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HETEROCYCLIC COMPOUNDS, COMPOSITIONS THEREOF, AND METHODS OF TREATMENT THEREWITH

Abstract

Provided herein are compounds having the following structure: ##STR00001## wherein the substituents are as defined herein, compositions comprising an effective amount of a compound, and methods for modulating the activity of KRAS G12D and/or G12V.

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Background/Summary

FIELD

[0001] Provided herein are heterocyclic compounds useful for treating cancer, a pharmaceutical composition comprising the compounds and, methods of using the compounds for treating cancer or a condition treatable or preventable by inhibition of KRAS activity, comprising administering an effective amount of the compounds to a subject in need thereof.

BACKGROUND

[0002] Ras is a family of proteins which are associated with cell membrane through their C-terminal membrane targeting region and well known as the molecular switch in intracellular signaling network (Cox A D, Der C J. Ras history: The saga continues. *Small GTPases.* 2010; 1(1):2-27). Ras proteins bind with either GTP or GDP and switch between "on" and "off" states. When Ras proteins bind with GDP, it is in the off (or inactive) state. And when Ras is switched on by certain growth promoting stimuli like growth factors, Ras proteins will be induced to exchange its bound GDP for a GTP and turn into on (or active) state (Malumbres M, Barbacid M. RAS oncogenes: the first 30 years. *Nat Rev Cancer.* 2003; 3(6):459-465). By switching to active state, Ras protein can interact with different downstream proteins and activate related signaling pathways (Berndt N, Hamilton A D, Sebti S M. Targeting protein prenylation for cancer therapy. *Nat Rev Cancer.* 2011; 11(11):775-791). Ras superfamily contains different subfamilies including Ras, Ral, Rap, Rheb, Rad, Rit and Miro (Wennerberg K, Rossman K L, Der C J. The Ras superfamily at a glance. *J Cell Sci.* 2005; 118(Pt 5):843-846). HRas, NRas and KRas are the most well studied proteins in Ras family since these proteins are the most common oncogenes in human cancers (O'Bryan J P. Pharmacological targeting of RAS: Recent success with direct inhibitors. *Pharmacol Res.* 2019; 139:503-511).

[0003] KRas is one of the most frequently mutated genes in human cancers. Based on data from Catalogue of Somatic Mutations (COSMIC) database, KRas mutation can be found in about 20% of human cancers, including pancreatic cancer, colorectal cancer, lung cancer, skin cancer etc. (O'Bryan J P. Pharmacological targeting of RAS: Recent success with direct inhibitors. *Pharmacol Res.* 2019; 139:503-511). The most common KRas mutations are found at position G12 and G13 by blocking the GTPase activating proteins (GAP) stimulated GTP hydrolysis activity of KRas (Wang W, Fang G, Rudolph J. Ras inhibition via direct Ras binding—is there a path forward?. *BioorgMed Chem Lett.* 2012; 22(18):5766-5776). That results in the over activation of KRas protein and ultimately leads to uncontrolled cell proliferation and cancer.

[0004] Among different cancers, pancreatic cancer is considered as the most KRas-addicted cancer type. KRas mutation is found in 94.1% of pancreatic ductal adenocarcinoma (PDAC). G12D (41%) and G12V (34%) mutations of KRas are the two most predominant mutations in all the KRas mutated PDAC (Waters A M, Der C J. KRAS: The Critical Driver and Therapeutic Target for Pancreatic Cancer. *Cold Spring Harb Perspect Med.* 2018; 8(9):a031435). In vivo data generated

by mouse models proves that the progression and maintenance of pancreatic cancer are highly rely on the constitutive activation of KRas downstream signaling (Siveke J T, Schmid R M. Chromosomal instability in mouse metastatic pancreatic cancer—it's Kras and Tp53 after all. *Cancer Cell.* 2005; 7(5):405-407). Which indicates that mutated KRas protein is a highly attractive drug target for pancreatic cancer and also other cancers with KRas mutation. Since WT KRas protein also plays a critical role in the function of normal tissue and WT KRas function is demonstrated to be essential for adult hematopoiesis (Malumbres M, Barbacid M. RAS oncogenes: the first 30 years. *Nat Rev Cancer.* 2003; 3(6):459-465). It is highly deserved that a potential drug molecule can selectively inhibit mutated Kras protein in cancer cells and spare its WT companion in normal cells.

[0005] Thus, KRas G12D and G12V mutations are a highly attractive target for cancer and other cancers with this mutation. As such, small-molecule therapeutic agents that are capable to selectively bind with Kras G12D or G12V and inhibit its function would be very useful.

[0006] Citation or identification of any reference in this section of this application is not to be construed as an admission that the reference is prior art to the present application.

SUMMARY

[0007] Provided herein are compounds having the following formula (II):

##STR00002## [0008] and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, atropisomers, isotopologues, and prodrugs thereof, wherein the substituents are as defined herein.

[0009] In one embodiment, the compound is selected from Table 1-Table 3.

[0010] In one embodiment, provided herein is a method for inhibiting the activity of KRAS mutant protein in a cell, comprising contacting said cell with an effective amount of a compound provided herein, or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer, enantiomer, atropisomer, or prodrug thereof, optionally wherein the KRAS mutant protein is KRAS G12D and/or G12V mutant protein.

[0011] In one embodiment, provided herein is a method for treatment or prevention of cancer, the method comprising administering to a subject in need thereof an effective amount of a compound provided herein, or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer, enantiomer, atropisomer, or prodrug thereof, optionally wherein the cancer is mediated by KRAS mutation; preferably KRAS G12D and/or G12V mutation.

