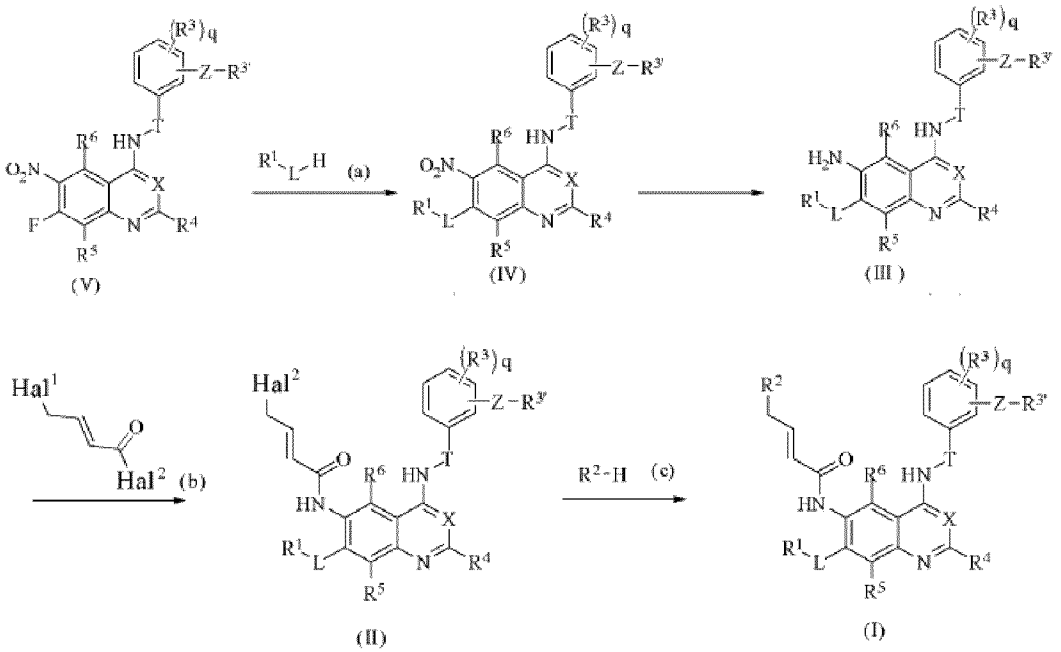
7. Composé selon l'une quelconque des revendications 1 à 3, ou un stéréoisomère de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci pour son utilisation dans le traitement d'une maladie proliférative excessive ou d'une bronchopneumopathie chronique obstructive.

8. Composé pour son utilisation selon la revendication 7, ou un stéréoisomère de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel ladite maladie proliférative excessive comprend une maladie cancéreuse et une maladie non cancéreuse, la maladie cancéreuse est choisie dans le groupe constitué d'un cérébrome, d'un cancer du poumon, d'un cancer du poumon non à petites cellules, d'un carcinome malpighien, d'un carcinome de la vessie, d'un cancer gastrique, d'un cancer des ovaires, d'un cancer péritonéal, d'un cancer pancréatique, d'un cancer mammaire, d'un cancer de la tête et du cou, d'un cancer du col de l'utérus, d'un cancer de l'endomètre, d'un cancer colorectal, d'un cancer du foie, d'un carcinome rénal, d'un adénocarcinome de l'oesophage, d'un cancer

malpighien de l'oesophage, d'une tumeur solide, d'un lymphome non hodgkinien, d'une tumeur du système nerveux central (gliome, glioblastome multiforme, gliome sarcomatose), d'un carcinome de la prostate ou d'un carcinome de la thyroïde ; et la maladie non cancéreuse est une maladie proliférative bénigne de la peau ou de la prostate.

