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(54) **HETEROCYCLIC COMPOUNDS AS BTK INHIBITORS**

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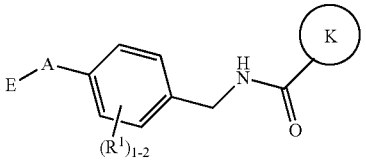
(57) **ABSTRACT**

The present invention relates to heterocyclic compounds or their pharmaceutically acceptable salts thereof as inhibitors of Bruton's tyrosine kinase (BTK) and its C481 mutant. The present invention relates to compounds shown in Formula (I) and their pharmaceutically acceptable salts thereof. The present invention also relates to methods for preparing compounds or their pharmaceutically acceptable salts thereof. Compounds of the present invention can be used to treat and/or prevent related diseases mediated by BTK or its C481 mutant, especially cancer and autoimmune diseases.

(I)



HETEROCYCLIC COMPOUNDS AS BTK INHIBITORS

[0001] This application is a continuation of PCT/CN2021/113535, filed Aug. 19, 2021, which claims the priority of Chinese Application No. 202010836243.4, filed Aug. 20, 2020. The contents of the above-identified applications are incorporated herein by reference in their entireties.

TECHNICAL FIELD

[0002] The invention relates to heterocyclic compounds or their pharmaceutically acceptable salts thereof, suitable for regulating or inhibiting activities of Bruton tyrosine kinase (BTK) and its C481 mutant. The present invention also relates to methods for preparing the compounds or their pharmaceutically acceptable salts thereof. The present invention further relates to the uses and methods of use of the compounds or their pharmaceutically acceptable salts thereof in the treatment and/or prevention of cancer and autoimmune diseases.

BACKGROUND ART

[0003] BTK is an important non-receptor tyrosine kinase that mediates cell signal transduction, which exists in plasma cells including B-cells. B-cells are activated through B-cell receptor (BCR) and BTK plays an important role in the BCR-mediated signaling pathway. After BCR on B-cells is activated, it causes the activation of BTK which leads to an increase in the concentration of downstream phospholipase C (PLC) and activates the IP3 and DAG signaling pathways. This signaling pathway can promote cell proliferation, adhesion and survival, and plays an important role in the development of B-cell lymphoma.

[0004] BTK inhibitors inhibit the proliferation of B lymphoma cells by inhibiting the activity of BTK, destroy adhesion of tumor cells, and promote tumor cell apoptosis, making BTK a compelling drug target for B-cell related cancers, such as non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia (WM), marginal zone Lymphoma (MZL), central nervous system leukemia (CNSL), etc. Several BTK inhibitors are currently on the market, including Abbvie/JNJ's ibrutinib, AZ's acalabrutinib, Beigene's zanubrutinib and Gilead/Ono's tirabrutinib, and more BTK inhibitors are in clinical research.

[0005] In addition to treating B-cell associated lymphomas, BTK inhibitors can also inhibit the production of B-cell autoantibodies and cytokines. In autoimmune diseases, B-cells present their own antigens, promote T-cell activation, secrete inflammatory factors that cause tissue damage, and at the same time activate B-cells to produce a large number of antibodies to trigger an autoimmune response. T- and B-cells interact to each other to form a positive feedback regulatory chain which leads to uncontrolled autoimmune responses and aggravates tissue pathological damage. Studies have shown that there are regulatory B-cells in the body which can negatively regulate the immune response and inhibit immune-mediated inflammation through the secretion of interleukin 10 (IL-10) or transforming growth factor β1 (TGF-β1) and other mechanisms. Therefore, BTK can be a drug target for autoimmune diseases, such as rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), pemphigus, etc. For autoimmune indications, BTK inhibitors are still in clinical research. Among them, Sanofi's rilzabrutinib and Merck Serono's evobrutinib have achieved effective results in the treatment of pemphigus and multiple sclerosis, respectively.

[0006] Most of BTK inhibitors on the market and under research are irreversible inhibitors which inhibit the activity of BTK by covalently binding to the cysteine residue located at 481 of the BTK protein. After some B-cell lymphoma patients received ibrutinib treatment for a period of time, BTK's C481 mutation, such as C481S, made ibrutinib lose its covalent binding point with the protein, resulting in a decrease in the activity of ibrutinib, thereby making patients resistant to the ibrutinib treatment (Quinquenel, et. al Blood 2019, 134, 641-644). There exists a need for BTK inhibitors which effectively inhibit the activities of BTK and its C481 mutant, thereby overcoming the drug resistance caused by the C481 mutation associated with irreversible BTK inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0007] Unless otherwise stated, the following terms used in this application have the following meanings.

[0008] "CSF/plasma ratio (Kp)" refers to the ratio of a compound concentration in cerebrospinal fluid (CSF) vs. in plasma. The ability of a compound to cross blood-brain barrier (BBB) is assessed by measuring its concentrations in CSF and plasma in rodents, and determining the ratio (Kp, CSF).

[0009] "C_{x-y}" refers to a range of the number of carbon atoms, where x and y are both integers, for example, C_{3-8} cycloalkyl stands for cycloalkyl having 3 to 8 carbon atoms.

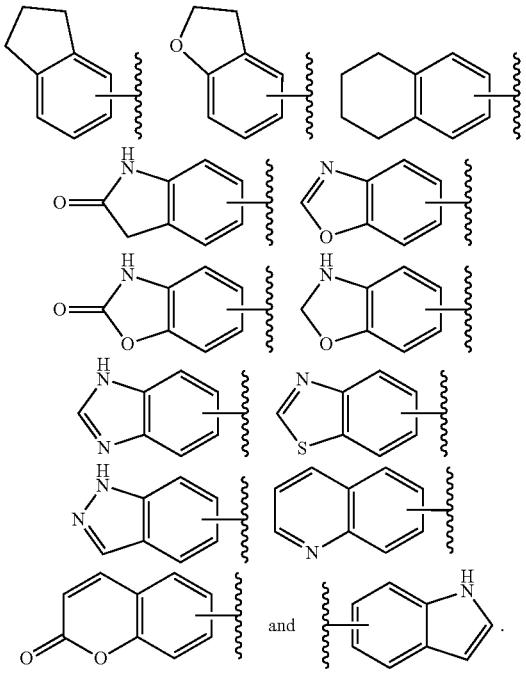
[0010] "Alkyl" refers to a saturated straight-chain or branched-chain hydrocarbyl substituent containing 1 to 20 carbon atoms, for example, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. Unrestricted examples of alkyl include but are not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl and 2-ethylbutyl.

[0011] "Cycloalkyl" refers to a saturated cyclic hydrocarbyl substituent containing 3 to 14 annular carbon atoms. Cycloalkyl may be a mono carbon ring substituent, typically containing 3 to 8, 3 to 7, or 3 to 6 carbon atoms. Unrestricted examples of monocyclic cycloalkyl include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cycloalkyl may also be a substituent with two or three mono rings that are fused together, such as decahydronaphthyl, bicyclo[2.2.2]octane and spiro[3.3]heptane.

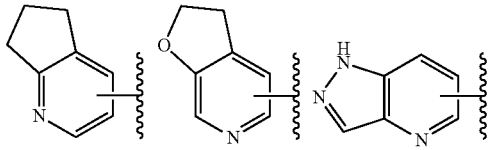
[0012] "Heterocyclyl or heterocycle" refers to a saturated or partially unsaturated monocyclic or polycyclic group containing 3 to 20 annular atoms, for example, 3 to 14, 3 to 12, 3 to 10, 3 to 8, 3 to 6, or 5 to 6 annular atoms in which one or more of the annular atoms are selected from N, O and $S(O)_m$ (where m is an integer from 0 to 2). Preferably, it may have 3 to 12 annular atoms, more preferably 3 to 10 ring atoms, more preferably 4 to 7 ring atoms, more preferably 4 to 6 ring atoms, most preferably 5 or 6 ring atoms, wherein

1 to 4 are heteroatoms, 1 to 3 are heteroatoms, or 1 to 2 are heteroatoms. Unrestricted examples of monocyclic heterocyclyl include but are not limited to pyrrolidinyl, oxetanyl, piperidyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, homopiperazinyl and azetidinyl. Polycyclic heterocyclyl includes fused, bridged or spiro polycyclic heterocycle, such as octahydrocyclopenta[c]pyrrole, octahydropyrrole[1,2-a]pyrazine, 3,8-diazabicyclo[3.2.1]octane, 5-azaspiro[2.4]heptane and 2-oxa-7-azaspiro[3.5]nonane.

[0013] "Aryl or aryl ring" refers to an aromatic monocyclic or fused polycyclic group containing 6 to 14 carbon atoms, preferably 6- to 10-membered, such as phenyl and naphthyl, most preferably phenyl. The aryl ring may be fused with a heteroaryl, heterocyclic or cycloalkyl ring. Unrestricted examples include but are not limited to:



[0014] "Heteroaryl or heteroaryl ring" refers to a heteroaromatic system containing 5 to 14 annular atoms, of which 1 to 4 annular atoms are selected from heteroatoms including O, S and N. Heteroaryl preferably is 5- to 10-membered, and more preferably 5- or 6-membered, such as furyl, thienyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, pyrazolyl, imidazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl and isoindolyl. The heteroaryl ring may be fused with an aryl, heterocyclyl or cycloalkyl ring. Unrestricted examples include but are not limited to:



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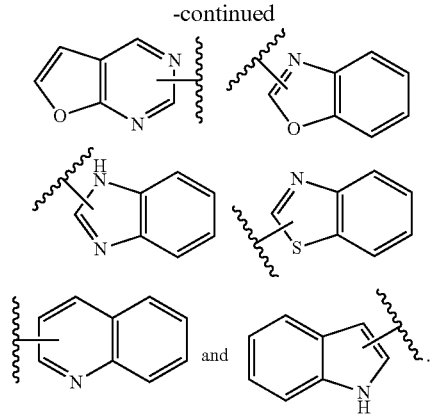


[0015] "Halogen" refers to F, Cl, Br, or I.

[0016] "Cyano" refers to —CN.

[0017] "Optional" means that the event or environment described later may but need not occur, and the expression includes the occurrence or non-occurrence of the event or environment. For example, "heterocyclic optionally substituted by an alkyl group" includes the case where the heterocyclic is substituted by an alkyl group and the case where the heterocyclic is not substituted by an alkyl group.

[0018] "Substitution" refers to one or more hydrogen atoms in a group, for example, 1 to 3 hydrogen atoms that are independently substituted by a corresponding number of substituents. The substituents are located only in their possible chemical positions understood by those skilled in the art. The substituents include but are not limited to halogen, hydroxyl, cyano, nitro, oxo, —SFS, C_{1-4} alkyl, C_{1-4} alkoxyl, etc.

[0019] "Isomers" refer to compounds that have the same molecular formula, but their atomic binding position or spatial arrangement is different. Isomers with different arrangement of their atoms in space are called "stereoisomers". Stereoisomers include optical isomers, geometric isomers, and conformational isomers.

[0020] Compounds of the present invention can exist as optical isomers. Optical isomers include enantiomers and diastereomers. An enantiomer is one of two stereoisomers that are mirror images of each other and are non-superposable. A racemic mixture or racemate is one that has equal amounts of left- and right-handed enantiomers of a chiral molecule. Diastereomers are stereoisomers that are not mirror images of one another and are non-superimposable on one another. When a compound is a single isomer and its absolute configuration is determined, it is referred as a "R" or "S" isomer according to the configuration of the substituents around the chiral carbon atom. When its absolute configuration is not determined, it is referred as a (+) or (−) isomer according to its measured optical rotation value. Methods for preparing and separating optical isomers are known to those skilled in the art.

[0021] Compounds of the present invention may also have geometric isomers resulting from the distribution of substituents around carbon-carbon double bonds, carbon-nitrogen double bonds, cycloalkyl or heterocyclyl groups. The substituents around the carbon-carbon double bond or carbon-nitrogen bond are designated to be in a Z or E configuration, and the substituents around the cycloalkyl or heterocycle are designated to be in a cis or trans configuration.

[0022] Compounds of the present invention may also show tautomerism, such as keto-enol tautomerism.

[0023] The present invention includes any tautomeric or stereoisomeric forms and mixtures thereof and is not limited to any tautomeric or stereoisomeric forms used in the compound nomenclature or chemical structural formulae.

[0024] "Isotopes" include all stable isotopes of the atoms appearing in the compounds of the present invention. Isotopes include those atoms with the same atomic number but in different masses. Examples of isotopes suitable for incorporation into the compounds of the present invention are isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, for example but not limited to ^{2}H (D), ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl. The isotopically labeled compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by methods similar to those described in the embodiments using appropriate isotopically labeled reagents instead of non-isotopically labeled reagents. Such compounds have various potential uses, for example, as standards and reagents in the determination of biological activities. In the case of stable isotopes, such compounds have the potential to beneficially alter biological, pharmacological, or pharmacokinetic properties. Deuterium ^{2}H (D) is a preferable isotope of the present invention. For example, hydrogen in methyl, methylene or methine can be replaced by deuterium.

[0025] Compounds of the present invention can be administered in form of prodrugs. "Prodrugs" refer to derivatives that are converted into biologically active compounds under the physiological condition in vivo, for example, by oxidation, reduction, and hydrolysis (each of which occurs with or without the participation of enzymes). Examples of a prodrug are a compound of the present invention in which an amino is acylated, alkylated or phoshorylated, for example eicosanoyl amino, alanyl amino and pivaloyloxymethyl amino; a hydroxyl is acylated, alkylated or phoshorylated or converted into borate, for example acetoxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaroyloxy and alanyloxy; a carbonyl is esterified or amidated; and a thiol forms a disulfide bridge with a carrier molecule that selectively delivers the drug to the target and/or to the cytosol of cells, such as peptide. Prodrugs may be prepared from the compounds of the present invention according to well-known methods.

[0026] "Pharmaceutically acceptable salts" refer to the salts made from compounds of the present invention with pharmaceutically acceptable bases or acids, including inorganic alkalis or acids and organic bases or acids, under the condition that the compounds contain one or more acidic or basic groups. Compounds of the present invention that contain acidic groups can exist in form of salts, for example, as alkali metal salts, alkaline earth metal salts, or ammonium salts. For example, such salts include sodium salts, potassium salts, calcium salts, magnesium salts or ammonia or organic amine salts such as salts of ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the present invention that contain basic groups can exist in form of salts as inorganic or organic acid salts. Examples of suitable acids include hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalene disulfonic acid, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propanoic acid, pivalic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfamic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid and other acids known to those skilled in the art. If compounds of the present invention contain both acidic and basic groups in the molecule, the present invention further includes internal salts in addition to the mentioned salt forms. Each salt can be obtained by conventional methods known to those skilled in the art, for example by mixing a compound of the present invention with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with another salt.

[0027] "Pharmaceutical composition" refers to a composition containing one or more of compounds of the present invention or their pharmaceutically acceptable salts, stable isotope derivatives, isomers, prodrugs, and mixtures thereof, and other components such as pharmaceutically acceptable carrier and excipients.

[0028] "Cancer or lymphoma or leukemia" includes but is not limited to B-cell malignancies, B-cell lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, non-Hodgkin Lymphoma (such as ABC-DLBCL), mantle cell lymphoma, follicular lymphoma, Waldenstrom's macroglobulinemia, marginal zone lymphoma, central nervous system lymphoma, chronic lymphocytic lymphoma, B-cell prelymphocytic leukemia, plasma cell lymphoma, multiple myeloma, various solid tumors (such as melanoma, bone cancer, brain cancer, colon cancer, liver cancer, skin cancer, kidney cancer, lung cancer, muscle cancer, bladder cancer, digestive tract/stomach Intestinal cancer, breast cancer, ovarian cancer, head and neck cancer, prostate cancer), etc.

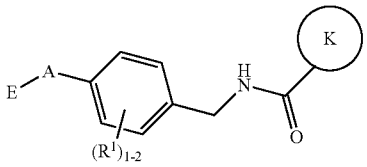
[0029] "Autoimmune or inflammatory disease" includes but is not limited to arthritis, multiple sclerosis, osteoporosis, inflammatory bowel disease, colitis, Crohn's disease, lupus, rheumatoid Arthritis, psoriatic arthritis, lupus nephritis, Sjogren's syndrome, IgG4-related diseases, idiopathic thrombocytopenic purpura, immune thrombocytopenia, Wright's syndrome, psoriasis, Behcet's disease, asthma, Pemphigus, diabetes, myasthenia gravis, Guillain-Barre syndrome, Graves' disease, Hashimoto's thyroiditis, vasculitis, autoimmune vasculitis, granuloma with multiple vasculitis, autoimmune hepatitis, etc.

[0030] "Therapeutically effective amount" refers to an amount of compounds of the present invention that can effectively inhibit activities of BTK and its C481 mutant, and/or treat or prevent the diseases mediated by BTK and its C481 mutant.

[0031] "Patients" refer to mammals, preferably humans.

[0032] The present invention are directed to compounds with a structure as shown in Formula (I) as reversible BTK inhibitors, which effectively inhibit the activities of BTK and its C481 mutant, thereby overcoming the drug resistance caused by the C481 mutation associated with irreversible BTK inhibitors.

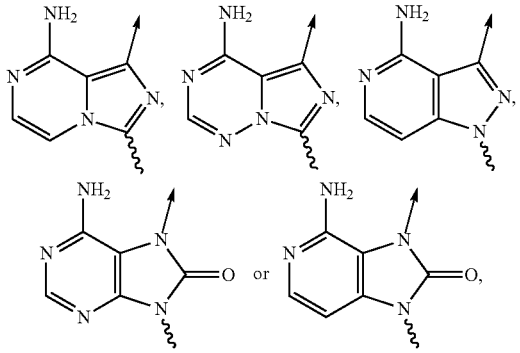
[0033] The present invention provides heterocyclic compounds as shown in Formula (I) or their pharmaceutically acceptable salts, stable isotope derivatives, isomers, and prodrugs thereof,



(I)

[0034] where:

[0035] A is



[0036] where → indicates that A is connected to the benzene ring and ∿∿ indicates that A is connected to E;

[0037] Ring K is phenyl or pyridyl, where the phenyl and pyridyl are optionally substituted by one or more substituents selected from halogen, cyano, C_{1-6} alkyl or —OR^a;

[0038] E is C_{1-6} alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl or 5-10 membered heteroaryl, where the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted by one or more substituents selected from D, halogen, cyano, —OR^b, —NR^bR^c, —$COOR^b$, —$C(O)R^b$, —$C(O)NR^bR^c$ or R^e;

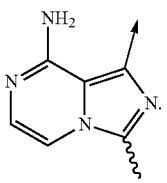
[0039] R^e is C_{1-6} alkyl, C_{3-10} cycloalkyl or 3-10 membered heterocyclyl, where one or more hydrogens of the alkyl, cycloalkyl and heterocyclyl are optionally substituted by halogen, cyano, —OR^b, —NR^bR^c, —$COOR^b$, —$C(O)R^b$ or —$C(O)NR^bR^c$;

[0040] R^1 is H, halogen, —OR^a or C_{1-6} alkyl;

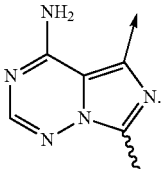
[0041] R^a is C_{1-6} alkyl, where one or more hydrogens of the alkyl are optionally substituted by D or fluorine; and

[0042] R^b and R^c are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 4-6 membered heterocyclyl.

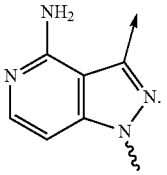
[0043] In one embodiment, A is



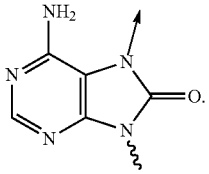
[0044] In one embodiment, A is



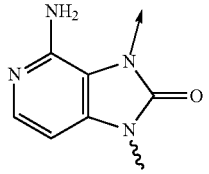
[0045] In another embodiment, A is



[0046] In another embodiment, A is

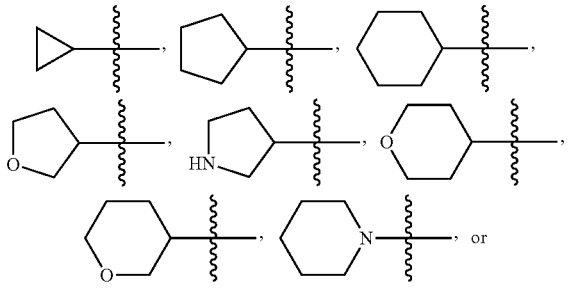


[0047] In another embodiment, A is



[0048] In one embodiment, E is C_{1-6} alkyl, wherein one or more hydrogens of the alkyl are optionally substituted by D or fluorine, for example —$CH(CH_3)(CF_3)$.

[0049] In one embodiment, E is C_{3-7} monocyclic cycloalkyl or 4-8 membered monocyclic heterocyclyl containing N and/or O. For example, E is



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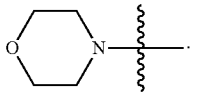
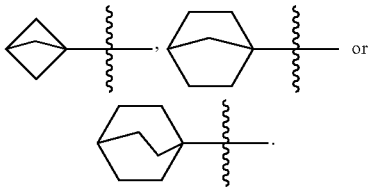
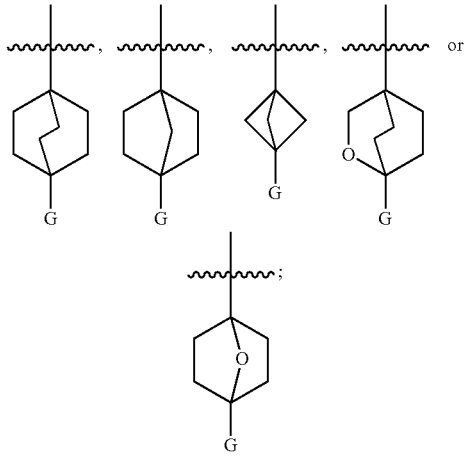


[0050] In one embodiment, E is C_{5-10} polycyclic cycloalkyl or 5-10 membered polycyclic heterocyclyl containing O. For example, E is



[0051] The monocyclic cycloalkyl, polycyclic cycloalkyl, monocyclic heterocyclyl, and polycyclic heterocyclyl are independently and optionally substituted by one or more substituents selected from D, halogen, —OR^b, —NR^bR^c, —$COOR^b$, —$C(O)R^b$, —$C(O)NR^bR^c$ or C_{1-6} alkyl, where one or more hydrogens of the alkyl are further optionally substituted by halogen, —OR^b or —NR^bR^c; R^b and R^c are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 4-6 containing N and/or O containing heterocyclic group (e.g., morpholinyl).

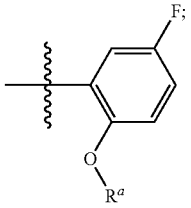
[0052] In a preferred embodiment, E is



G is H, fluorine, —OR^b, —NR^bR^c, —$COOR^b$, —$C(O)R^b$, —$C(O)NR^bR^c$ or C_{1-2} alkyl, where one or more hydrogens of the alkyl group are optionally substituted by fluorine, —OH or —NH_2; R^b and R^c are each independently selected from H, C_{1-2} alkyl, C_{3-6} cycloalkyl or N and/or O containing 4-6 membered heterocyclyl (for example, morpholinyl).

[0053] In a preferred embodiment, ring K is phenyl, where the phenyl is optionally substituted by one or two substituents selected from halogen or —OR^a; R^a is C_{1-2} alkyl, where one or more hydrogens of the alkyl is optionally substituted by D.

[0054] For example, ring K is



R^a is a C_{1-2} alkyl group, where one or more hydrogens of the alkyl are optionally substituted by D.

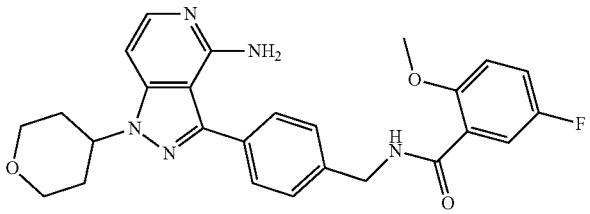
[0055] In one embodiment, R^1 is H.

[0056] In another embodiment, R^1 is halogen.

[0057] In one embodiment, the present invention relates to compounds that are have a substantial brain penetration and have a blood-brain barrier permeability.

[0058] In one embodiment, the present invention relates to CNS penetrant compounds that have CSF/plasma concentration ratio Kp, CSF≥0.15.

[0059] The present invention further relates to the following Compounds 1-29, and 31-54, or their pharmaceutically acceptable salts, prodrugs, stable isotope derivatives, isomers and mixtures thereof.

Compound No.	Compound Structure and Chemical Name
1.	 N-(4-(4-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide

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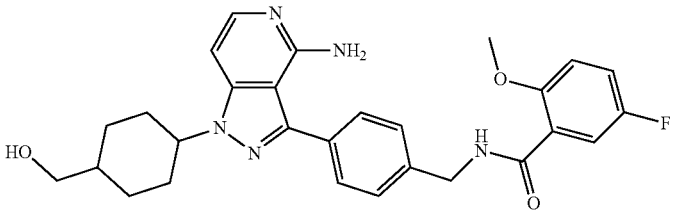
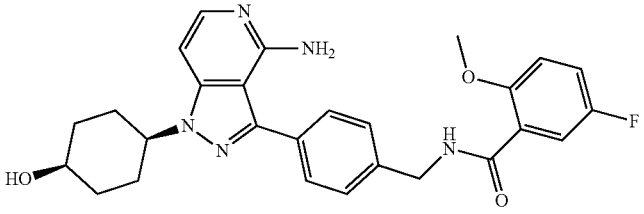
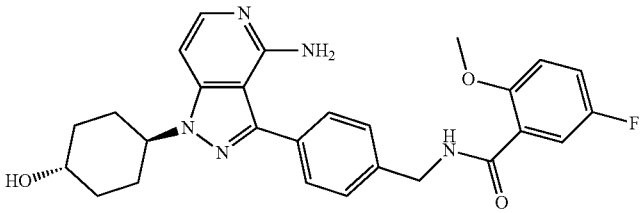
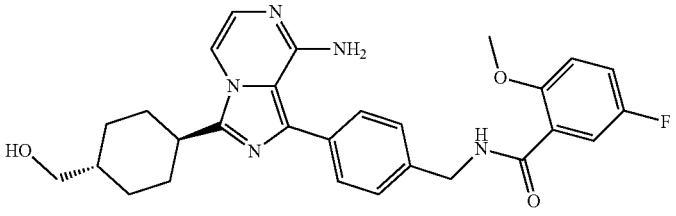
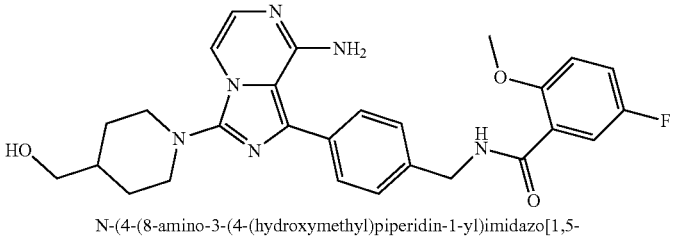
Compound No.	Compound Structure and Chemical Name
2.	 N-(4-(4-amino-1-(4-(hydroxymethyl)cyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide
3.	 N-(4-(4-amino-1-((1s,4s)-4-hydroxycyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide
4.	 N-(4-(4-amino-1-((1r,4r)-4-hydroxycyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide
5.	 N-(4-(8-amino-3-((1r,4r)-4-(hydroxymethyl)cyclohexyl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide
6.	 N-(4-(8-amino-3-(4-(hydroxymethyl)piperidin-1-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide

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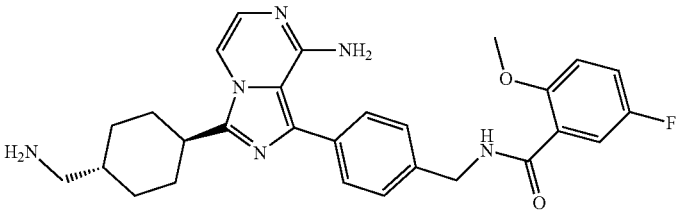
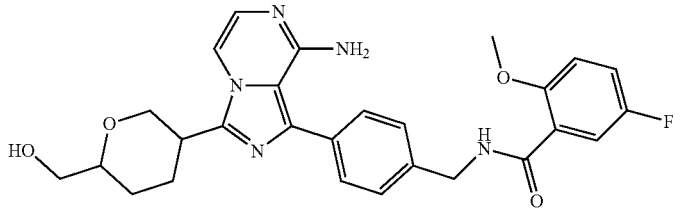
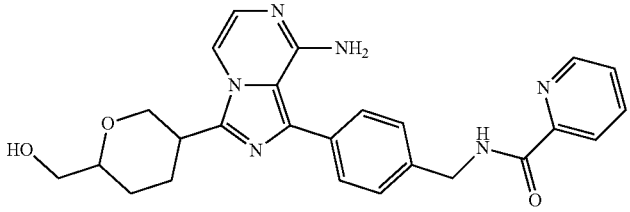
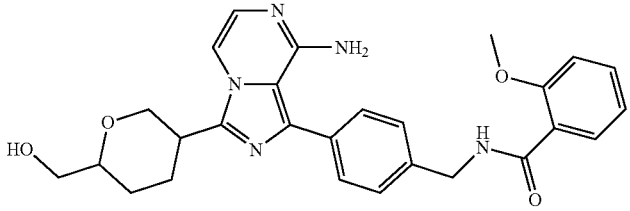
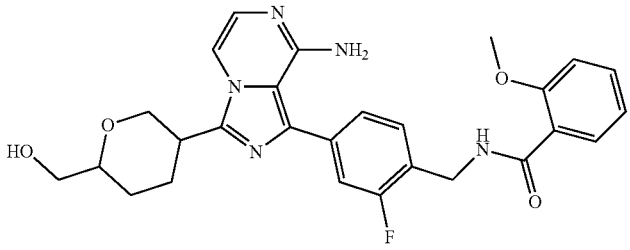
Compound No.	Compound Structure and Chemical Name
7.	 N-(4-(8-amino-3-((1r,4r)-4-(aminomethyl)cyclohexyl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide
8.	 N-(4-(8-amino-3-(6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide
9.	 N-(4-(8-amino-3-(6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)picolinamide
10.	 N-(4-(8-amino-3-(6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-2-methoxybenzamide
11.	 N-(4-(8-amino-3-(6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluorobenzyl)-2-methoxybenzamide

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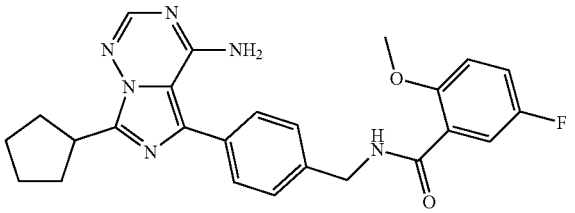
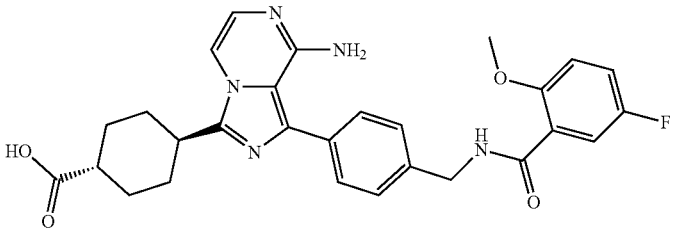
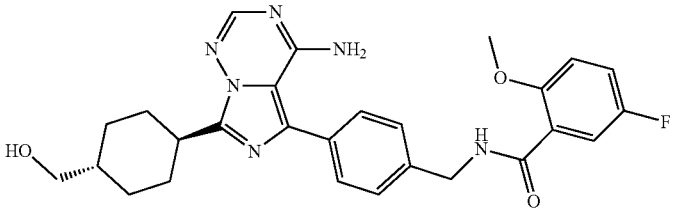
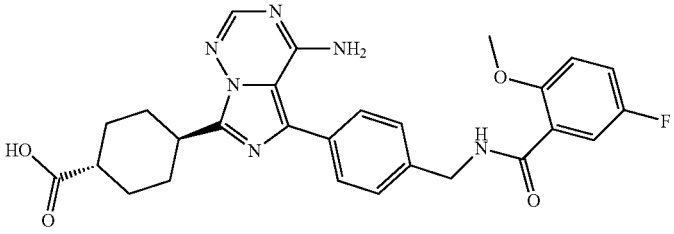
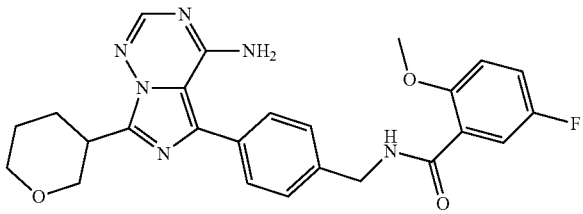
Compound No.	Compound Structure and Chemical Name
12.	 N-(4-(4-amino-7-cyclopentylimidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide
13.	 (1r,4r)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)cyclohexane-1-carboxylic acid
14.	 N-(4-(4-amino-7-((1r,4r)-4-(hydroxymethyl)cyclohexyl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide
15.	 (1r,4r)-4-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)cyclohexane-1-carboxylic acid
16.	 N-(4-(4-amino-7-(tetrahydro-2H-pyran-3-yl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide

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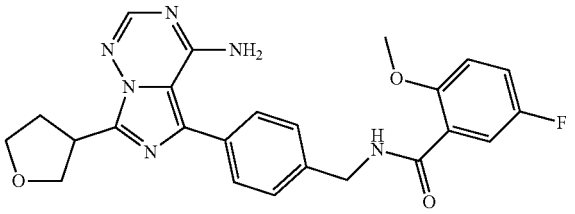
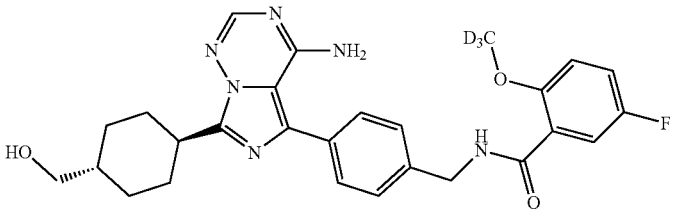
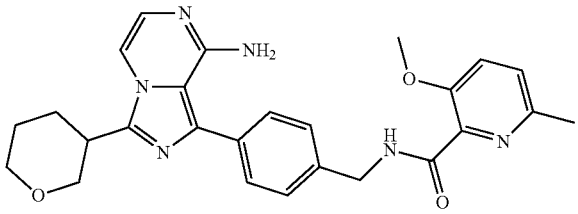
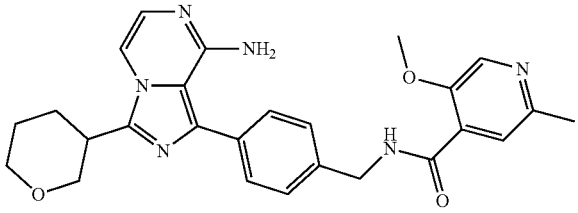
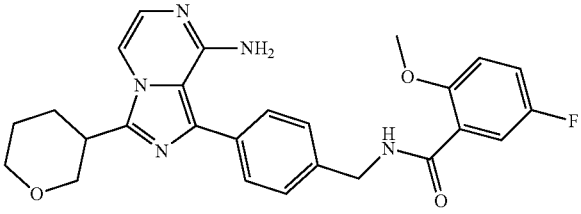
Compound No.	Compound Structure and Chemical Name
17.	 N-(4-(4-amino-7-(tetrahydrofuran-3-yl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide
18.	 N-(4-(4-amino-7-((1r,4r)-4-(hydroxymethyl)cyclohexyl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-(methoxy-d_3)benzamide
19.	 N-(4-(8-amino-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-3-methoxy-6-methylpicolinamide
20.	 N-(4-(8-amino-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-methoxy-2-methylisonicotinamide
21.	 N-(4-(8-amino-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide

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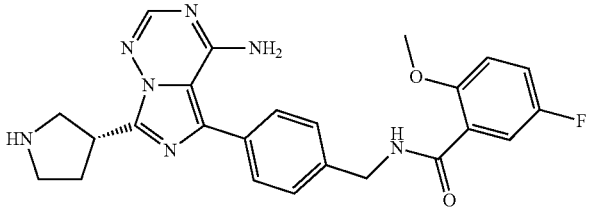
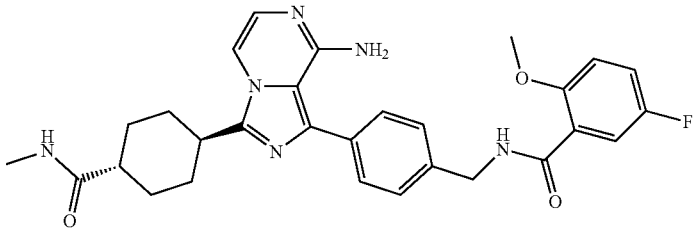
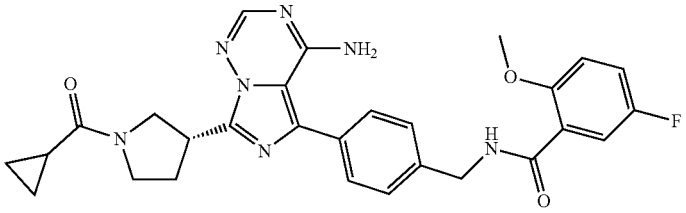
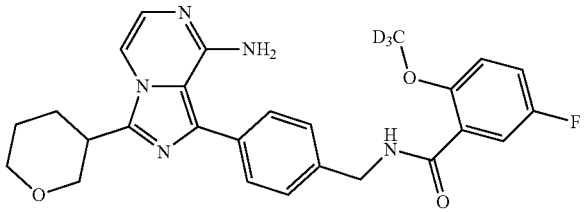
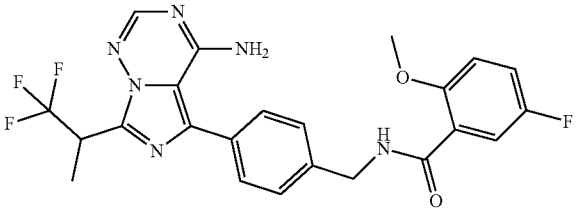
Compound No.	Compound Structure and Chemical Name
22.	 (R)-N-(4-(4-amino-7-(pyrrolidin-3-yl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide
23.	 N-(4-(8-amino-3-((1r,4r)-4-(methylcarbamoyl)cyclohexyl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide
24.	 (R)-N-(4-(4-amino-7-(1-(cyclopropanecarbonyl)pyrrolidin-3-yl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide
25.	 N-(4-(8-amino-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-(methoxy-dz)benzamide
26.	 N-(4-(4-amino-7-(1,1,1-trifluoropropan-2-yl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide

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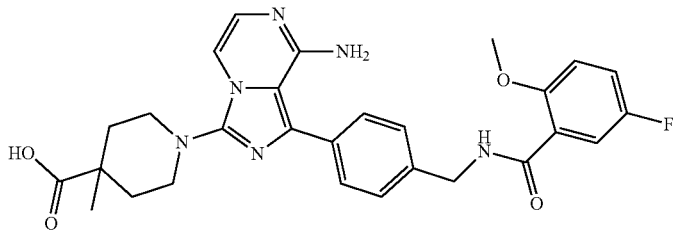
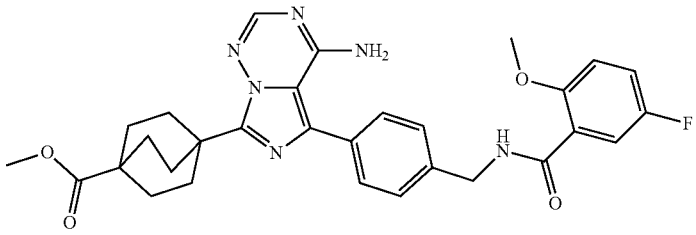
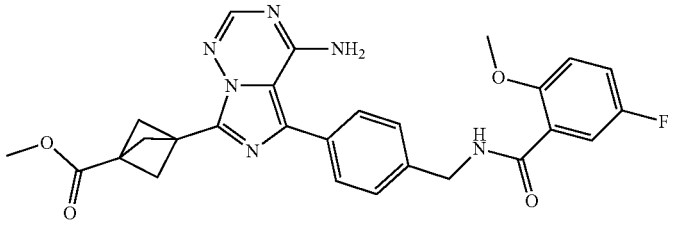
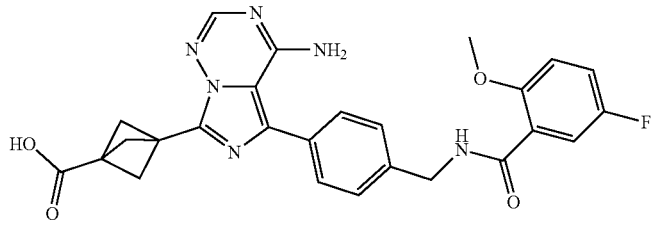
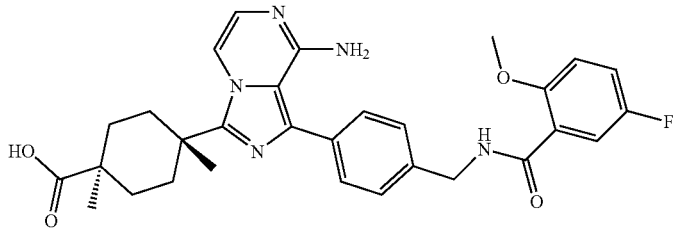
Compound No.	Compound Structure and Chemical Name
27.	 1-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-4-methylpiperidine-4-carboxylic acid
28.	 methyl 4-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)bicyclo[2.2.2]octane-1-carboxylate
29.	 methyl 3-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)bicyclo[1.1.1]pentane-1-carboxylate
31.	 3-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)bicyclo[1.1.1]pentane-1-carboxylic acid
32.	 (1r,4r)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-1,4-dimethylcyclohexane-1-carboxylic acid