Description

DETAILED DESCRIPTION

Definitions

[0012] As used herein, “KRAS gene” refers to a gene selected from the group consisting of: DIRAS1; DIRAS2; DIRAS3; ERAS; GEM; HRAS; KRAS; MRAS; NKIRAS1; NKIRAS2; NRAS; RALA; RALB; RAP1A; RAP1B; RAP2A; RAP2B; RAP2C; RASD1; RASD2; RASL10A; RASL10B; RASL11A; RASL11B; RASL12; REM1; REM2; RERG; RERGL; RRAD; RRAS; RRAS2, and mutants thereof.

[0013] As used herein, “KRAS protein” refers to a protein or an isoform thereof expressed by a KRAS gene (Scolnick E M, Papageoege A G, Shih T Y (1979), “Guanine nucleotide-binding activity for src protein of rat-derived murine sarcoma viruses,” Proc Natl Acad Sci USA. 76 (5): 5355-5559; Kranenburg O (November 2005) “The KRAS oncogene: past, present, and future,” Biochimica et Biophysica Acta (BBA)—Reviews on Cancer, 1756 (2): 81-2).

[0014] As used herein, “G12D mutation” refers to the mutation of the 12.sup.th amino acid residue located in the G domain of KRAS protein from glycine to aspartic acid.

[0015] As used herein, “KRAS G12D” or “G12D” refer to KRAS protein with G12D mutation.

[0016] As used herein, “G12V mutation” refers to the mutation of the 12.sup.th amino acid residue located in the G domain of KRAS protein from glycine to a valine.
[0017] As used herein, “KRAS G12V” or “G12V” refer to KRAS protein with G12V mutation.
[0018] As used herein, and in the specification and the accompanying claims, the indefinite articles “a” and “an” and the definite article “the” include plural as well as single referents, unless the context clearly indicates otherwise.
[0019] As used herein, and unless otherwise specified, the terms “about” and “approximately,” when used in connection with doses, amounts, or weight percents of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by one of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. In certain embodiments, the terms “about” and “approximately,” when used in this context, contemplate a dose, amount, or weight percent within 30%, within 20%, within 15%, within 10%, or within 5%, of the specified dose, amount, or weight percent.
[0020] As used herein, and unless otherwise specified, the terms “about” and “approximately,” when used in connection with a numeric value or range of values which is provided to characterize a particular solid form, e.g., a specific temperature or temperature range, such as, for example, that describes a melting, dehydration, desolvation, or glass transition temperature; a mass change, such as, for example, a mass change as a function of temperature or humidity; a solvent or water content, in terms of, for example, mass or a percentage; or a peak position, such as, for example, in analysis by, for example, IR or Raman spectroscopy or XRPD; indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the solid form. Techniques for characterizing crystal forms and amorphous solids include, but are not limited to, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), single-crystal X-ray diffractometry, vibrational spectroscopy, e.g., infrared (IR) and Raman spectroscopy, solid-state and solution nuclear magnetic resonance (NMR) spectroscopy, optical microscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies, and dissolution studies. In certain embodiments, the terms “about” and “approximately,” when used in this context, indicate that the numeric value or range of values may vary within 30%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. For example, in some embodiments, the value of an XRPD peak position may vary by up to +0.2° 20 (or +0.2 degree 20) while still describing the particular XRPD peak.
[0021] An “alkyl” group is a saturated, partially saturated, or unsaturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms, typically from 1 to 8 carbons or, in some embodiments, from 1 to 6, 1 to 4, or 2 to 6 or carbon atoms. Representative alkyl groups include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl; while saturated branched alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, tert-pentyl, -2-methylpentyl, -3-methylpentyl, -4-methylpentyl, -2,3-dimethylbutyl and the like. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, allyl, —CH═CH(CH.sub.3), —CH═C(CH.sub.3).sub.2, —C(CH.sub.3)═CH.sub.2, —C(CH.sub.3)═CH(CH.sub.3), —C(CH.sub.2CH.sub.3)═CH.sub.2, —C≡CH, —C≡C(CH.sub.3), —C≡C(CH.sub.2CH.sub.3), —CH.sub.2C≡CH, —CH.sub.2C≡C(CH.sub.3) and —CH.sub.2C≡C(CH.sub.7CH.sub.3), among others. An alkyl group can be substituted or unsubstituted. When the alkyl groups described herein are said to be “substituted,” they may be substituted with any substituent or substituents as those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); alkyl; hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; sulfonyl; sulfone; sulfonamide; ketone; aldehyde; ester; urea; urethane; oxime; hydroxyl amine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine;

hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; B(OH).sub.2, or O(alkyl)aminocarbonyl.

[0022] An “alkenyl” group is a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms, typically from 2 to 8 carbon atoms, and including at least one carbon-carbon double bond. Representative straight chain and branched (C.sub.2C.sub.8)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, 2pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, 2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, 3octenyl and the like. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. An alkenyl group can be unsubstituted or substituted.

[0023] An “alkynyl” group refers to a monovalent hydrocarbon radical moiety containing at least two carbon atoms and one or more carbon-carbon triple bonds. Alkynyl is optionally substituted and can be linear, branched, or cyclic. Alkynyl includes, but is not limited to, those radicals having 2-20 carbon atoms, i.e., C.sub.2-20 alkynyl; 2-12 carbon atoms, i.e., C.sub.2-12 alkynyl; 2-8 carbon atoms, i.e., C.sub.2-8 alkynyl; 2-6 carbon atoms, i.e., C.sub.2-6 alkynyl; and 2-4 carbon atoms, i.e., C.sub.2-4 alkynyl. Examples of alkynyl moieties include, but are not limited to ethynyl, propynyl, and butynyl.