9. Procédé de préparation d'un composé selon la revendication 1, comprenant les étapes suivantes :

Procédure réactionnelle :



dans lequel R^1, R^2, R^3, $R^{3'}$, R^4, R^5, R^6, X, L, T, Z et q sont tels définis dans la revendication 1, Hal^1 est choisi dans le groupe constitué de Cl, Br et I, Hal^2 est choisi dans le groupe constitué de Cl et Br, et Hal^1 et Hal^2 peuvent être identiques ou différents ;

1) la dissolution d'un composé du produit départ (a) dans un solvant organique, et sa réaction avec un composé de la formule (V) en présence d'une base inorganique pour produire un composé de la formule (IV) ;
2) la réaction du composé de la formule (IV) et d'un agent réducteur pour produire un composé de la formule (III) ;
3) la dissolution du composé de la formule (III) dans un solvant organique, et sa réaction avec un composé de la formule (b) pour produire un composé de la formule (II) ; et
4) la réaction du composé de la formule (II) et d'un composé de la formule (c) en présence d'une base pour produire un composé de la formule (I) ;

si nécessaire, un groupe fonctionnel qui doit être protégé peut être protégé, et ensuite déprotégé selon un procédé classique.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

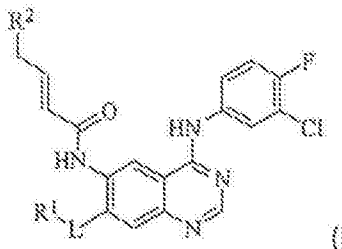
- WO 9738983 A **[0009]**
- US 20010044435 A1 **[0010]**
- US 20040044014 A1 **[0011]**

Non-patent literature cited in the description

- *Bioorganic & Medicinal Chemistry,* 2008, vol. 16, 3482-3488 **[0007]**
- *Adv Ther,* 2011, vol. 28 (2), 1-8 **[0012]**
- *Cancer Res,* 2007, vol. 67 (24), 11924-11932 **[0013]**
- *Mol Cancer Ther,* 2008, vol. 7 (7), 1880-1889 **[0013]**

Szabadalmi igénypontok

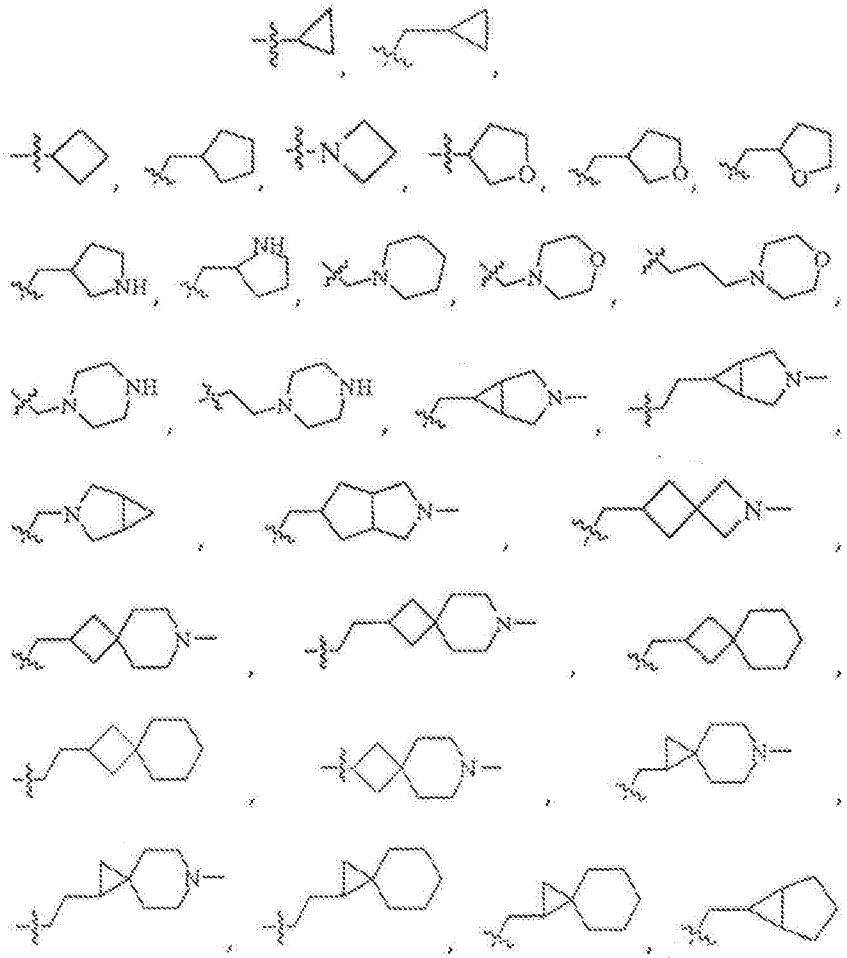
1. (I-2) általános képletű vegyületek, vagy ezek sztereoizomerjei, vagy ezek gyógyszerészetileg elfogadható sói:



(I-2),

ahol

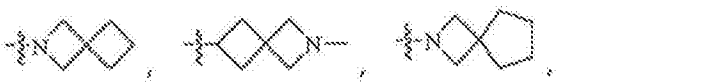
R^1 jelentését a szubsztituálatlan vagy halogén-, hidroxi-, amino-, karboxil-, ciano-, metil-, etil-, metoxi-, etoxi-, metil-amino-, etil-amino-, dimetil-amino-, vagy dietil-amino-csoporttal szubsztituált következő csoportokból: metil, etil,

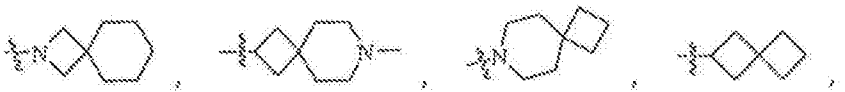


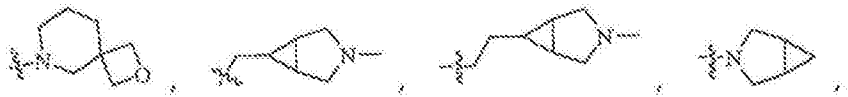
és

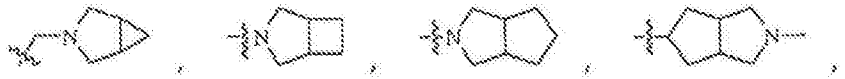
álló csoportból választjuk;

R^2 jelentését a szubsztituálatlan vagy halogén-, hidroxi-, amino-, metil-, etil-, metoxi-, etoxi-, metil-amino-, etil-amino-, dimetil-amino-, dietil-amino-, acetoxi-, acetil-amino-, metil-szulfonil-, vagy metil-szulfonil-amino-csoporttal szubsztituált következő csoportokból:





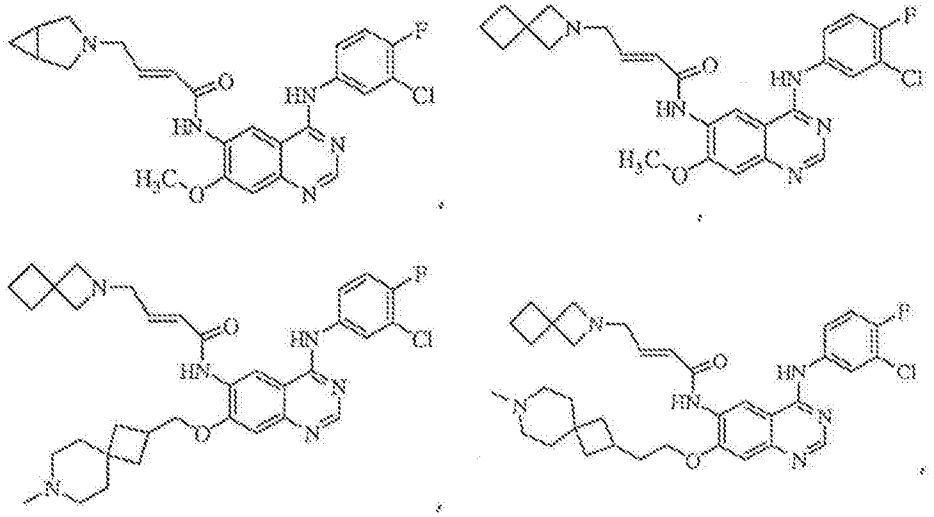


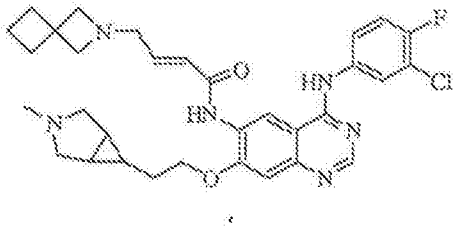


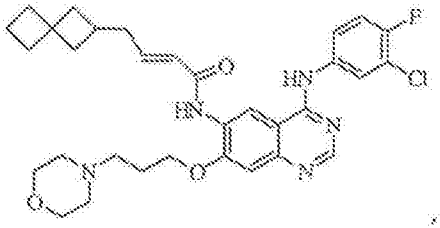
álló csoportból választjuk; és

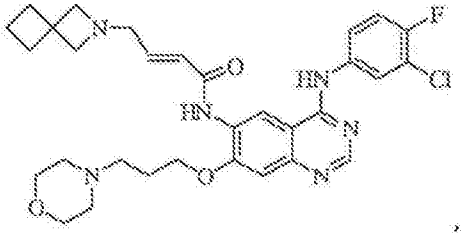
L jelentése O.

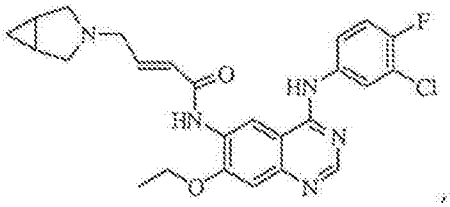
2. Az 1. igénypont szerinti vegyületek vagy ezek sztereoizomerjei, vagy ezek gyógyszerészetileg elfogadható sói, ahol a vegyületet az alábbiakból álló csoportból választjuk:

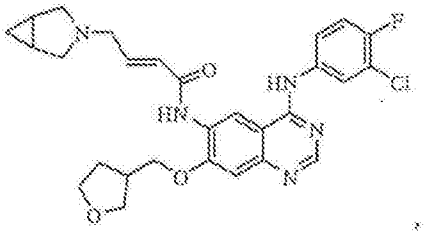


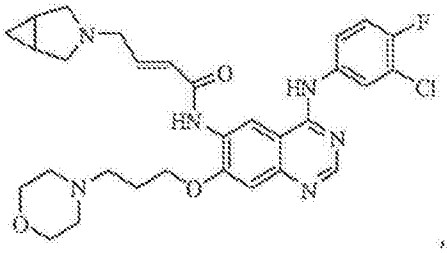


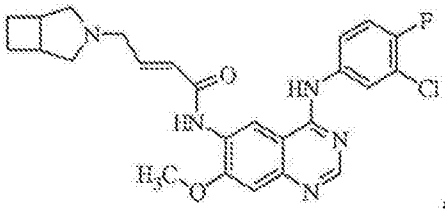


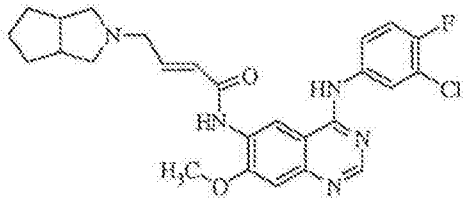


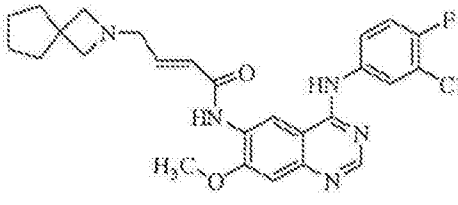


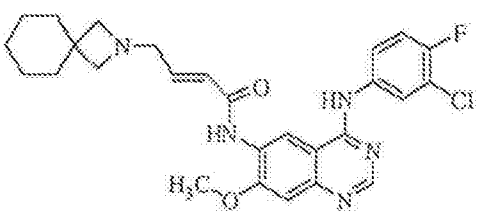


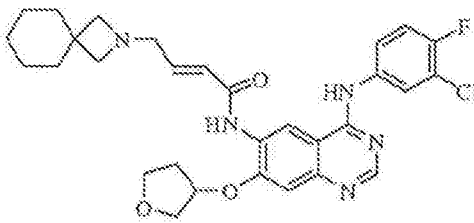


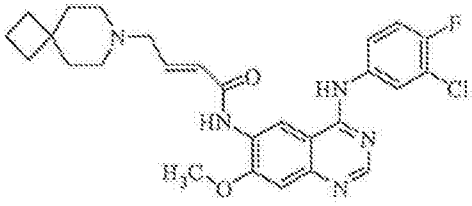


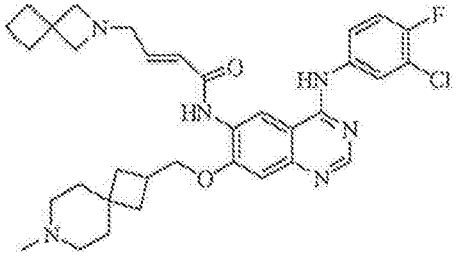


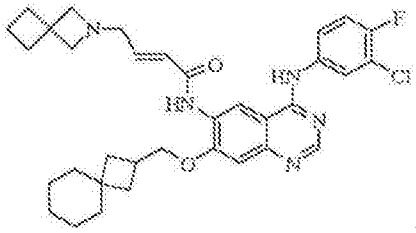




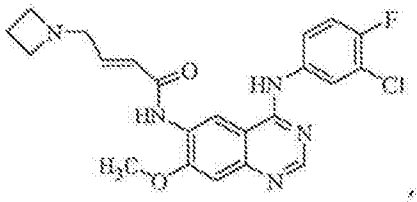


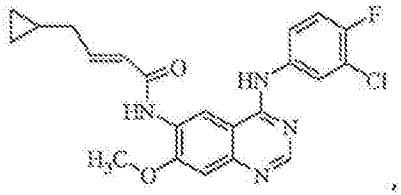


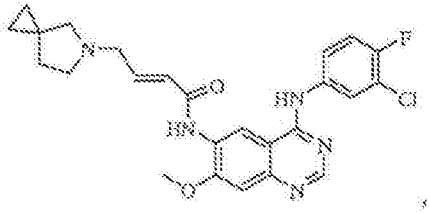


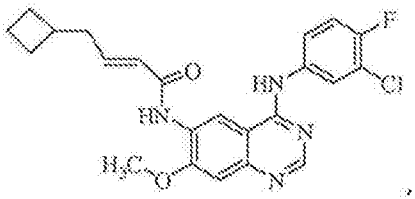


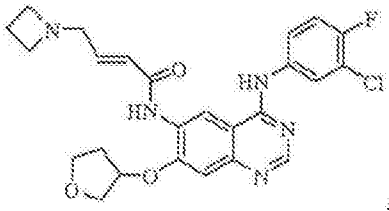
3. Vegyületek, vagy ezek sztereoizomerjei, vagy ezek gyógyszerészetileg elfogadható sói, ahol a vegyületet az alábbiakból álló csoportból választjuk:

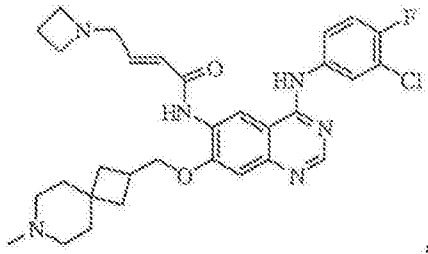


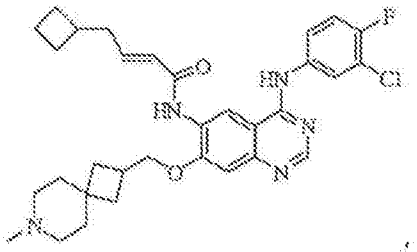


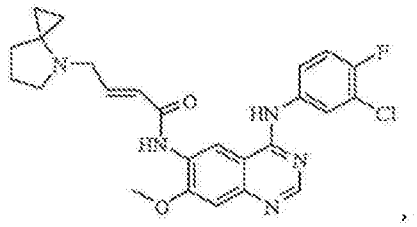


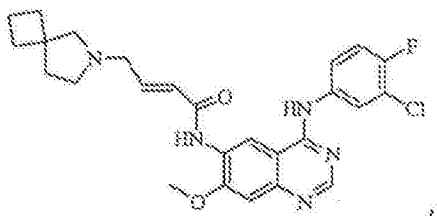


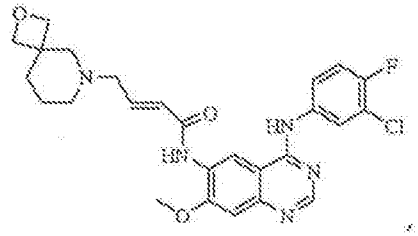












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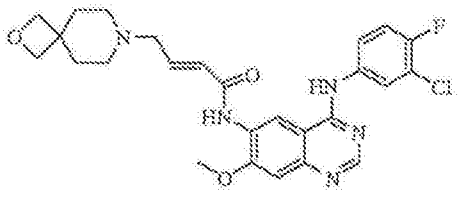
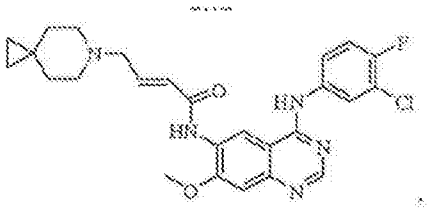




4. Gyógyszerkészítmény, amely az 1-3. igénypontok bármelyike szerinti vegyületet, vagy ennek sztereoizomerjeit, vagy ennek gyógyszerészetileg elfogadható sóit tartalmazza.

5. A 4. igénypont szerinti gyógyszerkészítmény, amely továbbá tartalmaz egy második hatóanyagot, amelyet az antineoplasztikus szerekből és az immunszupresszív szerekből álló csoportból választunk, a nevezett második hatóanyagot az antimetabolitokból, beleértve a kapecitabint és gemcitabint; a növekedési faktor inhibitorokból, beleértve a pazopanibot és az imatinibet; antitestekből, beleértve a herceptint és bevacizumabot; a mitotikus inhibitorokból, beleértve a paclitaxelt, vinorelbint, docetaxelt, és doxorubicint; az antineoplasz-

tikus hormonokból, beleértve a letrozolt, tamoxifent, és fulvestrantot; az alkilező szerekből, beleértve a ciklofoszfamidot és a karmusztint; a platina fémből, beleértve a karboplatint, ciszplatint, és oxaliplatint; a topoizomeráz inhibitorokból, beleértve a topotekánt; és az immunszupresszánsokból, beleértve az everolimuszt, álló csoportból választunk.

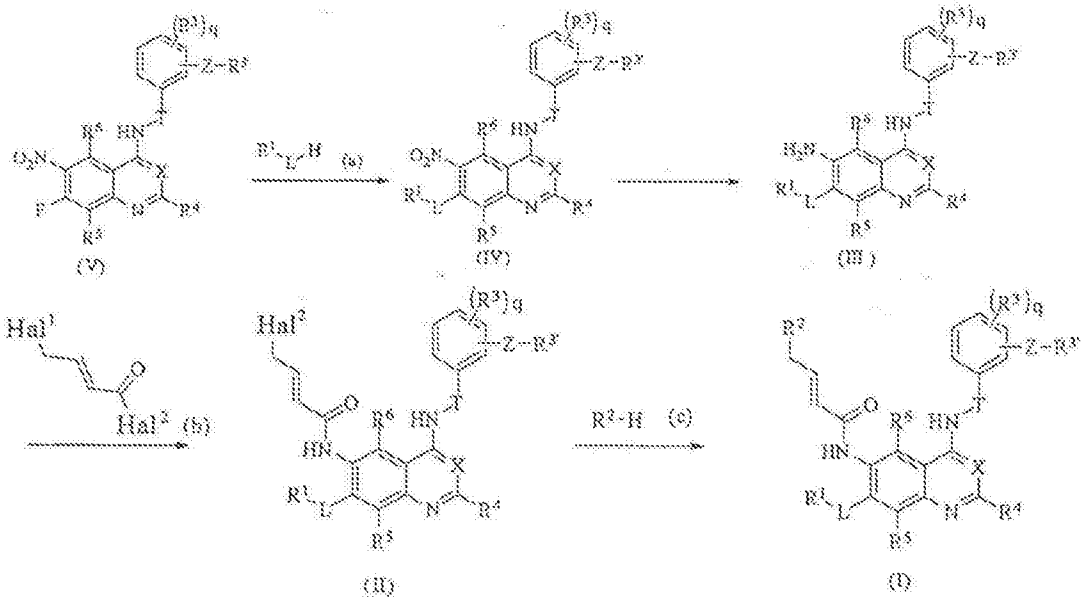
6. Gyógyszerkészítmény, amely az 1-3. igénypontok bármelyike szerinti vegyületeket, vagy ezek sztereoizomerjeit, vagy ezek gyógyszerészetileg elfogadható sóit és egy vagy több gyógyszerészetileg elfogadható hordozót tartalmaz.