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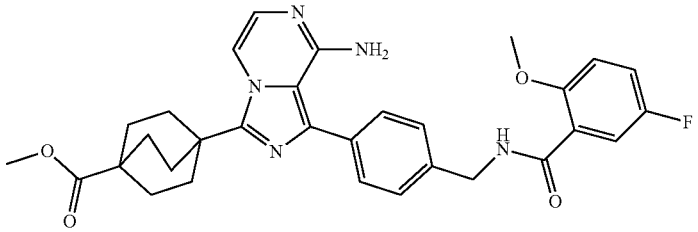
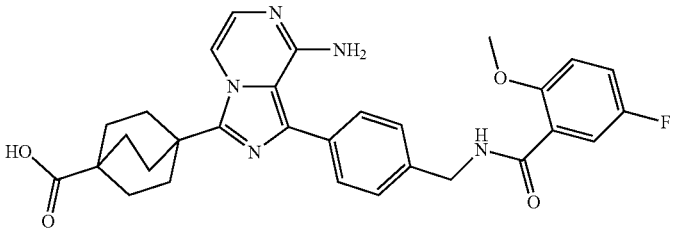
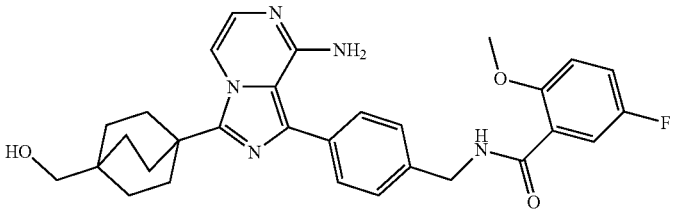
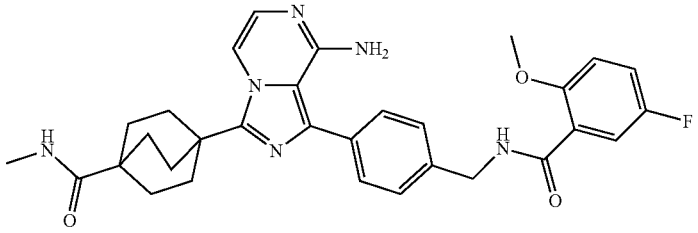
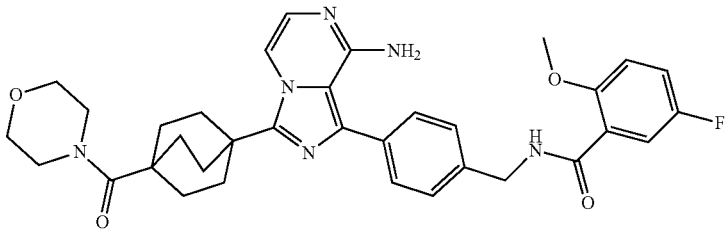
Compound No.	Compound Structure and Chemical Name
33.	 methyl 4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)bicyclo[2.2.2]octane-1-carboxylate
34.	 4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)bicyclo[2.2.2]octane-1-carboxylic acid
35.	 N-(4-(8-amino-3-(4-(hydroxymethyl)bicyclo[2.2.2]octan-1-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide
36.	 4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-N-methylbicyclo[2.2.2]octane-1-carboxamide
37.	 N-(4-(8-amino-3-(4-(morpholine-4-carbonyl)bicyclo[2.2.2]octan-1-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide

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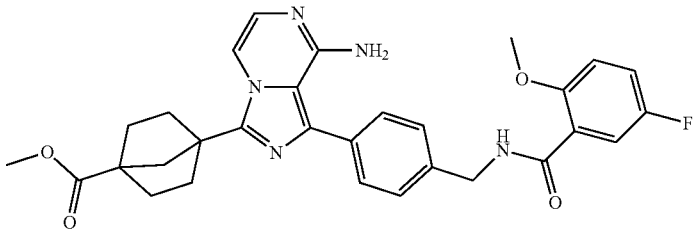
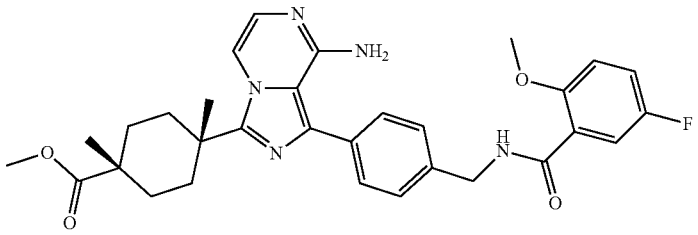
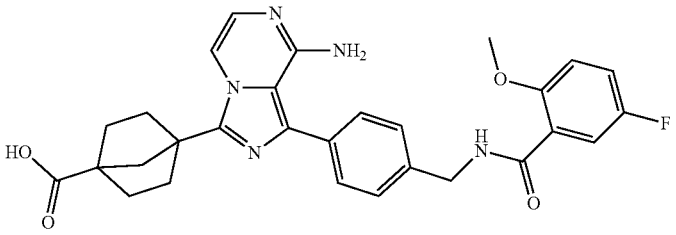
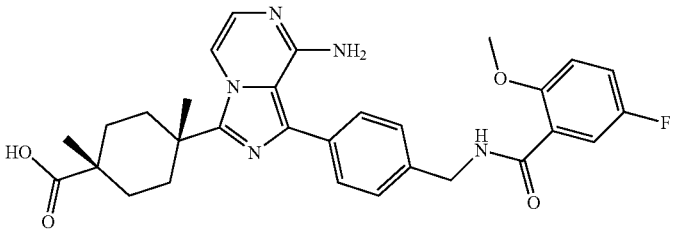
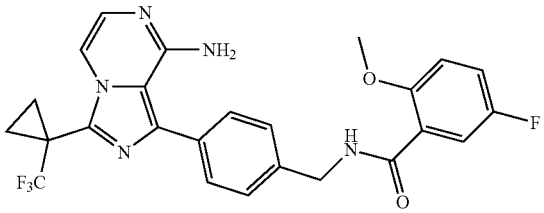
Compound No.	Compound Structure and Chemical Name
38.	 methyl 4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)bicyclo[2.2.1]heptane-1-carboxylate
39.	 methyl (1s,4s)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-1,4-dimethylcyclohexane-1-carboxylate
40.	 4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)bicyclo[2.2.1]heptane-1-carboxylic acid
41.	 (1s,4s)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-1,4-dimethylcyclohexane-1-carboxylic acid
42.	 N-(4-(8-amino-3-(1-(trifluoromethyl)cyclopropyl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide

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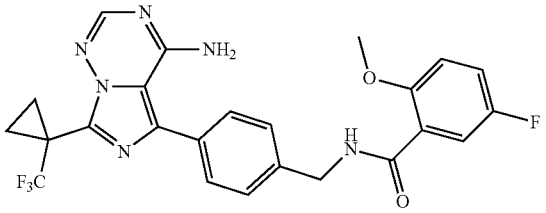
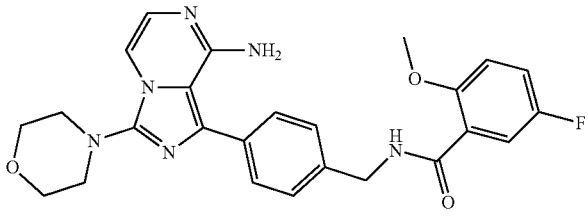
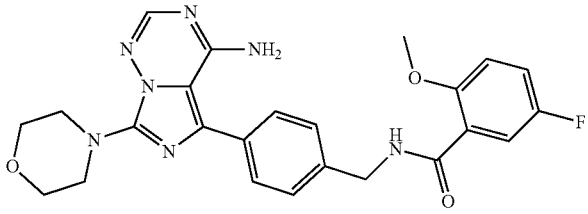
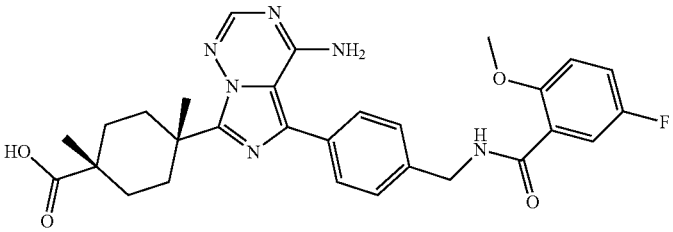
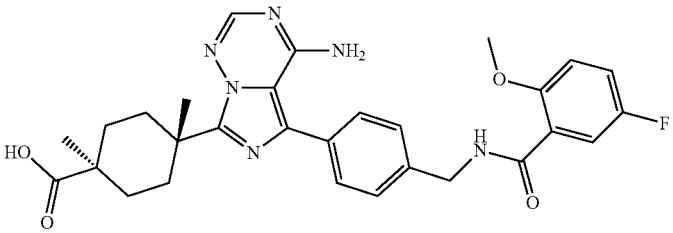
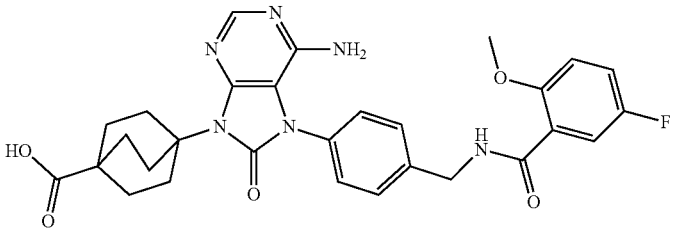
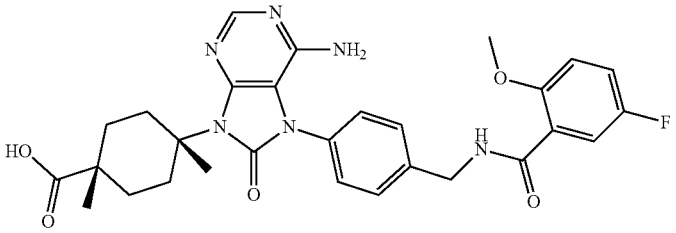
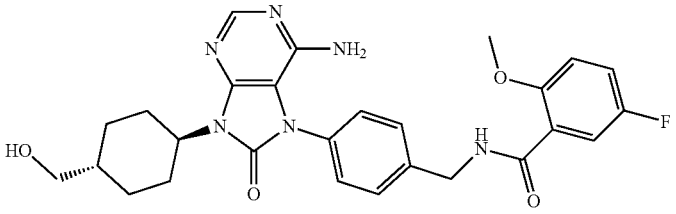
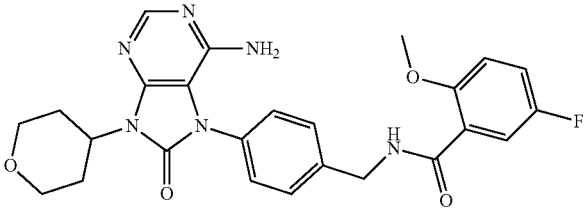
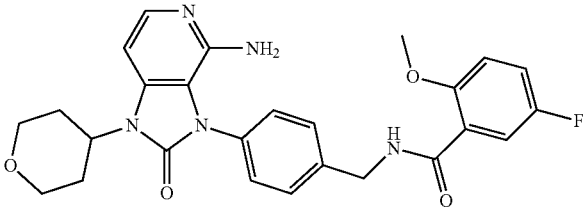
Compound No.	Compound Structure and Chemical Name
43.	 N-(4-(4-amino-7-(1-(trifluoromethyl)cyclopropyl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide
44.	 N-(4-(8-amino-3-morpholinoimidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide
45.	 N-(4-(4-amino-7-morpholinoimidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide
46.	 (1s,4s)-4-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)-1,4-dimethylcyclohexane-1-carboxylic acid
47.	 (1r,4r)-4-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)-1,4-dimethylcyclohexane-1-carboxylic acid

-continued

Compound No.	Compound Structure and Chemical Name
48.	 4-(6-amino-7-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-8-oxo-7,8-dihydro-9H-purin-9-yl)bicyclo[2.2.2]octane-1-carboxylic acid
49.	 (1s,4s)-4-(6-amino-7-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-8-oxo-7,8-dihydro-9H-purin-9-yl)-1,4-dimethylcyclohexane-1-carboxylic acid
50.	 N-(4-(6-amino-9-((1r,4r)-4-(hydroxymethyl)cyclohexyl)-8-oxo-8,9-dihydro-7H-purin-7-yl)benzyl)-5-fluoro-2-methoxybenzamide
51.	 N-(4-(6-amino-8-oxo-9-(tetrahydro-2H-pyran-4-yl)-8,9-dihydro-7H-purin-7-yl)benzyl)-5-fluoro-2-methoxybenzamide
52.	 N-(4-(4-amino-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-1,2-dihydro-3H-imidazo[4,5-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide

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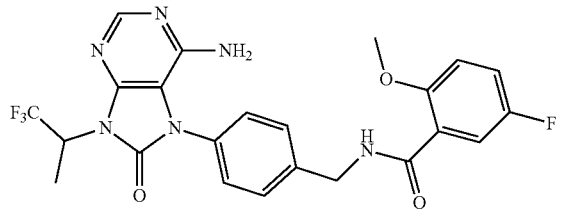
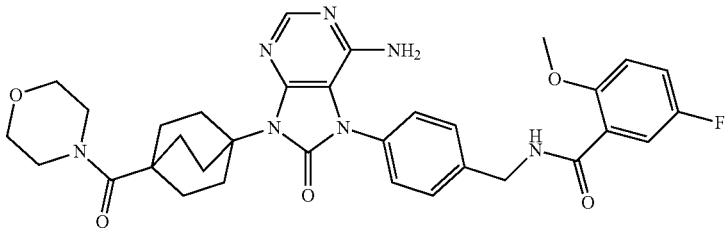
Compound No.	Compound Structure and Chemical Name
53.	 N-(4-(6-amino-8-oxo-9-(1,1,1-trifluoropropan-2-yl)-8,9-dihydro-7H-purin-7-yl)benzyl)-5-fluoro-2-methoxybenzamide
54.	 N-(4-(6-amino-9-(4-(morpholine-4-carbonyl)bicyclo[2.2.2]octan-1-yl)-8-oxo-8,9-dihydro-7H-purin-7-yl)benzyl)-5-fluoro-2-methoxybenzamide

[0060] Compounds of the present invention effectively inhibit the activities of BTK and its C481 mutant, preferably having an IC_{50} of less than 100 nM, and more preferably less than 10 nM.

[0061] The present invention also relates to pharmaceutical compositions comprising compounds of Formula (I) or their pharmaceutically acceptable salts, stable isotope derivatives, isomers and prodrugs thereof, and one or more pharmaceutically acceptable carriers or excipients.

[0062] The present invention further relates to a pharmaceutical composition comprising a compound of Formula (I) or its pharmaceutically acceptable salt, stable isotope derivative, isomer, prodrug and a mixture thereof, and at least one additional therapeutic agent, wherein the agent may be a small molecule chemotherapeutic drug (such as anti-inflammatory steroid drug, kinase targeting drug, apoptosis inhibitor, inflammation modulator, cytotoxic drug, DNA damage related drug) or a macromolecular immune and/or inflammation modulator (such as CD-20 antibody, CD19 antibody, PD-1 antibody).

[0063] Compounds of Formula (I) and another therapeutic agent may be present in the same pharmaceutical composition or in different pharmaceutical compositions. Compounds of Formula (I) and another agent may be administered simultaneously or sequentially in the same or different forms.

[0064] The present invention provides a method for treating or preventing diseases mediated by BTK or its C481 mutant. The method comprises administering to a patient in need a therapeutically effective amount of compounds of Formula (I) or their pharmaceutically acceptable salts, stable isotope derivatives, isomers, prodrugs and mixtures thereof, or pharmaceutical compositions containing compounds of Formula (I). The diseases include but are not limited to cancer, lymphoma, leukemia, autoimmune or inflammation diseases, such as B-cell malignancies, B-cell lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, non-Hodgkin's lymphoma (such as ABC-DLBCL), mantle cell lymphoma, follicular lymphoma, Waldenstrom's macroglobulinemia, marginal zone lymphoma, central nervous system lymphoma, chronic lymphocytic lymphoma, B-cell prelymphocytic leukemia, plasma cell lymphoma, multiple myeloma, various solid tumors (such as lung cancer, prostate cancer, head and neck cancer, breast cancer, ovarian cancer, uterine cancer, pancreatic cancer, colon cancer, rectal cancer, stomach cancer, esophageal cancer, brain cancer, liver cancer, kidney cancer, skin cancer, muscle cancer, epithelial cancer, bladder cancer, neuroblastoma, melanoma, bone cancer, melanoma), arthritis, multiple sclerosis, osteoporosis, inflammatory bowel disease, colitis, Crohn's disease, lupus, rheumatoid arthritis, psoriatic arthritis, lupus nephritis, Sjogren's syndrome, IgG4-related diseases, idiopathic thrombocytopenic purpura, immune thrombocytopenia, Wright syndrome, psoriasis, Behcet's disease, asthma, pemphigus, diabetes, myasthenia gravis, Guillain-Barre syndrome, Graves' disease, Hashimoto's thyroiditis, vasculitis, autoimmune vasculitis, granuloma with multiple vasculitis, autoimmune hepatitis, especially B-cell lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, non-Hodgkin's lymphoma (such as ABC-DLBCL), mantle cell lymphoma, filtration alveolar lymphoma, Waldenstrom's macroglobulinemia, marginal zone lymphoma, central nervous system lymphoma, chronic lymphocytic lymphoma, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, lupus nephritis, dryness Syndrome, IgG4-related diseases, idiopathic thrombocytopenic purpura, immune thrombocytopenia, pemphigus, urticaria, etc.

[0065] According to the present invention, the pharmaceutical composition may be in any dosage form, including but not limited to tablets, capsules, solutions, freeze-dried preparations and injectable.

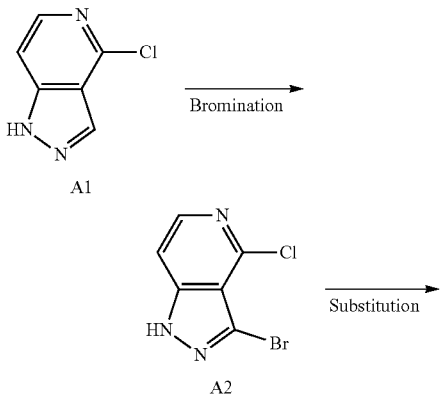
[0066] The pharmaceutical formulation of the present invention may be administered in form of a dosage unit containing a predetermined amount of active ingredient.

Such a unit may contain 1 mg to 1 g, preferably 5 mg to 700 mg, particularly preferably 10 mg to 500 mg of a compound of the present invention, depending on the disease being treated, the method of administration, as well as age, weight, and condition of the patients. The pharmaceutical formulation may be prepared using methods well-known in the pharmaceutical field, for example, by formulating the active ingredient with one or more excipients or one or more adjuvants.

[0067] The pharmaceutical formulation of the present invention is suitable for administration by any appropriate method, such as by oral (including oral or sublingual) or parenteral (including subcutaneous, intramuscular, intravenous, or intradermal).

[0068] The present invention also provides methods for preparing compounds. The preparation of compounds of the present invention may be accomplished by the following exemplary methods and examples, but these methods and examples should not be considered as limitation of the scope of the present invention in any way. Compounds of the present invention may also be synthesized by synthetic techniques known to those skilled in the art or by combinations of methods known in the art and of the present invention. The products obtained at each step of reaction are isolated by separation techniques known in the art, including but not limited to extraction, filtration, distillation, crystallization, and chromatographic separation. The starting materials and chemical reagents used for syntheses may be conventionally made based on literature (for example, SciFinder) or purchased.

[0069] Heterocyclic compounds shown in Formula (I) of the present invention can be synthesized according to the route shown below: 1) bromination of A1 with NBS to give A2; 2) substitution of A2 by a protected amine (for example, 2,4-dimethoxybenzylamine) to give A3; 3) Mitsunobu reaction between A3 and E-OH to provide A4; 4) Suzuki coupling of A4 with a phenylboronic acid to give A5; 5) deprotection of A5 to give A6. A functional group of E can be further derivatized to afford various target compounds. For example, an ester in E can be hydrolyzed by alkali (such as LiOH) to form an acid and E containing protected amine or alcohol can be deprotected to give amine or alcohol, and the amine can be further amidated to afford amides, etc.



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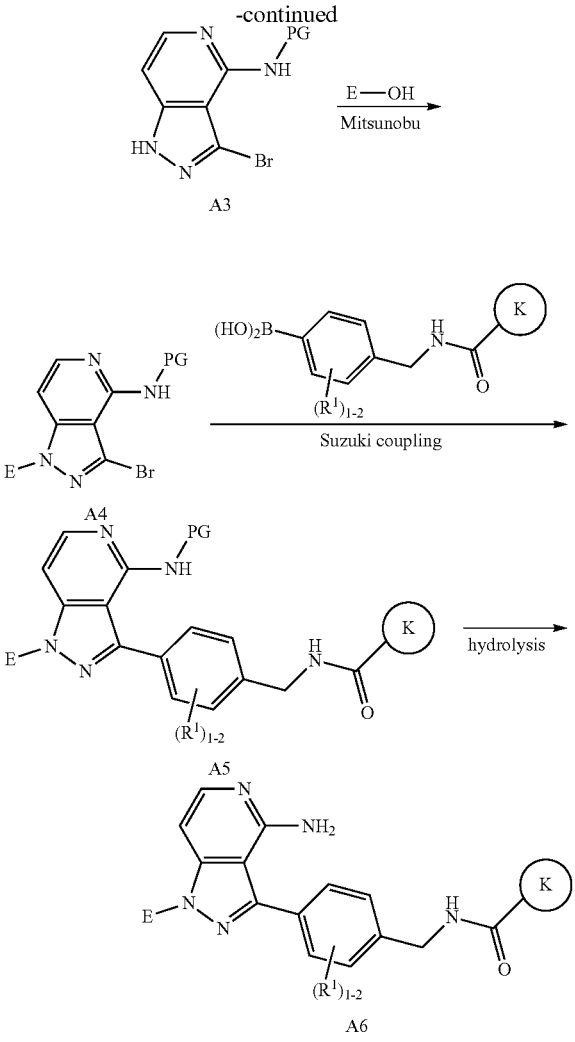
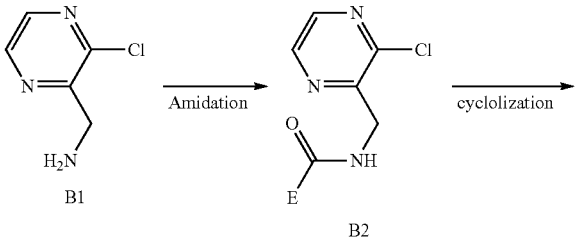


[0070] Heterocyclic compounds shown in Formula (I) of the present invention may also be synthesized according to the route shown below: 1) amide formation between B1 and E-COOH to give B2; 2) cyclization of B2 in phosphine oxychloride under heated to give B3; 3) bromination of B3 with NBS to give B4; 4) substitution of B4 by a protected amine (for example, 2,4-dimethoxybenzylamine) under base catalysis to give B5; 5) Suzuki coupling of B5 with a phenylboronic acid to give B6; 6) deprotection of B6 to give B7. Similarly, a functional group of B7 can be further derivatized to afford various target compounds.



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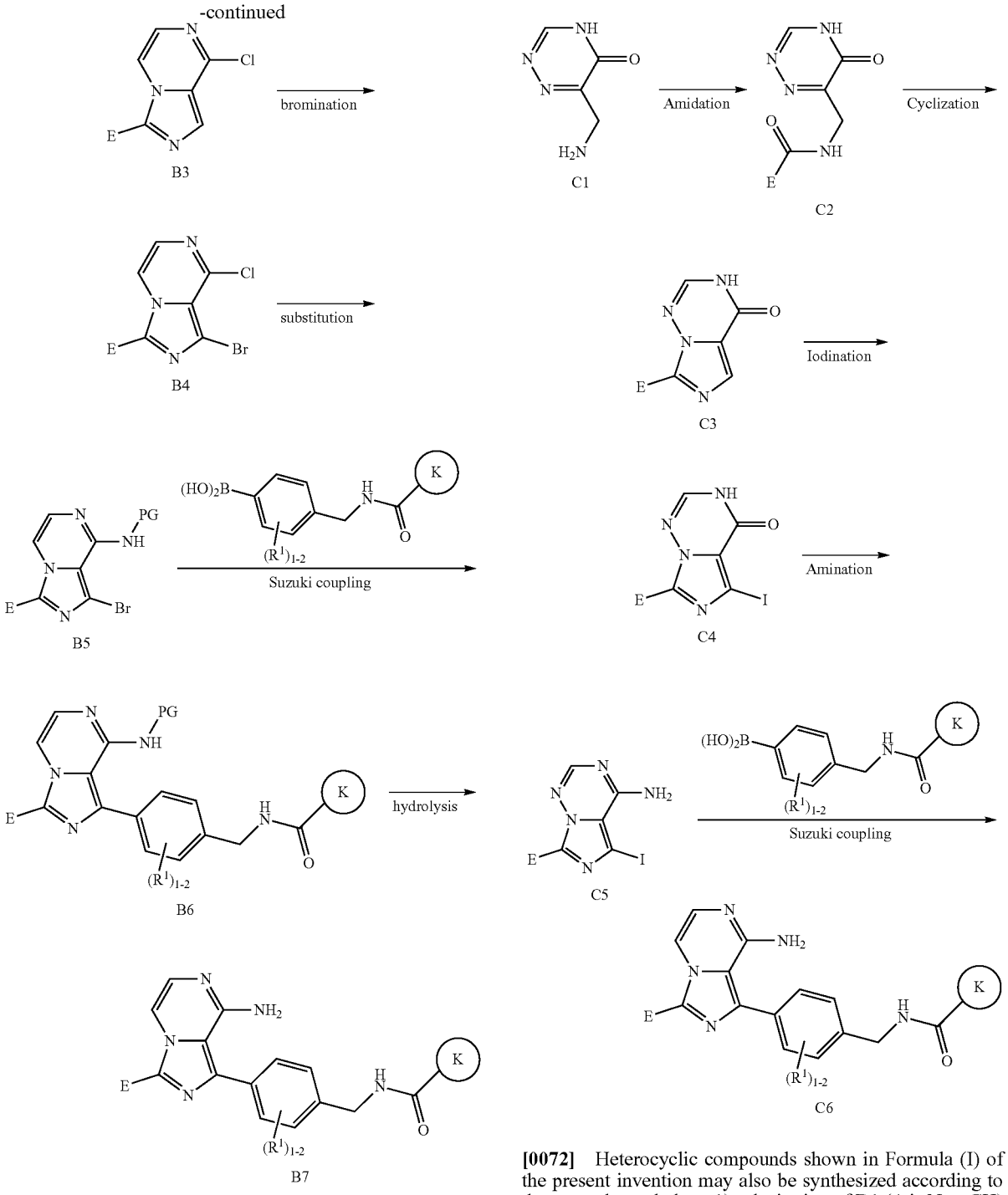
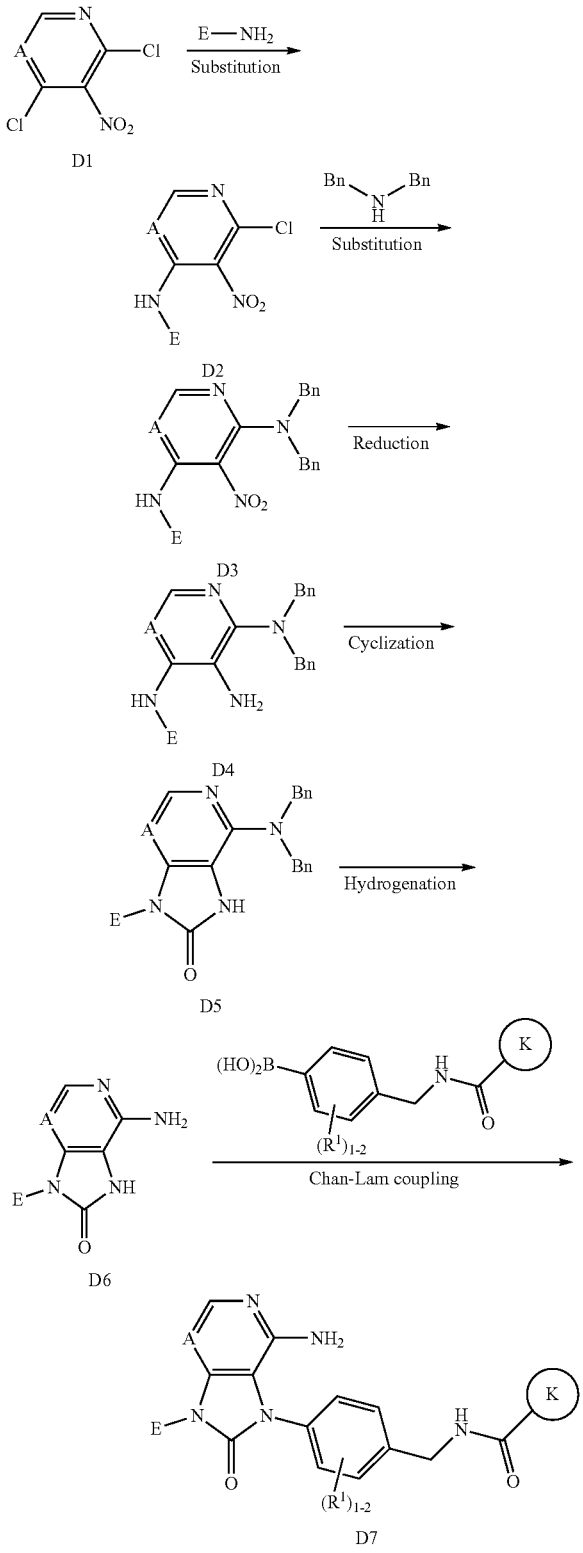


[0071] Heterocyclic compounds shown in Formula (I) of the present invention may also be synthesized according to the route shown below: 1) amide formation of C1 with E-COOH to give C2; 2) cyclization of C2 in phosphine oxychloride under heat to give C3; 3) iodination of C3 with NIS to give C4; 4) amination of C4 to give C5; 5) Suzuki coupling of C5 a phenylboronic acid to give C6. Similarly, a functional group of C6 can be further derivatized to afford various target compounds.

[0072] Heterocyclic compounds shown in Formula (I) of the present invention may also be synthesized according to the route shown below: 1) substitution of D1 (A is N or CH) by E-NH_2 under base catalysis to give D2; 2) further substitution of D2 by a protected amine (such as dibenzylamine) to give D3; 3) reduction of D3 to give D4 (for example, with a reducing agent Zn/NH_4Cl); 4) cyclization of D4 with carbonyl diimidazole or triphosgene in the present of a base (such as NEt_3) to give D5; 5) deprotection of D5 to give D6; 6) Chan-Lam coupling of D6 with a phenylboronic acid to give D7. Similarly, a functional group of D7 can be further derivatized to afford various target compounds.



EXAMPLES

[0073] The starting materials in the present invention were synthesized according to methods known in the art or purchased from ABCR GmbH & Co. KG, Acros Organics, Aldrich Chemical Company, Accela ChemBio Inc., Beijing Ouhe, etc.

[0074] The structure of a compound was determined by nuclear magnetic resonance (NMR) or mass spectrometry (MS). NMR determination used a Bruker ASCEND-400 NMR spectrometer. The solvent for the determination was deuterated dimethyl sulfoxide (DMSO-d_6), deuterated chloroform ($CDCl_3$) or deuterated methanol (CD_3OD). The internal standard was tetramethylsilane (TMS) and the chemical shift was given in a unit of 10^{-6} (ppm). MS determination used an Agilent SQD (ESI) mass spectrometer (Agilent 6120).

[0075] HPLC determination used Agilent 1260 DAD high pressure liquid chromatograph (column: Poroshell 120 EC-C18, 50×3.0 mm, 2.7 μm) or Waters Arc high pressure liquid chromatograph (column: Sunfire C18, 150×4.6 mm, 5 μm).

[0076] Thin layer chromatography (TLC) used GF254 silica gel plates from Qingdao Haiyang Chemical Co., Ltd. with a thickness of 0.15 to 0.2 mm, and the separation/purification of products by thin layer chromatography used silica plates with a thickness 0.4 to 0.5 mm.

[0077] Column chromatography generally used 200 to 300 mesh silica gel from Qingdao Haiyang Chemical Co., Ltd.

[0078] Unless otherwise specified in the examples, reactions were run in room temperature (20-30° C.) and under an atmosphere of argon or nitrogen using a balloon with a volume of about 1 L.

[0079] Hydrogenation was carried out under an atmosphere of hydrogen using a balloon with a volume of about 1 L that was attached to the reaction vessel after being vacuumed and filled with hydrogen repeatedly for 3 times.

[0080] The microwave reaction used a CEM Discover-SP microwave reactor.

[0081] The reaction was monitored using Agilent LCMS (1260/6120) or thin layer chromatography. The solvent eluting systems for column chromatography and TLC included a) dichloromethane/methanol, b) petroleum ether/ethyl acetate, or other systems as indicated. The ratio of the solvents was adjusted according to the polarity of the compound, and further adjusted by addition of a small amount of TEA, or an acidic or alkaline reagent as needed. The compound purification was alternatively done using Waters' MS-guided automated preparation system (abbreviated as prep-HPLC) with a MS detector (SQD2), eluting at a flow rate of 20 mL/min in an appropriate acetonitrile/water (containing 0.1% TFA or formic acid) or acetonitrile/water (containing 0.05% of 25-28% ammonium hydroxide) gradient (XBridge-C18, 19×150 mm, 5 μm). Some compounds were prepared as HCl salts after prep-HPLC purification by addition of 1 N HCl to the collected fractions, followed by drying under reduced pressure.

[0082] The abbreviation DMF refers to N,N-dimethylformamide.

[0083] The abbreviation DIPEA refers to N,N-diisopropylethylamine.

[0084] The abbreviation DBU refers to 1,8-diazabicycloundec-7-ene.

[0085] The abbreviation NBS refers to N-bromosuccinimide.

[0086] The abbreviation NIS refers to N-iodosuccinimide.

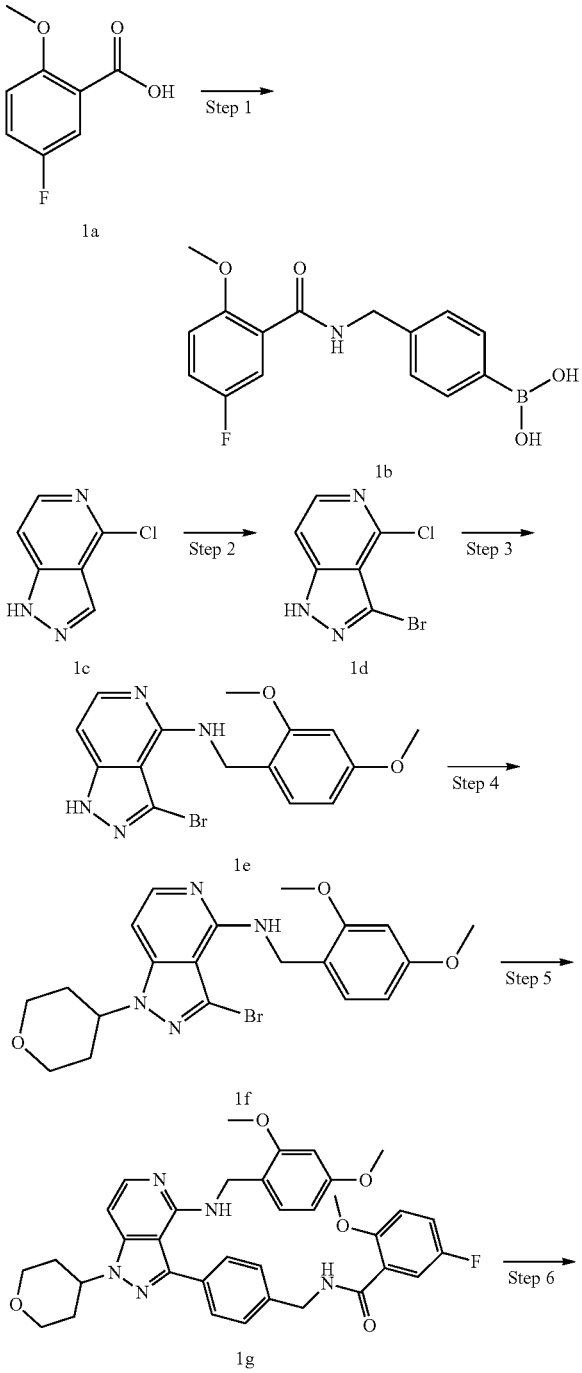
[0087] $Pd(dppf)Cl_2$ refers to [1,1'-bis(diphenylphosphino) ferrocene]dichloropalladium.

[0088] The abbreviation HATU refers to 2-(7-azabenzotriazole)-N,N,N',N'-tetramethylurea hexafluorophosphate.

[0089] The abbreviation LDA refers to lithium diisopropylamide.

Example 1. N-(4-(4-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 1)

[0090]



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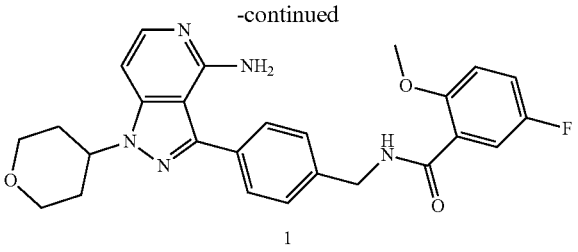


1

Step 1. (4-((5-fluoro-2-methoxybenzamido)methyl) phenyl)boronic acid (1b)

[0091] To a solution of 5-fluoro-2-methoxybenzoic acid 1a (340 mg, 2 mmol) in DMF (0.05 mL) and dichloromethane (10 mL) at 0° C. was added oxalyl chloride (279 mg, 2.2 mmol). The mixture was gradually warmed to room temperature and stirred for 1 hour, then cooled to 0° C. again, followed by addition of a suspension of (4-(aminomethyl) phenyl)boronic acid hydrochloride (374 mg, 2 mmol) and DIPEA (516 mg, 4 mmol) in THE (20 mL). After stirring at room temperature for 15 hours, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and washed with saturated ammonium chloride (50 mL) and brine (50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was dried to give the title compound 1b (460 mg, 76%).

[0092] MS m/z (ESI): 304 [M+1]

Step 2. 3-bromo-4-chloro-1H-pyrazolo[4,3-c]pyridine (1d)

[0093] To a solution of 4-chloro-1H-pyrazolo[4,3-c]pyridine 1c (921 mg, 6 mmol) in acetonitrile (60 mL) was added NBS (1.12 g, 6.3 mmol). After stirring for 5 hours, the solvent was removed under reduced pressure and the residue was dried to give the title compound 1d (2.1 g). The product was used directly in the next step without further purification.