[0024] A “cycloalkyl” group is a saturated, partially saturated, or unsaturated cyclic alkyl group of from 3 to 10 carbon atoms having a single cyclic ring or multiple condensed or bridged rings which can be optionally substituted with from 1 to 3 alkyl groups. In some embodiments, the cycloalkyl group has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms ranges from 3 to 5, 3 to 6, or 3 to 7. A cycloalkyl comprising more than one ring may be fused, spiro, or bridged, or combinations thereof. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like, or multiple or bridged ring structures such as 1-bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, adamantyl and the like. Examples of unsaturated cycloalkyl groups include cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, hexadienyl, among others. A cycloalkyl group can be substituted or unsubstituted. Such substituted cycloalkyl groups include, by way of example, cyclohexanol and the like.

[0025] A “bridged” bicyclic ring system includes two rings sharing three, four, or five adjacent ring atoms. As used herein, the term “bridge” refers to an atom or chain of atoms that connects two different parts of a molecule. Two atoms connected through a bridge (usually but not always two tertiary carbon atoms) are called “bridgeheads”. In addition to the bridge, the two bridgeheads are connected by at least two individual atoms or atomic chains. Examples of bridged bicyclic ring systems include adamantanyl, norbornanyl, bicyclo [3.2.1]octyl, bicyclo [2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.2.3]nonyl, 2-oxa-bicyclo [2.2.2]octyl, 1-aza-bicyclo [2.2.2]octyl, 3-aza-bicyclo [3.2.1]octyl, and 2, Examples include, but are not limited to, 6-dioxa-tricyclo [3.3.1.03,7]nonyl. In one embodiment, the bridge is unsubstituted or substituted —(CH.sub.2).sub.n—, wherein n is 1, 2, 3, 4, or 5. In one embodiment, the bridge is —CH.sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—. A “spiro” bicyclic ring system shares a single ring atom (usually a quaternary carbon atom) between two rings.

[0026] An “aryl” group is an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl). In some embodiments, aryl groups contain 6-14 carbons, and in others from 6 to 12 or even 6 to 10 carbon atoms in the ring portions of the groups. Particular aryls include phenyl, biphenyl, naphthyl and the like. An aryl group can be substituted or unsubstituted. The phrase “aryl groups” also includes groups containing fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl,

tetrahydronaphthyl, and the like).

[0027] A “heterocyclyl” is an aromatic (also referred to as heteroaryl) or non-aromatic cycloalkyl in which one to four of the ring carbon atoms are independently replaced with a heteroatom from the group consisting of O, S and N. In some embodiments, heterocyclyl groups include 3 to 10 ring members, whereas other such groups have 3 to 5, 3 to 6, or 3 to 8 ring members. Heterocyclyls can also be bonded to other groups at any ring atom (i.e., at any carbon atom or heteroatom of the heterocyclic ring). A heterocyclyl group can be substituted or unsubstituted. A heterocyclyl group may include multiple condensed rings including, but are not limited to, bicyclic, tricyclic, and quadracyclic rings, as well as bridged or spirocyclic ring systems. Heterocyclyl groups encompass unsaturated, partially saturated and saturated ring systems, such as, for example, imidazolyl, imidazolinyl and imidazolidinyl (e.g., imidazolidin-4-one or imidazolidin-2,4-dionyl) groups. The phrase heterocyclyl includes fused ring species, including those comprising fused aromatic and non-aromatic groups, such as, for example, 1- and 2-aminotetraline, benzotriazolyl (e.g., 1H-benzo[d][1,2,3]triazolyl), benzimidazolyl (e.g., 1H-benzo[d]imidazolyl), 2,3-dihydrobenzo[1,4]dioxinyl, and benzo[1,3]dioxolyl. The phrase also includes bridged polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. Representative examples of a heterocyclyl group include, but are not limited to, aziridinyl, azetidinyl, azepanyl, oxetanyl, pyrrolidyl, imidazolidinyl (e.g., imidazolidin-4-onyl or imidazolidin-2,4-dionyl), pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, dioxolyl, furanyl, thiophenyl, pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, benzisoxazolyl (e.g., benzo[d]isoxazolyl), thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, piperidyl, piperazinyl (e.g., piperazin-2-onyl), morpholinyl, thiomorpholinyl, tetrahydropyranyl (e.g., tetrahydro-2H-pyranyl), tetrahydrothiopyranyl, oxathianyl, dioxyl, dithianyl, pyranyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, dihydropyridyl, dihydrodithiinyl, dihydrodithionyl, 1,4-dioxaspiro[4.5]decanyl, 2-oxo-1-oxa-3,8-diazaspiro[4.5]decane, 1-oxo-2,8-diazaspiro[4.5]decane, 3-oxo-2,8-diazaspiro[4.5]decane, 3-oxo-1-oxa-4,9-diazaspiro[5.5]undecane, 2-oxo-1-oxa-3,9-diazaspiro[5.5]undecane, homopiperazinyl, quinuclidyl, indolyl (e.g., indolyl-2-onyl or isoindolin-1-onyl), indolinyl, isoindolyl, isoindolinyl, azaindolyl (pyrrolopyridyl or 1H-pyrrolo[2,3-b]pyridyl), indazolyl, indolizinyl, benzotriazolyl (e.g., 1H-benzo[d][1,2,3]triazolyl), benzimidazolyl (e.g., 1H-benzo[d]imidazolyl or 1H-benzo[d]imidazol-2(3H)-onyl), benzofuranyl, benzothiophenyl, benzothiazolyl, benzoxadiazolyl, benzoxazinyl, benzodithiinyl, benzoxathiinyl, benzothiazinyl, benzoxazolyl (i.e., benzo[d]oxazolyl), benzothiazolyl, benzothiadiazolyl, benzo[1,3]dioxolyl, pyrazolopyridyl (for example, 1H-pyrazolo[3,4-b]pyridyl, 1H-pyrazolo[4,3-b]pyridyl), imidazopyridyl (e.g., azabenzimidazolyl or 1H-imidazo[4,5-b]pyridyl), triazolopyridyl, isoxazolopyridyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl (e.g., 3,4-dihydroisoquinolin-1(2H)-onyl), quinolizinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, pteridinyl, thianaphthalenyl, dihydrobenzothiazinyl, dihydrobenzofuranyl, dihydroindolyl, dihydrobenzodioxinyl, tetrahydroindolyl, tetrahydroindazolyl, tetrahydrobenzimidazolyl, tetrahydrobenzotriazolyl, tetrahydropyrrolopyridyl, tetrahydropyrazolopyridyl, tetrahydroimidazopyridyl, tetrahydrotriazolopyridyl, tetrahydropyrimidin-2(1H)-one and tetrahydroquinolinyl groups. Representative non-aromatic heterocyclyl groups do not include fused ring species that comprise a fused aromatic group. Examples of non-aromatic heterocyclyl groups include aziridinyl, azetidinyl, azepanyl, pyrrolidyl, imidazolidinyl (e.g., imidazolidin-4-onyl or imidazolidin-2,4-dionyl), pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, piperidyl, piperazinyl (e.g., piperazin-2-onyl), morpholinyl, thiomorpholinyl, tetrahydropyranyl (e.g., tetrahydro-2H-pyranyl), tetrahydrothiopyranyl, oxathianyl, dithianyl, 1,4-dioxaspiro[4.5]decanyl, homopiperazinyl, quinuclidyl, or tetrahydropyrimidin-2(1H)-one. Representative substituted heterocyclyl groups may be mono-substituted or substituted more than once, such as, but not limited to, pyridyl or morpholinyl groups, which are 2-, 3-, 4-, 5-, or 6-