7. Az 1-3. igénypontok bármelyike szerinti vegyületek, vagy ezek sztereoizomerjei, vagy ezek gyógyszerészetileg elfogadható sói excesszív proliferációs betegség vagy krónikus obstruktív légúti betegség kezelésében történő alkalmazásra.

8. Vegyületek, vagy ezek sztereoizomerjei, vagy ezek gyógyszerészetileg elfogadható sói a 7. igénypont szerinti alkalmazásra, ahol az excesszív proliferációs betegség rákos megbetegedésre és nem-rákos megbetegedésre vonatkozik, a rákos megbetegedést az alábbiakból álló csoportból választjuk: cerebróma, tüdőrák, nem-kisejtes tüdőrák, laphám sejt, hólyag karcinóma, gyomorrák, petefészekrák, peritoneális rák, hasnyálmirigy rák, emlőrák, fej és nyaki rák, méhnyak rák, méhtestrák, végbélrák, májrák, vese karcinóma, nyelőcső adenokarcinóma, nyelőcső laphámsejt rák, szolid tumor, nem-Hodgkin limfóma, központi idegrendszeri tumor (glioma, gliobasztoma multiform, glioma szarkomatozis), prosztata karcinóma vagy pajzsmirigy karcinóma; és a nem-rákos megbetegedés a bőr vagy prosztata jóindulatú burjánzásos megbetegedései.

9. Eljárás 1. igénypont szerinti vegyületek előállítására, amely a következő lépéseket tartalmazza:

A reakció folyamata:



ahol R^1, R^2, R^3, R^{3a}, R^4, R^5, R^6, X, L, T, Z és q jelentése az 1. igénypontban meghatározott, Hal^1 jelentését a Cl, Br és I által alkotott csoportból választjuk, Hal^2 jelentését a Cl és Br által alkotott csoportból választjuk, és Hal^1 és Hal^2 jelentése lehet azonos vagy különböző;

1) A kiindulási anyag (a) vegyületének feloldása egy szerves oldószerben, és reagáltatása (V) képletű vegyülettel egy szervetlen bázis jelenlétében (IV) képletű vegyület előállítására;

2) A (IV) képletű vegyület és egy redukáló szer reagáltatása a (III) képletű vegyület előállítására;

3) A (III) képletű vegyület feloldása egy szerves oldószerben, és reagáltatása (b) képletű vegyülettel (II) képletű vegyület előállítására; és

4) A (II) képletű vegyület és (c) képletű vegyület reagáltatása bázis jelenlétében (I) képletű vegyület előállítására;

ahol, ha szükséges, egy védendő funkciós csoport védhető, és ezután egy szokásos eljárással a védőcsoport eltávolítható.

A meghatalmazott:

Dr. Gál Melinda
Szabadalmi Ügyvivői Iroda
H-1062 Budapest, Andrássy út 113.
Telefon: 461-1000 Fax: 461-1099
Email: gal@mgk.hu