[0094] MS m/z (ESI): 232 [M+1]

Step 3. 3-bromo-N-(2,4-dimethoxybenzyl)-1H-pyrazolo[4,3-c]pyridin-4-amine (1e)

[0095] A mixture of 1d (2.1 g, crude product), 2,4-dimethoxybenzylamine (2 g, 12 mmol) and DIPEA (3.1 g, 24 mmol) in acetonitrile (50 mL) was heated to 120° C. and stirred for 15 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=30/1 to 1/2) to give the title compound 1e (1.2 g, 55% over two steps).

[0096] MS m/z (ESI): 363 [M+1]

Step 4. 3-bromo-N-(2,4-dimethoxybenzyl)-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[4,3-c]pyridin-4-amine (1f)

[0097] To a mixture of 1e (363 mg, 1 mmol), tetrahydro-2H-pyran-4-ol (306 mg, 3 mmol) and triphenylphosphine (524 mg, 2 mmol) in THE (5 mL) was added a solution of diisopropyl azodicarboxylate (404 mg, 2 mmol) in THE (5 mL) dropwise. After stirring for 3 hours, the solvent was

removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 1/1) to give the title compound 1f (220 mg, 49%).

[0098] MS m/z (ESI): 447 [M+1]

Step 5. N-(4-(4-((2,4-dimethoxybenzyl)amino)-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (1g)

[0099] A mixture of 1f (134 mg, 0.3 mmol), 1b (90 mg, 0.3 mmol), potassium carbonate (83 mg, 0.6 mmol) and $PdCl_2$ (dppf) (22 mg, 0.03 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated to 120° C. under a nitrogen atmosphere and stirred for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=20/1 to 1/5) to give the title compound 1g (80 mg, 42%).

[0100] MS m/z (ESI): 626 [M+1]

Step 6. N-(4-(4-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (1)

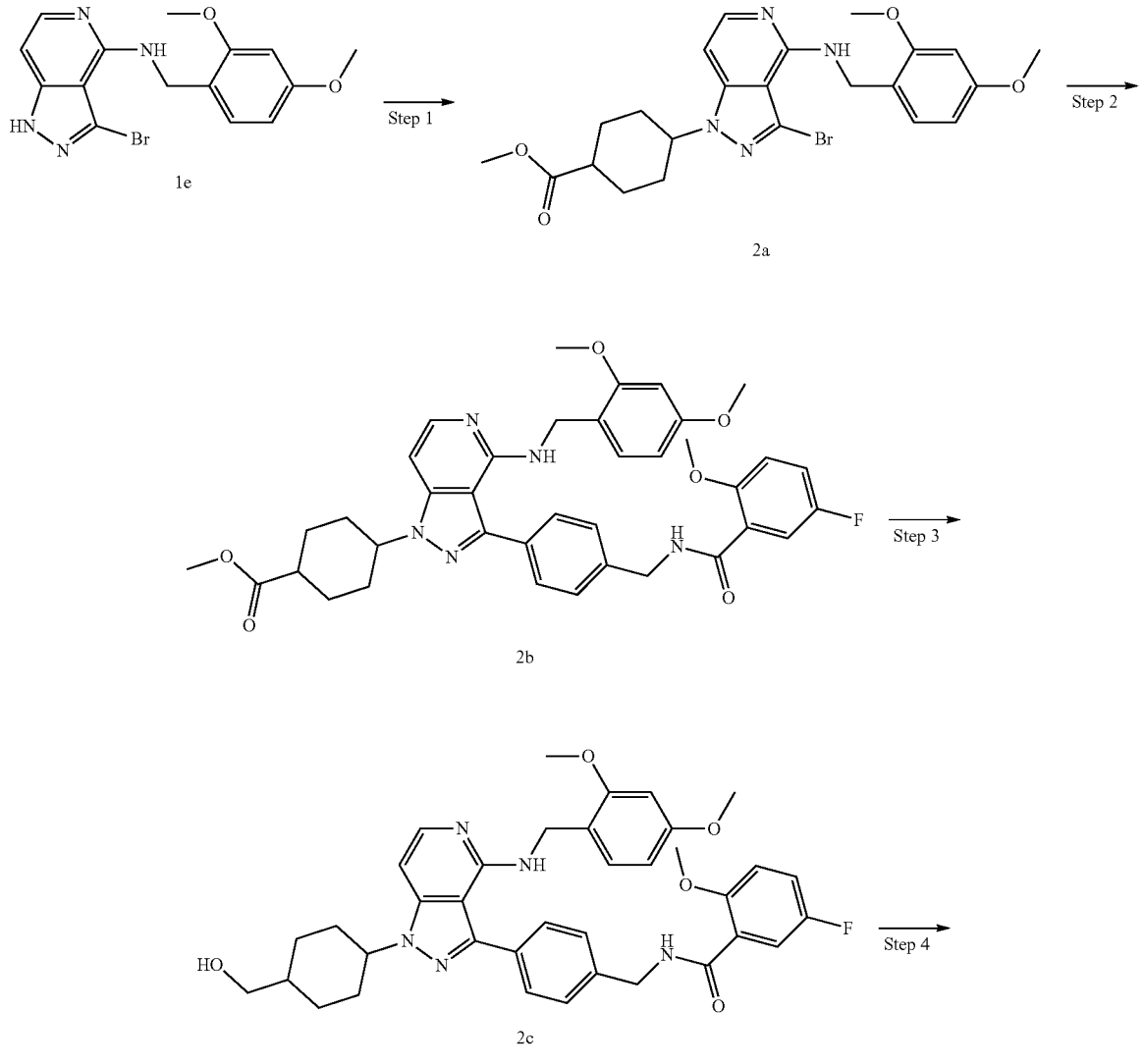
[0101] Trifluoroacetic acid (5 mL) was added to a solution of 1g (80 mg, 0.13 mmol) in dichloromethane (2 mL) and the resulting mixture was heated to 40° C. and stirred for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 1 (21 mg, solid, 34%).

[0102] MS m/z (ESI): 476 [M+1]

[0103] ^{1}H NMR (400 MHz, CD_3OD) δ 7.83-7.50 (m, 6H), 7.32-7.25 (m, 1H), 7.24-7.11 (m, 2H), 4.84 (d, J=11.7 Hz, 1H), 4.73 (s, 2H), 4.13 (dd, J=11.4, 3.7 Hz, 2H), 4.00 (s, 3H), 3.68 (t, J=11.2 Hz, 2H), 2.37 (ddd, J=16.7, 12.5, 4.8 Hz, 2H), 1.98 (dd, J=11.2, 9.0 Hz, 2H).

Example 2. N-(4-(4-amino-1-(4-(hydroxymethyl)cyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 2)

[0104]



1e

2a

2b

2c

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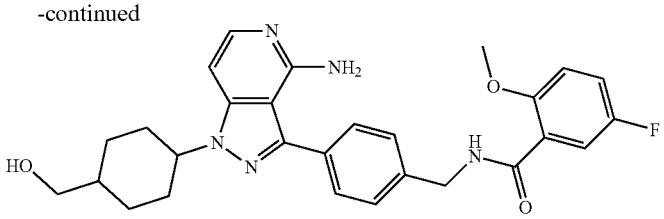


2

Step 1. methyl 4-(3-bromo-4-((2,4-dimethoxybenzyl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexane-1-carboxylate (2a)

[0105] To a mixture of 1e (726 mg, 2 mmol), methyl 4-hydroxycyclohexane-1-carboxylate (948 mg, 6 mmol) and triphenylphosphine (733 mg, 2.8 mmol) in THE (30 mL) was added diisopropyl azodicarboxylate (566 mg, 2.8 mmol) dropwise. After stirring for 15 hours, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 2a (130 mg, 13%).

[0106] MS m/z (ESI): 503 [M+1]

Step 2. methyl 4-(4-((2,4-dimethoxybenzyl)amino)-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexane-1-carboxylate (2b)

[0107] A mixture of 2a (130 mg, 0.26 mmol), 1b (94 mg, 0.32 mmol), potassium carbonate (72 mg, 0.52 mmol) and $PdCl_2(dppf)$ (19 mg, 0.026 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated to 120° C. and stirred for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=20/1 to 0/100) to give the title compound 2b (70 mg, 39%).

[0108] MS m/z (ESI): 682 [M+1]

Step 3. N-(4-(4-((2,4-dimethoxybenzyl)amino)-1-(4-(hydroxymethyl)cyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (2c)

[0109] To a solution of 2b (70 mg, 0.1 mmol) in THE (10 mL) at 0° C. was added lithium aluminum hydride (76 mg, 2 mmol). After stirring for 1 hour at 0° C., saturated brine (0.5 mL) was added, and the mixture was filtered. The filtrate was concentrated to dryness to afford the title compound 2c (45 mg, 69%).

[0110] MS m/z (ESI): 654 [M+1]

Step 4. N-(4-(4-amino-1-(4-(hydroxymethyl)cyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (2)

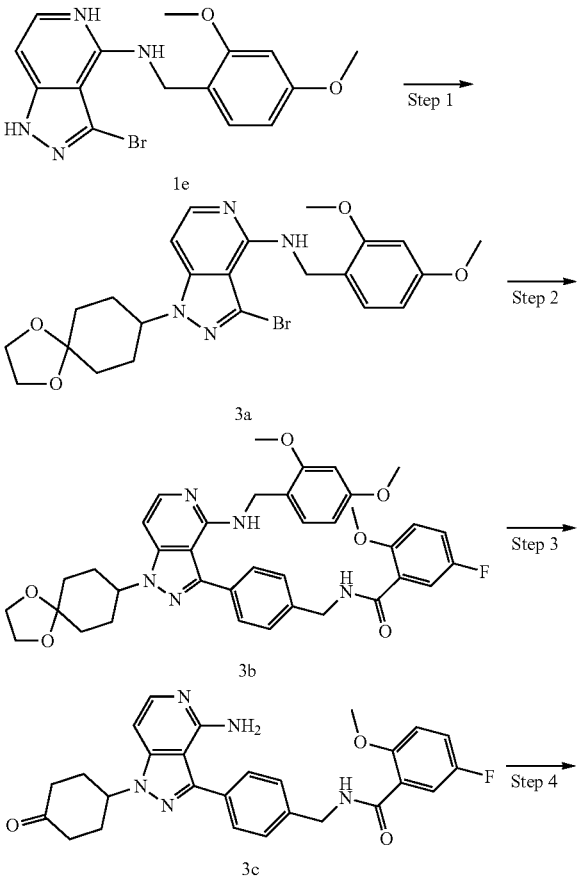
[0111] To a solution of 2c (45 mg, 0.069 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (3 mL). The resulting mixture was heated to 50° C. and stirred for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 2 (2.8 mg, solid, 8%).

[0112] MS m/z (ESI): 504 [M+1]

[0113] ^1H NMR (400 MHz, CD_3OD) δ 7.78-7.62 (m, 4H), 7.58 (d, J=8.1 Hz, 2H), 7.32-7.24 (m, 1H), 7.20 (dd, J=9.1, 4.2 Hz, 1H), 6.91 (d, J=6.4 Hz, 1H), 4.73 (s, 2H), 4.61-4.55 (m, 1H), 4.00 (s, 3H), 3.68 (d, J=7.3 Hz, 2H), 2.21 (dd, J=21.5, 10.1 Hz, 2H), 2.00-1.75 (m, 7H).

Example 3. N-(4-(4-amino-1-((1s,4s)-4-hydroxycyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 3) and N-(4-(4-amino-1-((1r,4r)-4-hydroxycyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 4)

[0114]



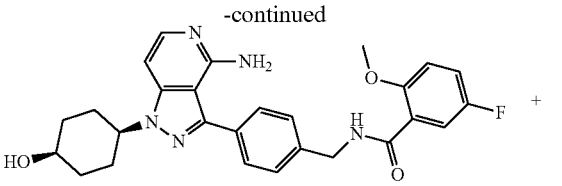
1e

3a

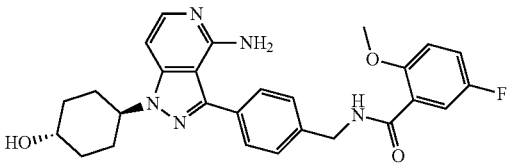
3b

3c

-continued



3



4

Step 1. 3-bromo-N-(2,4-dimethoxybenzyl)-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazolo[4,3-c]pyridin-4-amine (3a)

[0115] To a mixture of 1e (600 mg, 1.65 mmol), 1,4-dioxaspiro[4.5]decane-8-ol (521 mg, 3.3 mmol) and triphenylphosphine (864 mg, 3.3 mmol) in THE (30 mL) was added diisopropyl azodicarboxylate (667 mg, 3.3 mmol) dropwise. After stirring for 15 hours, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 2/1) to give the title compound 3a (440 mg, 53%).

[0116] MS m/z (ESI): 503 [M+1]

Step 2. N-(4-(4-((2,4-dimethoxybenzyl)amino)-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (3b)

[0117] A mixture of 3a (250 mg, 0.5 mmol), 1b (151 mg, 0.5 mmol), potassium carbonate (138 mg, 1 mmol) and $PdCl_2$(dppf) (36 mg, 0.05 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was heated to 120° C. under a nitrogen atmosphere and stirred for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 1/3) to give the title compound 3b (100 mg, 29%).

[0118] MS m/z (ESI): 682 [M+1]

Step 3. N-(4-(4-amino-1-(4-oxocyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (3c)

[0119] To a solution of 3b (100 mg, 0.15 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (4 mL). The resulting mixture was heated to 50° C. and stirred for 3 hours. After cooling to room temperature, the solvent was removed under reduced pressure to give the title compound 3c (110 mg). The product was used directly in the next step without further purification.

[0120] MS m/z (ESI): 488 [M+1]

Step 4. N-(4-(4-amino-1-((1s,4s)-4-hydroxycyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 3) and N-(4-(4-amino-1-((1r,4r)-4-hydroxycyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 4)

[0121] To a solution of 3c (110 mg, crude product) in THE (15 mL) at 0° C. was added lithium aluminum hydride (56 mg, 1.47 mmol). After stirring for 1 hour, the mixture was added with saturated brine (1 mL), filtered, and concentrated to dryness. The residue was purified by prep-HPLC to give the title compound 3 (7.3 mg, solid, 10%) and 4 (5.1 mg, solid, 7%).

N-(4-(4-amino-1-((1s,4s)-4-hydroxycyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (3)

[0122] MS m/z (ESI): 490 [M+1]

[0123] ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (d, J=6.3 Hz, 1H), 7.66 (td, J=6.2, 2.8 Hz, 3H), 7.58 (d, J=8.3 Hz, 2H), 7.28 (ddd, J=9.1, 7.6, 3.3 Hz, 1H), 7.19 (dd, J=9.1, 4.2 Hz, 1H), 6.94 (d, J=6.4 Hz, 1H), 4.73 (s, 2H), 4.52 (t, J=11.5 Hz, 1H), 3.99 (s, 3H), 3.76-3.70 (m, 1H), 2.21-2.03 (m, 6H), 1.63-1.53 (m, 2H).

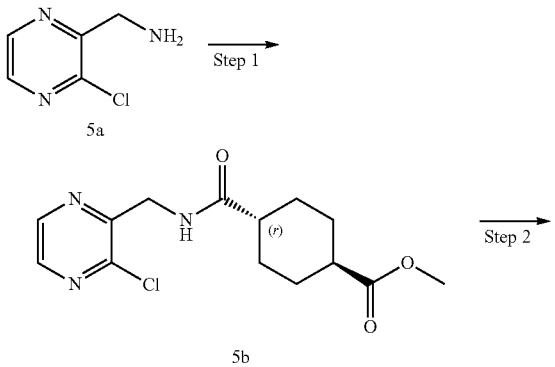
N-(4-(4-amino-1-((1r,4r)-4-hydroxycyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (4)

[0124] MS m/z (ESI): 490 [M+1]

[0125] ^{1}H NMR (400 MHz, CD_3OD) δ 7.72-7.64 (m, 4H), 7.58 (d, J=8.2 Hz, 2H), 7.28 (ddd, J=9.1, 7.6, 3.3 Hz, 1H), 7.20 (dd, J=9.1, 4.2 Hz, 1H), 7.02 (d, J=6.5 Hz, 1H), 4.73 (s, 2H), 4.60-4.54 (m, 1H), 4.06 (s, 1H), 4.00 (s, 3H), 2.49 (dd, J=13.3, 10.3 Hz, 2H), 2.01 (d, J=12.9 Hz, 2H), 1.82 (t, J=13.7 Hz, 4H).

Example 4. N-(4-(4-amino-1-((1r,4r)-4-hydroxycyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 5)

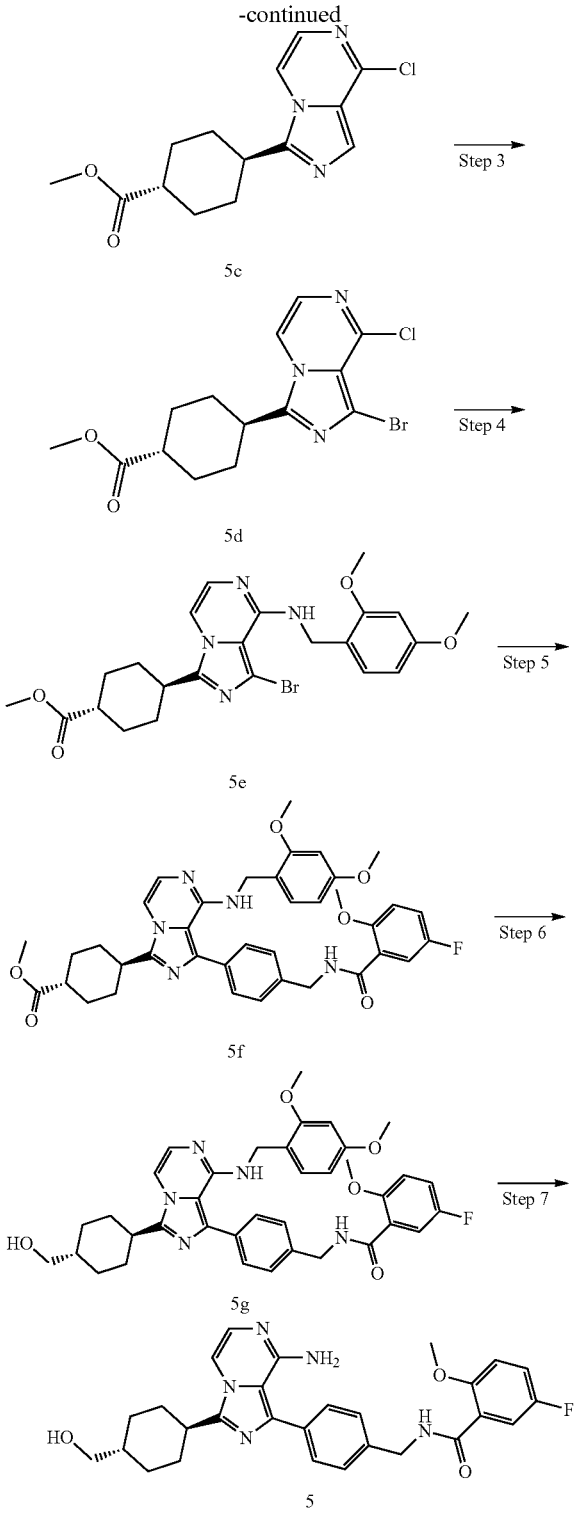
[0126]



5a

5b

-continued



Step 1. methyl (1r,4r)-4-(((3-chloropyrazin-2-yl) methyl)carbamoyl)cyclohexane-1-carboxylate (5b)

[0127] To a mixture of (3-chloropyrazin-2-yl)methylamine hydrochloride 5a (360 mg, 2 mmol), (1r,4r)-4-(methoxycarbonyl)cyclohexane-1-carboxylic acid (373 mg, 2 mmol) and triethylamine (606 mg, 6 mmol) in DMF (10 mL) was added HATU (836 mg, 2.2 mmol). After stirring for 16 hours, the reaction mixture was added with water (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=10/1 to 4/1) to give the title compound 5b (520 mg, 84%).

[0128] MS m/z (ESI): 312 [M+1]

Step 2. methyl (1r,4r)-4-(8-chloroimidazo[1,5-a] pyrazin-3-yl)cyclohexane-1-carboxylate (5c)

[0129] To a solution of 5b (520 mg, 1.67 mmol) in acetonitrile (10 mL) at 0° C. was added phosphine oxychloride (2.55 g, 16.7 mmol) in portions. The resulting mixture was heated to 100° C. and stirred for 2 hours. After cooling to 0° C., the solvent was removed under reduced pressure to give the title compound 5c (420 mg, 86%). The product was used directly in the next reaction without further purification.

[0130] MS m/z (ESI): 294 [M+1]

Step 3. methyl (1r,4r)-4-(1-bromo-8-chloroimidazo [1,5-a]pyrazin-3-yl)cyclohexane-1-carboxylate (5d)

[0131] To a solution of 5c (420 mg, 1.43 mmol) in acetonitrile (100 mL) at 0° C. was added NBS (280 mg, 1.57 mmol). After stirring at room temperature for 1 hour, the mixture was quenched with water (20 mL) and extracted with dichloromethane (2×20 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give the title compound 5d (180 mg, 34%).

[0132] MS m/z (ESI): 372 [M+1]

Step 4. methyl (1r,4r)-4-(1-bromo-8-((2,4-dimethoxybenzyl)amino)imidazo[1,5-a]pyrazin-3-yl)cyclohexane-1-carboxylate (5e)

[0133] To a solution of 5d (160 mg, 0.43 mmol) in acetonitrile (5 mL) were added 2,4-dimethoxybenzylamine (49 mg, 0.47 mmol) and DIPEA (166 mg, 1.3 mmol). The mixture was heated to 50° C. and stirred for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/0 to 7/3) to give the title compound 5e (160 mg, 74%).

[0134] MS m/z (ESI): 503 [M+1]

Step 5. methyl (1r,4r)-4-(8-((2,4-dimethoxybenzyl) amino)-1-(4-((5-fluoro-2-methoxybenzamido) methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)cyclohexane-1-carboxylate (5f)

[0135] To a solution of 5e (160 mg, 0.318 mmol) in 1,4-dioxane (5 mL) were added 1b (191 mg, 0.636 mmol), potassium carbonate (132 mg, 0.954 mmol) and $PdCl_2$(dppf) (24 mg, 0.032 mmol).

[0136] The mixture was heated to 100° C. under a nitrogen atmosphere and stirred for 4 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column

chromatography (petroleum ether/ethyl acetate=100/0 to 7/3) to give the title compound 5f (140 mg, 64%).

[0137] MS m/z (ESI): 682 [M+1]

Step 6. N-(4-(8-((2,4-dimethoxybenzyl)amino)-3-((1r,4r)-4-(hydroxymethyl)cyclohexyl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (5g)

[0138] To a solution of 5f (140 mg, 0.204 mmol) in THE (5 mL) at 0° C. was added lithium aluminum hydride (23 mg, 0.616 mmol). After stirring at room temperature for 1 hour, it was cooled to 0° C. and to which 20% NaOH aqueous solution (0.1 mL) was added dropwise. The resulting mixture was stirred at room temperature for 1 hour, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/0 to 1/1) to give the title compound 5g (100 mg, 75%).

[0139] MS m/z (ESI): 654 [M+1]

Step 7. N-(4-(4-amino-1-((1r,4r)-4-hydroxycyclohexyl)-1H-pyrazolo[4,3-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (5)

[0140] A mixture of 5g (80 mg, 0.122 mmol) and trifluoroacetic acid (5 mL) was heated to 80° C. and stirred for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 5 (12.0 mg, solid, 20%).

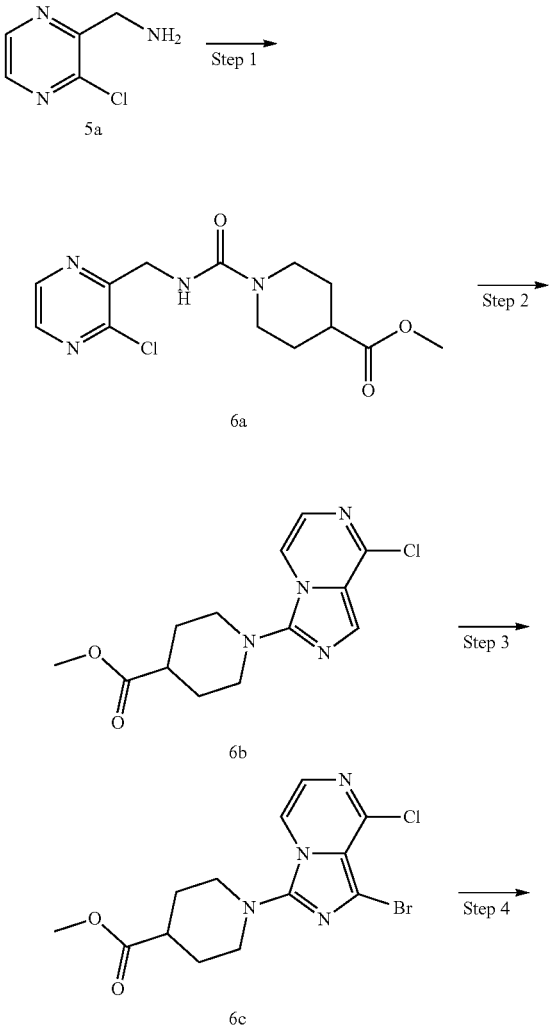
[0141] MS m/z (ESI): 504 [M+1]

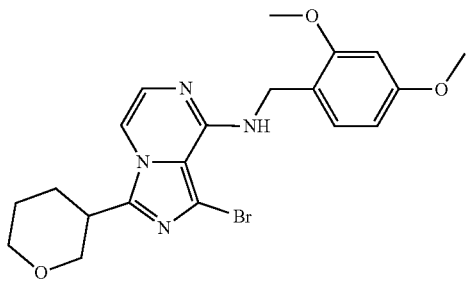
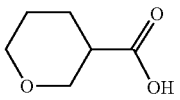
[0142] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91-8.76 (m, 1H), 7.61 (d, J=5.1, 1H), 7.58-7.50 (m, 3H), 7.45 (d, J=8.1, 2H), 7.40-7.28 (m, 1H), 7.19 (dd, J=9.0, 4.3, 1H), 7.00 (d, J=4.9, 1H), 5.94 (s, 2H), 4.57 (d, J=6.0, 2H), 4.51-4.34 (m, 1H), 3.90 (s, 3H), 3.27 (d, J=5.6, 1H), 3.12-3.00 (m, 2H), 1.97 (d, J=11.5, 2H), 1.85 (d, J=10.7, 2H), 1.62 (d, J=14.0, 2H), 1.45 (s, 2H), 1.25 (d, J=9.5, 1H).

[0143] The intermediate as shown below was synthesized according to the procedures for the first to fourth steps in Example 4, except that tetrahydro-2H-pyran-3-carboxylic acid was used instead of (1r,4r)-4-(methoxycarbonyl)cyclohexane-1-carboxylic acid in the first step.

Example 5. N-(4-(8-amino-3-(4-(hydroxymethyl)piperidin-1-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 6)

[0144]



Intermediate No.	Structure	Compound replacing (1r,4r)-4-(methoxycarbonyl)cyclohexane-1-carboxylic acid	MS m/z (ESI)
19e			447

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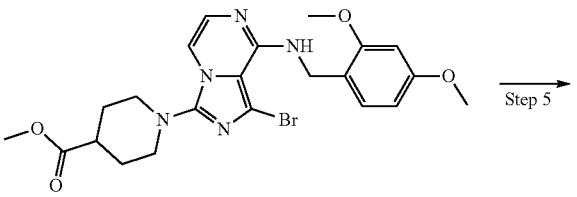
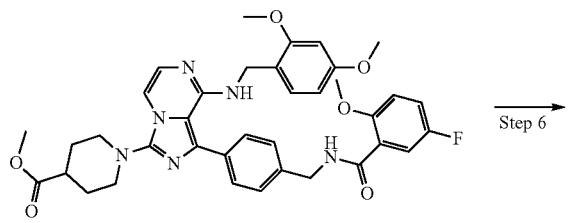
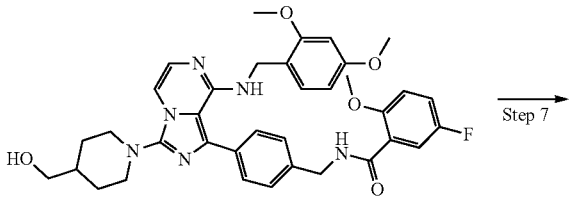


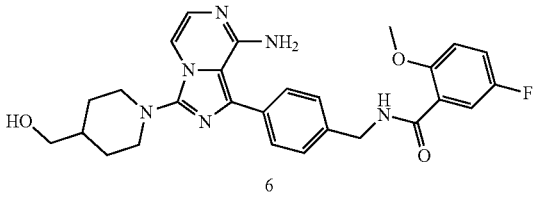
6d



6e



6f



6

Step 1. methyl 1-(((3-chloropyrazin-2-yl)methyl) carbamoyl)piperidine-4-carboxylate (6a)

[0145] To a solution of (3-chloropyrazine-2-yl) methylamine hydrochloride 5a (1.80 g, 10 mmol) and DIPEA (1.29 g, 10 mmol) in DMF (10 mL) was added N,N'-carbonyldiimidazole (1.62 g, 10 mmol). The mixture was stirred for 3 hours and then added with methyl piperidine-4-carboxylate (1.43 g, 10 mmol). The mixture was stirred for additional 18 hours and then filtered. The filter cake was washed with ethyl acetate (3×10 mL). The combined filtrates were washed with water (3×10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound 6a (3 g, 96%). The product was used directly in the next step without further purification.

[0146] MS m/z (ESI): 313 [M+1]

Step 2. methyl 1-(8-chloroimidazo[1,5-a]pyrazin-3-yl)piperidine-4-carboxylate (6b)

[0147] To a solution of 6a (3 g, 9.6 mmol) in acetonitrile (10 mL) was added phosphorus oxychloride (2.98 g, 19.2 mmol). The mixture was heated to 100° C. and stirred for 3 hours. After cooling to room temperature, the residue was dispersed in ethyl acetate (10 mL) and adjusted to pH=9 with saturated sodium carbonate solution. The resulting mixture was extracted with ethyl acetate (3×20 mL). The combined organic phase was washed with water (3×10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/1 to 4/1) to give the title compound 6b (260 mg, 9%).

[0148] MS m/z (ESI): 295 [M+1]

Step 3. methyl 1-(1-bromo-8-chloroimidazo[1,5-a] pyrazin-3-yl)piperidine-4-carboxylate (6c)

[0149] To a solution of 6b (260 mg, 0.88 mmol) in acetonitrile (5 mL) was added NBS (189 mg, 1.1 mmol). After the mixture was stirred for 5 hours, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/1 to 17/3) to give the title compound 6c (200 mg, 67%).

[0150] MS m/z (ESI): 373 [M+1]

Step 4. methyl 1-(1-bromo-8-((2,4-dimethoxybenzyl)amino)imidazo[1,5-a]pyrazin-3-yl)piperidine-4-carboxylate (6d)

[0151] To a solution of 6c (200 mg, 0.54 mmol) and 2,4-dimethoxybenzylamine (99 mg, 0.59 mmol) in acetonitrile (5 mL) was added DIPEA (208 mg, 1.6 mmol). The mixture was heated to 60° C. and stirred for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/1 to 7/3) to give the title compound 6d (200 mg, 74%).

[0152] MS m/z (ESI): 504 [M+1]

Step 5. methyl 1-(8-((2,4-dimethoxybenzyl)amino)-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-4-carboxylate (6e)

[0153] To a mixture of 6d (200 mg, 0.4 mmol), 1b (145 mg, 0.48 mmol) and $PdCl_2(dppf)$ (29 mg, 0.04 mmol) in 1,4-dioxane (10 mL) were added potassium carbonate (82 mg, 0.6 mmol) and water (2 mL). The mixture was heated to 100° C. under a nitrogen atmosphere and stirred for 3 hours. After cooling to room temperature, the mixture was extracted with ethyl acetate (3×10 mL). The combined organic phase was washed with water (3×10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/1 to 4/1) to give the title compound 6e (170 mg, 63%).

[0154] MS m/z (ESI): 683 [M+1]

Step 6. N-(4-(8-((2,4-dimethoxybenzyl)amino)-3-(4-(hydroxymethyl)piperidin-1-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (6f)

[0155] To a solution of 6e (90 mg, 0.13 mmol) in THE (3 mL) at 0° C. was added lithium aluminum hydride (10 mg, 0.26 mmol). After the mixture was gradually warmed to room temperature and stirred for 3 hours, ethyl acetate (1 mL) and water (1 mL) were added. After stirring for 10 minutes, the mixture was extracted with ethyl acetate (3×5 mL). The combined organic phase was washed with water (3×5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound 6f (100 mg). The product was used directly in the next step without further purification.

[0156] MS m/z (ESI): 655 [M+1]

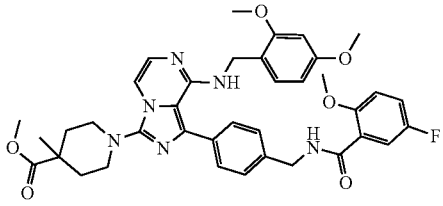
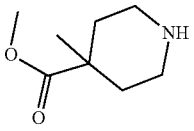
Step 7. N-(4-(8-amino-3-(4-(hydroxymethyl)piperidin-1-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (6)

[0157] To a solution of 6f (100 mg, 0.15 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (2 mL). The mixture was heated to 50° C. and stirred for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in methanol (2 mL) and to which potassium carbonate (138 mg) was added. The mixture was stirred for 3 hours, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give the title compound 6 (27.6 mg, solid, 42%).

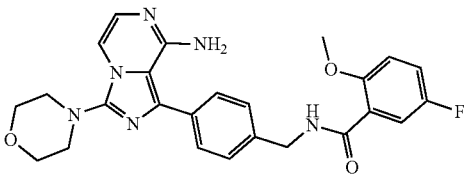
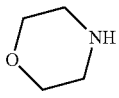
[0158] MS m/z (ESI): 505 [M+1]

[0159] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (t, J=6.1 Hz, 1H), 7.62-7.48 (m, 3H), 7.44 (d, J=8.2 Hz, 2H), 7.37-7.31 (m, 1H), 7.22-7.14 (m, 2H), 6.95 (d, J=4.9 Hz, 1H), 5.99-5.87 (m, 2H), 4.61-4.48 (m, 3H), 3.90 (s, 3H), 3.42-3.33 (m, 4H), 2.89-2.79 (m, 2H), 1.82-1.74 (m, 2H), 1.59-1.52 (m, 1H), 1.44-1.34 (m, 2H).

[0160] The intermediate as shown below was synthesized according to the procedures for the first to the fifth steps in Example 5, except that methyl 4-methylpiperidine-4-carboxylate was used instead of methyl piperidine-4-carboxylate in the first step.

Intermediate No.	Structure	Compound replacing methyl piperidine-4-carboxylate	MS m/z (ESI)
27a			697

[0161] Compound 44 was synthesized according to the procedure in Example 5 (without the sixth step), except that morpholine was used instead of methyl piperidine-4-carboxylate in the first step.

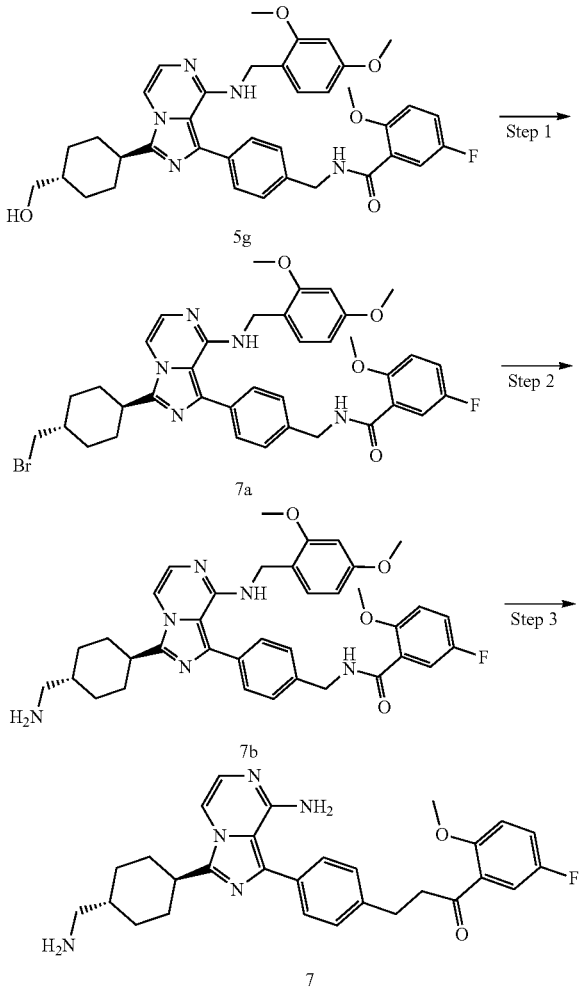
Compound No.	Structure	Compound replacing methyl piperidine-4-carboxylate	MS m/z (ESI)
44			477

[0162] ^{1}H NMR data of Compound 44 is shown below:

Compound	^{1}H NMR
N-(4-(8-amino-3-morpholinoimidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (44)	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (t, J = 6.1 Hz, 1H), 8.14 (s, 0.5H), 7.59 (d, J = 8.2 Hz, 2H), 7.52 (m, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.40-7.30 (m, 2H), 7.19(m, 1H), 6.96 (d, J = 5.2 Hz, 1H), 6.54 (brs, 2.5 H), 4.57 (d, J = 6.1 Hz, 2H), 3.90 (s, 3H), 3.84-3.75 (m, 4H), 3.18-3.10 (m, 4H).

Example 6. N-(4-(8-amino-3-((1r,4r)-4-(aminomethyl)cyclohexyl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 7)

[0163]



Step 1. N-(4-(3-((1r,4r)-4-(bromomethyl)cyclohexyl)-8-((2,4-dimethoxybenzyl)amino)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (7a)

[0164] To a slurry of 5g (160 mg, 0.25 mmol) in dichloromethane (10 mL) were added triphenylphosphine (96 mg, 0.37 mmol) and carbon tetrabromide (122 mg, 0.37 mmol) in sequence under a nitrogen atmosphere. The mixture was heated to reflux and stirred for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=4/1 to 1/1) to give the title compound 7a (170 mg, 97%).

[0165] MS m/z (ESI): 716 [M+1]

Step 2. N-(4-(3-((1r,4r)-4-(aminomethyl)cyclohexyl)-8-((2,4-dimethoxybenzyl)amino)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (7b)

[0166] A mixture of 7a (110 mg, 0.16 mmol) and a solution of ammonia in THE (4 M, 5 mL) in a sealed tube was heated to 100° C. and stirred for 48 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane/methanol=100/0=50/1) to give the title compound 7b (60 mg, 58%).

[0167] MS m/z (ESI): 653 [M+1]

Step 3. N-(4-(8-amino-3-((1r,4r)-4-(aminomethyl)cyclohexyl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (7)

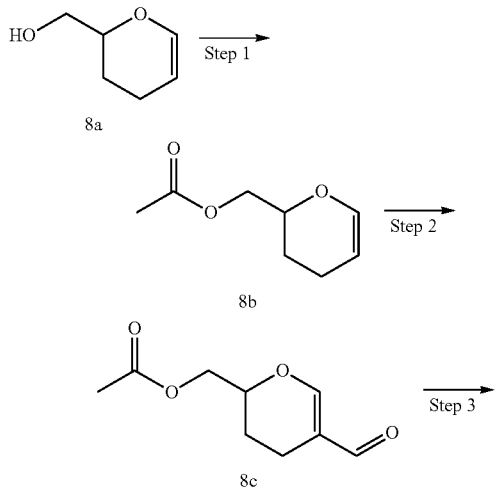
[0168] A mixture of 7b (60 mg, 0.092 mmol) and trifluoroacetic acid (10 mL) was heated to 80° C. and stirred for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by reversed phase preparative high performance liquid chromatography to give the title compound 7 (4.5 mg, solid, 10%).

[0169] MS m/z (ESI): 503 [M+1]

[0170] ^{1}H NMR (400 MHz, CD_3OD) δ 7.73-7.41 (m, 6H), 7.37-7.15 (m, 2H), 7.00 (s, 1H), 4.70 (s, 2H), 3.97 (s, 3H), 3.24-3.11 (m, 1H), 2.87 (d, J=6.1, 2H), 2.20-2.00 (m, 5H), 1.92-1.66 (m, 4H).