substituted, or disubstituted with various substituents such as those listed below.
[0028] A “heteroaryl” group is an aryl ring system having one to four heteroatoms as ring atoms in a heteroaromatic ring system, wherein the remainder of the atoms are carbon atoms. In some embodiments, heteroaryl groups contain 3 to 6 ring atoms, and in others from 6 to 9 or even 6 to 10 atoms in the ring portions of the groups. Suitable heteroatoms include oxygen, sulfur and nitrogen. In certain embodiments, the heteroaryl ring system is monocyclic or bicyclic. Non-limiting examples include but are not limited to, groups such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, benzisoxazolyl (e.g., benzo[d]isoxazolyl), thiazolyl, pyrolyl, pyridazinyl, pyrimidyl, pyrazinyl, thiophenyl, benzothiophenyl, furanyl, benzofuranyl, indolyl (e.g., indolyl-2-onyl or isoindolin-1-onyl), azaindolyl (pyrrolopyridyl or 1H-pyrrolo[2,3-b]pyridyl), indazolyl, benzimidazolyl (e.g., 1H-benzo[d]imidazolyl), imidazopyridyl (e.g., azabenzimidazolyl or 1H-imidazo[4,5-b]pyridyl), pyrazolopyridyl, triazolopyridyl, benzotriazolyl (e.g., 1H-benzo[d][1,2,3]triazolyl), benzoxazolyl (e.g., benzo[d]oxazolyl), benzothiazolyl, benzothiadiazolyl, isoxazolopyridyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl (e.g., 3,4-dihydroisoquinolin-1(2H)-onyl), tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups.
[0029] As used herein, “spirocyclic ring” refers to two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings.
[0030] A “cycloalkylalkyl” group is a radical of the formula: -alkyl-cycloalkyl, wherein alkyl and cycloalkyl are as defined above. Substituted cycloalkylalkyl groups may be substituted at the alkyl, the cycloalkyl, or both the alkyl and the cycloalkyl portions of the group. Representative cycloalkylalkyl groups include but are not limited to methylcyclopropyl, methylcyclobutyl, methylcyclopentyl, methylcyclohexyl, ethylcyclopropyl, ethylcyclobutyl, ethylcyclopentyl, ethylcyclohexyl, propylcyclopentyl, propylcyclohexyl and the like.
[0031] An “aralkyl” group is a radical of the formula: -alkyl-aryl, wherein alkyl and aryl are defined above. Substituted aralkyl groups may be substituted at the alkyl, the aryl, or both the alkyl and the aryl portions of the group. Representative aralkyl groups include but are not limited to benzyl and phenethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl.
[0032] An “heterocyclylalkyl” group is a radical of the formula: -alkyl-heterocyclyl, wherein alkyl and heterocyclyl are defined above. Substituted heterocyclylalkyl groups may be substituted at the alkyl, the heterocyclyl, or both the alkyl and the heterocyclyl portions of the group. Representative heterocylylalkyl groups include but are not limited to 4-ethyl-morpholinyl, 4-propylmorpholinyl, furan-2-yl methyl, furan-3-yl methyl, pyridin-3-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl.
[0033] A “halogen” is fluorine, chlorine, bromine or iodine.
[0034] A “hydroxyalkyl” group is an alkyl group as described above substituted with one or more hydroxy groups.
[0035] An “alkoxy” or “alkoxyl” group is —O-(alkyl), wherein alkyl is defined above.
[0036] An “alkoxyalkyl” group is -(alkyl)-O-(alkyl), wherein alkyl is defined above.
[0037] An “amino” group is a radical of the formula: —NH.sub.2.
[0038] An “alkylamino” group is a radical of the formula: —NH-alkyl or —N(alkyl).sub.2, wherein each alkyl is independently as defined above.
[0039] A “carboxy” group is a radical of the formula: —C(O)OH.
[0040] An “aminocarbonyl” group is a radical of the formula: —C(O)N(R.sup.#).sub.2, —C(O)NH(R.sup.#) or —C(O)NH.sub.2, wherein each R.sup.# is independently a substituted or unsubstituted alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl or heterocyclyl group as defined herein.
[0041] An “acylamino” group is a radical of the formula: —NHC(O)(R.sup.#) or —N(alkyl)C(O)(R.sup.#), wherein each alkyl and R.sup.# are independently as defined above.