Example 7. N-(4-(8-amino-3-(6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 8)

[0171]



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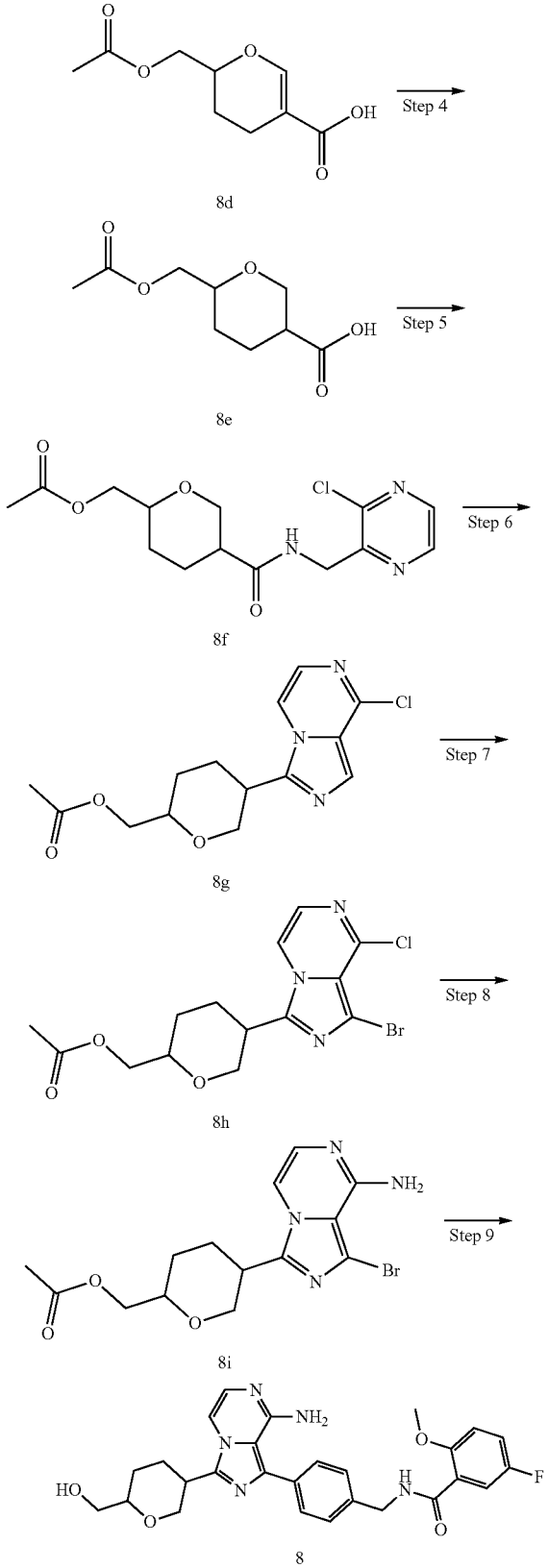


Step 1. (3,4-dihydro-2H-pyran-2-yl)methyl acetate (8b)

[0172] To a solution of (3,4-dihydro-2H-pyran-2-yl)-methanol 8a (12.5 g, 110 mmol) in dichloromethane (50 mL) were added triethylamine (16.7 g, 165 mmol) and acetic anhydride (16.8 g, 165 mmol). After stirring for 15 hours, the mixture was diluted with dichloromethane (200 mL) and washed with saturated ammonium chloride solution (50 mL), water (50 mL) and saturated brine (50 mL) in sequence. The solvent was removed from the organic phase under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=30/1 to 1/2) to give the title compound 8b (15 g, 87%).

[0173] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (dd, J=4.5, 1.7 Hz, 1H), 4.71 (dddd, J=6.2, 4.9, 2.6, 1.2 Hz, 1H), 4.17 (qd, J=11.6, 5.2 Hz, 2H), 4.11-3.99 (m, 1H), 2.14-2.06 (m, 4H), 2.01 (dddd, J=15.7, 11.0, 2.9, 1.6 Hz, 1H), 1.89-1.82 (m, 1H), 1.69 (dtd, J=13.5, 10.3, 6.0 Hz, 1H).

Step 2. (5-formyl-3,4-dihydro-2H-pyran-2-yl)methyl acetate (8c)

[0174] To DMF (80 mL) was added phosphine oxychloride (25.5 g, 166 mmol). The resulting mixture was stirred for 30 minutes, cooled to 0° C. and added with 8b (13 g, 83 mmol). After warming to room temperature, the mixture was stirred for 15 hours, then added with saturated sodium bicarbonate solution (50 mL) and stirred for additional 15 hours. The mixture was extracted with ethyl acetate (3×200 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 3/1) to give the title compound 8c (8 g, 52%).

[0175] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.33 (d, J=9.4 Hz, 1H), 4.34-4.20 (m, 3H), 2.43 (ddd, J=17.0, 5.5, 3.2 Hz, 1H), 2.25-2.14 (m, 1H), 2.12 (s, 3H), 2.04-1.94 (m, 1H), 1.76

[0176] 1.62 (m, 1H).

Step 3. 2-(acetoxymethyl)-3,4-dihydro-2H-pyran-5-carboxylic acid (8d)

[0177] To a mixture of 8c (1.5 g, 8.1 mmol), sodium phosphate monobasic (2.43 g, 20.3 mmol), acetonitrile (16 mL), n-butanol (16 mL) and water (8 mL) was added hydrogen peroxide (30%, 3.67 mL, 32.4 mmol). After stirring for 30 minutes, to the mixture was added sodium chlorite (3.66 g, 40.5 mmol) and stirring was continued for additional 15 hours. The reaction mixture was diluted with saturated brine (80 mL) and extracted with ethyl acetate (2×100 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtrated, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 3/1) to afford the title compound 8d (1.03 g, 63%).

[0178] MS m/z (ESI): 201 [M+1]

Step 4. 6-(acetoxymethyl)tetrahydro-2H-pyran-3-carboxylic acid (8e)

[0179] A mixture of 8d (1 g, 5 mmol) and palladium on carbon (10%, 0.7 g) in ethyl acetate (80 mL) was stirred for

48 hours under a hydrogen atmosphere. The mixture was filtered and concentrated to dryness to give the title compound 8e (1.05 g, 100%). The product was used directly in the next step without further purification.

[0180] MS m/z (ESI): 203 [M+1]

Step 5. (5-(((3-chloropyrazin-2-yl)methyl)carbamoyl)tetrahydro-2H-pyran-2-yl)methyl acetate (8)

[0181] To a mixture of 5a (890 mg, 5.0 mmol), 8e (1.05 g, crude product) and DIPEA (1.28 g, 9.9 mmol) in DMF (15 mL) was added HATU (2.26 g, 5.9 mmol). After stirring for 30 minutes, the mixture was purified by reversed phase preparative high performance liquid chromatography to give the title compound 8f (1.5 g, 72%).

[0182] MS m/z (ESI): 328 [M+1]

Step 6. (5-(8-chloroimidazo[1,5-a]pyrazin-3-yl)tetrahydro-2H-pyran-2-yl)methyl acetate (8g)

[0183] A mixture of 8f (229 mg, 0.7 mmol) and phosphine oxychloride (215 mg, 1.4 mmol) in acetonitrile (20 mL) was heated to 80° C. and stirred for 6 hours. After cooling to 0° C., saturated sodium bicarbonate solution (30 mL) was added, and the mixture was extracted with ethyl acetate (2×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 2/1) to give the title compound 8g (150 mg, 69%).

[0184] MS m/z (ESI): 310 [M+1]

Step 7. (5-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)tetrahydro-2H-pyran-2-yl)methyl acetate (8h)

[0185] To a solution of 8g (150 mg, 0.48 mmol) in acetonitrile (20 mL) at 0° C. was added NBS (112 mg, 0.63 mmol). The mixture was allowed to warm to room temperature and stirred for 30 minutes. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 2/1) to give the title compound 8h (170 mg, 89%).

[0186] MS m/z (ESI): 388 [M+1]

Step 8. (5-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)tetrahydro-2H-pyran-2-yl)methyl acetate (8i)

[0187] A mixture of 8h (150 mg, 0.386 mmol) and ammonium hydroxide (10 mL) in acetonitrile (10 mL) was heated to 80° C. and stirred for 4.5 hours in a sealed tube. After cooling to room temperature, the solvent was removed under reduced pressure to give the title compound 8i (145 mg). The product was used directly in the next step without further purification

[0188] MS m/z (ESI): 369 [M+1]

Step 9. N-(4-(8-amino-3-(6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (8)

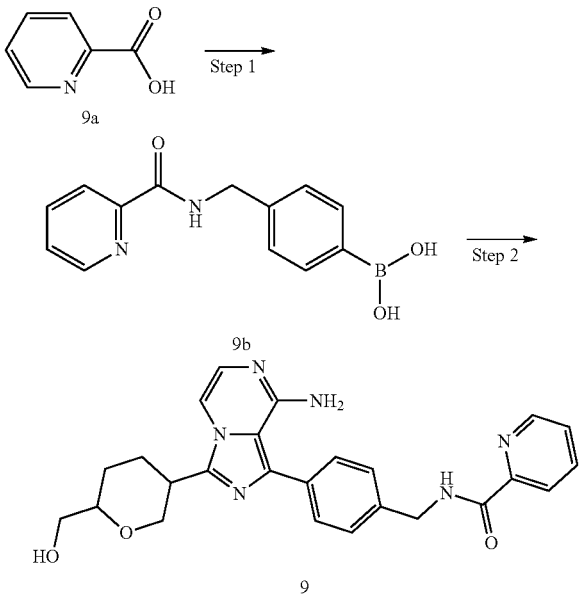
[0189] A mixture of 8i (145 mg, 0.39 mmol), 1b (174 mg, 0.58 mmol), potassium carbonate (106 mg, 0.77 mmol), $PdCl_2(dppf)$ (29 mg, 0.04 mmol), 1,4-dioxane (5 mL) and water (1 mL) was heated to 120° C. under a nitrogen atmosphere and stirred for 2 hours. After cooling to room temperature, it was diluted with saturated brine (3 mL) and extracted with ethyl acetate (3×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give the title compound 8 (32 mg, solid, 16%).

[0190] MS m/z (ESI): 506 [M+1]

[0191] ^1H NMR (400 MHz, CD_3OD) δ 7.62 (dd, J=9.1, 3.1 Hz, 3H), 7.56-7.47 (m, 3H), 7.29-7.20 (m, 1H), 7.17 (dd, J=9.1, 4.2 Hz, 1H), 6.99 (d, J=5.1 Hz, 1H), 4.70 (s, 2H), 4.29 (dd, J=11.8, 3.0 Hz, 1H), 3.97 (s, 3H), 3.90 (dd, J=11.8, 3.5 Hz, 1H), 3.64 (dd, J=9.6, 4.2 Hz, 2H), 3.56 (t, J=7.1 Hz, 1H), 3.38 (s, 1H), 2.29 (dd, J=13.6, 4.2 Hz, 1H), 2.14-2.03 (m, 1H), 1.96-1.86 (m, 1H), 1.67-1.59 (m, 1H).

Example 8. N-(4-(8-amino-3-(6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)picolinamide (Compound 9)

[0192]



Step 1. (4-(picolinamidomethyl)phenyl)boronic acid (9b)

[0193] To a mixture of picolinic acid 9a (240 mg, 1.95 mmol), (4-(aminomethyl)phenyl) borate hydrochloride (280 mg, 1.5 mmol), DIPEA (387 mg, 3 mmol) and DMF (4 mL) was added HATU (855 mg, 2.25 mmol). After stirring for 1 hour, the mixture was purified by prep-HPLC to give the title compound 9b (295 mg, 77%).

[0194] MS m/z (ESI): 257 [M+1]

Step 2. N-(4-(8-amino-3-(6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)picolinamide (9)

[0195] A mixture of 8i (125 mg, 0.25 mmol), 9b (128 mg, 0.5 mmol), $PdCl_2(dppf)$ (18 mg, 0.025 mmol), potassium carbonate (69 mg, 0.5 mmol), 1,4-dioxane (4 mL) and water (1 mL) was heated to 120° C. under a nitrogen atmosphere

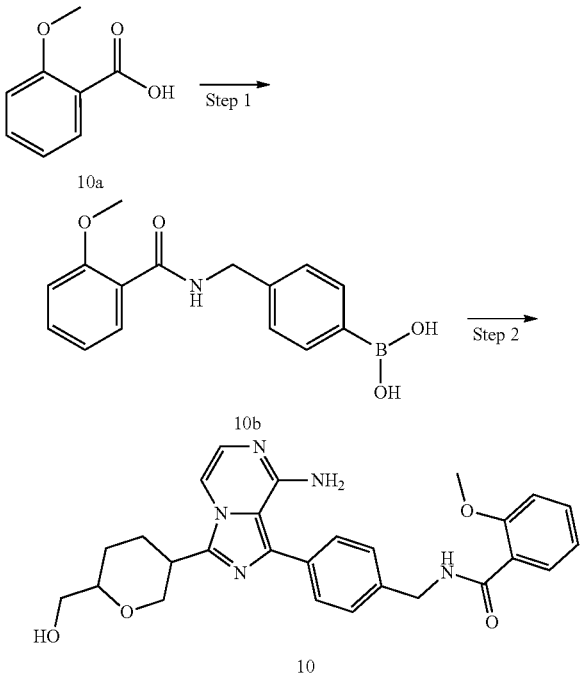
and stirred for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 9 (12 mg, solid, 11%).

[0196] MS m/z (ESI): 459 [M+1]

[0197] ^{1}H NMR (400 MHz, CD_3OD) δ 8.67 (d, J=4.1 Hz, 1H), 8.15 (d, J=7.8 Hz, 1H), 7.99 (td, J=7.7, 1.7 Hz, 1H), 7.80-7.31 (m, 6H), 7.01 (d, J=5.2 Hz, 1H), 4.74 (s, 2H), 4.31 (dd, J=11.8, 2.3 Hz, 1H), 3.92 (dd, J=11.8, 3.6 Hz, 1H), 3.71-3.54 (m, 3H), 3.40 (dd, J=7.5, 3.4 Hz, 1H), 2.36-2.26 (m, 1H), 2.11 (ddd, J=15.3, 9.7, 4.5 Hz, 1H), 1.99-1.88 (m, 1H), 1.69-1.60 (m, 1H).

Example 9. N-(4-(8-amino-3-(6-(hydroxymethyl) tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-2-methoxybenzamide (Compound 10)

[0198]



Step 1. (4-((2-methoxybenzamido)methyl)phenyl)boronic acid (10b)

[0199] To a mixture of 2-methoxybenzoic acid (296 mg, 1.95 mmol), (4-(aminomethyl)phenyl)boronic acid hydrochloride (280 mg, 1.5 mmol), DIPEA (387 mg, 3 mmol) and DMF (4 mL) was added HATU (855 mg, 2.25 mmol). After stirring for 1 hour, the mixture was purified by prep-HPLC to give the title compound 10b (270 mg, 63%).

[0200] MS m/z (ESI): 286 [M+1]

Step 2. N-(4-(8-amino-3-(6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl) benzyl)-2-methoxybenzamide (9)

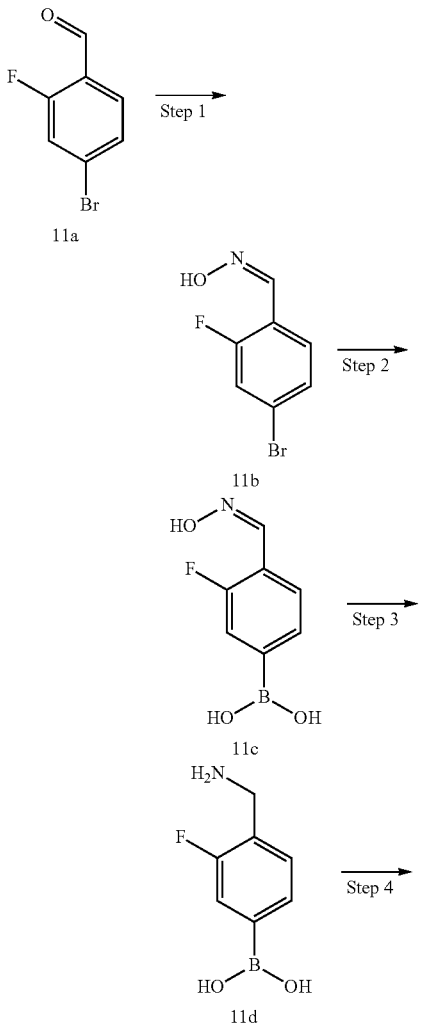
[0201] A mixture of 8i (125 mg, 0.25 mmol), 10b (143 mg, 0.5 mmol), potassium carbonate (69 mg, 0.5 mmol), $PdCl_2$ (dppf) (18 mg, 0.025 mmol), 1,4-dioxane (4 mL) and water (1 mL) was heated to 120° C. under a nitrogen atmosphere and stirred for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane/methanol=50/1 to 20/1) to give the title compound 10 (73 mg, solid, 60%).

[0202] MS m/z (ESI): 488 [M+1]

[0203] ^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (dd, J=7.7, 1.8 Hz, 1H), 7.64 (d, J=8.2 Hz, 2H), 7.60-7.49 (m, 4H), 7.18 (d, J=8.2 Hz, 1H), 7.12-7.06 (m, 1H), 7.01 (d, J=5.2 Hz, 1H), 4.73 (s, 2H), 4.32 (dd, J=11.7, 2.4 Hz, 1H), 4.04-3.95 (m, 3H), 3.93 (dd, J=11.8, 3.6 Hz, 1H), 3.72-3.62 (m, 2H), 3.57 (dd, J=14.2, 6.9 Hz, 1H), 3.40 (dd, J=8.4, 4.3 Hz, 1H), 2.35-2.27 (m, 1H), 2.17-2.06 (m, 1H), 1.99-1.89 (m, 1H), 1.69-1.61 (m, 1H).

Example 10. N-(4-(8-amino-3-(6-(hydroxymethyl) tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluorobenzyl)-2-methoxybenzamide (Compound 11)

[0204]



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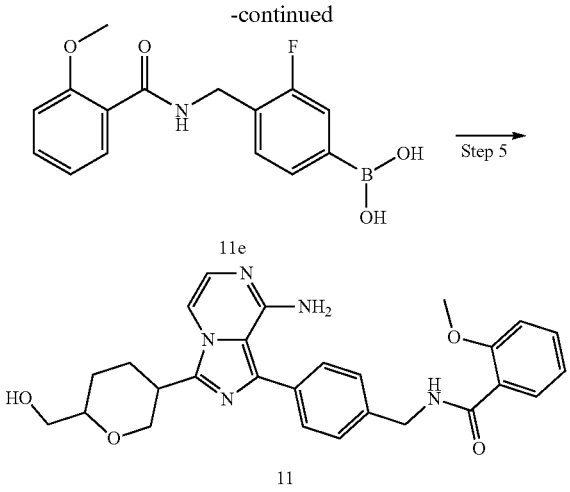


Step 1. 4-bromo-2-fluorobenzaldehyde oxime (11 b)

[0205] To a solution of 4-bromo-2-fluorobenzaldehyde 11a (4.06 g, 20 mmol) in ethanol (50 mL) was added hydroxylamine hydrochloride (1.53 g, 22 mmol). After stirring for 2 hours, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=20/1 to 10/1) to give the title compound 11b (2.18 g, 50%).

[0206] MS m/z (ESI): 218 [M+1]

Step 2. (3-fluoro-4-((hydroxyimino)methyl)phenyl) boronic acid (11c)

[0207] To a solution of 11b (2.18 g, 10 mmol) and triisopropyl borate (3.76 g, 20 mmol) in THE (50 mL) at −78° C. was added n-butyl lithium (2.5 M, 12 mL, 30 mmol). After stirring for 2 hours at −78° C., water (2 mL) was added, and the resulting mixture was warmed to room temperature and stirred for 30 minutes. The mixture was adjusted to pH=5-6 with 1 N hydrochloric acid and filtered. The filter cake was dried to give the title compound 11c (3.78 g). The product was used directly in the next step without further purification.

[0208] MS m/z (ESI): 184 [M+1]

Step 3. (4-(aminomethyl)-3-fluorophenyl)boronic acid (11d)

[0209] A mixture of 11c (3.7 g, 10 mmol) and palladium on carbon (10%, 500 mg) in methanol (80 mL) was stirred under a hydrogen atmosphere for 4 hours. The mixture was filtered and concentrated to dryness under reduced pressure to give the title compound 11d (2.9 g). The product was used directly in the next step without further purification.

[0210] MS m/z (ESI): 170 [M+1]

Step 4. (3-fluoro-4-((2-methoxybenzamido)methyl) phenyl)boronic acid (11e)

[0211] To a mixture of 2-methoxybenzoic acid (2.28 g, 15 mmol), 11d (1.69 g, 10 mmol), DIPEA (3.9 g, 30 mmol) and DMF (30 mL) was added HATU (5.7 g, 15 mmol). After stirring for 3 hours, the mixture was purified by prep-HPLC to give the title compound Ile (720 mg, 24%).

[0212] MS m/z (ESI): 304 [M+1]

Step 5. N-(4-(8-amino-3-(6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluorobenzyl)-2-methoxybenzamide (11)

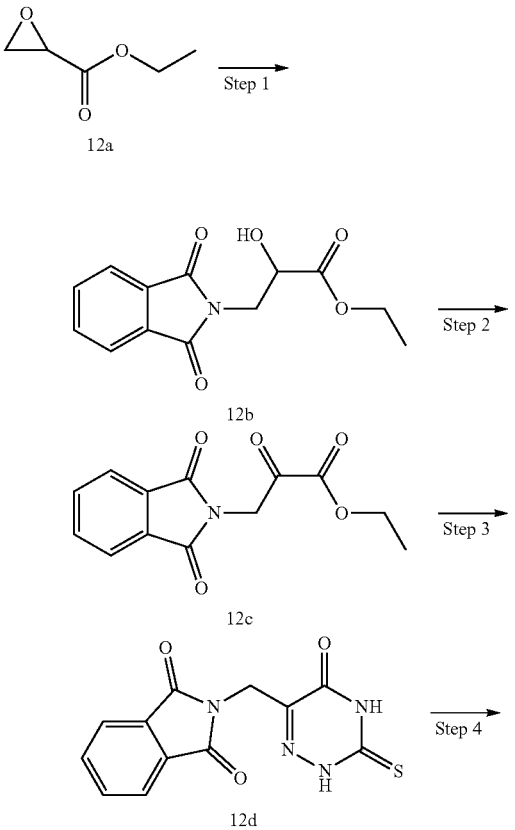
[0213] A mixture of 8i (125 mg, 0.25 mmol), Ile (151 mg, 0.5 mmol), potassium carbonate (69 mg, 0.5 mmol), $PdCl_2$ (dppf) (18 mg, 0.025 mmol), 1,4-dioxane (4 mL) and water (1 mL) was heated to 120° C. under a nitrogen atmosphere and stirred for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane/methanol=50/1 to 20/1) to give the title compound 11 (55.4 mg, solid, 43%).

[0214] MS m/z (ESI): 506 [M+1]

[0215] ^1H NMR (400 MHz, CD_3OD) δ 7.91 (dd, J=7.8, 1.8 Hz, 1H), 7.59-7.48 (m, 3H), 7.43 (ddd, J=8.2, 5.4, 1.6 Hz, 2H), 7.16 (d, J=8.2 Hz, 1H), 7.06 (td, J=7.7, 0.9 Hz, 1H), 7.01 (d, J=5.1 Hz, 1H), 4.74 (s, 2H), 4.29 (dd, J=11.8, 1.9 Hz, 1H), 3.98 (d, J=5.7 Hz, 3H), 3.90 (dd, J=11.8, 3.5 Hz, 1H), 3.66-3.60 (m, 2H), 3.56 (t, J=7.1 Hz, 1H), 3.38 (t, J=4.0 Hz, 1H), 2.33-2.26 (m, 1H), 2.14-2.05 (m, 1H), 1.95 (s, 1H), 1.62 (dd, J=9.6, 4.2 Hz, 1H).

Example 11. N-(4-(4-amino-7-cyclopentylimidazo [5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 12)

[0216]



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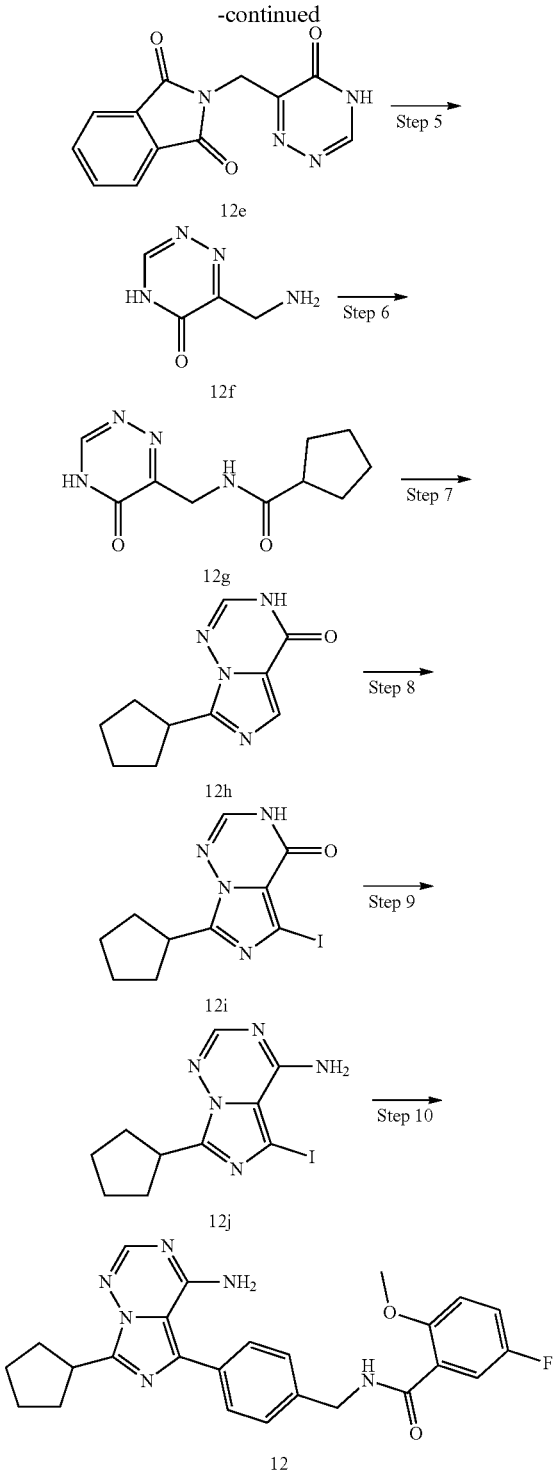


Step 1. ethyl 3-(1,3-dioxoisoindolin-2-yl)-2-hydroxypropanoate (12b)

[0217] To a solution of ethyl oxirane-2-carboxylate 12a (30 g, 259 mmol) in DMF (300 mL) were added phthalimide (34.2 g, 233 mmol) and potassium phthalimide (9.6 g, 52 mmol) in sequence. The mixture was heated to 90° C. and stirred for 8 hours, then cooled to room temperature, diluted with water (600 mL), and extracted with ethyl acetate (3×600 mL). The combined organic phase was washed with water (3×600 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound 12b (57.5 g, 84%). The product was used directly in the next step without further purification.

[0218] MS m/z (ESI): 264 [M+1]

[0219] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.85 (m, 2H), 7.80-7.69 (m, 2H), 4.50 (t, J=5.9 Hz, 1H), 4.32-4.18 (m, 2H), 4.09-3.98 (m, 2H), 3.03 (s, 1H), 1.30-1.22 (m, 3H).

Step 2. ethyl 3-(1,3-dioxoisoindolin-2-yl)-2-oxopropanoate (12c)

[0220] To solution of 12b (57.5 g, 218 mmol) in acetonitrile (500 mL) at 0° C. was added 2-iodoxybenzoic acid (91.7 g, 328 mmol) in portions. The mixture was heated to 90° C. and stirred for 18 hours. After cooling to room temperature, it was filtered. The filtrate was concentrated to a volume of about 150 mL and the newly formed precipitate was filtered out. The new filtrate was concentrated to dryness, added with dichloromethane (250 mL) and filtered. The newly obtained filtrate was concentrated to dryness under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/0 to 1/1) to give the title compound 12c (40 g, 70%).

[0221] MS m/z (ESI): 262 [M+1]

[0222] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.85 (m, 2H), 7.80-7.74 (m, 2H), 4.99 (s, 2H), 4.41 (q, J=7.1 Hz, 2H), 1.41 (t, J=7.1 Hz, 3H).

Step 3. 2-((5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)methyl)isoindoline-1,3-dione (12d)

[0223] To solution of 12c (40 g, 153 mmol) in acetic acid (300 mL) was added hydrazinocarbothioformamide (14 g, 153 mmol). The mixture was heated to 120° C. and stirred for 16 hours. After cooling to room temperature, the precipitate was collected by filtration, and washed with acetic acid (2×50 mL) and petroleum ether (200 mL) to give the title compound 12d (16 g, 36%).

[0224] MS m/z (ESI): 289 [M+1]

[0225] ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.38 (s, 1H), 13.29 (s, 1H), 7.96-7.85 (m, 4H), 4.68 (s, 2H).

Step 4. 2-((5-oxo-4,5-dihydro-1,2,4-triazin-6-yl) methyl)isoindoline-1,3-dione (12e)

[0226] To a mixture of 12d (16 g, 56 mmol) in ethanol (6 mL) was added Raney nickel (8 g, 50% wt). The mixture was heated to 85° C. and stirred for 72 hours under a hydrogen atmosphere. The reaction was not complete. The reaction mixture was cooled to room temperature and added with additional Raney nickel (8 g, 50% wt). The mixture was heated to 85° C. and stirred for 6 hours under a hydrogen atmosphere. The hydrogen atmosphere was replaced with a nitrogen atmosphere, and the reaction mixture was quickly filtered while it was hot. The filter cake was dissolved in ethanol (200 mL), refluxed for 1 hour and filtered (this operation was repeated 4 times). The combined filtrate was concentrated to dryness under reduced pressure to give the title compound 12e (11.56 g, 81%).

[0227] MS m/z (ESI): 127 [M+1]

[0228] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.78 (s, 3H), 3.87 (s, 2H).

Step 5. 6-(aminomethyl)-1,2,4-triazin-5(4H)-one (12f)

[0229] To a mixture of 12e (11.56 g, 45 mmol) in ethanol (200 mL) was added hydrazine hydrate (22.5 g, 450 mmol) dropwise. The resulting solution was stirred for 16 hours and then slurried with ethanol (300 mL). After filtration, the solvent was removed from the filtrate under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane/methanol (containing 10% water)=2/3 to 7/3) to give the title compound 12f (700 mg). The filter cake was slurried with water (400 mL) and filtered. The solvent was removed from the filtrate under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane/methanol (containing 10% water)=2/3 to 7/3) to give the title compound 12f (3.35 g). The two portions of the product were combined to give the title compound 12f (4.05 g, 71%).

[0230] MS m/z (ESI): 127 [M+1]

[0231] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.78 (s, 3H), 3.87 (s, 2H)

Step 6. N-((5-oxo-4,5-dihydro-1,2,4-triazin-6-yl) methyl)cyclopentanecarboxamide (12g)

[0232] To a mixture of 12f (600 mg, 4.76 mmol), triethylamine (721 mg, 7.14 mmol) and cyclopentanecarboxylic acid (597 mg, 5.23 mmol) in dichloromethane (20 mL) was added HATU (2.72 g, 7.14 mmol). The mixture was stirred for 18 hours, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/1 to 1/100) to give the title compound 12g (400 mg, 38%).

[0233] MS m/z (ESI): 223 [M+1]

Step 7. 7-cyclopentylimidazo[5,1-f][1,2,4]triazin-4 (3H)-one (12h)

[0234] To a mixture of 12g (400 mg, 1.8 mmol) in acetonitrile (10 mL) was added phosphine oxychloride (551 mg, 3.6 mmol). The mixture was heated to 100° C. and stirred for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/1 to 1/100) to give the title compound 12h (210 mg, 54%).

[0235] MS m/z (ESI): 205 [M+1]

Step 8. 7-cyclopentyl-5-iodoimidazo[5,1-f][1,2,4] triazin-4(3H)-one (12i)

[0236] To a solution of 12h (210 mg, 1.03 mmol) in DMF (2 mL) was added NIS (242 mg, 1.08 mmol). After stirring for 18 hours, the mixture was quenched with water (5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic phase was washed with water (3×5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/1 to 1/1) to give the title compound 12i (110 mg, 31%).

[0237] MS m/z (ESI): 331 [M+1]

Step 9. 7-cyclopentyl-5-iodoimidazo[5,1-f][1,2,4] triazin-4-amine (12j)

[0238] To a solution of 1,2,4-triazole (188 mg, 2.73 mmol) in pyridine (1 mL) was added phosphine oxychloride (139 mg, 0.91 mmol). After stirring for 15 minutes, a solution of 12i (110 mg, 0.33 mmol) in pyridine (1 mL) was added and stirring was continued for 2 hours. The mixture was cooled to 0° C., and a solution of ammonia in isopropanol (2 M, 0.3 mL) was added. After stirring for 18 hours, the mixture was filtered, and the filter cake was washed with dichloromethane (5 mL). The combined filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/1 to 1/1) to give the title compound 12j (60 mg, 70%).

[0239] MS m/z (ESI): 330 [M+1]

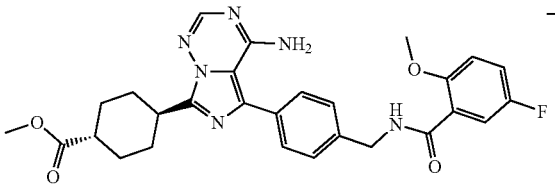
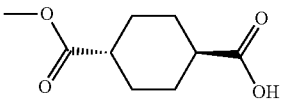
Step 10. N-(4-(4-amino-7-cyclopentylimidazo[5,1-f] [1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (12)

[0240] A mixture of 12j (40 mg, 0.12 mmol), 1b (45 mg, 0.15 mmol), potassium carbonate (26 mg, 0.18 mmol), $PdCl_2$(dppf) (9 mg, 0.012 mmol) and 1,4-dioxane (2 mL) was heated to 120° C. under a nitrogen atmosphere and stirred for 18 hours. After cooling to room temperature, the mixture was filtered and concentrated under reduced pressure. The residue was purified by preparative silica gel thin-layer chromatography (ethyl acetate as the developing solvent) to give the title compound 12 (5.1 mg, solid, 9%).

[0241] MS m/z (ESI): 461 [M+1]

[0242] ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (s, 1H), 7.57-7.49 (m, 3H), 7.44 (d, J=8.2 Hz, 2H), 7.18-7.13 (m, 1H), 7.09-7.05 (m, 1H), 4.60 (s, 2H), 3.87 (s, 3H), 3.66-3.61 (m, 1H), 2.07-2.00 (m, 2H), 1.92-1.78 (m, 4H), 1.68-1.61 (m, 2H).

[0243] The compounds or intermediates as shown below were synthesized according to the procedures in Example 11, except that a different carboxylic acid was used instead of cyclopentanecarboxylic acid in the sixth step.

Compound/ Intermediate No.	Structure	Compound replacing cyclopentanecarboxylic acid	MS m/z (ESI)
14a			533

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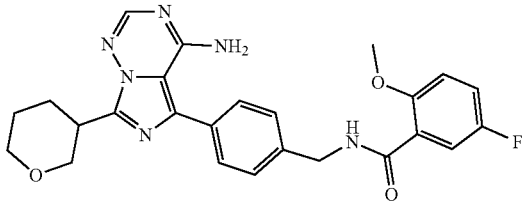
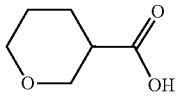
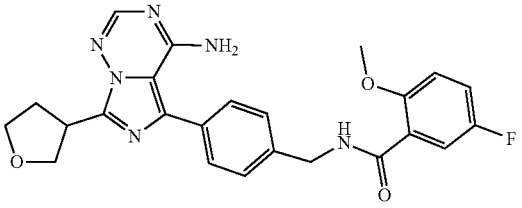
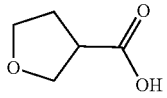
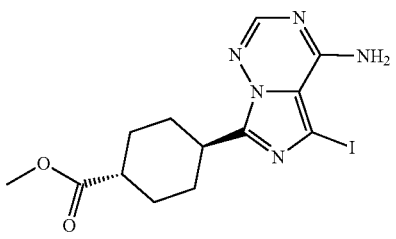
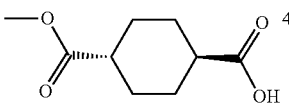
Compound/ Intermediate No.	Structure	Compound replacing cyclopentanecarboxylic acid	MS m/z (ESI)
16			477
17			463

[0244] The NMR data of compounds 16 and 17 are shown below:

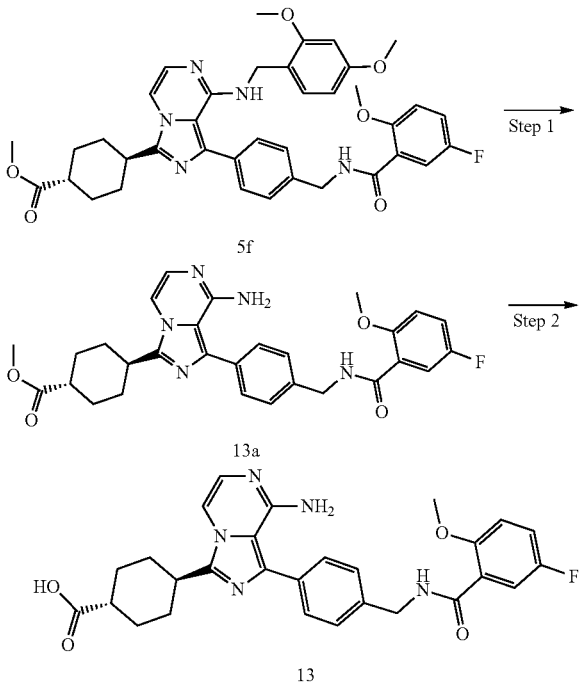
Compound	^{1}H NMR
N-(4-(4-amino-7-(tetrahydro-2H-pyran-3-yl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (16)	^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (s, 1H), 7.67-7.61 (m, 3H), 7.59-7.54 (m, 2H), 7.30-7.25 (m, 1H), 7.21-7.17 (m, 1H), 4.72 (s, 2H), 4.13 (dd, J = 11.5, 2.7 Hz, 1H), 4.04-3.97 (m, 4H), 3.79-3.73 (m, 1H), 3.71-3.65 (m, 1H), 3.59-3.52 (m, 1H), 2.19-2.07 (m, 2H), 1.86-1.77 (m, 2H).
N-(4-(4-amino-7-(tetrahydrofuran-3-yl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (17)	^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (s, 1H), 7.86 (s, 1H), 7.65-7.60 (m, 2H), 7.58-7.49 (m, 2H), 7.28-7.23 (m, 1H), 7.19-7.15 (m, 1H), 4.69 (s, 2H), 4.23 (t, J = 7.8 Hz, 1H), 4.13-4.05 (m, 2H), 4.03-3.91 (m, 4H), 2.46-2.42 (m, 1H), 1.32-1.26 (m, 2H).

[0245] The intermediate as shown below was synthesized according to the procedures for the sixth to ninth step in Example 11, except that (1r,4r)-4-(methoxycarbonyl)cyclohexane-1-carboxylic acid was used instead of cyclopentanecarboxylic acid in the sixth step.

Compound/ Intermediate No.	Structure	Compound replacing cyclopentanecarboxylic acid	MS m/z (ESI)
18e			402

Example 12. (1r,4r)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)cyclohexane-1-carboxylic acid (Compound 13)

[0246]



Step 1. methyl (1r,4r)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)cyclohexane-1-carboxylate (13a)

[0247] A mixture of 5f (100 mg, 0.147 mmol) and trifluoroacetic acid (10 mL) was heated to 80° C. and stirred for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure to give the title compound 13a (100 mg). The product was used directly in the next step without further purification.

[0248] MS m/z (ESI): 532 [M+1]

Step 2. (1r,4r)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)cyclohexane-1-carboxylic acid (13)

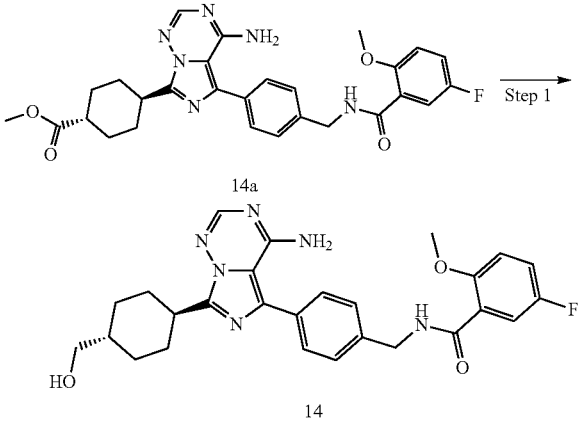
[0249] To a solution of 13a (100 mg, crude product) in methanol (5 mL) was added lithium hydroxide (11 mg, 0.45 mmol). After stirring for 1 hour, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 13 (26.5 mg, solid, 35%).

[0250] MS m/z (ESI): 518 [M+1]

[0251] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 1H), 8.85 (s, 1H), 7.66 (d, J=5.0, 1H), 7.59-7.50 (m, 3H), 7.46 (d, J=8.1, 2H), 7.38-7.31 (m, 1H), 7.19 (dd, J=9.1, 4.3, 1H), 7.02 (d, J=4.9, 1H), 5.96 (s, 2H), 4.58 (d, J=6.0, 2H), 3.91 (s, 3H), 3.12 (t, J=11.4, 1H), 2.36-2.26 (m, 1H), 2.01 (t, J=10.0, 4H), 1.74-1.50 (m, 4H).

Example 13. N-(4-(4-amino-7-((1r,4r)-4-(hydroxymethyl)cyclohexyl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 14)

[0252]



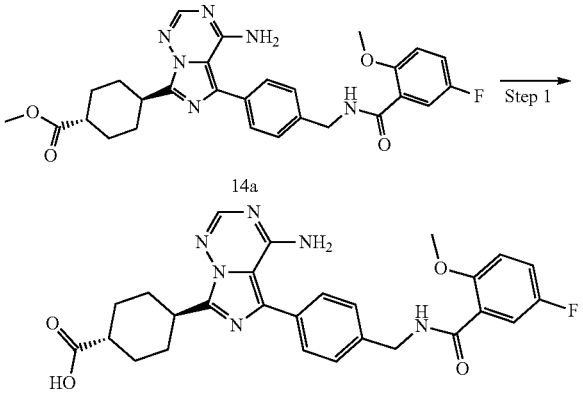
[0253] To a solution of 14a (40 mg, 0.075 mmol) in THE (3 mL) at 0° C. was added lithium aluminum hydride (6 mg, 0.15 mmol) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 hour, quenched with water (0.2 mL) and filtered. The solvent was removed from the filtrate under reduced pressure and the residue was purified by prep-HPLC to give the title compound 14 (15.7 mg, solid, 42%).

[0254] MS m/z (ESI): 505 [M+1]

[0255] ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (s, 1H), 7.55-7.50 (m, 3H), 7.46-7.42 (m, 2H), 7.17-7.13 (m, 1H), 7.09-7.05 (m, 1H), 4.60 (s, 2H), 3.87 (s, 3H), 3.33 (d, J=6.3 Hz, 2H), 2.00-1.94 (m, 2H), 1.90-1.84 (m, 2H), 1.79-1.67 (m, 3H), 1.14-1.01 (m, 3H).

Example 14. (1r,4r)-4-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)cyclohexane-1-carboxylic acid (Compound 15)

[0256]



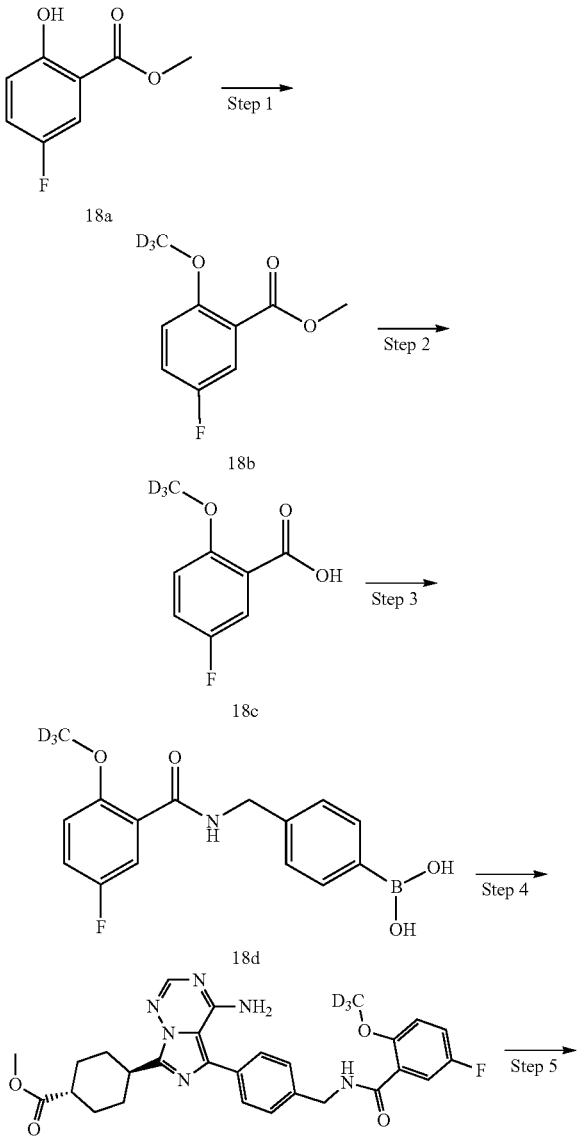
[0257] To a mixture of 14a (40 mg, 0.075 mmol), THE (3 mL) and methanol (3 mL) was added lithium hydroxide monohydrate (13 mg, 0.3 mmol). After stirring for 3 hours, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 15 (23.1 mg, solid, 59%).

[0258] MS m/z (ESI): 519 [M+1]

[0259] ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.68-7.61 (m, 3H), 7.59-7.54 (m, 2H), 7.31-7.25 (m, 1H), 7.21-7.17 (m, 1H), 4.72 (s, 2H), 3.99 (s, 3H), 3.44-3.38 (m, 1H), 2.45-2.38 (m, 1H), 2.20-2.09 (m, 4H), 1.90-1.80 (m, 2H), 1.70-1.61 (m, 2H).

Example 15. N-(4-(4-amino-7-((1r,4r)-4-(hydroxymethyl)cyclohexyl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-(methoxy-d_3)benzamide (Compound 18)

[0260]



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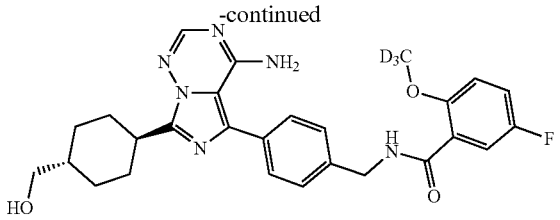


18

Step 1. methyl 5-fluoro-2-(methoxy-d_3)benzoate (18b)

[0261] To a mixture of methyl 5-fluoro-2-hydroxybenzoate 18a (1.7 g, 10 mmol) and potassium carbonate (2.07 g, 15 mmol) in acetonitrile (10 mL) was added deuterated methyl iodide (1.45 g, mmol). After stirring for 24 hours, it was filtered. The filtrate was removed from the solvent under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/1 to 4/1) to give the title compound 18b (900 mg, 48%).

[0262] MS m/z (ESI): 188 [M+1]

Step 2. 5-fluoro-2-(methoxy-d_3)benzoic acid (18c)

[0263] To a solution of 18b (900 mg, 4.81 mmol) in THE (5 mL) was added an aqueous solution of sodium hydroxide (231 mg, 5.77 mmol, 2 mL). After stirring for 5 hours, the mixture was adjusted to pH=4 with a solution of hydrogen chloride in ethyl acetate (4 M) and extracted with ethyl acetate (3×10 mL). The combined organic phase was washed with water (3×10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was removed from the solvent under reduced pressure to give the title compound 18c (600 mg, 72%). The product was used directly in the next step without further purification.

[0264] MS m/z (ESI): 173 [M+1]

Step 3. (4-((5-fluoro-2-(methoxy-d_3)benzamido)methyl)phenyl)boronic acid (18d)

[0265] To a mixture of 18c (600 mg, 3.47 mmol), (4-(aminomethyl)phenyl)boronic acid hydrochloride (649 mg, 3.47 mmol) and DIPEA (895 mg, 6.93 mmol) in DMF (5 mL) was added HATU (1.58 g, 4.16 mmol). The mixture was stirred for 18 hours and then purified by prep-HPLC to give the title compound 18d (360 mg, 34%).

[0266] MS m/z (ESI): 307 [M+1]

Step 4. methyl (1r,4r)-4-(4-amino-5-(4-((5-fluoro-2-(methoxy-d_3)benzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)cyclohexane-1-carboxylate (18e)

[0267] A mixture of 18e (50 mg, 0.12 mmol), 18d (46 mg, 0.15 mmol), $PdCl_2$(dppf) (10 mg, 0.012 mmol), potassium carbonate (26 mg, 0.19 mmol), 1,4-dioxane (2 mL) and water (0.2 mL) was heated to 130° C. under a nitrogen atmosphere and stirred for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/1 to 1/100) to give the title compound 18f (50 mg, 75%).

[0268] MS m/z (ESI): 536 [M+1]

Step 5. N-(4-(4-amino-7-((1r,4r)-4-(hydroxymethyl) cyclohexyl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-(methoxy-d_3)benzamide (18)

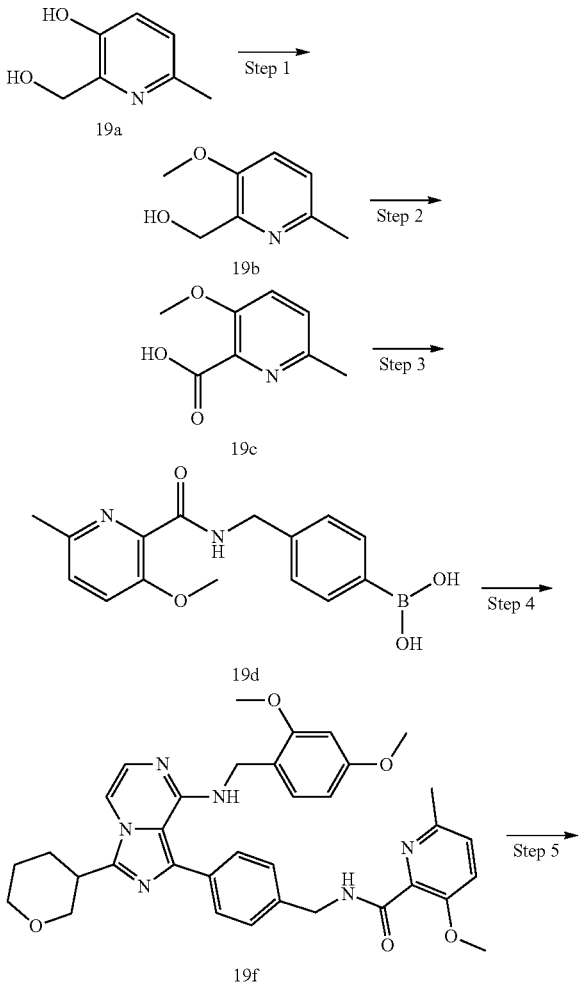
[0269] Lithium aluminum hydride (8 mg, 0.19 mmol) was added to a solution of 18f (50 mg, 0.093 mmol) in THE (3 mL) at 0° C. The mixture was gradually warmed to room temperature and stirred for 3 hours. It was quenched with water (0.1 mL) and filtered. The filtrate was removed from the solvent under reduced pressure and the residue was purified by prep-HPLC to give the title compound 18 (15.4 mg, solid, 33%).

[0270] MS m/z (ESI): 508 [M+1]

[0271] ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.67-7.61 (m, 3H), 7.58-7.54 (m, 2H), 7.30-7.25 (m, 1H), 7.21-7.17 (m, 1H), 4.72 (s, 2H), 3.45 (d, J=6.3 Hz, 2H), 2.12-2.06 (m, 2H), 2.02-1.96 (m, 2H), 1.90-1.80 (m, 2H), 1.69-1.56 (m, 2H), 1.25-1.15 (m, 2H).

Example 16. N-(4-(8-amino-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-3-methoxy-6-methylpicolinamide (Compound 19)

[0272]



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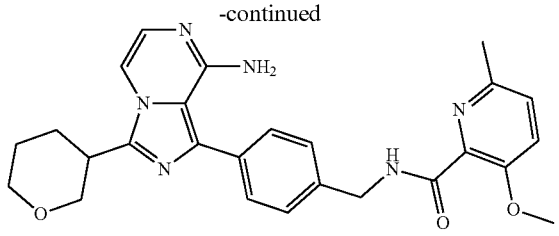


19

Step 1. (3-methoxy-6-methylpyridin-2-yl)methanol (19b)

[0273] To a mixture of 2-(hydroxymethyl)-6-methylpyridin-3-ol 19a (700 mg, 5 mmol) and potassium carbonate (2.07 g, 15 mmol) in DMF (10 mL) was added methyl iodide (1.42 g, 10 mmol). After stirring for 1 hour, the mixture was added with water (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic phase was dried over anhydrous sodium sulfate and the solvent was removed from the filtrate under reduced pressure to give the title compound 19b (600 mg, crude). The product was used directly in the next step without further purification.

[0274] MS m/z (ESI): 154 [M+1]

Step 2. 3-methoxy-6-methylpicolinic acid (19c)

[0275] To a mixture of 19b (600 mg, 4 mmol) and water (40 mL) were added a potassium hydroxide aqueous solution (1 N, 20 mL) and potassium permanganate (1.26 g, 8 mmol) in sequence. After stirring for 1.5 hours, the mixture was adjusted to pH=4-6 with dilute hydrochloric acid (1 N) and extracted with dichloromethane (5×20 mL). The combined organic phase was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane/methanol=100/0 to 4/1) to give the title compound 19c (150 mg, 18%).

[0276] MS m/z (ESI): 168 [M+1]

Step 3. (4-((3-methoxy-6-methylpicolinamido) methyl)phenyl)boronic acid (19d)

[0277] To a mixture of 19c (150 mg, 0.90 mmol), (4-(aminomethyl)phenyl)boronic acid hydrochloride (187 mg, 1.00 mmol) and DIPEA (258 mg, 2.0 mmol) in DMF (2 mL) was added HATU (380 mg, 1.0 mmol). After stirring for one hour, the mixture was added with water (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give the title compound 19d (30 mg, 11%).

[0278] MS m/z (ESI): 301 [M+1]

Step 4. N-(4-(8-((2,4-dimethoxybenzyl)amino)-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-3-methoxy-6-methylpicolinamide (19f)

[0279] A mixture of 19e (59 mg, 0.13 mmol), 19d (30 mg, 0.13 mmol), potassium carbonate (51 mg, 0.39 mmol), $PdCl_2$(dppf) (10 mg, 0.013 mmol), 1,4-dioxane (3 mL) and water (0.3 mL) was heated to 100° C. under a nitrogen atmosphere and stirred for 18 hours. After cooling to room temperature, the solvent was removed under reduced pres-

sure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/0 to 3/2) to give the title compound 19f (30 mg, 37%).

[0280] MS m/z (ESI): 623 [M+1]

Step 5. N-(4-(8-amino-3-(tetrahydro-2H-pyran-3-yl) imidazo[1,5-a]pyrazin-1-yl)benzyl)-3-methoxy-6-methylpicolinamide (19)

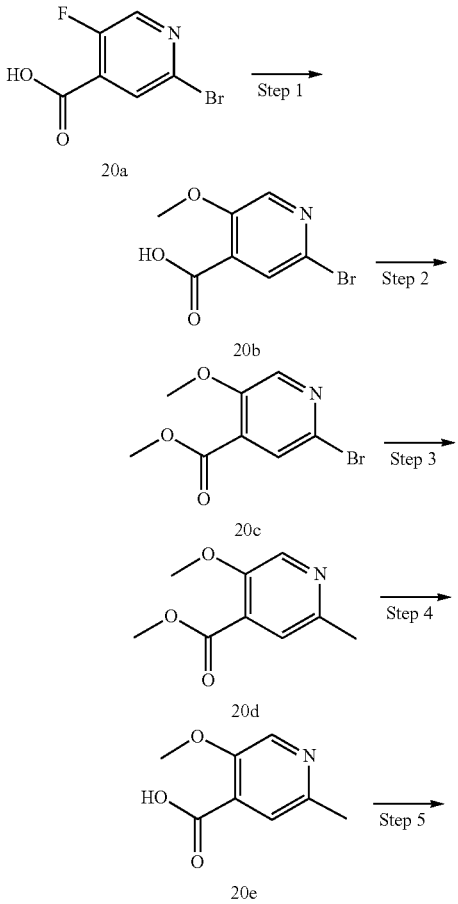
[0281] A mixture of 19f (30 mg, 0.048 mmol) and trifluoroacetic acid (5 mL) was heated to 100° C. and stirred for one hour. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 19 (6.0 mg, solid, 27%).

[0282] MS m/z (ESI): 473 [M+1]

[0283] ^{1}H NMR (400 MHz, CD_3OD) δ 7.73-7.45 (m, 6H), 7.39 (s, 1H), 7.00 (d, J=4.9 Hz, 1H), 4.70 (s, 2H), 4.11-3.85 (m, 5H), 3.71 (t, J=10.9 Hz, 1H), 3.53 (t, J=10.6 Hz, 1H), 3.44 (t, J=11.1 Hz, 1H), 2.48 (s, 3H), 2.15 (d, J=11.9 Hz, 1H), 2.09-1.93 (m, 1H), 1.89 (dd, J=23.3, 10.2 Hz, 1H), 1.77 (d, J=13.1 Hz, 1H).

Example 17. N-(4-(8-amino-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-methoxy-2-methylisonicotinamide (Compound 20)

[0284]



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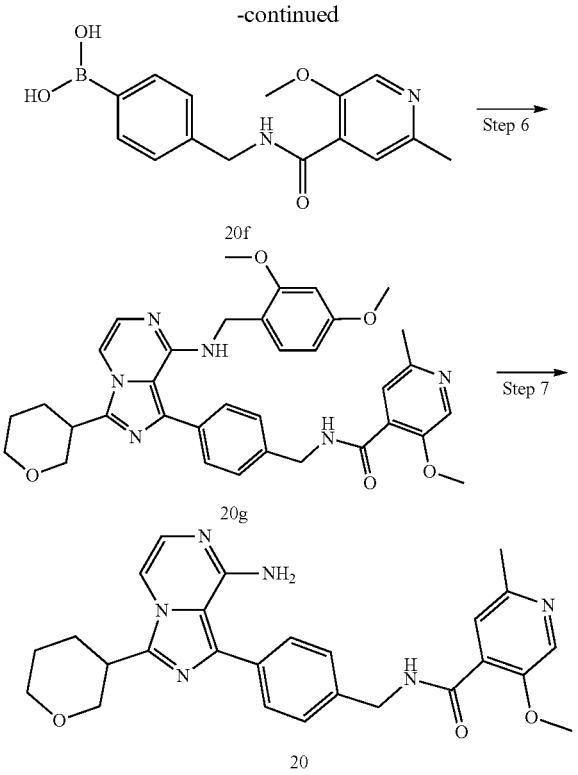


Step 1. 2-bromo-5-methoxyisonicotinic acid (20b)

[0285] To a solution of 2-bromo-5-fluoroisonicotinic acid 20a (2.2 g, 10 mmol) in methanol (40 mL) was added sodium methoxide (2.7 g, 30% in methanol, 15 mmol). The mixture was heated to 60° C. and stirred for 4 hours. After cooling to room temperature, sodium methoxide (1.8 g, 30% in methanol, 10 mmol) was added and the mixture was heated to 60° C. again and stirred for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in water (20 mL) and the mixture was adjusted to pH=4 with hydrochloric acid (12 N). After filtration, the precipitate was collected to give the title compound 20b (2.06 g, 89%).

[0286] MS m/z (ESI): 232 [M+1]

[0287] ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.62 (s, 1H), 8.34 (s, 1H), 7.70 (s, 1H), 3.92 (s, 3H).

Step 2. methyl 2-bromo-5-methoxyisonicotinate (20c)

[0288] To a solution of 20b (2.06 g, 8.9 mmol) in methanol (60 mL) was added concentrated sulfuric acid (1.13 g, 1.3 mmol) and the mixture was heated to reflux for 16 hours. After cooling to room temperature, the solvent was removed under reduced pressure, and to which was added saturated sodium bicarbonate solution (100 mL) The mixture was then extracted with dichloromethane (3×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/0 to 2/3) to give the title compound 20c (1.86 g, 85%).

[0289] MS m/z (ESI): 246 [M+1]

[0290] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.74 (s, 1H), 3.99 (s, 3H), 3.93 (s, 3H).

Step 3. methyl 5-methoxy-2-methylisonicotinate (20d)

[0291] To solution of 20c (1.61 g, 6.6 mmol) in THE (24 mL) were added trimethylaluminum (2 M in hexane, 3.94 mL, 7.9 mmol) and palladium tetrakis(triphenylphosphine) (758 mg, 0.66 mmol) under nitrogen atmosphere. The mixture was heated to 70° C. and stirred for 4 hours. After cooling to room temperature, saturated ammonium chloride solution (100 mL) and ethyl acetate (100 mL) were added sequentially. The precipitate was filtered out and the filtrate was allowed to stand. The separated aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate=100/0 to 2/3) to give the title compound 20d (1.43 g, mixed with triphenylphosphine). The product was used directly in the next step without further purification.

[0292] MS m/z (ESI): 182 [M+1]

[0293] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.44 (s, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 2.54 (s, 3H).

Step 4. 5-methoxy-2-methylisonicotinic acid (20e)

[0294] To a mixture of 20d (1.43 g, mixed with triphenylphosphine) in methanol (6 mL) and THE (6 mL) was added sodium hydroxide solution (2.5 N, 6 mL, 15 mmol). The mixture was stirred for 16 hours, and the solvent was removed under reduced pressure. The residue was dissolved in water (20 mL) and washed with isopropyl ether (3×20 mL). The aqueous layer was acidified with concentrated hydrochloric acid to pH=4, concentrated to a volume of about 2 mL and extracted with THF (100 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound 20e (633 mg, 50% over two steps).

[0295] MS m/z (ESI): 168 [M+1]

[0296] ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H), 8.36 (s, 1H), 7.36 (s, 1H), 3.88 (s, 3H), 2.43 (s, 3H).

Step 5. (4-((5-methoxy-2-methylisonicotinamido) methyl)phenyl)boronic acid (20f)

[0297] To a mixture of 20e (119 mg, 0.71 mmol) and (4-(aminomethyl)phenyl)boronic acid hydrochloride (133 mg, 0.71 mmol) in dichloromethane (2 mL) were added DIPEA (367 mg, 2.84 mmol) and HATU (270 mg, 0.71 mmol). The mixture was stirred for one hour and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/methanol=100/0 to 19/1) to give the title compound 20f (80 mg, 38%).

[0298] MS m/z (ESI): 301 [M+1]

Step 6. N-(4-(8-((2,4-dimethoxybenzyl)amino)-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-methoxy-2-methylisonicotinamide (20g)

[0299] A mixture of 20f (80 mg, 0.27 mmol), 19e (119 mg, 0.27 mmol), potassium carbonate (149 mg, 1.1 mmol), $PdCl_2$(dppf) (20 mg, 0.027 mmol), 1,4-dioxane (20 mL) and water (2 mL) was heated to 100° C. and stirred for 8 hours under a nitrogen atmosphere. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane/methanol=100/0 to 26/1) to give the title compound 20g (54 mg, 32%).

[0300] MS m/z (ESI): 623 [M+1]

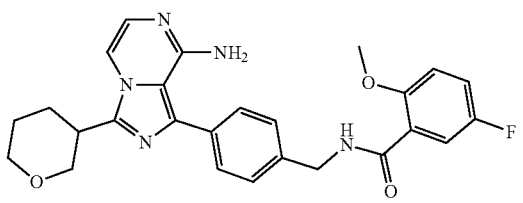
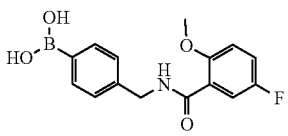
Step 7. N-(4-(8-amino-3-(tetrahydro-2H-pyran-3-yl) imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-methoxy-2-methylisonicotinamide (20)

[0301] A solution of 20g (54 mg, 0.087 mmol) in trifluoroacetic acid (5 mL) was heated to 80° C. and stirred for 20 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 20 (10.8 mg, solid, 26%).

[0302] MS m/z (ESI): 473 [M+1]

[0303] ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 7.70-7.52 (m, 6H), 7.04 (d, J=4.7 Hz, 1H), 4.72 (s, 2H), 4.13-3.99 (m, 2H), 4.07 (s, 3H), 3.74 (t, J=10.9 Hz, 1H), 3.56 (td, J=11.5, 2.5 Hz, 1H), 3.51-3.43 (m, 1H), 2.54 (s, 3H), 2.18 (d, J=12.7 Hz, 1H), 2.04 (ddd, J=15.7, 12.4, 4.2 Hz, 1H), 1.95-1.84 (m, 1H), 1.83-1.75 (m, 1H).

[0304] Compounds as shown below were synthesized according to the procedures for the sixth step to the seventh step in Example 20, except that a different phenylboronic acid was used instead of (4-((5-methoxy-2-methylisonicotinamido)methyl)phenyl)boronic acid 20f in the sixth step.

Compound No.	Structure	Replacement of 20f	MS m/z (ESI)
21			1b 476

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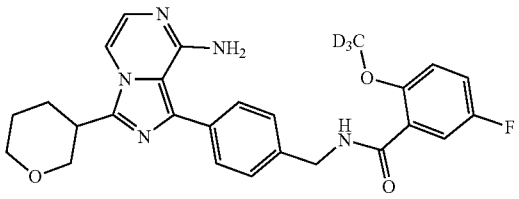
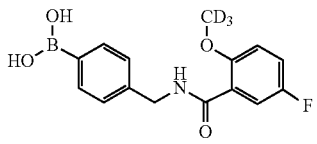
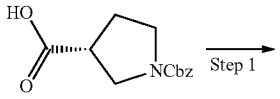
Compound No.	Structure	Replacement of 20f	MS m/z (ESI)
25			18d 479

[0305] The NMR data of compounds 21 and 25 are shown below:

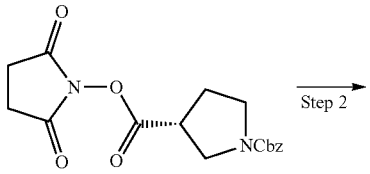
Compound	^{1}H NMR
N-(4-(8-amino-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (21)	^{1}H NMR (400 MHz, DMSO-d_6) δ12.68 (s, 1H), 8.85 (t, J = 6.0 Hz, 1H), 8.13 (s, 1H) 7.70 (d, J = 5.1 Hz, 1H), 7.58-7.49 (m, 3H), 7.45 (d, J = 8.1 Hz, 2H), 7.39-7.30 (m, 1H), 7.19 (dd, J = 9.1, 4.3 Hz, 1H), 7.03 (d, J = 5.0 Hz, 1H), 5.99 (s, 2H), 4.57 (d, J = 6.1 Hz, 2H), 4.00 (d, J = 11.0 Hz, 1H), 3.90 (s, 3H), 3.58 (t, J = 10.8 Hz, 1H), 3.47-3.36 (m, 2H), 2.08 (d, J = 11.2 Hz, 1H), 1.94-1.65 (m, 4H).
N-(4-(8-amino-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-(methoxy-d_3)benzamide (25)	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (t, J = 5.9 Hz, 1H), 7.70 (d, J = 5.0 Hz, 1H), 7.60-7.40 (m, 5H), 7.37-7.31 (m, 1H), 7.18 (dd, J = 9.1, 4.2 Hz, 1H), 7.02 (d, J = 4.9 Hz, 1H), 5.98 (s, 2H), 4.57 (d, J = 6.0 Hz, 2H), 3.95 (dd, J = 35.6, 10.9 Hz, 2H), 3.59 (t, J = 10.8 Hz, 1H), 3.46-3.36 (m, 2H), 2.08 (d, J = 7.8 Hz, 1H), 1.92-1.69 (m, 3H).

Example 18. (R)—N-(4-(4-amino-7-(pyrrolidin-3-yl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 22)

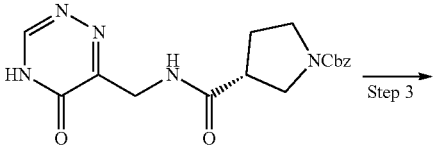
[0306]



22a



22b



22c

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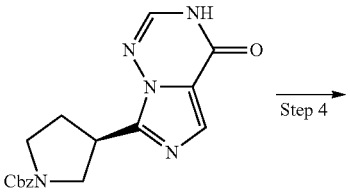
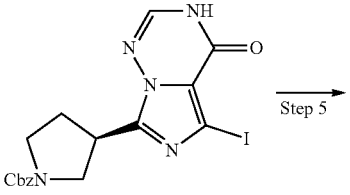
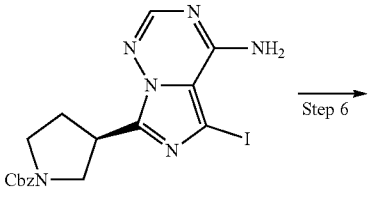


22d



22e



22f

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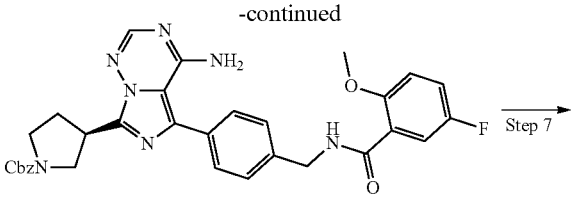
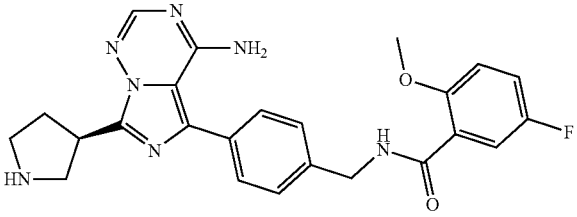


22g



22

Step 1. 1-benzyl 3-(2,5-dioxopyrrolidin-1-yl) (R)-pyrrolidine-1,3-dicarboxylate (22b)

[0307] A mixture of (R)-1-((benzyloxy)carbonyl)pyrrolidine-3-carboxylic acid 22a (748 mg, 3 mmol) and 1-hydroxy-pyrrolidine-2,5-dione (380 mg, 3.3 mmol) in THE (30 mL) was cooled to 0° C. and added with dicyclohexylcarbodiimide (743 mg, 3.6 mmol). After warming to room temperature and stirring for 4 hours, the mixture was cooled to 0° C. and filtered. The filtrate was concentrated to dryness under reduced pressure to give the title compound 22b (1.1 g, 100%). The product was used directly in the next step without further purification.

[0308] MS m/z (ESI): 347 [M+1]

Step 2. benzyl (R)-3-(((5-oxo-4,5-dihydro-1,2,4-triazin-6-yl)methyl)carbamoyl)pyrrolidine-1-carboxylate (22c)

[0309] To a mixture of 12f (915 mg, 6 mmol) and DBU (4.6 g, 30 mmol) in DMF (10 mL) was added 22b (1.1 g, 3 mmol) in THE (10 mL). After stirring for 4 hours, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 22c (240 mg, 22%).

[0310] MS m/z (ESI): 358 [M+1]

Step 3. benzyl (R)-3-(4-oxo-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate (22d)

[0311] To a solution of 22c (240 mg, 0.67 mmol) in acetonitrile (15 mL) was added phosphine oxychloride (5 mL). The resulting mixture was heated to 80° C. and stirred for 5 hours. After cooling to room temperature, the solvent was removed under reduced pressure to give the title compound 22d (270 mg, crude). The product was used directly in the next step without further purification.

[0312] MS m/z (ESI): 340 [M+1]

Step 4. benzyl (R)-3-(5-iodo-4-oxo-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate (22e)

[0313] To a solution of 22d (270 mg, crude, 0.67 mmol) in DMF (10 mL) was added NIS (1.51 g, 6.7 mmol). The resulting mixture was heated to 50° C. and stirred for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 22e (140 mg, 45%).

[0314] MS m/z (ESI): 466 [M+1]

Step 5. benzyl (R)-3-(4-amino-5-iodoimidazo[5,1-J][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate (22f)

[0315] To a solution of 1H-[1,2,4]triazole (207 mg, 3 mmol) in pyridine (1 mL) was added phosphine oxychloride (138 mg, 0.9 mmol). After stirring for 10 minutes, a solution of 22e (140 mg, 0.3 mmol) in pyridine (1 mL) was added. After stirring for additional 2 hours, a solution of ammonia in isopropanol (2 M, 5 mL, 10 mmol) was added and stirring was continued for another hour. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=20/1 to 1/2) to give the title compound 22f (220 mg, crude). The product was used directly in the next step without further purification.

[0316] MS m/z (ESI): 465 [M+1]

Step 6. benzyl (R)-3-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate (22g)

[0317] A mixture of 22f (220 mg, crude product), 1b (136 mg, 0.45 mmol), potassium carbonate (83 mg, 0.6 mmol), $PdCl_2$(dppf) (44 mg, 0.06 mmol), 1,4-dioxane (4 mL) and water (1 mL) were heated to 105° C. under a nitrogen atmosphere and stirred for 1.5 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 22g (45 mg, 25%).

[0318] MS m/z (ESI): 596 [M+1]

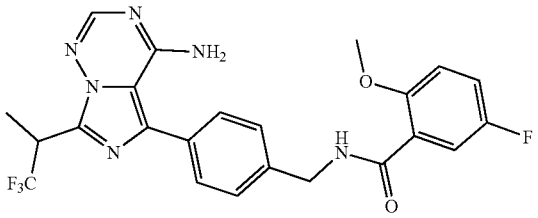
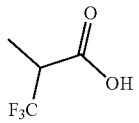
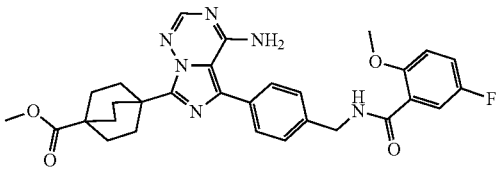
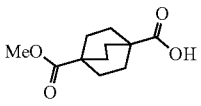
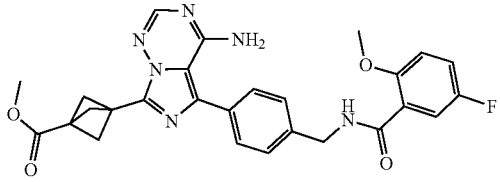
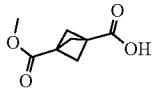
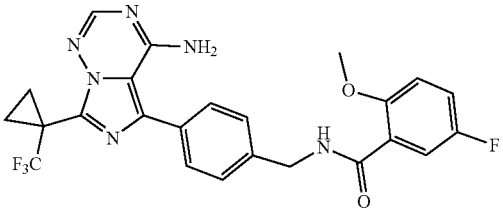
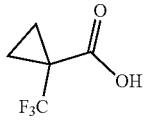
Step 7. (R)—N-(4-(4-amino-7-(pyrrolidin-3-yl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (22)

[0319] To a solution of 22g (45 mg, 0.076 mmol) in dichloromethane (10 mL) at 0° C. was added trimethylsilyl iodide (30 mg, 0.15 mmol). The mixture was warmed to room temperature and stirred for 2 hours. The solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 22 (20 mg, solid, 57%).

[0320] MS m/z (ESI): 462 [M+1]

[0321] ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (s, 1H), 7.67-7.59 (m, 3H), 7.55 (d, J=8.3 Hz, 2H), 7.26 (ddd, J=9.1, 7.6, 3.3 Hz, 1H), 7.18 (dd, J=9.1, 4.2 Hz, 1H), 4.69 (s, 2H), 4.32-4.25 (m, 1H), 3.97 (d, J=8.2 Hz, 3H), 3.81-3.73 (m, 2H), 3.60-3.54 (m, 1H), 3.47 (dd, J=7.4, 4.2 Hz, 1H), 2.57 (dd, J=13.4, 6.3 Hz, 1H), 2.46-2.39 (m, 1H).

[0322] Compounds shown below were synthesized according to the procedures for the first to sixth steps in Example 18, except that a different carboxylic acid was used instead of (R)-1-((benzyloxy)carbonyl)pyrrolidine-3-carboxylic acid 22a in the first step.

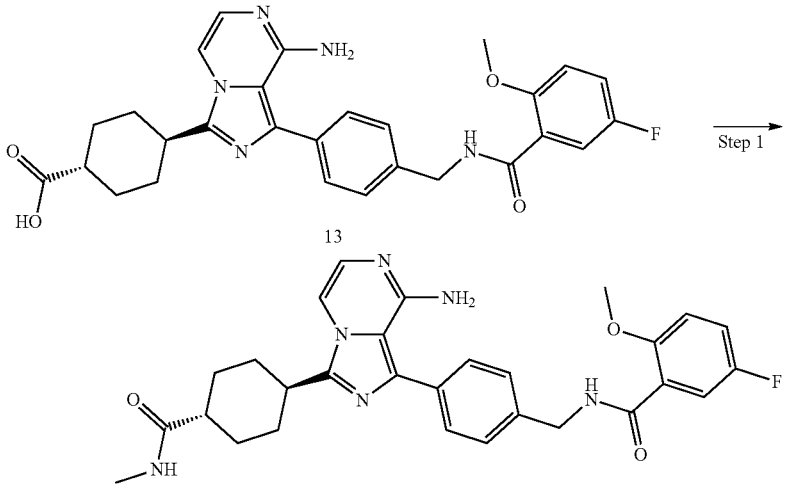
Compound No.	Structure	Compound replacing 22a	MS m/z (ESI)
26			489
28			559
29			517
43			501

[0323] The NMR data of compounds 26, 28, 29 and 43 are shown below:

Compound	^{1}H NMR
N-(4-(4-amino-7-(1,1,1-trifluoropropan-2-yl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (26)	^{1}H NMR (400 MHz, CD_3OD) δ 7.91 (s, 1H), 7.65-7.61 (m, 3H), 7.55 (d, J = 8.3 Hz, 2H), 7.26 (ddd, J = 9.1, 7.6, 3.3 Hz, 1H), 7.17 (dd, J = 9.1, 4.2 Hz, 1H), 4.70 (s, 2H), 4.58-4.51 (m, 1H), 3.97 (s, 3H), 1.66 (d, J = 7.3 Hz, 3H).
methyl 4-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)bicyclo[2.2.2]octane-1-carboxylate (28)	^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (s, 1H), 7.64-7.57 (m, 3H), 7.52 (d, J = 8.3 Hz, 2H), 7.25 (ddd, J = 9.1, 7.6, 3.3 Hz, 1H), 7.17 (dd, J = 9.1, 4.2 Hz, 1H), 4.69 (s, 2H), 3.96 (s, 3H), 3.66 (s, 3H), 2.26 (dd, J = 9.7, 6.2 Hz, 6H), 1.93 (dd, J = 9.7, 6.3 Hz, 6H).
methyl 3-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)bicyclo[1.1.1]pentane-1-carboxylate (29)	^{1}H NMR (400 MHz, CD_3OD) δ7.85 (s, 1H), 7.65-7.59 (m, 3H), 7.54 (d, J = 8.3 Hz, 2H), 7.28-7.22 (m, 1H), 7.17 (dd, J = 9.1, 4.2 Hz, 1H), 4.69 (s, 2H), 3.97 (s, 3H), 3.71 (s, 3H), 2.63 (s, 6H).
N-(4-(4-amino-7-(1-(trifluoromethyl)cyclopropyl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (43)	^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (s, 1H), 7.62 (dd, J = 8.7, 2.4 Hz, 3H), 7.55 (d, J = 8.1 Hz, 2H), 7.28-7.22 (m, 1H), 7.17 (dd, J = 9.1, 4.2 Hz, 1H), 4.70 (s, 2H), 3.97 (s, 3H), 1.59 (dd, J = 7.6, 5.5 Hz, 2H), 1.43 (d, J = 6.0 Hz, 2H).