[0042] A “sulfonylamino” group is a radical of the formula: —NHSO.sub.2(R.sup.#) or —N(alkyl)SO.sub.2(R.sup.#), wherein each alkyl and R.sup.# are defined above.
[0043] A “urea” group is a radical of the formula: —N(alkyl)C(O)N(R.sup.#).sub.2, —N(alkyl)C(O)NH(R.sup.#), —N(alkyl)C(O)NH.sub.2, —NHC(O)N(R.sup.#).sub.2, —NHC(O)NH(R.sup.#), or —NH(CO)NHR.sup.#, wherein each alkyl and R.sup.# are independently as defined above.
[0044] When the groups described herein, with the exception of alkyl group, are said to be “substituted,” they may be substituted with any appropriate substituent or substituents. Illustrative examples of substituents are those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); alkyl; hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; sulfonyl; sulfone; sulfonamide; ketone; aldehyde; ester; urea; urethane; oxime; hydroxyl amine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; oxygen (═O); B(OH).sub.2, O(alkyl)aminocarbonyl; cycloalkyl, which may be monocyclic or fused or non-fused polycyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), or a heterocyclyl, which may be monocyclic or fused or non-fused polycyclic (e.g., pyrrolidyl, piperidyl, piperazinyl, morpholinyl, or thiazinyl); monocyclic or fused or non-fused polycyclic aryl or heteroaryl (e.g., phenyl, naphthyl, pyrrolyl, indolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, tetrazolyl, pyrazolyl, pyridyl, quinolinyl, isoquinolinyl, acridinyl, pyrazinyl, pyridazinyl, pyrimidyl, benzimidazolyl, benzothiophenyl, or benzofuranyl) aryloxy; aralkyloxy; heterocyclyloxy; and heterocyclyl alkoxy.
[0045] As used herein, the term “pharmaceutically acceptable salt(s)” refers to a salt prepared from a pharmaceutically acceptable non-toxic acid or base including an inorganic acid and base and an organic acid and base. Suitable pharmaceutically acceptable base addition salts of the compounds of formula (I) include, but are not limited to those well-known in the art, see for example, *Remington's Pharmaceutical Sciences*, 18.sup.th eds., Mack Publishing, Easton PA (1990) or *Remington: The Science and Practice of Pharmacy,* 19.sup.th eds., Mack Publishing, Easton PA (1995).
[0046] As used herein and unless otherwise indicated, the term “stereoisomer” or “stereomerically pure” means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. The compounds can have chiral centers and can occur as racemates, individual enantiomers or diastereomers, and mixtures thereof. All such isomeric forms are included within the embodiments disclosed herein, including mixtures thereof.
[0047] The use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms, are encompassed by the embodiments disclosed herein. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular compound may be used in methods and compositions disclosed herein. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. See, e.g., Jacques, J., et al., *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981);

Wilen, S. H., et al., *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E. L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[0048] It should also be noted the compounds can include E and Z isomers, or a mixture thereof, and cis and trans isomers or a mixture thereof. In certain embodiments, the compounds are isolated as either the E or Z isomer. In other embodiments, the compounds are a mixture of the E and Z isomers.

[0049] As used herein and unless otherwise indicated, “atropisomers” refer to stereoisomers resulting from hindered rotation about a single bond axis where the rotational barrier is high enough to allow for the isolation of the individual rotational isomers

[0050] “Tautomers” refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. For example, in aqueous solution, pyrazoles may exhibit the following isomeric forms, which are referred to as tautomers of each other:

##STR00003##

[0051] As readily understood by one skilled in the art, a wide variety of functional groups and other structures may exhibit tautomerism and all tautomers of compounds of formula (I) are within the scope of the present invention.

[0052] It should also be noted the compounds can contain unnatural proportions of atomic isotopes at one or more of the atoms. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (H), iodine-125 (.sup.125I), sulfur-35 (.sup.35S), or carbon-14 (.sup.14C), or may be isotopically enriched, such as with deuterium (.sup.2H), carbon-13 (.sup.13C), or nitrogen-15 (.sup.15N). As used herein, an “isotopologue” is an isotopically enriched compound. The term “isotopically enriched” refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. “Isotopically enriched” may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom. The term “isotopic composition” refers to the amount of each isotope present for a given atom. Radiolabeled and isotopically enriched compounds are useful as therapeutic agents, e.g., cancer and inflammation therapeutic agents, research reagents, e.g., binding assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the compounds as described herein, whether radioactive or not, are intended to be encompassed within the scope of the embodiments provided herein. In some embodiments, there are provided isotopologues of the compounds, for example, the isotopologues are deuterium, carbon-13, or nitrogen-15 enriched compounds.