Example 19. N-(4-(8-amino-3-((1r,4r)-4-(methylcarbamoyl)cyclohexyl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 23)

[0324]



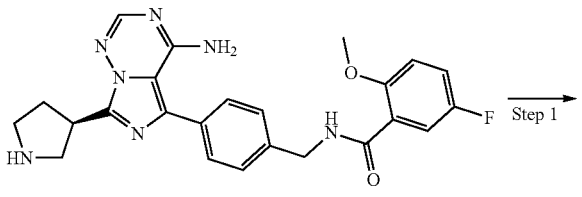
[0325] To a mixture of 13 (8 mg, 0.015 mmol), ammonium chloride (3 mg, 0.045 mmol) and DIPEA (8 mg, 0.06 mmol) in DMF (2 mL) was added HATU (11 mg, 0.03 mmol). After stirring for 30 minutes, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 23 as a formate salt (5.5 mg, solid, 63%).

[0326] MS m/z (ESI): 531 [M+1]

[0327] 1H NMR (400 MHz, CD_3OD) δ 9.02 (s, 1H), 7.88 (d, J=4.9 Hz, 1H), 7.71 (d, J=5.6 Hz, 1H), 7.60 (dt, J=24.3, 6.5 Hz, 4H), 7.29-7.22 (m, 1H), 7.18 (dd, J=9.1, 4.2 Hz, 1H), 6.98 (d, J=5.5 Hz, 1H), 4.71 (d, J=3.9 Hz, 2H), 3.98 (s, 3H), 3.22-3.14 (m, 1H), 2.73 (d, J=4.5 Hz, 3H), 2.31 (dd, J=13.4, 9.8 Hz, 1H), 2.08 (d, J=13.4 Hz, 2H), 1.96 (d, J=12.4 Hz, 2H), 1.87-1.65 (m, 4H).

Example 20. (R)—N-(4-(4-amino-7-(1-(cyclopropanecarbonyl)pyrrolidin-3-yl)imidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 24)

[0328]



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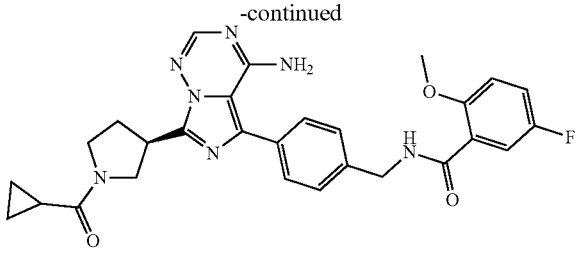


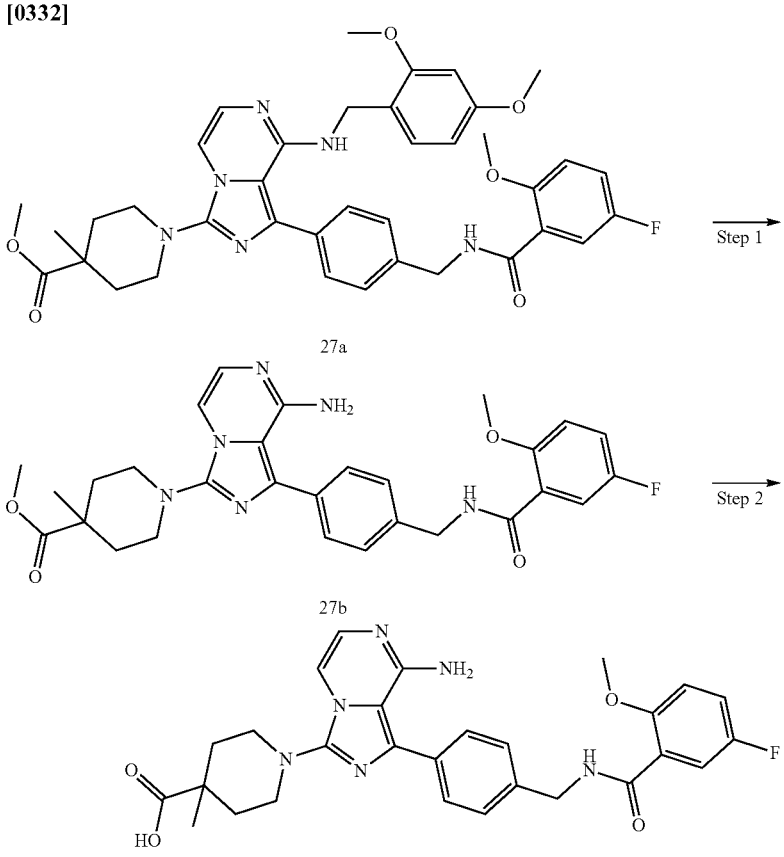
[0329] To a mixture of 22 (110 mg, 0.24 mmol) and saturated sodium bicarbonate solution (5 mL) in THE (10 mL) at 0° C. was added cyclopropylformyl chloride (37 mg, 0.36 mmol). After warming to room temperature, the mixture was stirred for 30 minutes, diluted with saturated brine (10 mL) and extracted with ethyl acetate (2×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/methanol=100/1 to 15/1) to give the title compound 24 (57.5 mg, solid, 45%).

[0330] MS m/z (ESI): 530 [M+1]

[0331] ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (dd, J=6.5, 2.7 Hz, 1H), 7.62 (dd, J=9.1, 3.0 Hz, 3H), 7.53 (d, J=8.1 Hz, 2H), 7.28-7.22 (m, 1H), 7.17 (dd, J=9.1, 4.2 Hz, 1H), 4.69 (s, 2H), 4.30-4.19 (m, 1H), 4.11-3.99 (m, 2H), 3.97 (s, 3H), 3.91-3.68 (m, 2H), 2.55-2.37 (m, 2H), 1.87-1.78 (m, 1H), 0.93-0.81 (m, 4H).

Example 21. 1-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-4-methylpiperidine-4-carboxylic acid (Compound 27)

[0332]



27a

27b

27

Step 1. methyl 1-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-4-methylpiperidine-4-carboxylate (27b)

[0333] A mixture of 27a (360 mg, 0.52 mmol) and trifluoroacetic acid (5 mL) was heated to 90° C. and stirred for 5 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 27b (180 mg, 64%).

[0334] MS m/z (ESI): 547 [M+1]

Step 2. 1-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-4-methylpiperidine-4-carboxylic acid (27)

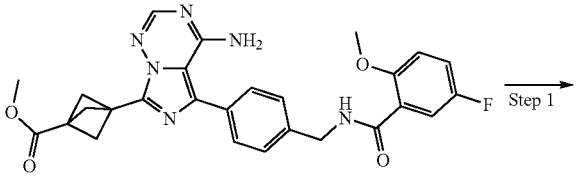
[0335] A mixture of 27b (180 mg, 0.33 mmol), water (2 mL), methanol (2 mL) and lithium hydroxide (79 mg, 3.3 mmol) was stirred for two hours. The solvent was then removed under reduced pressure and the residue was purified by prep-HPLC to give the title compound 27 (21.2 mg, solid, 12%).

[0336] MS m/z (ESI): 533 [M+1]

[0337] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 8.84 (t, J=5.6 Hz, 1H), 7.57 (d, J=8.2 Hz, 2H), 7.52 (dd, J=9.2, 3.3 Hz, 1H), 7.44 (d, J=8.2 Hz, 2H), 7.37-7.31 (m, 1H), 7.23 (d, J=5.0 Hz, 1H), 7.19 (dd, J=9.1, 4.3 Hz, 1H), 6.95 (d, J=5.0 Hz, 1H), 6.01 (s, 2H), 4.56 (d, J=6.0 Hz, 2H), 3.90 (s, 3H), 3.22 (m, 2H), 2.96 (m, 2H), 2.11 (d, J=13.4 Hz, 2H), 1.63 (m, 2H), 1.22 (s, 3H).

Example 22. 3-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (Compound 31)

[0338]



29

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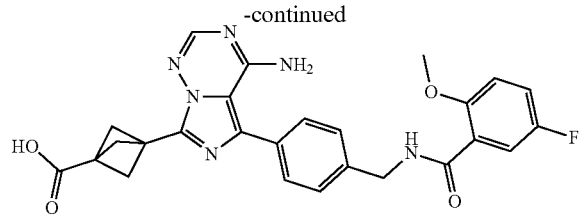


31

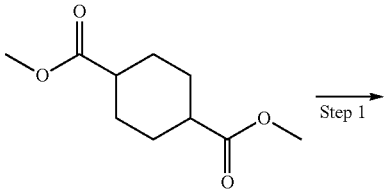
[0339] A mixture of 29 (65 mg, 0.13 mmol) and aqueous lithium hydroxide (1 N, 2 mL) in THF (10 mL) was stirred for four hours. The mixture was adjusted to pH=7-8 with glacial acetic acid and extracted with ethyl acetate (2×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give the title compound 31 (50 mg, solid, 79%).

[0340] MS m/z (ESI): 503 [M+1]

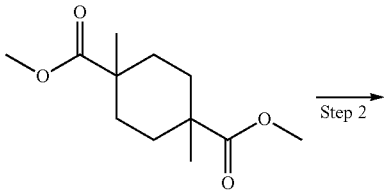
[0341] ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.64-7.59 (m, 3H), 7.54 (d, J=8.3 Hz, 2H), 7.25 (ddd, J=9.1, 7.6, 3.3 Hz, 1H), 7.17 (dd, J=9.1, 4.2 Hz, 1H), 4.70 (d, J=4.0 Hz, 2H), 3.97 (s, 3H), 2.62 (s, 6H).

Example 23. (1r,4r)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-1,4-dimethylcyclohexane-1-carboxylic acid (Compound 32)

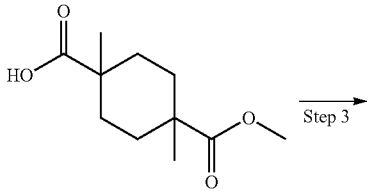
[0342]



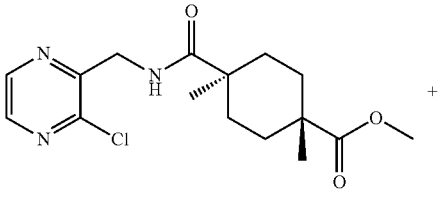
32a



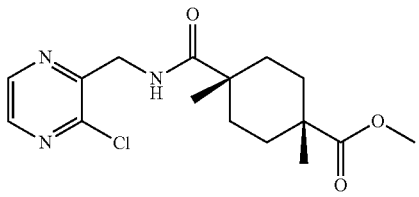
32b



32c



32d



32e

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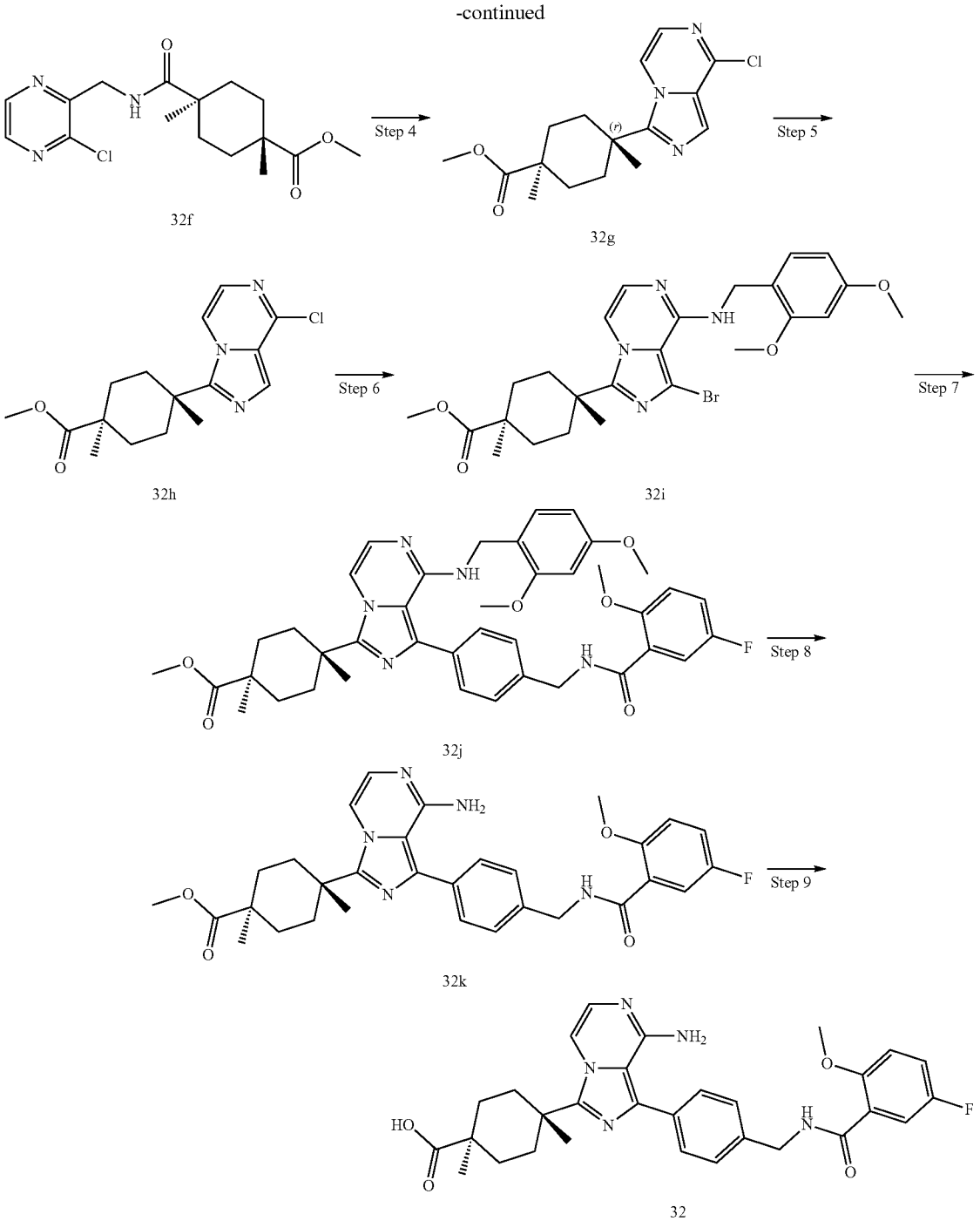


Step 1. dimethyl 1,4-dimethylcyclohexane-1,4-dicarboxylate (32b)

[0343] To a solution of LDA (2 M, 12.5 mL, 25 mmol) and hexamethylphosphoric triamide (13.9 mL, 79.9 mmol) in THE (25 mL) at −78° C. was added dimethyl cyclohexane-1,4-dicarboxylate 32a (2 g, 10 mmol) in THE (2 mL). After stirring for one hour, the mixture was warmed to 0° C. and stirred for another hour. The mixture was re-cooled to −78° C. and methyl iodide (7.75 g, 54.6 mmol) was added. The resulting mixture was stirred at room temperature for two hours, added with 1 N hydrochloric acid (3 mL) and extracted with ethyl acetate (50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=78/22) to give the title compound 32b (450 mg, 20%).

[0344] ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.59 (s, 6H), 1.79-1.70 (m, 4H), 1.47-1.38 (m, 4H), 1.13 (s, 6H).

Step 2. 4-(methoxycarbonyl)-1,4-dimethylcyclohexane-1-carboxylic acid (32c)

[0345] A mixture of 32b (387 mg, 1.70 mmol), potassium hydroxide (476 mg, 8.5 mmol), methanol (2 mL) and water (2 mL) were heated to 80° C. and stirred for 16 hours. After cooling to room temperature, the reaction mixture was concentrated to dryness under reduced pressure, added with 1 N hydrochloric acid (5 mL) and extracted with ethyl acetate (8 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under reduced pressure to give the title compound 32c (325 mg, crude, 90%).

[0346] ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.59 (s, 3H), 1.82-1.70 (m, 4H), 1.46-1.32 (m, 4H), 1.12 (d, J=7.6 Hz, 6H).

Step 3. methyl (1r,4r)-4-(((3-chloropyrazin-2-yl)methyl)carbamoyl)-1,4-dimethylcyclohexane-1-carboxylate (32d) and methyl (1s,4s)-4-(((3-chloropyrazin-2-yl)methyl)carbamoyl)-1,4-dimethylcyclohexane-1-carboxylate (32e)

[0347] To a mixture of 32c (492 mg, 2.30 mmol) and (3-chloro-pyrazin-2-yl)methylamine hydrochloride (621 mg, 3.45 mmol) in DMF (15 mL) were added DIPEA (1.48 g, 11.45 mmol) and HATU (1.31 g, 15 mL). After stirring for 2 hours, the mixture was purified by prep-HPLC and then by silica gel column chromatography (petroleum ether/ethyl acetate=1/1) to give the title compound 32d (190 mg, 24%) and 32e (60 mg, 8%)

[0348] MS m/z (ESI): 340 [M+1]

Step 4 through Step 7. methyl (1r,4r)-4-(8-((2,4-dimethoxybenzyl)amino)-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-1,4-dimethylcyclohexane-1-carboxylate (32j)

[0349] 32j was synthesized according to the procedures for step 2 to 5 in Example 4, except that 32d was used instead of 5b.

[0350] MS m/z (ESI): 710 [M+1]

Step 8. methyl (1r,4r)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-1,4-dimethylcyclohexane-1-carboxylate (32k)

[0351] A solution of 32j (60 mg, 0.084 mmol) in trifluoroacetic acid (3 mL) was heated to 90° C. and stirred for 5 hours. After cooling to room temperature, the mixture was concentrated to dryness and the residue was purified by prep-HPLC to give the title compound 32k (30 mg, 63%).

[0352] MS m/z (ESI): 560 [M+1]

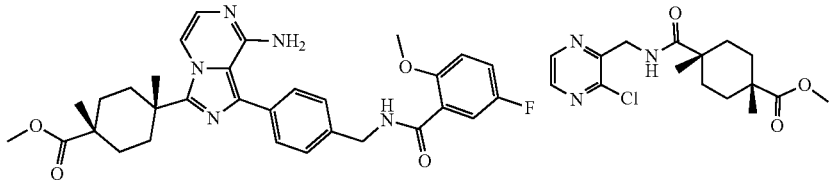
Step 9. (1r,4r)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-1,4-dimethylcyclohexane-1-carboxylic acid (32)

[0353] A mixture of 32k (30 mg, 0.054 mmol), lithium hydroxide monohydrate (9.6 mg, 0.24 mmol), water (1 mL) and methanol (1 mL) was stirred for 2 hours and then concentrated to dryness under reduced pressure. The residue was purified by prep-HPLC to give the title compound 32 (9 mg, solid, 31%).

[0354] MS m/z (ESI): 546 [M+1]

[0355] ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 7.73 (d, J=5.5 Hz, 1H), 7.63 (dd, J=9.0, 3.1 Hz, 3H), 7.54 (d, J=8.3 Hz, 2H), 7.26 (ddd, J=9.1, 7.6, 3.3 Hz, 1H), 7.17 (dd, J=9.1, 4.2 Hz, 1H), 6.94 (d, J=5.4 Hz, 1H), 4.70 (s, 2H), 3.97 (s, 3H), 2.58 (d, J=14.4 Hz, 2H), 2.09 (d, J=13.8 Hz, 2H), 1.65 (t, J=11.9 Hz, 2H), 1.39 (s, 5H), 1.09 (s, 3H).

[0356] Compound 39 was synthesized according to the procedures for the fourth to eighth step in Example 23, except that 32e was used instead of 32d in the fourth step.

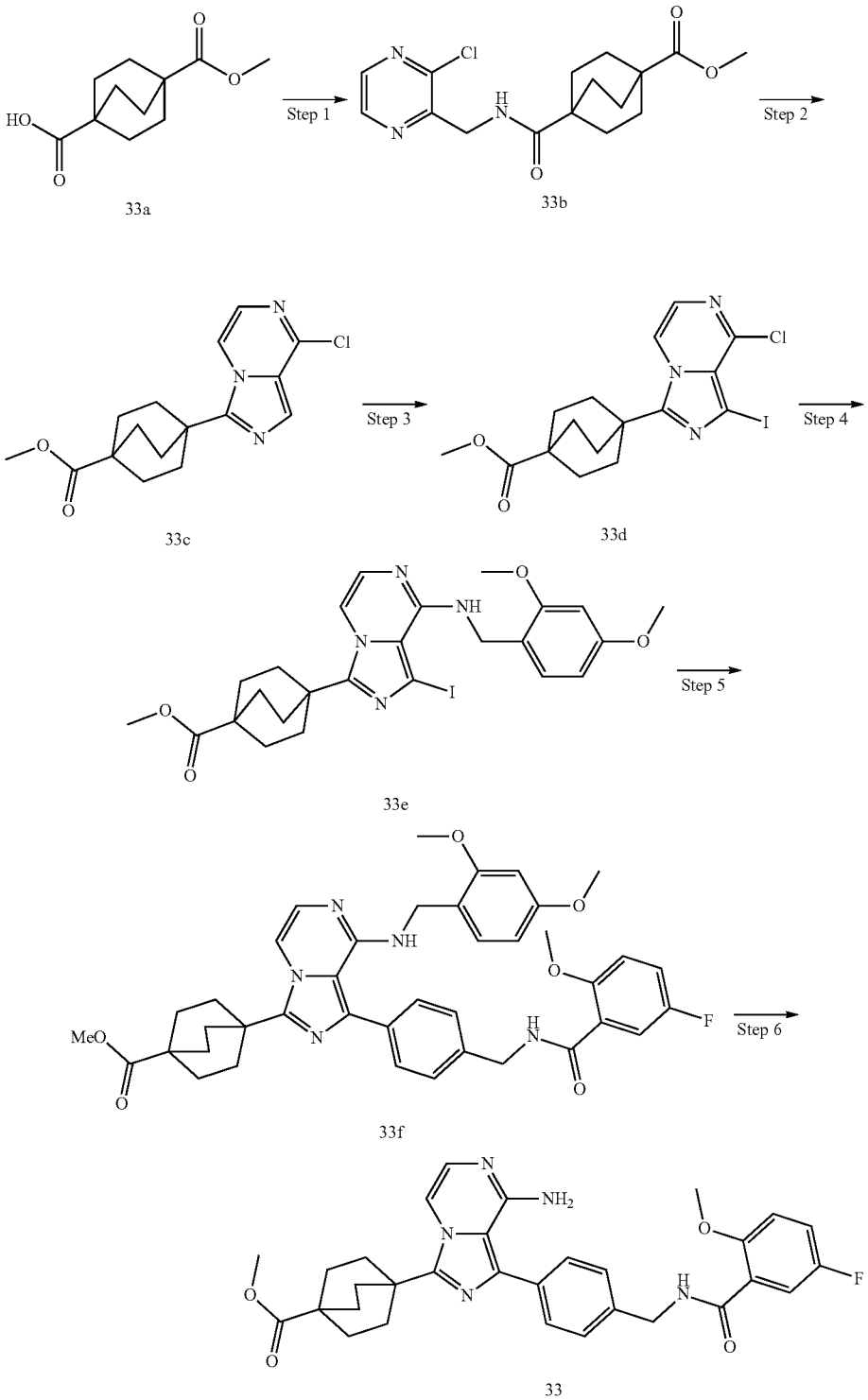
Compound No.	Structure	Compound replacing 32d	MS m/z (ESI)
39		32e	546

[0357] The NMR data of Compound 39 is shown below:

Compound	^{1}H NMR
methyl (1s,4s)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-1,4-dimethylcyclohexane-1-carboxylate (39)	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 7.79 (d, J = 5.5 Hz, 1H), 7.53 (m, 5H), 7.38-7.30 (m, 1H), 7.19 (m, 1H), 6.98 (d, J = 5.5 Hz, 1H), 6.85 (s, 2H), 4.58 (d, J = 6.1 Hz, 2H), 3.90 (s, 3H), 3.57 (s, 3H), 2.08 (t, J = 10.4 Hz, 2H), 2.01-1.81 (m, 4H), 1.53 (s, 2H), 1.43 (s, 3H), 1.21 (s, 3H).

Example 24. methyl 4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)bicyclo[2.2.2]octane-1-carboxylate (Compound 33)

[0358]



Step 1. methyl 4-(((3-chloropyrazin-2-yl)methyl) carbamoyl)bicyclo[2.2.2]octane-1-carboxylate (33b)

[0359] To a mixture of 4-(methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid 33a (1.06 g, 5 mmol), (3-chloropyrazin-2-yl)methylamine hydrochloride 5a (900 mg, 5 mmol) and DIPEA (1.94 g, 15 mmol) in DMF (10 mL) was added HATU (2.47 g, 6.5 mmol). After stirring for 30 minutes, the mixture was diluted with water (40 mL) and extracted with ethyl acetate (2×100 mL). The combined organic phase was washed with saturated brine (80 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 2/1) to give the title compound 33b (1.5 g, 89%).

[0360] MS m/z (ESI): 338 [M+1]

Step 2. methyl 4-(8-chloroimidazo[1,5-a]pyrazin-3-yl)bicyclo[2.2.2]octane-1-carboxylate (33c)

[0361] A mixture of 33b (1.5 g, 4.44 mmol) and phosphine oxychloride (20 mL) in acetonitrile (10 mL) was heated to 120° C. and stirred for 4 hours. After cooling to room temperature, the solvent was removed under reduced pressure to give the title compound 33c (1.4 g, crude). The product was used directly in the next step without further purification.

[0362] MS m/z (ESI): 320 [M+1]

Step 3. methyl 4-(8-chloro-1-iodoimidazo[1,5-a] pyrazin-3-yl)bicyclo[2.2.2]octane-1-carboxylate (33d)

[0363] To a mixture of 33c (1.4 g, crude product) in DMF (10 mL) was added NIS (2 g, 8.9 mmol). The resulting mixture was heated to 50° C. and stirred for 2 hours. After cooling to room temperature, the mixture was diluted with water (30 mL) and extracted with ethyl acetate (2×100 mL). The combined organic phase was washed with saturated brine (80 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 2/1) to give the title compound 33d (1.5 g, 76% in two steps).

[0364] MS m/z (ESI): 446 [M+1]

Step 4. methyl 4-(8-((2,4-dimethoxybenzyl)amino)-1-iodoimidazo[1,5-a]pyrazin-3-yl)bicyclo[2.2.2] octane-1-carboxylate (33e)

[0365] A mixture of 33d (1.5 g, 3.4 mmol), 2,4-dimethoxybenzylamine (675 mg, 4.0 mmol) and DIPEA (868 mg, 6.7 mmol) in acetonitrile (30 mL) was heated at 90° C. and stirred for 15 hours in a sealed tube. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 3/1) to give the title compound 33e (1.7 g, 88%).

[0366] MS m/z (ESI): 577 [M+1]

Step 5. methyl 4-(8-((2,4-dimethoxybenzyl)amino)-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)bicyclo[2.2.2]octane-1-carboxylate (33f)

[0367] A mixture of 33e (1.7 g, 3 mmol), 1b (1.36 g, 4.5 mmol), potassium carbonate (828 mg, 6 mmol), $PdCl_2$(dppf) (219 mg, 0.3 mmol), 1,4-dioxane (16 mL) and water (4 mL) was heated to 100° C. under a nitrogen atmosphere and stirred for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 1/2) to give the title compound 33f (1.7 g, 80%).

[0368] MS m/z (ESI): 708 [M+1]

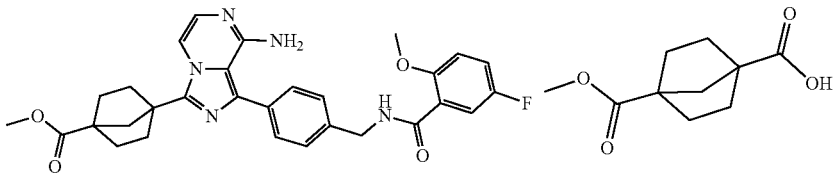
Step 6. methyl 4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a] pyrazin-3-yl)bicyclo[2.2.2]octane-1-carboxylate (33)

[0369] A mixture of 33f (1.7 g, 2.4 mmol), dichloromethane (5 mL) and trifluoroacetic acid (30 mL) was heated to reflux and stirred for 5 hours. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in methanol (50 mL) and adjusted to pH 7-8 with saturated sodium bicarbonate solution. The solvent was then removed under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane/methanol=100/1 to 20/1) to give the title compound 33 (1.2 g, solid, 89%).

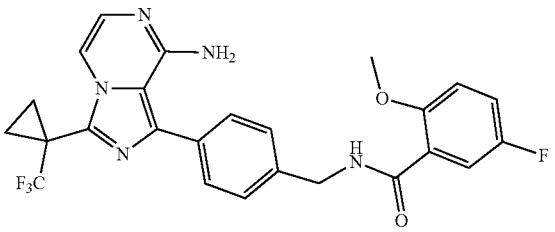
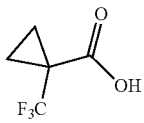
[0370] MS m/z (ESI): 558 [M+1]

[0371] ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J=5.3 Hz, 1H), 7.62 (dd, J=9.2, 3.2 Hz, 1H), 7.55 (dd, J=19.7, 8.3 Hz, 4H), 7.28-7.22 (m, 1H), 7.17 (dd, J=9.1, 4.2 Hz, 1H), 6.93 (d, J=5.3 Hz, 1H), 4.69 (s, 2H), 3.96 (s, 3H), 3.67 (s, 3H), 2.18 (dd, J=9.8, 5.9 Hz, 6H), 1.98 (dd, J=9.7, 5.9 Hz, 6H).

[0372] The compounds as shown below were synthesized according to the procedures in Example 24, except that a different carboxylic acid was used instead of 4-(methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid 33a in the first step.

Compound No.	Structure	Compound replacing 33a	MS m/z (ESI)
38			544

-continued

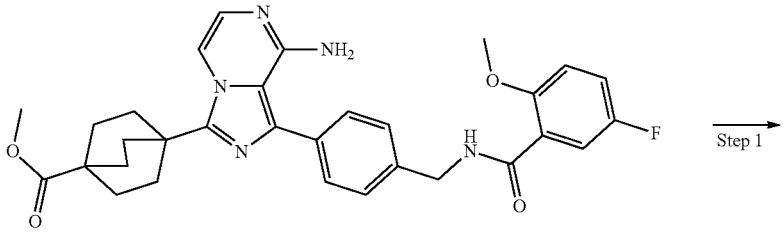
Compound No.	Structure	Compound replacing 33a	MS m/z (ESI)
42			500

[0373] The NMR data of compounds 38 and 42 are shown below:

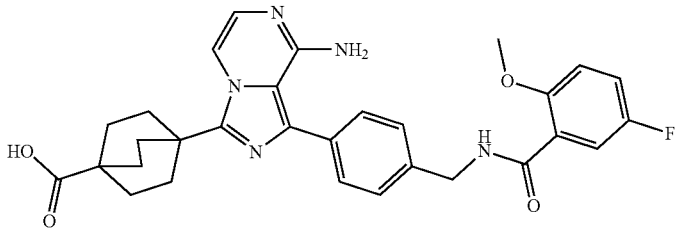
Compound	^{1}H NMR
methyl 4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)bicyclo[2.2.1]heptane-1-carboxylate (38)	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.68 (d, J = 5.1 Hz, 1H), 7.58-7.49 (m, 3H), 7.45 (d, J = 8.2 Hz, 2H), 7.37-7.30 (m, 1H), 7.19 (m, 1H), 6.99 (d, J = 5.0 Hz, 1H), 5.96 (s, 2H), 4.57 (d, J = 6.1 Hz, 2H), 3.90 (s, 3H), 3.65 (s, 3H), 2.19 (s, 2H), 2.09 (m, 6H), 1.77 (m, 2H).
N-(4-(8-amino-3-(1-(trifluoromethyl)cyclopropyl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (42)	^{1}H NMR (400 MHz, CD_3OD) δ 7.69 (d, J = 5.1 Hz, 1H), 7.66-7.58 (m, 3H), 7.54 (d, J = 8.2 Hz, 2H), 7.25 (ddd, J = 9.1, 7.7, 3.3 Hz, 1H), 7.20-7.11 (m, 2H), 4.70 (s, 2H), 3.97 (s, 3H), 1.66 (dd, J = 7.3, 5.4 Hz, 2H), 1.41 (s, 2H).

Example 25. 4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)bicyclo[2.2.2]octane-1-carboxylic acid (Compound 34)

[0374]



33



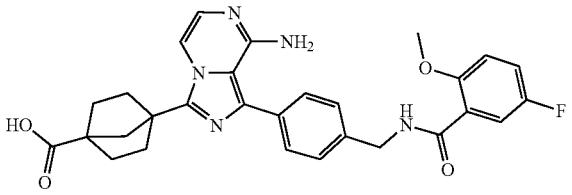
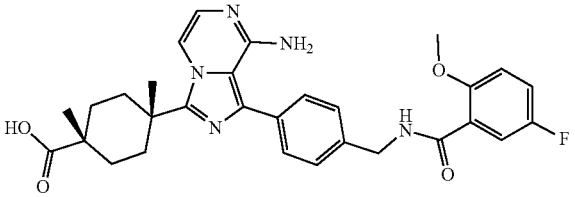
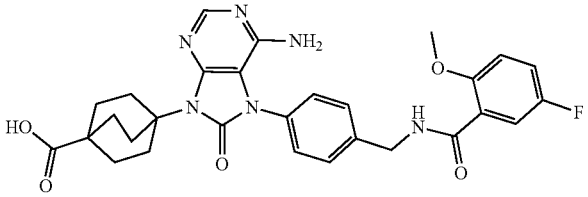
34

[0375] A mixture of 33 (1 g, 1.8 mmol) and aqueous lithium hydroxide solution (1 N, 6 mL) in THE (20 mL) was heated to 50° C. and stirred for 15 hours. After cooling to room temperature, glacial acetic acid (1 mL) was added to the mixture and the solvent was removed under reduced pressure. The residue was purified by prep-HPLC to give the title compound 34 (300 mg, solid, 31%).

[0376] MS m/z (ESI): 544 [M+1]

[0377] ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, J=5.3 Hz, 1H), 7.62 (dd, J=9.2, 3.2 Hz, 1H), 7.55 (dd, J=20.5, 8.3 Hz, 4H), 7.28-7.23 (m, 1H), 7.17 (dd, J=9.1, 4.2 Hz, 1H), 6.93 (d, J=5.3 Hz, 1H), 4.70 (s, 2H), 3.96 (s, 3H), 2.18 (dd, J=9.6, 5.9 Hz, 6H), 1.99 (dd, J=9.8, 5.8 Hz, 6H).

[0378] The compounds as shown below were synthesized according to the procedures in Example 25, except that different esters were used instead of 33.

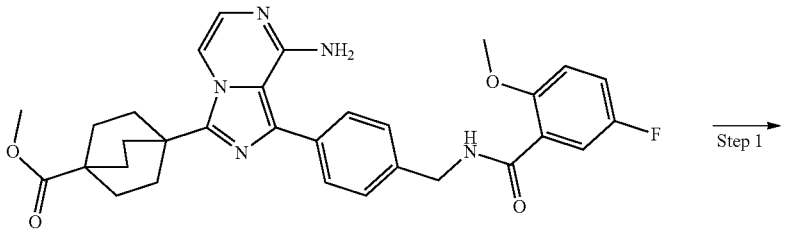
Compound No.	Structure	Compound replacing 33	MS m/z (ESI)
40		38	530
41		39	546
48		48a	561

[0379] The NMR data of compounds 40, 41 and 48 are shown below:

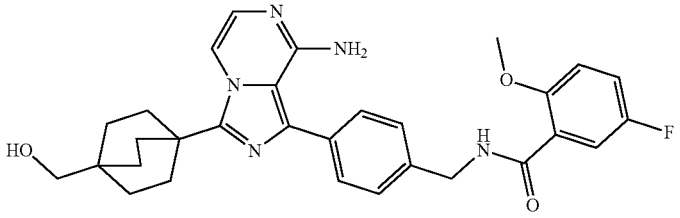
Compound	^{1}H NMR
4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)bicyclo[2.2.1]heptane-1-carboxylic acid (40)	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1H), 8.85 (t, J = 6.1 Hz, 1H), 7.68 (d, J = 4.6 Hz, 1H), 7.58-7.50 (m, 3H), 7.45 (d, J = 8.2 Hz, 2H), 7.34 (m, 1H), 7.19 (m, 1H), 6.99 (s, 1H), 5.96 (s, 2H), 4.57 (d, J = 6.1 Hz, 2H), 3.90 (s, 3H), 2.09 (m, 8H), 1.73 (d, J = 9.2 Hz, 2H).
(1s,4s)-4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-1,4-dimethylcyclohexane-1-carboxylic acid (41)	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (s, 1H), 8.84 (s, 1H), 7.69 (d, J = 5.2 Hz, 1H), 7.58-7.50 (m, 3H), 7.45 (d, J = 8.1 Hz, 2H), 7.33 (m, 1H), 7.19 (m, 1H), 6.95 (d, J = 5.1 Hz, 1H), 5.95 (s, 2H), 4.57 (d, J = 6.1 Hz, 2H), 3.90 (s, 3H), 2.14 (s, 2H), 1.99-1.88 (m, 2H), 1.81 (d, J = 13.8 Hz, 2H), 1.53-1.37 (m, 5H), 1.19 (s, 3H).
4-(6-amino-7-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-8-oxo-7,8-dihydro-9H-purin-9-yl)bicyclo[2.2.2]octane-1-carboxylic acid (48)	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 7.63 (dd, J = 9.2, 3.2 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.47-7.37 (m, 2H), 7.26 (dd, J = 7.6, 3.3 Hz, 1H), 7.23-7.15 (m, 1H), 4.71 (s, 2H), 3.99 (s, 3H), 2.62 (dd, J = 9.6, 6.4 Hz, 6H), 2.02 (dd, J = 9.5, 6.5 Hz, 6H).

Example 26. N-(4-(8-amino-3-(4-(hydroxymethyl) bicyclo[2.2.2]octan-1-yl)imidazo[1,5-a]pyrazin-1-yl) benzyl)-5-fluoro-2-methoxybenzamide (Compound 35)

[0380]



33



35

[0381] To a solution of 33 (100 mg, 0.18 mmol) in THE (20 mL) at 0° C. was added lithium aluminum hydride (7 mg, 0.18 mmol). After stirring for 1 hour, the mixture was added with saturated brine (0.5 mL) and the solvent was removed under reduced pressure. The residue was purified by TLC (dichloromethane/methanol=12/1) to give the title compound 35 (32.2 mg, solid, 34%).

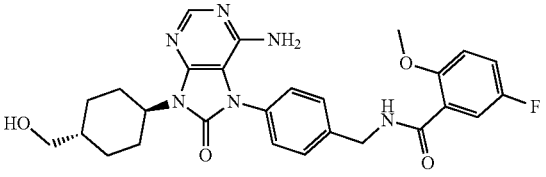
[0382] MS m/z (ESI): 530 [M+1]

[0383] ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (d, J=5.3 Hz, 1H), 7.62 (dd, J=9.2, 3.2 Hz, 1H), 7.59-7.50 (m, 4H), 7.25 (ddd, J=9.1, 7.6, 3.3 Hz, 1H), 7.17 (dd, J=9.1, 4.2 Hz, 1H), 6.92 (d, J=5.3 Hz, 1H), 4.69 (s, 2H), 3.96 (s, 3H), 3.26 (s, 2H), 2.14 (dd, J=9.4, 6.3 Hz, 6H), 1.65-1.59 (m, 6H).

[0384] The compound as shown below was synthesized according to the procedures in Example 26, except that a different ester was used instead of 33.