[0053] “Treating” as used herein, means an alleviation, in whole or in part, of a disorder, disease or condition, or one or more of the symptoms associated with a disorder, disease, or condition, or slowing or halting of further progression or worsening of those symptoms, or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself. In some embodiments, “treating” means an alleviation, in whole or in part, of a disorder, disease or condition, or a slowing, or halting of further progression or worsening of those symptoms. In another embodiment, “treating” means and alleviation, in whole or in part, of a disorder, disease or condition, or symptoms associated with a condition, wherein the condition is treatable or preventable by inhibition of KRAS; preferably G12D and/or G12V.

[0054] “Preventing” as used herein, means a method of delaying and/or precluding the onset, recurrence or spread, in whole or in part, of a disorder, disease or condition; barring a subject from acquiring a disorder, disease, or condition; or reducing a subject's risk of acquiring a disorder, disease, or condition. In one embodiment, the condition is a condition, treatable or preventable by inhibition of KRAS; preferably G12D and/or G12V.

[0055] The term “effective amount” in connection with a compound means an amount capable of

treating or preventing a disorder, disease or condition, or symptoms thereof, disclosed herein.
[0056] The term “subject” includes an animal, including, but not limited to, an animal such a cow, monkey, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig, in one embodiment a mammal, in another embodiment a human.

Compounds

[0057] Aspect 1: Provided herein are compounds having the following formula (I):

##STR00004## [0058] and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, atropisomers, isotopologues, and prodrugs thereof, [0059] wherein: [0060] ring A is unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; [0061] moiety B is unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocyclyl, or unsubstituted or substituted C.sub.2-5alkyl; [0062] X is N, or C—R.sup.8; [0063] W is O, NH, N—R.sup.9, N—C(═O)—R.sup.10, or O═S═O; [0064] each of R.sup.0 is, independently, H, halogen, amino, —CN, —OH, unsubstituted or substituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkenyl, unsubstituted or substituted C.sub.1-4 alkynyl, unsubstituted or substituted C.sub.1-4alkoxy, unsubstituted or substituted C.sub.3-5cycloalkyl, unsubstituted or substituted 3-member to 5-member heterocyclyl, unsubstituted or substituted C.sub.1-4alkylamino, carboxy, nitro, thiol, or thioether; or one or more pairs of the R.sup.0 groups, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; [0065] each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, is, independently, H, halogen, amino, —CN, —OH, unsubstituted or substituted C.sub.1-4alkyl, unsubstituted or substituted C.sub.1-4alkoxy, unsubstituted or substituted C.sub.3-5cycloalkyl, unsubstituted or substituted 3-member to 5-member heterocyclyl, unsubstituted or substituted C.sub.1-4alkylamino, carboxy, nitro, thiol, or thioether; or [0066] optionally, R.sup.3a, and R.sup.3b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0067] R.sup.4a, and R.sup.4b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0068] R.sup.6a, and R.sup.6b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0069] R.sup.7a, and R.sup.7b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0070] R.sup.8a, and R.sup.8b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0071] R.sup.6a, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0072] R.sup.6a, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0073] R.sup.5, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0074] R.sup.5, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; [0075] R.sup.8 is H, halogen, unsubstituted or substituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkenyl, unsubstituted or substituted C.sub.3-5 cycloalkyl, unsubstituted or substituted C.sub.1-4 alkoxyl, unsubstituted or substituted C.sub.1-4 halogenated alkyl, unsubstituted or substituted C.sub.3-5 halogenated cycloalkyl, unsubstituted or substituted C.sub.1-4 halogenated alkoxyl, CN, OH, or amino; [0076] R.sup.9 is substituted or unsubstituted C.sub.1-4 alkyl, or unsubstituted or substituted C.sub.3-5 cycloalkyl; [0077] R.sup.10 is substituted or unsubstituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkoxy, unsubstituted or substituted C.sub.3-5 cycloalkyl, or unsubstituted or substituted 3-member to 5-member heterocyclyl; [0078] t is 0, or 1; and [0079] each of m, and q is, independently, an integer between 0 and the maximum number of the substituent groups allowed on rings A, and B, respectively.

[0080] Provided herein are compounds having the following formula (IA):