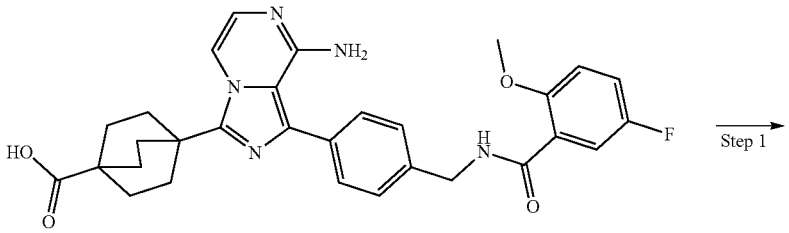
[0385] The NMR data of Compound 50 is shown below:

Compound	^{1}H NMR
N-(4-(6-amino-9-((1r,4r)-4-(hydroxymethyl)cyclohexyl)-8-oxo-8,9-dihydro-7H-purin-7-yl)benzyl)-5-fluoro-2-methoxybenzamide (50)	^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 7.64 (dd, J = 9.2, 3.3 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.28 (ddd, J = 9.1, 7.6, 3.3 Hz, 1H), 7.19 (dd, J = 9.2, 4.2 Hz, 1H), 4.72 (s, 2H), 4.45-4.32 (m, 1H), 3.99 (s, 3H), 3.44 (d, J = 6.4 Hz, 2H), 2.53-2.43 (m, 2H), 2.00 (d, J = 13.9 Hz, 2H), 1.90 (d, J = 9.2 Hz, 2H), 1.62 (s, 1H), 1.21-1.12 (m, 2H).

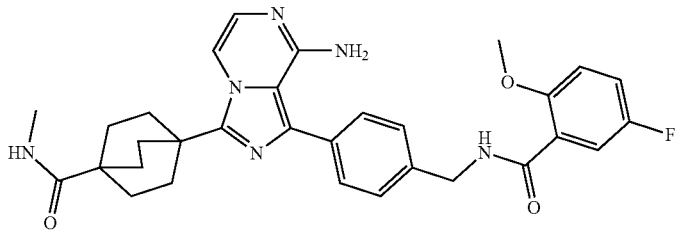
Compound No.	Structure	Compound replacing 33	MS m/z (ESI)
50		50a	521

Example 27. 4-(8-amino-1-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-N-methylbicyclo[2.2.2]octane-1-carboxamide (Compound 36)

[0386]



34



36

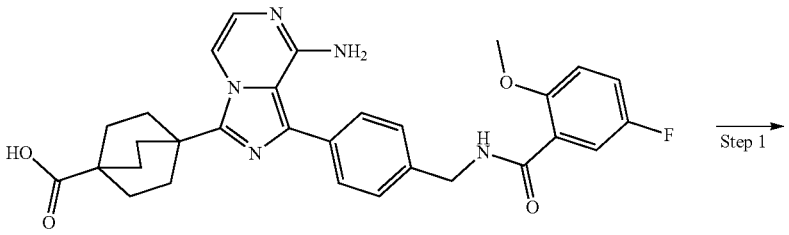
[0387] To a mixture of 34 (82 mg, 0.15 mmol), methylamine hydrochloride (20 mg, 0.3 mmol) and DIPEA (78 mg, 0.6 mmol) in DMF (1.5 mL) was added HATU (114 mg, 0.3 mmol). After stirring for 30 minutes, the mixture was purified by prep-HPLC to give the title compound 36 (11.5 mg, solid, 14%).

[0388] MS m/z (ESI): 557 [M+1]

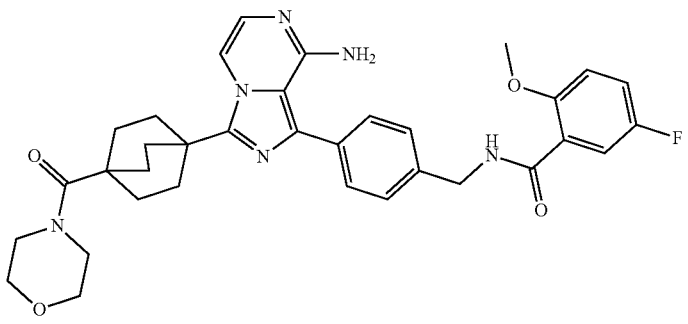
[0389] 1H NMR (400 MHz, CD_3OD) δ 7.83 (d, J=5.4 Hz, 1H), 7.70-7.50 (m, 5H), 7.26 (ddd, J=9.1, 7.6, 3.3 Hz, 1H), 7.17 (dd, J=9.1, 4.2 Hz, 1H), 6.93 (d, J=5.4 Hz, 1H), 4.70 (d, J=4.0 Hz, 2H), 3.97 (s, 3H), 2.72 (t, J=5.0 Hz, 3H), 2.19 (dd, J=9.6, 6.0 Hz, 6H), 1.93 (dd, J=9.5, 6.1 Hz, 6H).

Example 28. N-(4-(8-amino-3-(4-(morpholine-4-carbonyl)bicyclo[2.2.2]octan-1-yl)imidazo[1,5-a]pyrazin-1-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 37)

[0390]



34



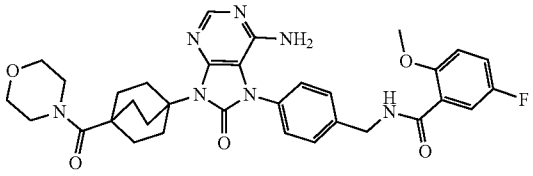
37

[0391] To a mixture of 34 (82 mg, 0.15 mmol), morpholine (26 mg, 0.3 mmol) and DIPEA (78 mg, 0.6 mmol) in DMF (1.5 mL) was added HATU (114 mg, 0.3 mmol). After stirring for 30 minutes, the mixture was purified by prep-HPLC to give the title compound 37 (17.2 mg, solid, 19%).

[0392] MS m/z (ESI): 613 [M+1]

[0393] ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (d, J=5.4 Hz, 1H), 7.62 (dd, J=9.2, 3.2 Hz, 1H), 7.55 (dd, J=20.6, 8.3 Hz, 4H), 7.26 (ddd, J=9.1, 7.6, 3.3 Hz, 1H), 7.17 (dd, J=9.1, 4.2 Hz, 1H), 6.93 (d, J=5.4 Hz, 1H), 4.69 (s, 2H), 3.97 (s, 3H), 3.71 (d, J=5.0 Hz, 4H), 3.67 (d, J=4.9 Hz, 4H), 2.25-2.15 (m, 6H), 2.08 (dd, J=9.7, 5.4 Hz, 6H).

[0394] The compound as shown below was synthesized according to the procedures in Example 28, except that a different acid was used instead of 34.

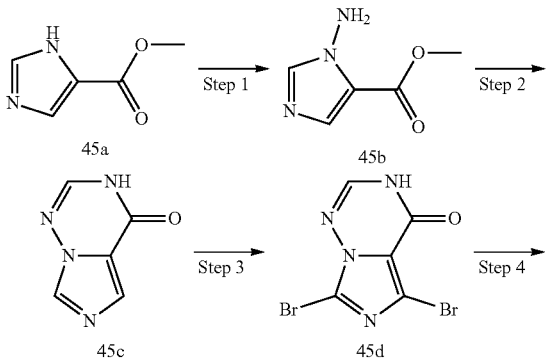
Compound No.	Structure	Compound replacing 34	MS m/z (ESI)
54		48	630

[0395] The NMR data of compounds 54 are shown below:

Compound	^{1}H NMR
N-(4-(6-amino-9-(4-(morpholine-4-carbonyl)bicyclo[2.2.2]octan-1-yl)-8-oxo-8,9-dihydro-7H-purin-7-yl)benzyl)-5-fluoro-2-methoxybenzamide (54)	^{1}H NMR (400 MHz, CD_3OD) δ8.10 (s, 1H), 7.63 (dd, J = 9.2, 3.3 Hz, 1H), 7.59 (s, 1H), 7.57 (s, 1H), 7.43 (s, 1H), 7.41 (s, 1H), 7.31-7.25 (m, 1H), 7.19 (dd, J = 9.2, 4.3 Hz, 1H), 4.71 (s, 2H), 3.99 (s, 3H), 3.70 (s, 4H), 3.67 (d, J = 4.8 Hz, 4H), 2.64 (d, J = 8.4 Hz, 6H), 2.13-2.09 (m, 6H).

Example 29. N-(4-(4-amino-7-morpholinoimidazo[5,1-f][1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 45)

[0396]



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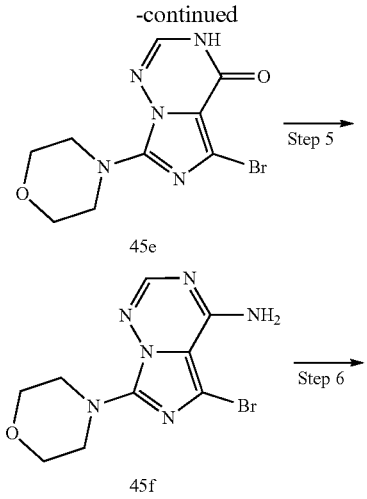

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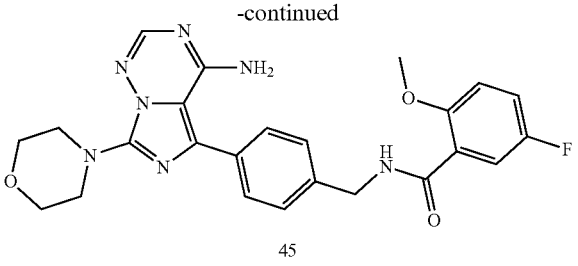


Step 1. methyl 1-amino-1H-imidazole-5-carboxylate (45b)

[0397] To a solution of methyl 1H-imidazole-5-carboxylate 45a (630 mg, 5.0 mmol) in THE at −78° C. was added a solution of LiHMDS in THF (1 M, 5 mL). The solution was warmed to −10° C., stirred for 3 hours and then added with diphenylphosphonylhydroxylamine (1.28 g, 5.5 mmol). The mixture was warmed to room temperature and stirred for additional 12 hours. It was concentrated to dryness under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane/methanol=10/1) to give the title compound 45b (450 mg, 63%).

[0398] MS m/z (ESI): 142 [M+1]

Step 2. imidazo[5,1-f][1,2,4]triazin-4(3H)-one (45c)

[0399] A mixture of 45b (450 mg, 3.17 mmol) and formamidine acetate (1.65 g, 15.85 mmol) in ethanol (10 mL) was heated to 85° C. and stirred for 2 days. After cooling to room temperature, the mixture was concentrated to dryness to which was added water (50 mL). The mixture was filtered, and the filter cake was collected to give the title compound 45c (330 mg, 76%).

[0400] MS m/z (ESI): 137 [M+1]

[0401] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.47 (d, J=0.7 Hz, 1H), 7.93 (s, 1H), 7.79 (d, J=0.7 Hz, 1H).

Step 3. 5,7-dibromoimidazo[5,1-f][1,2,4]triazin-4 (3H)-one (45d)

[0402] To a solution of 45c (450 mg, 3.3 mmol) in DMF (5 mL) at 0° C. was added liquid bromine (1.6 g). After stirring for 3 hours, the mixture was filtered to give the title compound 45d (550 mg, 77%).

[0403] MS m/z (ESI): 293 [M+1]

Step 4. 5-bromo-7-morpholinoimidazo[5,1-f][1,2,4] triazin-4(3H)-one (45e)

[0404] A mixture of 45d (300 mg, 1.02 mmol), morpholine (89 mg, 1.02 mmol), DMSO (1 mL) and DIPEA (263 mg, 2.04 mmol) was heated to 95° C. and stirred for 12 hours. After cooling to room temperature, the mixture was concentrated to dryness. The residue was dispersed in water (5 mL) and extracted with ethyl acetate (2×10 mL). The combined organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/methanol=10/1) to give the title compound 45e (220 mg, 72%).

[0405] MS m/z (ESI): 300 [M+1]

Step 5. 5-bromo-7-morpholinoimidazo[5,1-f][1,2,4] triazin-4-amine (45f)

[0406] To a solution of 1H-[1,2,4]triazole (455 mg, 6.6 mmol) in pyridine (5 mL) was added phosphine oxychloride (335 mg, 2.19 mmol). The mixture was stirred for 10 minutes, and then cooled to 0° C. to which was added a solution of 45e (220 mg, 0.73 mmol) in pyridine (3 mL). After stirring for 2 hours at 0° C., a solution of ammonia in isopropanol (2 M, 3.65 mL) was added. The resulting mixture was stirred at room temperature for 12 hours and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/methanol=10/1) to give the title compound 45f (86.5 mg, 59.3%).

[0407] MS m/z (ESI): 299 [M+1]

Step 6. N-(4-(4-amino-7-morpholinoimidazo[5,1-f] [1,2,4]triazin-5-yl)benzyl)-5-fluoro-2-methoxybenzamide (45)

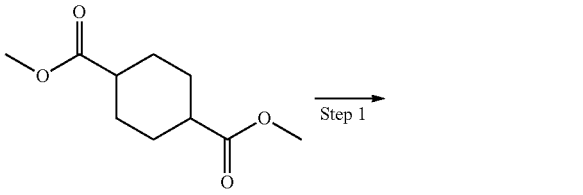
[0408] To a mixture of 45f (86.5 mg, 0.3 mmol), 1b (115.5 mg, 0.3 mmol), potassium carbonate (82.8 mg, 0.6 mmol), 1,4-dioxane (5 mL) and water (1 mL) was added $PdCl_2$ (dppf) (24.5 mg, 0.03 mmol). The mixture was heated to 90° C. and stirred for 2 hours. After cooling to room temperature, the reaction mixture was concentrated to dryness. The residue was dispersed in water (10 mL) and extracted with ethyl acetate (2×20 mL). The combined organic phase was washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under reduced pressure. The residue was purified by prep-HPLC to give the title compound 45 (10 mg, solid, 7%).

[0409] MS m/z (ESI): 478 [M+1]

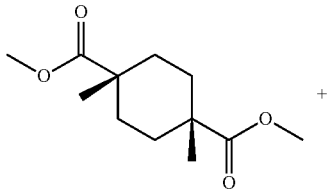
[0410] ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (s, 1H), 7.66-7.58 (m, 3H), 7.52 (d, J=8.3 Hz, 2H), 7.26 (ddd, J=9.1, 7.6, 3.3 Hz, 1H), 7.17 (dd, J=9.1, 4.2 Hz, 1H), 4.68 (s, 2H), 3.97 (s, 3H), 3.89-3.81 (m, 4H), 3.63-3.53 (m, 4H).

Example 30. (1s,4s)-4-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)-1,4-dimethylcyclohexane-1-carboxylic acid (Compound 46)

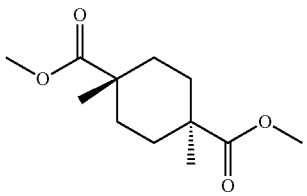
[0411]



32a

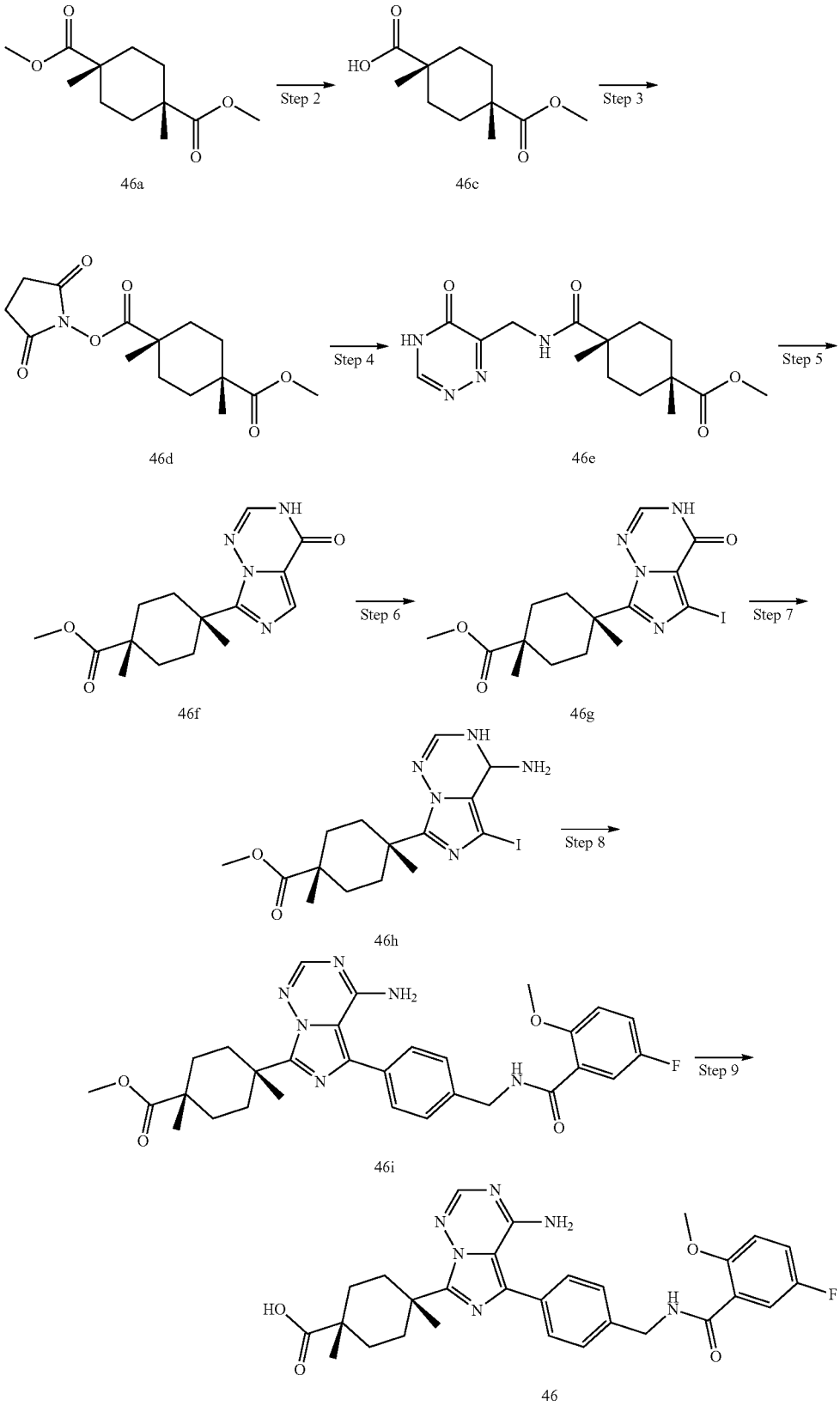


46a



46b

-continued


Step 2
Step 3
46a
46c
Step 4
Step 5
46d
46e
Step 6
Step 7
46f
46g
Step 8
46h
Step 9
46i
46

Step 1. dimethyl (1s,4s)-1,4-dimethylcyclohexane-1,4-dicarboxylate (46a) and dimethyl (1r,4r)-1,4-dimethylcyclohexane-1,4-dicarboxylate (46b)

[0412] To a solution of LDA (2 M, 62.5 mL, 125 mmol) and hexamethylphosphoric triamide (69.5 mL, 400 mmol) in THF (125 mL) at −50° C. was added a solution of 32a (10 g, 50 mmol) in 1,4-dioxane solution (10 mL) dropwise. After stirring for 1 hour, the solution was warmed to 0° C. and stirred for another hour. After cooling to −50° C. again, iodomethane (31 g, 218.4 mmol) was added to the solution and stirring was continued at room temperature for 16 hours. The solution was added with 1 N hydrochloric acid (30 mL) and extracted with ethyl acetate (50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=78/22) to give the title compound 46a (2.9 g, 250%) and 46b (1.4 g, 12%).

Step 2. (1s,4s)-4-(methoxycarbonyl)-1,4-dimethylcyclohexane-1-carboxylic acid (46c)

[0413] A mixture of 46a (1 g, 4.38 mmol), potassium hydroxide (334 mg, 6.0 mmol), methanol (20 mL) and water (20 mL) was heated to 80° C. and stirred for 16 hours. After cooling to room temperature, the solution was concentrated to dryness. The residue was added with 1 N hydrochloric acid (20 mL) and extracted with ethyl acetate (30 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give the title compound 46c (795 mg, 85%).

Step 3 to 8. methyl (1s,4s)-4-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)-1,4-dimethylcyclohexane-1-carboxylate (46i)

[0414] 46i was synthesized according to the procedures for the first to sixth step in Example 18, except that 46c was used instead of (R)-1-((benzyloxy)carbonyl)pyrrolidine-3-carboxylic acid 22a in the third step.

[0415] MS m/z (ESI): 561 [M+1]

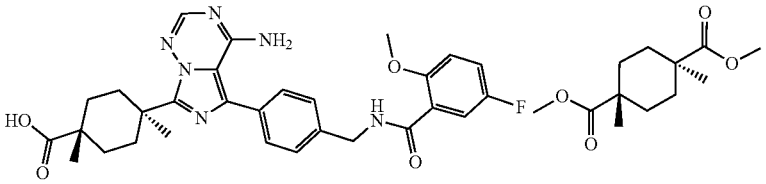
Step 9. (1s,4s)-4-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)-1,4-dimethylcyclohexane-1-carboxylic acid (46)

[0416] 46 was synthesized according to the procedures for the first to the sixth step in Example 26, except that 46i was used instead of 33 in the third step.

[0417] MS m/z (ESI): 547 [M+1]

[0418] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 8.84 (t, J=6.0 Hz 1H), 7.87 (s, 1H), 7.59 (d, J=8.2 Hz, 2H), 7.53 (m, 1H), 7.47 (d, J=8.2 Hz, 2H), 7.34 (s, 1H), 7.19 (m, 1H), 4.57 (d, J=6.1 Hz, 2H), 3.90 (s, 3H), 3.29 (s, 2H), 2.33 (s, 2H), 1.88 (m, 4H), 1.44 (m, 5H), 1.18 (s, 3H).

[0419] Compound 47 as shown below was synthesized according to the procedures for the second to the ninth step in Example 30, except that 46b was used instead of 46a in the second step.

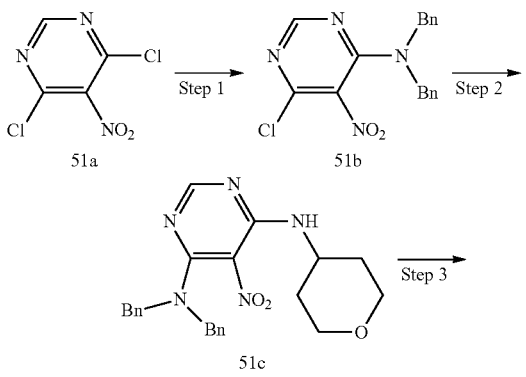
Compound No.	Structure	Compound replacing 46a	MS m/z (ESI)
47			547

[0420] The NMR data of Compound 47 is shown below:

Compound	^{1}H NMR
(1r,4r)-4-(4-amino-5-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)imidazo[5,1-f][1,2,4]triazin-7-yl)-1,4-dimethylcyclohexane-1-carboxylic acid (47)	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 8.84 (t, J = 6.0 Hz, 1H), 7.89 (s, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.53 (m, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.37-7.31 (m, 1H), 7.19 (m, 1H), 4.57 (d, J = 6.0 Hz, 2H), 3.90 (s, 3H), 3.31 (s, 2H), 2.75 (d, J = 13.1 Hz, 2H), 1.93 (d, J = 13.6 Hz, 2H), 1.45 (t, J = 11.7 Hz, 2H), 1.33 (m, 5H), 1.00 (s, 3H).

Example 31. N-(4-(6-amino-8-oxo-9-(tetrahydro-2H-pyran-4-yl)-8,9-dihydro-7H-purin-7-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 51)

[0421]



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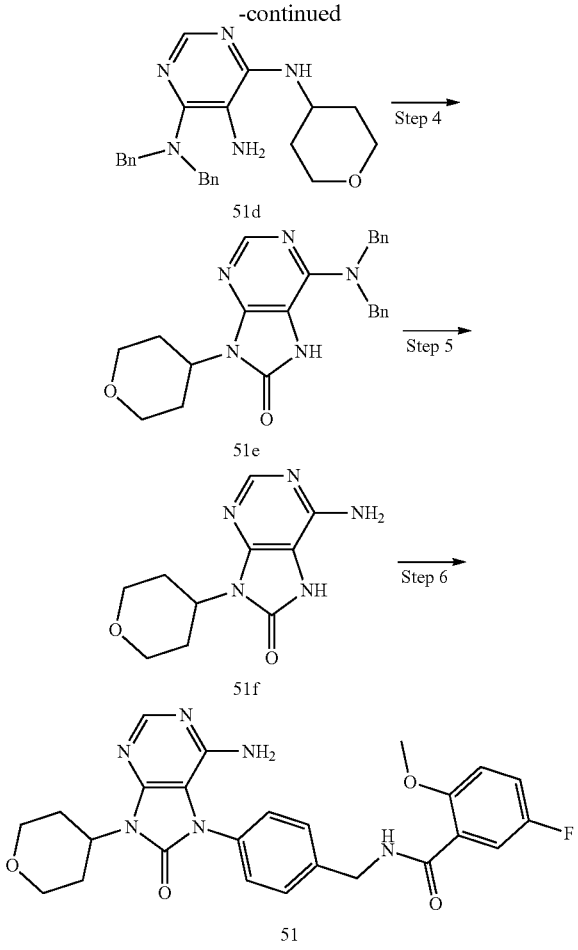


51d

51e

51f

51

Step 1. N,N-dibenzyl-6-chloro-5-nitropyrimidin-4-amine (51a)

[0422] To a mixture of 4,6-dichloro-5-nitropyrimidine 51a (1.93 g, 10 mmol) and triethylamine (2.02 g, 20 mmol) in dichloromethane (10 mL) was added a solution of dibenzylamine (1.97 g, mmol) in dichloromethane (5 mL) over 10 minutes. The resulting mixture was stirred at 0° C. for 1 hour and concentrated to dryness under reduced pressure. The residue was suspended in water (70 mL) and extracted with ethyl acetate (2×100 mL). The combined organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/0 to 9/1) to give the title compound 51b (3.21 g, 91%).

[0423] MS m/z (ESI): 355[M+1]

Step 2. N^4,N^4-dibenzyl-5-nitro-NY-(tetrahydro-2H-pyran-4-yl)pyrimidine-4,6-diamine (51c)

[0424] To a mixture of 51b (0.8 g, 2.25 mmol) and triethylamine (455 mg, 4.5 mmol) in dichloromethane (5 mL) was added tetrahydro-2H-pyran-4-amine (227 mg, 2.25 mmol) in dichloromethane (3 mL). The resulting mixture was stirred for 1 hour and then concentrated to dryness under reduced pressure. The residue was suspended in water (70 mL) and extracted with ethyl acetate (2×50 mL). The combined organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/0 to 4/1) to give the title compound 51c (0.68 g, 72%).

[0425] MS m/z (ESI): 420[M+1]

Step 3. N^4,N^4-dibenzyl-N-(tetrahydro-2H-pyran-4-yl)pyrimidine-4,5,6-triamine (51d)

[0426] To a mixture of 51c (0.68 g, 1.62 mmol), ammonium chloride (433 mg, 8.1 mmol), ethyl acetate (10 mL) and water (10 mL) was added zinc powder (526 mg, 8.1 mmol). The resulting mixture was stirred for 6 hours and extracted with ethyl acetate (2×50 mL). The combined organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/0 to 1/1) to give the title compound 51d (0.52 g, 82%).

[0427] MS m/z (ESI): 390[M+1]

Step 4. 6-(dibenzylamino)-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8H-purin-8-one (51e)

[0428] To a mixture of triphosgene (520 mg, 1.33 mmol) and triethylamine (404 mg, 4 mmol) in THE (10 mL) was added a solution of 51d (520 mg, 1.33 mmol) in THE (3 mL). The resulting mixture was stirred for 1 hour and then concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/0 to 1/1) to give the title compound 51e (0.35 g, 82%).

[0429] MS m/z (ESI): 416[M+1]

Step 5. 6-amino-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8H-purin-8-one (51f)

[0430] To a solution of 51e (350 mg, 0.84 mmol) in acetic acid (10 mL) was added palladium on carbon (10%, 100 mg). The resulting mixture was stirred for 12 hours under a hydrogen atmosphere and then filtered. The filtrate was concentrated to dryness under reduced pressure to give the title compound 51f (165 mg, 83%).

[0431] MS m/z (ESI): 236[M+1]

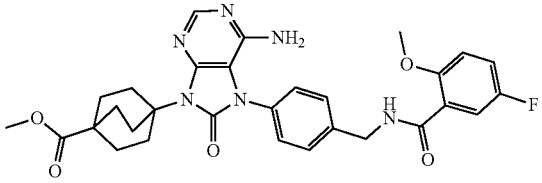
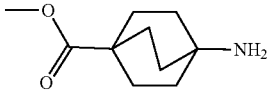
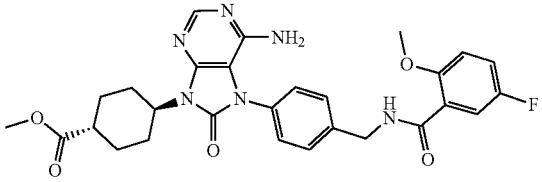
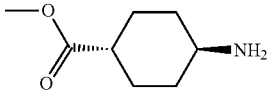
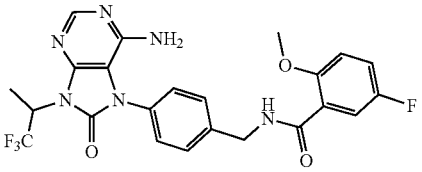
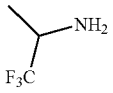
Step 6. N-(4-(6-amino-8-oxo-9-(tetrahydro-2H-pyran-4-yl)-8,9-dihydro-7H-purin-7-yl)benzyl)-5-fluoro-2-methoxybenzamide (51)

[0432] To a mixture of 51f (248 mg, 1.05 mmol) and 1b (636 mg, 2.1 mmol) in acetonitrile (5 mL) were added $Cu(OAc)_2$ (381 mg, 2.1 mmol) and triethylamine (530 mg, 5.25 mmol)). The resulting mixture was stirred under an air atmosphere for 12 hours and concentrated to dryness under reduced pressure. The residue was purified by prep-HPLC to give the title compound 51 (85.3 mg, solid, 17%).

[0433] MS m/z (ESI): 493[M+1]

[0434] ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (s, 1H), 7.67-7.57 (m, 3H), 7.51-7.42 (m, 2H), 7.28 (ddd, J=9.1, 7.6, 3.3 Hz, 1H), 7.20 (d, J=4.2 Hz, 1H), 4.72 (s, 2H), 4.64 (tt, J=12.6, 4.4 Hz, 1H), 4.15-4.05 (m, 2H), 3.99 (s, 3H), 3.57 (d, J=1.3 Hz, 2H), 2.77 (qd, J=12.6, 4.7 Hz, 2H), 1.79 (s, 2H).

[0435] The compounds or intermediates as shown below were synthesized according to the procedures in Example 31, except that a different amine was used instead of tetrahydro-2H-pyran-4-amine in the second step.

Compound/ Intermediate No.	Structure	Compound replacing tetrahydro-2H-pyran-4-amine	MS m/z (ESI)
48a			575
50a			549
53			505

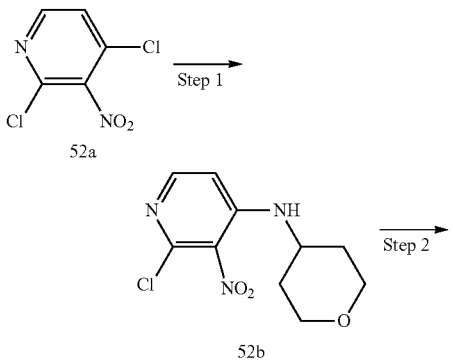
[0436] The NMR data of Compound 47 is shown below:

Compound	^{1}H NMR
N-(4-(6-amino-8-oxo-9-(1,1,1-trifluoropropan-2-yl)-8,9-dihydro-7H-purin-7-yl)benzyl)-5-fluoro-2-methoxybenzamide (53)	^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (s, 1H), 7.69-7.57 (m, 3H), 7.52-7.43 (m, 2H), 7.32-7.24 (m, 1H), 7.19 (dd, J = 9.1, 4.2 Hz, 1H), 5.23 (s, 1H), 4.72 (s, 2H), 3.99 (s, 3H), 1.93 (d, J = 7.4 Hz, 3H).

[0437] Compound 49 can be synthesized according to the procedures in Example 32.

Example 32. N-(4-(4-amino-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-1,2-dihydro-3H-imidazo[4,5-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (Compound 52)

[0438]



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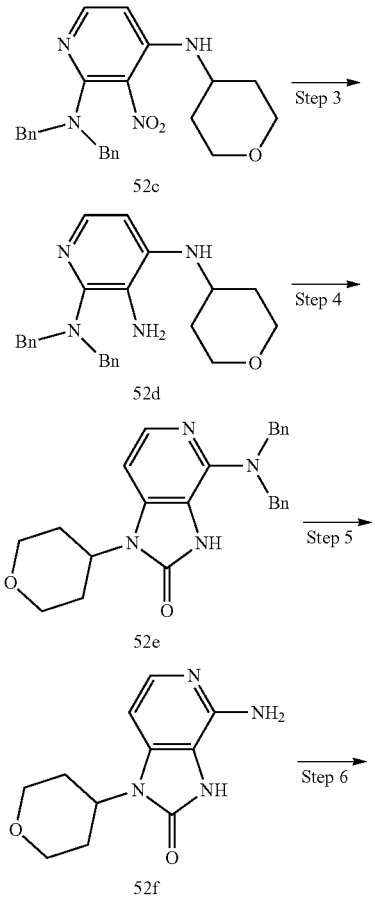

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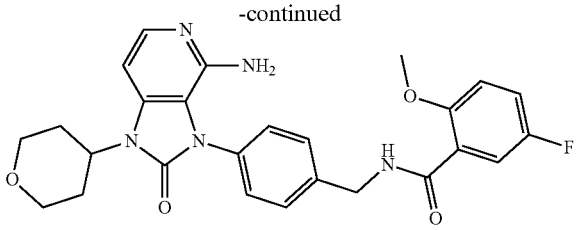


52

Step 1. 2-chloro-3-nitro-N-(tetrahydro-2H-pyran-4-yl)pyridin-4-amine (52b)

[0439] To a mixture of 2,4-dichloro-3-nitropyridine 52a (1.93 g, 10 mmol) and triethylamine (1.31 g, 13 mmol) in DMF (12 mL) was added tetrahydro-2H-pyran-4-amine (1.01 g, 10 mmol). The resulting mixture was stirred for 1 hour and then concentrated to dryness under reduced pressure.

[0440] The residue was suspended in water (70 mL) and extracted with ethyl acetate (2×100 mL). The combined organic phase was washed with saturated brine (50 mL)c dried over anhydrous sodium sulfate, filtered and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/0 to 9/1) to give the title compound 52b (2.33 g, 91%).

[0441] MS m/z (ESI): 258 [M+1]

Step 2. N^2,N^2-dibenzyl-3-nitro-N^4-(tetrahydro-2H-pyran-4-yl)pyridine-2,4-diamine (52c)

[0442] To a mixture of 52b (2.33 g, 9.07 mmol) and triethylamine (1.83 g, 18.1 mmol) in acetonitrile (10 mL) was added dibenzylamine (1.78 g, 9.07 mmol). The resulting mixture was heated to 80° C. and stirred for 20 minutes. After cooling to room temperature, the reaction mixture was concentrated to dryness under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100/0 to 4/1) to give the title compound 52c (3.22 g, 85%).

[0443] MS m/z (ESI): 419 [M+1]

Step 3 to 6. N-(4-(4-amino-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-1,2-dihydro-3H-imidazo[4,5-c]pyridin-3-yl)benzyl)-5-fluoro-2-methoxybenzamide (52)

[0444] 52 was synthesized according to the procedures for the third to the sixth step in Example 31.

[0445] MS m/z (ESI): 492 [M+1]

[0446] ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (s, 1H), 7.69-7.57 (m, 3H), 7.51-7.43 (m, 2H), 7.28 (ddd, J=9.1, 7.6, 3.3 Hz, 1H), 7.20 (d, J=4.2 Hz, 1H), 6.95 (s, 1H), 4.73 (s, 2H), 4.54 (tt, J=12.4, 4.2 Hz, 1H), 4.20-4.07 (m, 2H), 3.99 (s, 3H), 3.60 (d, J=1.6 Hz, 2H), 2.56 (qd, J=12.6, 4.7 Hz, 2H), 1.82 (dd, J=12.5, 2.6 Hz, 2H).

Biological Experiments

Example 33. BTK Activity Inhibition Assay

[0447] In vitro kinase assay was used to evaluate the effects of compounds of the present invention on BTK activity (Table 1).

[0448] The experimental method is summarized below:

[0449] By using the homogeneous time-resolved fluorescence (HTRF) kinase detection kit (Cisbio, catalog number 62TK0PEC), the enzymatic activity of BTK is determined by detecting the phosphorylation level of the substrate in the kinase reaction. The reaction buffer contains the enzyme reaction buffer (1×) from the kit, 5 mM $MgCl_2$, 1 mM DTT, 10 nM SEB and 0.01% Tween-20; the kinase reaction solution contains human-derived recombinant BTK protein (Carna Biosciences, Catalog No. 08-180) diluted to 0.2 ng/μL with the reaction buffer; the substrate reaction solution contains biotin-labeled tyrosine kinase substrate diluted to 0.5 μM with the reaction buffer and 40 μM ATP; the detection buffer contains Eu^{3+}-labeled cage antibody diluted to 0.05 ng/μL and streptavidin-labeled XL665 antibody diluted to 31.25 nM with the reaction buffer; the test compound is dissolved and diluted to 100 μM with DMSO, followed by a 4-fold serial dilution with DMSO to the lowest concentration of 6.1 nM and finally 40-time dilution with the reaction buffer for each concentration point. If the IC_{50} value of the compound is very low, the initial concentration of the compound is reduced.

[0450] Add 4 μL test compound solution and 2 μL kinase reaction solution to a 384-well detection plate (Corning, catalog number 3674), mix well and incubate at room temperature for 15 minutes; add 4 μL substrate reaction solution and incubate for 50 minutes; add 10 μL detection buffer, mix well and stand for 60 minutes; detect signal at 620 nm and 665 nm using an Envision plate reader (Perkin Elmer). The signal value (absorbance at 665 nm/absorbance at 620 nm) is positively correlated with the degree of phosphorylation of the substrate, thereby detecting the kinase activity of BTK. In this experiment, the group without BTK is the negative control (100% inhibition) and the group with BTK but no compound is the positive control (0% inhibition). The inhibition curve is plotted and the corresponding IC_{50} value of the test compound is calculated using XLfit software (ID Business Solutions Ltd., UK).

Example 34. BTK C481S Activity Inhibition Assay

[0451] In vitro kinase assay was used to evaluate the effects of compounds of the present invention on BTK C481S activity (Table 1).

[0452] The experimental method is summarized below:

[0453] By using the homogeneous time-resolved fluorescence (HTRF) kinase detection kit (Cisbio, catalog number 62TK0PEC), the enzymatic activity of BTK C481S is determined by detecting the phosphorylation level of the substrate in the kinase reaction. The reaction buffer contains the enzyme reaction buffer (1×) from the kit, 5 mM $MgCl_2$, 1 mM DTT, 10 nM SEB, and 0.01% Tween-20; the kinase reaction solution contains human recombinant BTK C481S protein (purified in-house) diluted to 1.5 ng/μL with the reaction buffer; the substrate reaction solution contains biotin-labeled tyrosine kinase substrate diluted to 0.5 μM with the reaction buffer and 35 μM ATP; the detection buffer contains Eu^{3+}-labeled cage antibody diluted to 0.05 ng/μL and streptavidin-labeled XL665 antibody diluted to 31.25 nM with the reaction buffer; the test compound is dissolved and diluted to 100 μM with DMSO, followed by a 4-fold serial dilution with DMSO to the lowest concentration of 6.1 nM and finally 40-time dilution with the reaction buffer for each concentration point. If the IC_{50} value of the compound is very low, the initial concentration of the compound is reduced.

[0454] Add 4 μL test compound solution and 2 μL kinase reaction solution to a 384-well detection plate (Corning, catalog number 3674), mix well and incubate at room temperature for 15 minutes; add 4 μL substrate reaction solution and incubate for 50 minutes; add 10 μL detection

buffer, mix well and stand for 60 minutes; detect signal at 620 nm and 665 nm using an Envision plate reader (Perkin Elmer). The signal value (absorbance at 665 nm/absorbance at 620 nm) is positively correlated with the degree of phosphorylation of the substrate, thereby detecting the kinase activity of BTK C481S. In this experiment, the group without BTK is the negative control (100% inhibition) and the group with BTK C481 S but no compound is the positive control (0% inhibition). The inhibition curve is plotted and the corresponding IC_{50} value of the test compound is calculated using XLfit software (TD Business Solutions Ltd., UK).

TABLE 1

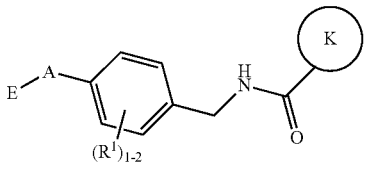
Compound No.	BTK IC_{50} (nM)	BTK C481S IC_{50} (nM)
1.	17	3.5
2.	1.7	2.5
3.	3.2	4.6
4.	2.3	3.0
5.	4.6	2.6
6.	4.6	3.3
7.	3.4	1.7
8.	1.2	0.8
9.	718	498
10.	14	3.6
11.	20	3.9
12.	3.0	
13.	1.4	0.8
14.	3.2	2.9
15.	1.4	1.1
16.	1.8	1.1
17.	6.3	2.4
18.	0.7	0.8
19.	212	201
21.	1.7	1.8
22.	155	36
23.	1.0	3.0
24.	3.9	2.5
25.	1.1	1.5
26.	3.8	11
27.	2.7	1.3
28.	1.0	2.2
29.	1.2	2.1
31.	0.6	3.0
32.	2.4	6.3
33.	0.8	1.8
34.	0.9	1.5
35.	0.6	1.5
36.	0.9	3.4
37.	1.3	1.9
38.	2.9	2.1
39.	3.3	0.6
40.	0.4	1.1
41.	2.6	5.3
42.	1.7	4.3
43.	2.7	5.4
44.	10	7.1
45.	9.4	2.6
46.	7.7	1.6
47.	1.3	1.4
48.	1.2	8.2
50.	2.4	20
51.	4.0	9.2
52.	7.2	30
53.	5.6	21
54.	5.8	6.1

[0455] The invention, and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude the specification.

What is claimed is:

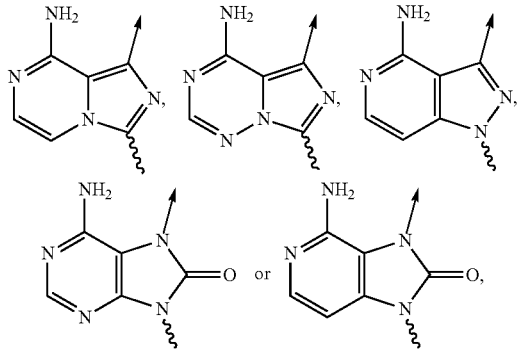
1. A compound represented by general formula (I), or a pharmaceutically acceptable salt, stable isotope derivative, or stereo isomer thereof:

(I)



wherein:

A is



where → indicates that A is connected to the benzene ring, and ∿∿ indicates that A is connected to E;

Ring K is phenyl or pyridyl, where phenyl and pyridyl are optionally substituted by one or more substituents selected from halogen, cyano, C_{1-6} alkyl or $—OR^a$;

E is C_{1-6} alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl or 5-10 membered heteroaryl, where the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted by one or more substituents selected from D, halogen, cyano, $—OR^b$, $—NR^bR^c$, $—COOR^b$, $—C(O)R^b$, $—C(O)NR^bR^c$, or R^e;

R^e is C_{1-6} alkyl, C_{3-10} cycloalkyl or 3-10 membered heterocyclyl, where the alkyl, cycloalkyl and heterocyclyl are optionally substituted by halogen, cyano, $—OR^b$, $—NR^bR^c$, $—COOR^b$, $—C(O)R^b$ or $—C(O)NR^bR^c$;

R^1 is H, halogen, $—OR^a$ or C_{1-6} alkyl;

R^a is C_{1-6} alkyl, where one or more hydrogens of the alkyl are optionally substituted by D or fluorine; and

R^b and R^c are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl,

wherein the compound is a CNS penetrant having a Kp, CSF value of at least 0.15.

2. The compound according to claim **1**, or a pharmaceutically acceptable salt, stable isotope derivative, or a stereo

isomer thereof, wherein E is a C_{1-6} alkyl group, wherein one or more hydrogens of the alkyl group are optionally substituted by D or fluorine.

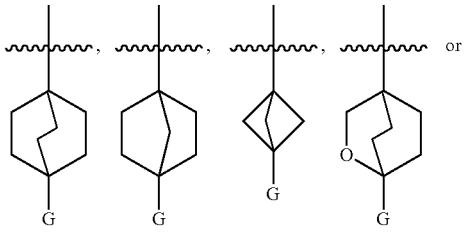
3. The compound according to claim **1**, or a pharmaceutically acceptable salt, stable isotope derivative, or a stereo isomer thereof, wherein E is C_{3-7} monocyclic cycloalkyl or 4-8 membered monocyclic heterocyclyl containing N and/or O, the monocyclic cycloalkyl and the monocyclic heterocyclyl are optionally substituted by one or more substituents selected from D, halogen, —OR^b, —NR^bR^c, —$COOR^b$, —$C(O)R^b$, —$C(O)NR^bR^c$ or C_{1-6} alkyl, where one or more hydrogens of the alkyl group are further optionally substituted by halogen, —OR^b or —NR^bR^c; R^b and R^c are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or N and/or O containing 4-6-membered heterocyclyl.

4. The compound according to claim **1**, or a pharmaceutically acceptable salt, stable isotope derivative, or a stereo isomer thereof, wherein E is cyclopropanyl, cyclobutanyl, cyclopentyl, cyclohexane, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl, the cycloalkyl and heterocyclic groups are optionally selected from one or more D, fluorine, —OR^b, —NR^bR^c, —$COOR^b$, —$C(O)R^b$, —$C(O)NR^bR^c$ or C_{1-2} alkyl substituent substituted, wherein one or more hydrogens of the alkyl substituents are further optionally substituted by fluorine, —OH or —NH_2; R^b and R^c are each independently selected from H, C_{1-2} alkyl, C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl containing N and/or O (for example, morpholinyl).

5. The compound according to claim **1**, or a pharmaceutically acceptable salt, stable isotope derivative, or a stereo isomer thereof, wherein E is a C_{5-10} polycyclic cycloalkyl group or an 0-containing 5-10 membered polycyclic heterocyclic group, the polycyclic cycloalkyl and polycyclic heterocyclic groups are optionally substituted by one or more substituents selected from D, halogen, —OR^b, —NR^bR^c, —$COOR^b$, —$C(O)R^b$, —$C(O)NR^bR^c$ or C_{1-6} alkyl substituents, wherein one or more hydrogens of the alkyl substituents are further optionally substituted by halogen, —OR^b or —NR^bR^c; R^b and R^c are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 4-6 membered heterocyclic group containing N and/or O.

6. The compound according to claim **1**, or a pharmaceutically acceptable salt, stable isotope derivative, or a stereo isomer thereof,

wherein E is



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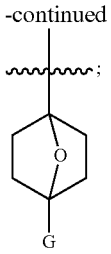
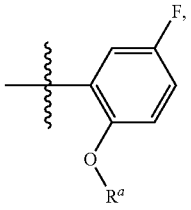


G is H, fluorine, —OR^b, —NR^bR^c, —$COOR^b$, —$C(O)R^b$, —$C(O)NR^bR^c$ or C_{1-2} alkyl, wherein one or more hydrogens of the alkyl are optionally substituted by fluorine, —OH or —NH_2; R^b and R^c are each independently selected from H, C_{1-2} alkyl, C_{3-6} cycloalkyl or 4-6 membered heterocyclic group containing N and/or O (for example, morpholinyl).

7. The compound according to claim **1**, or a pharmaceutically acceptable salt, stable isotope derivative, or a stereo isomer thereof, wherein ring K is a phenyl group, wherein the phenyl group is optionally selected from halogen or —OR^a by one or two groups.

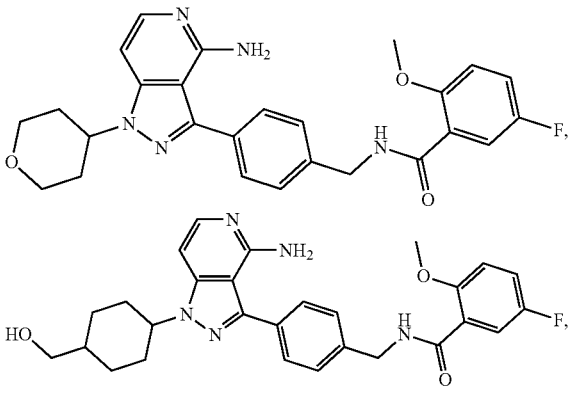
8. The compound according to claim **1**, or a pharmaceutically acceptable salt, stable isotope derivative, or a stereo isomer thereof, wherein ring K is



R^a is C_{1-2} alkyl, wherein one or more hydrogens of the alkyl group are optionally substituted by D.

9. The compound according to claim **1**, or its pharmaceutically acceptable salt, stable isotope derivative and isomer thereof, wherein R^1 is H or fluorine.

10. A compound having the following structure, or its pharmaceutically acceptable salt, stable isotope derivative, and stereoisomer thereof:



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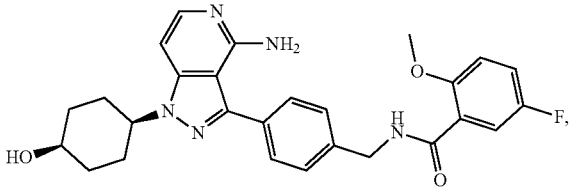

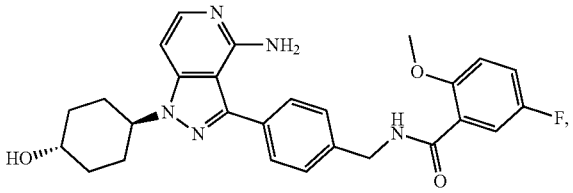

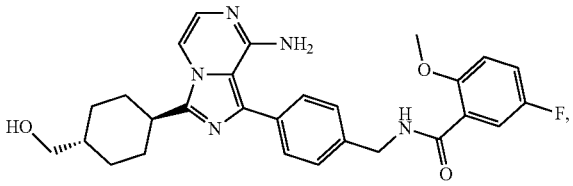

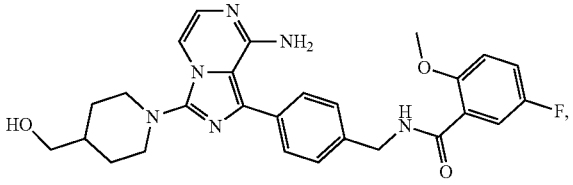

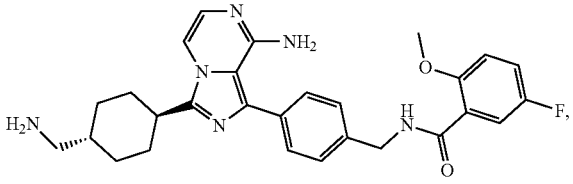

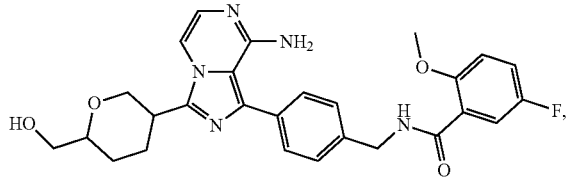

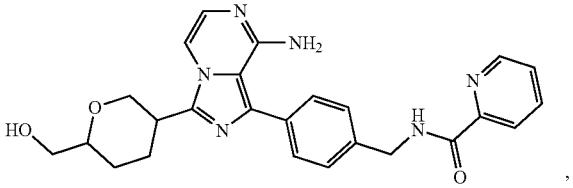

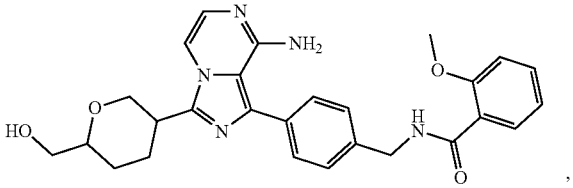

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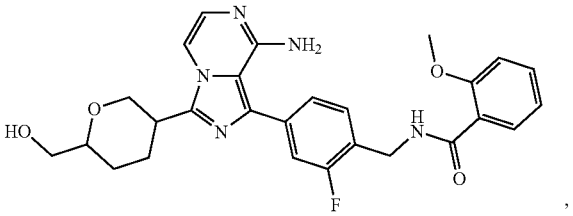

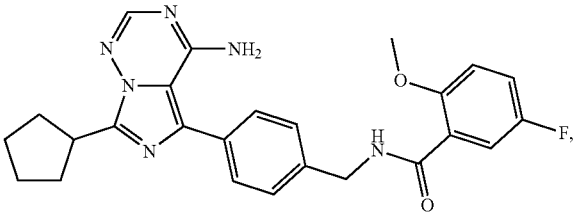

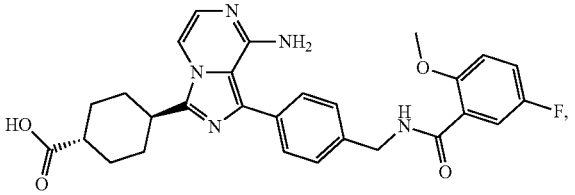

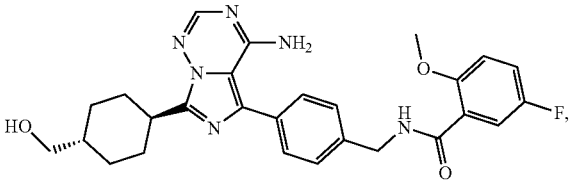

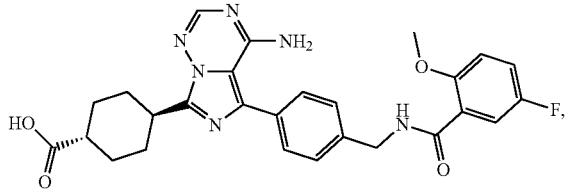

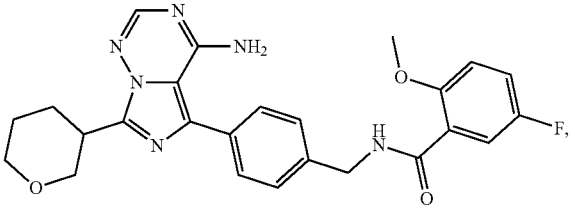

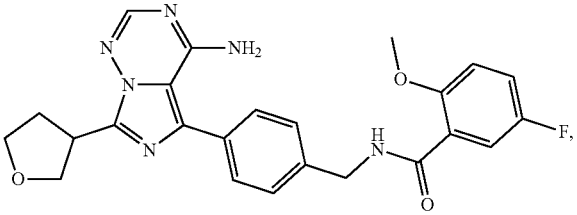

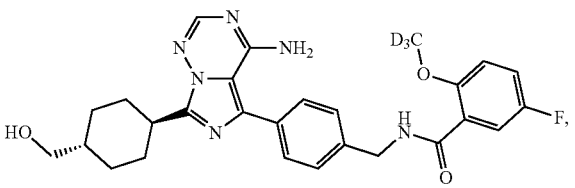

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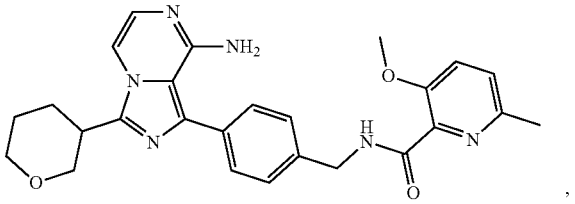

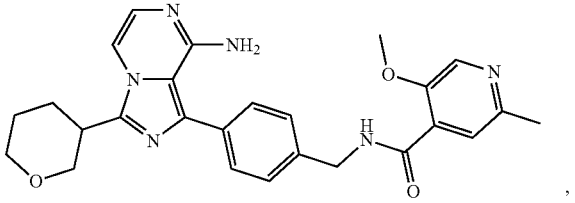

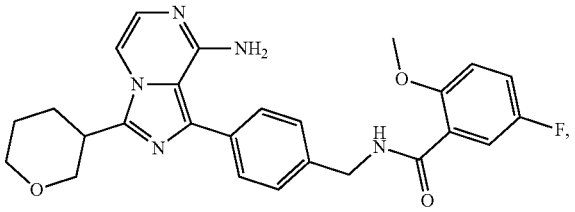

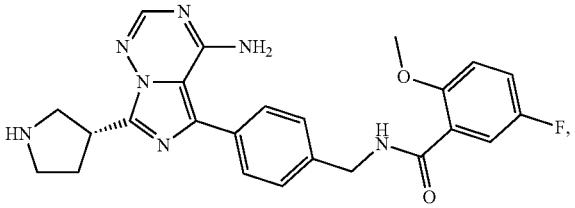

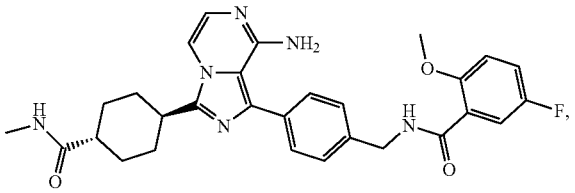

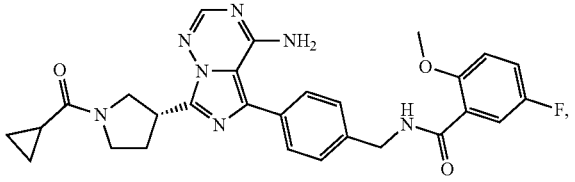

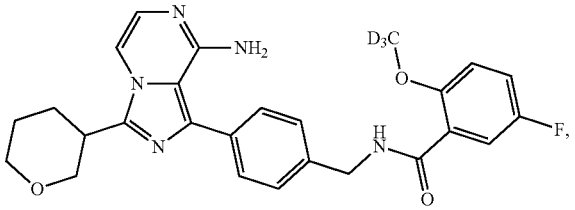

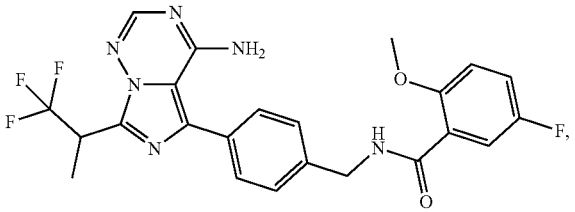

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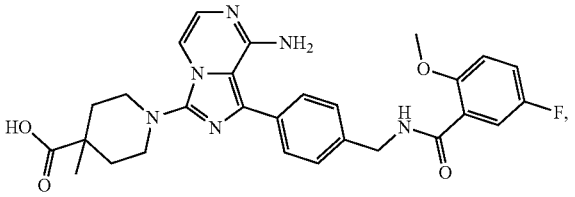

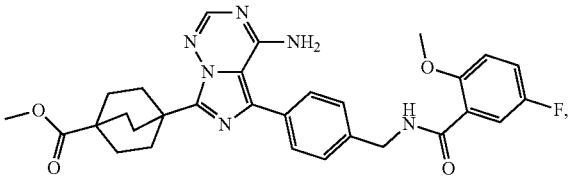

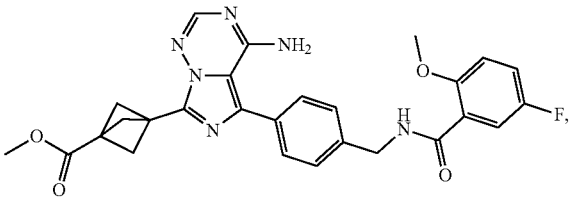

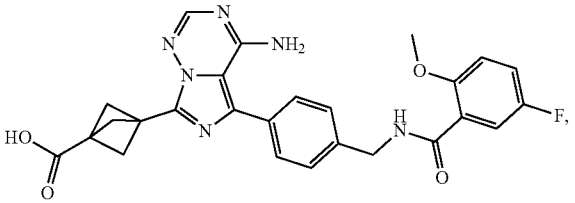

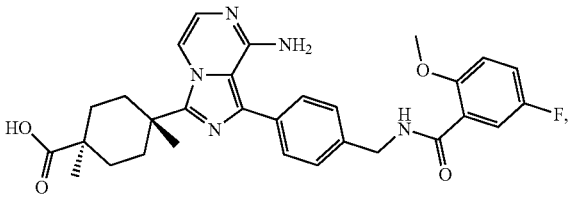

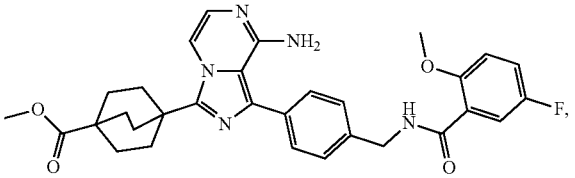

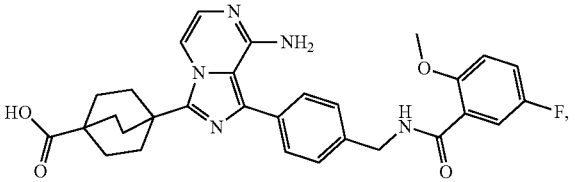

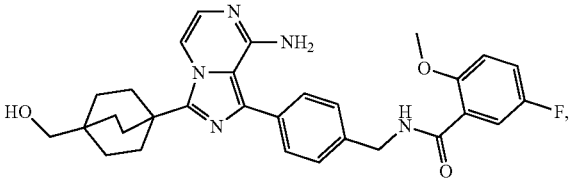

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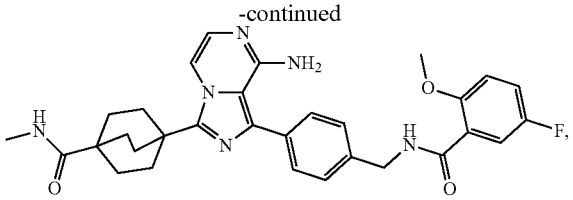

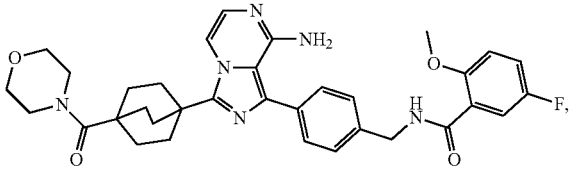

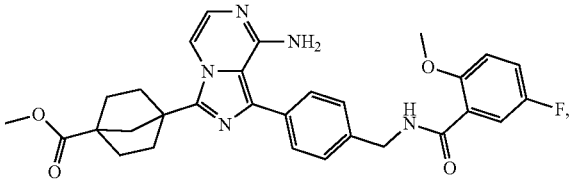

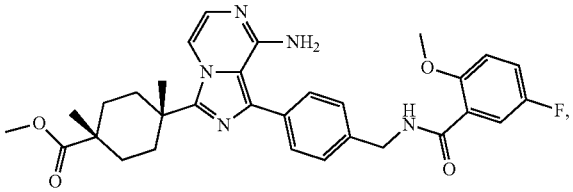

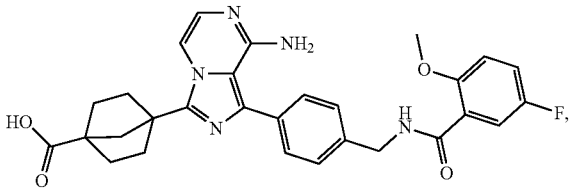

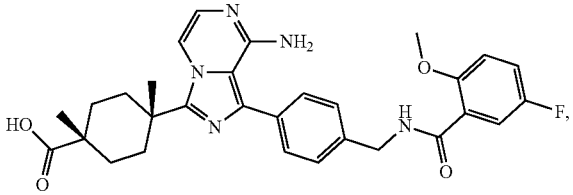

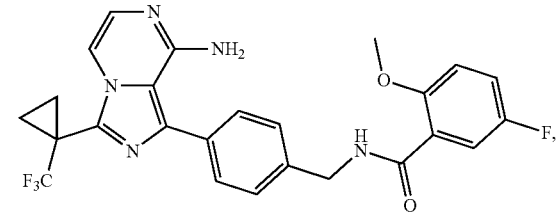

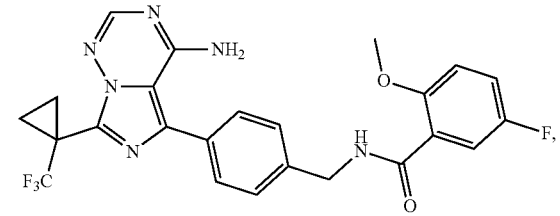

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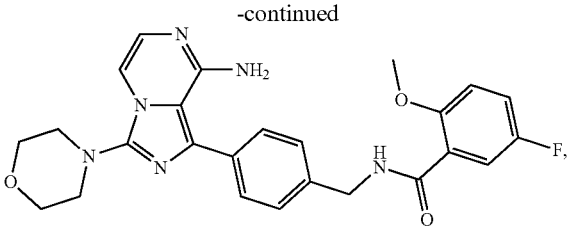

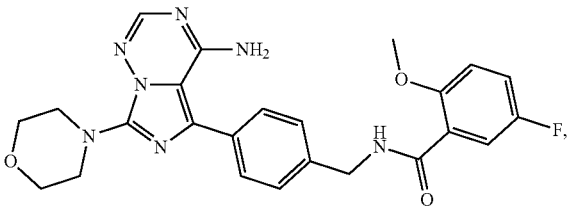

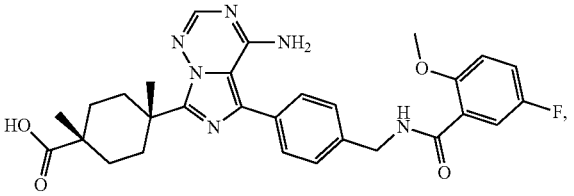

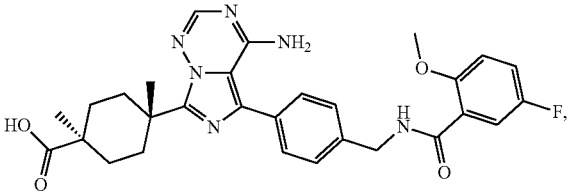

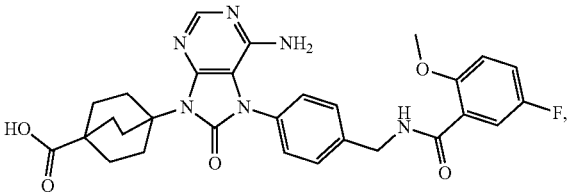

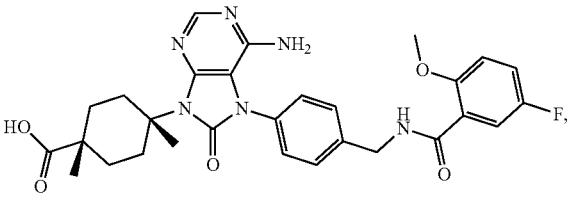

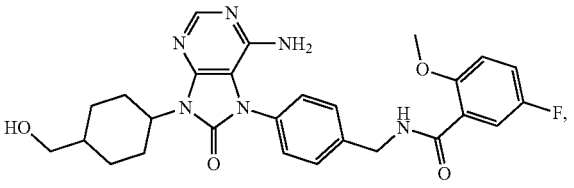

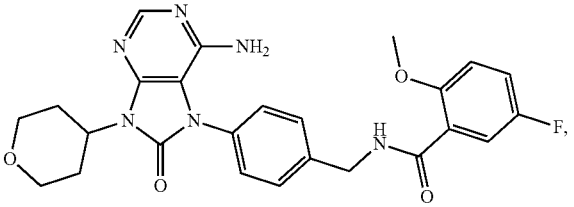

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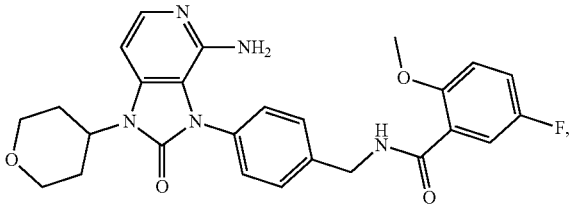

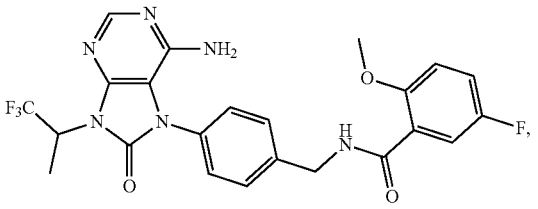

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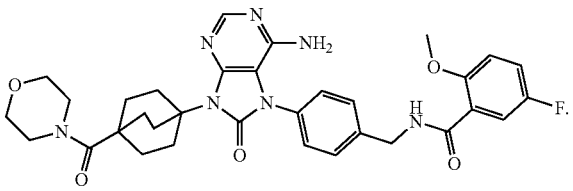
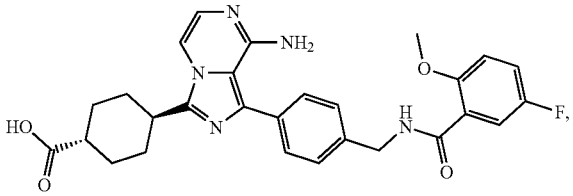
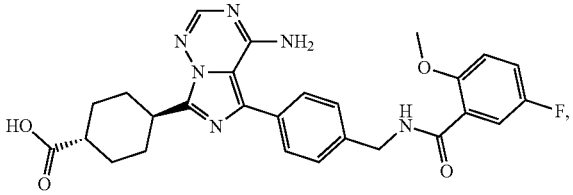
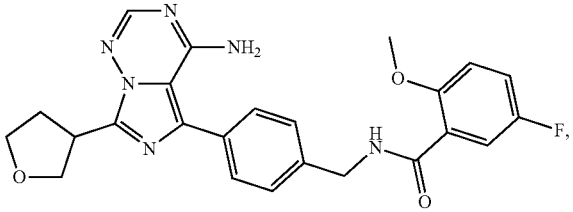
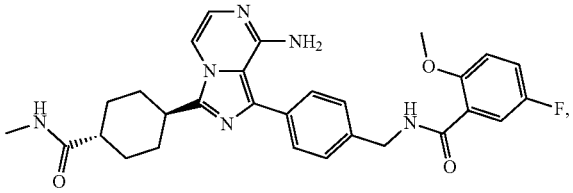


11. The compound of claim **10**, which is:









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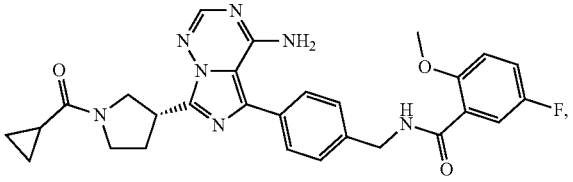

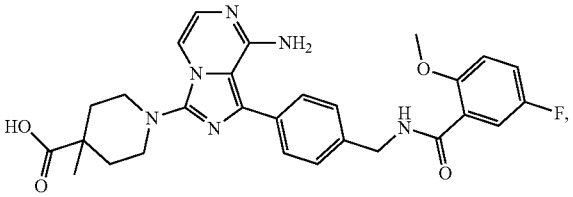

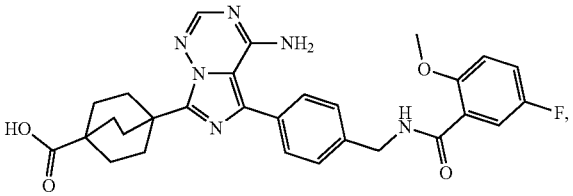

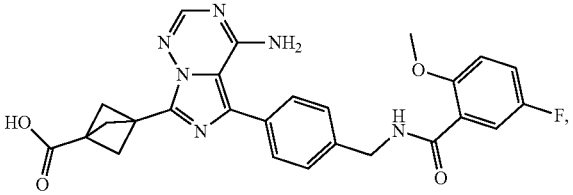

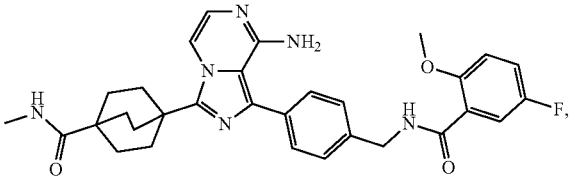

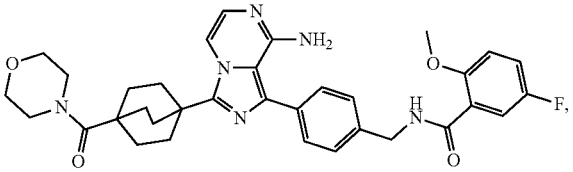

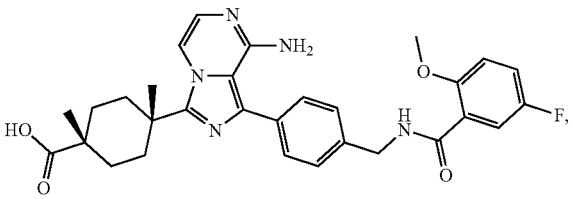

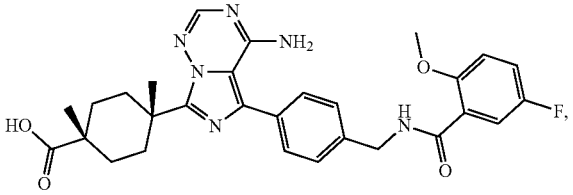

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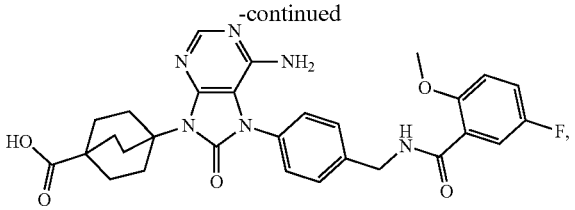
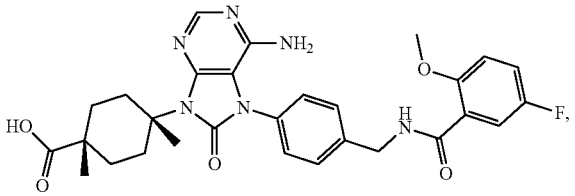
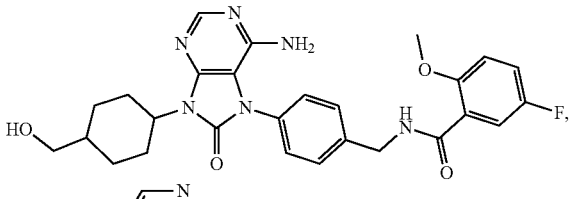
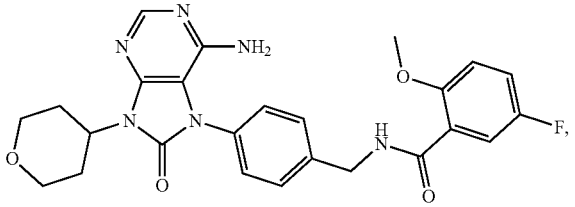
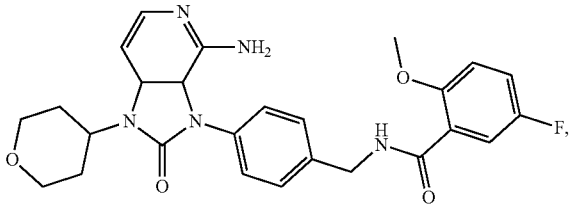
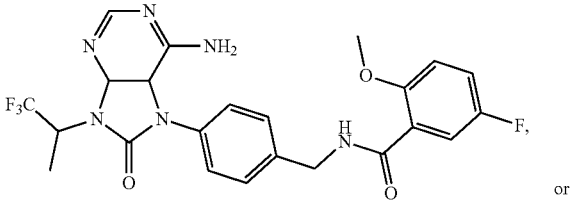


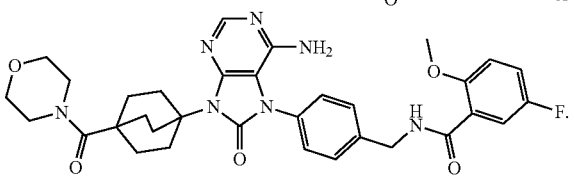






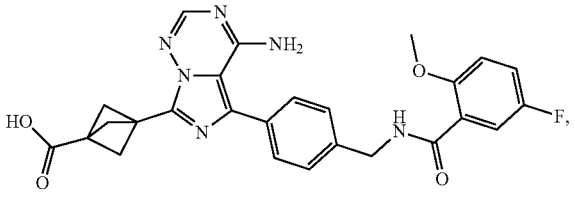






or

12. The compound of claim **10**, which is:



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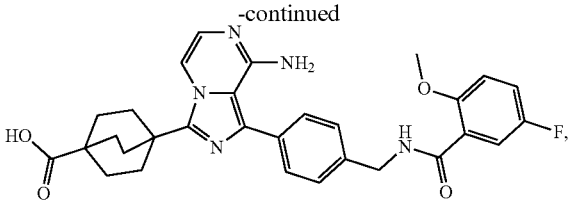
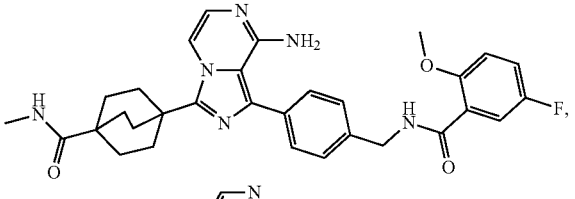
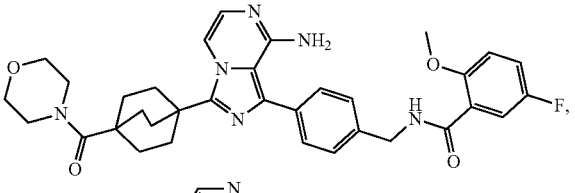
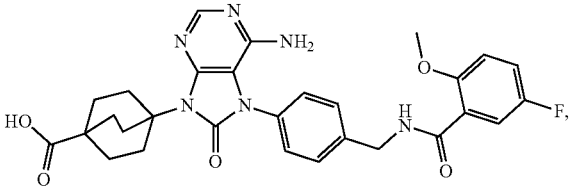
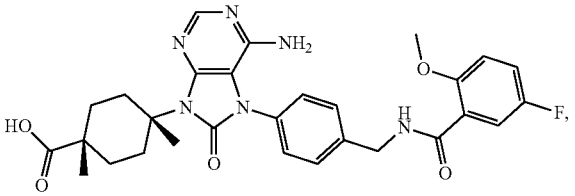
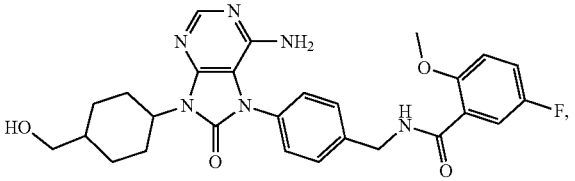


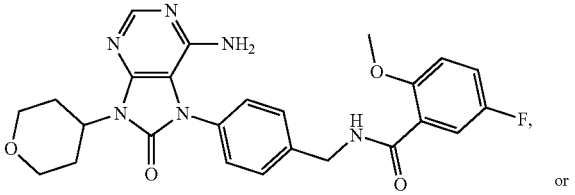




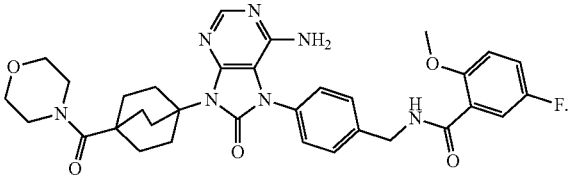








or



13. A pharmaceutical composition comprising the compound according to claim **10**, or a pharmaceutically acceptable salt, stable isotope derivative, or a stereoisomer thereof, and a pharmaceutically acceptable carrier.

14. A method for preventing or treating related diseases mediated by BTK or its C481 mutant, the method compris-

ing administering to a patient in need a therapeutically effective amount of the compound according to claim **10** or a pharmaceutically acceptable salt, stable isotope derivative, or a stereoisomer thereof, wherein the diseases mediated by BTK and its C481 mutant are cancer, lymphoma, leukemia, an autoimmune disease or an inflammatory disease.

15. The method according to claim **14**, wherein the disease is B-cell lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, mantle cell lymphoma, Waldenstrom's macroglobulinemia, marginal zone lymphoma, follicular lymphoma, central nervous system lymphoma, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, multiple myeloma, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, lupus nephritis, Sjogren's syndrome, IgG4-related diseases, idiopathic thrombocytopenic purpura, immune thrombocytopenia, or pemphigus.

* * * * *