##STR00005## [0081] and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, atropisomers, isotopologues, and prodrugs thereof, [0082] wherein: [0083] ring A is unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; [0084] moiety B is unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; [0085] X is N, or C—R.sup.8; [0086] W is O, NH, N—R.sup.9, N—C(═O)—R.sup.10, or O═S═O; [0087] each of R.sup.0 is, independently, H, halogen, amino, —CN, —OH, unsubstituted or substituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkenyl, unsubstituted or substituted C.sub.1-4 alkynyl, unsubstituted or substituted C.sub.1-4alkoxy, unsubstituted or substituted C.sub.3-5cycloalkyl, unsubstituted or substituted 3-member to 5-member heterocyclyl, unsubstituted or substituted C.sub.1-4alkylamino, carboxy, nitro, thiol, or thioether; or one or more pairs of the R.sup.0 groups, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; [0088] each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, is, independently, H, halogen, amino, —CN, —OH, unsubstituted or substituted C.sub.1-4alkyl, unsubstituted or substituted C.sub.1-4alkoxy, unsubstituted or substituted C.sub.3-5cycloalkyl, unsubstituted or substituted 3-member to 5-member heterocyclyl, unsubstituted or substituted C.sub.1-4alkylamino, carboxy, nitro, thiol, or thioether; or [0089] optionally, R.sup.3a, and R.sup.3b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0090] R.sup.4a, and R.sup.4b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0091] R.sup.6a, and R.sup.6b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0092] R.sup.7a, and R.sup.7b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0093] R.sup.8a, and R.sup.8b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0094] R.sup.6a, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0095] R.sup.6a, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0096] R.sup.5, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0097] R.sup.5, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; [0098] R.sup.8 is H, halogen, unsubstituted or substituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkenyl, unsubstituted or substituted C.sub.3-5 cycloalkyl, unsubstituted or substituted C.sub.1-4 alkoxyl, unsubstituted or substituted C.sub.1-4 halogenated alkyl, unsubstituted or substituted C.sub.3-5 halogenated cycloalkyl, unsubstituted or substituted C.sub.1-4 halogenated alkoxyl, CN, OH, or amino; [0099] R.sup.9 is substituted or unsubstituted C.sub.1-4 alkyl, or unsubstituted or substituted C.sub.3-5 cycloalkyl; [0100] R.sup.10 is substituted or unsubstituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkoxy, unsubstituted or substituted C.sub.3-5 cycloalkyl, or unsubstituted or substituted 3-member to 5-member heterocyclyl; [0101] t is 0, or 1; and [0102] each of m, and q is, independently, an integer between 0 and the maximum number of the substituent groups allowed on rings A, and B, respectively.

[0103] Provided herein are compounds having the following formula (II):

##STR00006## [0104] and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, atropisomers, isotopologues, and prodrugs thereof, [0105] wherein: [0106] ring A is unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; [0107] moiety B is unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocyclyl, or unsubstituted or substituted C.sub.2-5alkyl; [0108] X is N, or C—R.sup.8; [0109] W is O, NH, N—R.sup.9, N—C(═O)—R.sup.10, or O═S═O; [0110] each of R.sup.0 is, independently, H, halogen, amino, —

CN, —OH, unsubstituted or substituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkenyl, unsubstituted or substituted C.sub.1-4 alkynyl, unsubstituted or substituted C.sub.1-4alkoxy, unsubstituted or substituted C.sub.3-5cycloalkyl, unsubstituted or substituted 3-member to 5-member heterocyclyl, unsubstituted or substituted C.sub.1-4alkylamino, carboxy, nitro, thiol, or thioether; or one or more pairs of the R.sup.0 groups, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; [0111] each of R.sup.3a, R.sup.3b, R.sup.4, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, is, independently, H, halogen, amino, —CN, —OH, unsubstituted or substituted C.sub.1-4alkyl, unsubstituted or substituted C.sub.1-4alkoxy, unsubstituted or substituted C.sub.3-5cycloalkyl, unsubstituted or substituted 3-member to 5-member heterocyclyl, unsubstituted or substituted C.sub.1-4alkylamino, carboxy, nitro, thiol, or thioether; or [0112] optionally, R.sup.3a, and R.sup.3b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0113] R.sup.4a, and R.sup.4b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0114] R.sup.6a, and R.sup.6b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0115] R.sup.7a, and R.sup.7b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0116] R.sup.8a, and R.sup.8b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0117] R.sup.6a, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0118] R.sup.6a, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0119] R.sup.5, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0120] R.sup.5, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; [0121] R.sup.8 is H, halogen, unsubstituted or substituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkenyl, unsubstituted or substituted C.sub.3-5 cycloalkyl, unsubstituted or substituted C.sub.1-4 alkoxyl, unsubstituted or substituted C.sub.1-4 halogenated alkyl, unsubstituted or substituted C.sub.3-5 halogenated cycloalkyl, unsubstituted or substituted C.sub.1-4 halogenated alkoxyl, CN, OH, or amino; [0122] R.sup.9 is substituted or unsubstituted C.sub.1-4 alkyl, or unsubstituted or substituted C.sub.3-5 cycloalkyl; [0123] R.sup.10 is substituted or unsubstituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkoxy, unsubstituted or substituted C.sub.3-5 cycloalkyl, or unsubstituted or substituted 3-member to 5-member heterocyclyl; [0124] t is 0, or 1; [0125] each of s and r, is independently, is 1, or 2; and [0126] each of m, and q is, independently, an integer between 0 and the maximum number of the substituent groups allowed on rings A, and B, respectively.

[0127] Provided herein are compounds having the following formula (IIA):

##STR00007## [0128] an pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, atropisomers, isotopologues, and prodrugs thereof, [0129] wherein: [0130] ring A is unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; [0131] moiety B is unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; [0132] X is N, or C—R.sup.8; [0133] W is O, NH, N—R.sup.9, N—C(═O)—R.sup.10, or O═S═O; [0134] each of R.sup.0 is, independently, H, halogen, amino, —CN, —OH, unsubstituted or substituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkenyl, unsubstituted or substituted C.sub.1-4 alkynyl, unsubstituted or substituted C.sub.1-4alkoxy, unsubstituted or substituted C.sub.3-5cycloalkyl, unsubstituted or substituted 3-member to 5-member heterocyclyl, unsubstituted or substituted C.sub.1-4alkylamino, carboxy, nitro, thiol, or thioether; or one or more pairs of the R.sup.0 groups, together with the atom to which they are attached to, form

unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; [0135] each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, is, independently, H, halogen, amino, —CN, —OH, unsubstituted or substituted C.sub.1-4alkyl, unsubstituted or substituted C.sub.1-4alkoxy, unsubstituted or substituted C.sub.3-5cycloalkyl, unsubstituted or substituted 3-member to 5-member heterocyclyl, unsubstituted or substituted C.sub.1-4alkylamino, carboxy, nitro, thiol, or thioether; or [0136] optionally, R.sup.3a, and R.sup.3b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0137] R.sup.4a, and R.sup.4b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0138] R.sup.6a, and R.sup.6b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0139] R.sup.7a, and R.sup.7b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0140] R.sup.8a, and R.sup.8b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or [0141] R.sup.6a, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0142] R.sup.6a, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0143] R.sup.5, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or [0144] R.sup.5, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; [0145] R.sup.8 is H, halogen, unsubstituted or substituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkenyl, unsubstituted or substituted C.sub.3-5 cycloalkyl, unsubstituted or substituted C.sub.1-4 alkoxyl, unsubstituted or substituted C.sub.1-4 halogenated alkyl, unsubstituted or substituted C.sub.3-5 halogenated cycloalkyl, unsubstituted or substituted C.sub.1-4 halogenated alkoxyl, CN, OH, or amino; [0146] R.sup.9 is substituted or unsubstituted C.sub.1-4 alkyl, or unsubstituted or substituted C.sub.3-5 cycloalkyl; [0147] R.sup.10 is substituted or unsubstituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkoxy, unsubstituted or substituted C.sub.3-5 cycloalkyl, or unsubstituted or substituted 3-member to 5-member heterocyclyl; [0148] t is 0, or 1; [0149] each of s and r, is independently, is 1, or 2; and [0150] each of m, and q is, independently, an integer between 0 and the maximum number of the substituent groups allowed on rings A, and B, respectively.

[0151] In one embodiment, s is 1. In one embodiment, s is 2. In some embodiment, m is an integer between 0 and 5. In some embodiment, m is an integer between 1 and 4. In some embodiment, m is an integer between 2 and 3. In some embodiment, m is an integer of 2 or 3. In some embodiment, q is an integer between 0 and 5. In some embodiment, q is an integer between 1 and 4. In some embodiment, q is an integer between 1 and 3. In some embodiment, q is an integer of 1 or 2.

[0152] In one embodiment, X is N. In one embodiment, X is C—R.sup.8. In one embodiment, X is C—H, C—F, C—Cl, or C—CF.sub.3. In one embodiment, X is C—Cl. In one embodiment, X is C—CF.sub.3.

[0153] In some embodiments for any one of formulas (I), (IA), (II), or (IIA), R.sup.6a, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or R.sup.6a, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or R.sup.5, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or R.sup.5, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In some embodiments for any one of formulas (I), (IA), (II), or (IIA), R.sup.6a, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In some embodiments for any one of formulas (I), (IA), (II), or (IIA), R.sup.6a, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In some

embodiments for any one of formulas (I), (IA), (II), or (IIA), R.sup.5, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In some embodiments for any one of formulas (I), (IA), (II), or (IIA), R.sup.5, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge.

Aspect 2:

[0154] In one embodiment, ring A is an aryl group (e.g., phenyl or naphthyl) optionally substituted with one or more substituents. In one embodiment, the substituent is F, Cl, Br, amino, —CN, OH, —CF.sub.3, —CHF.sub.2, —CH.sub.2F, —CF.sub.2CH.sub.3, —CF.sub.2CF.sub.3, —OCHF.sub.2, —OCF.sub.3, vinyl(—CH═CH), -propylenyl (e.g., —C(CH.sub.3)═CH), —CF═CH, aryl, heteroaryl, ethynyl, propynyl, butynyl, pentynyl, hexynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, vinyl, propylenyl, allyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl, hexadienyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, or hexoxy. In one embodiment, the substituent is F, Cl, Br, amino, —CN, OH, —CF.sub.3, —CHF.sub.2, —CH.sub.2F, —CF.sub.2CH.sub.3, —CF.sub.2CF.sub.3, —OCHF.sub.2, —OCF.sub.3, vinyl(—CH═CH), -propylenyl (such as —C(CH.sub.3)═CH), —CF═CH, aryl, heteroaryl, ethynyl, propynyl, butynyl, pentynyl, hexynyl, cyclopropyl, methylcyclopropyl, fluorocyclopropyl, difluorocyclopropyl, fluoromethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, vinyl, propylenyl, allyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl, hexadienyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, or hexoxy.

[0155] In one embodiment, ring A is a 5- to 7-membered monocyclic heteroaryl or 8- to 12-membered bicyclic heteroaryl group optionally substituted with one or more substituents. In some preferred embodiments, ring A is pyridyl, benzothiazolyl, quinolinyl, isoquinolinyl, pyrazolopyridinyl, benzoimidazolyl, quinazolinyl, or quinazolinyl. In one embodiment, the substituent is F, Cl, Br, C(CH.sub.3)═CH or —CH═CH, —CF═CH, —CN, OH, —NH.sub.2, —CF.sub.3, —CHF.sub.2, —CH.sub.2F, —CF.sub.2CH.sub.3, —CF.sub.2CF.sub.3, —OCHF.sub.2, —OCF.sub.3, aryl, ethynyl, propynyl, butynyl, pentynyl, hexynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, vinyl, propylenyl, allyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl, hexadienyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, or hexoxy. In one embodiment, the substituent is F, Cl, Br, C(CH.sub.3)═CH or —CH═CH, —CF═CH, —CN, OH, NH.sub.2, —CF.sub.3, —CHF.sub.2, —CH.sub.2F, —CF.sub.2CH.sub.3, —CF.sub.2CF.sub.3, —OCHF.sub.2, —OCF.sub.3, aryl, ethynyl, propynyl, butynyl, pentynyl, hexynyl, cyclopropyl, methylcyclopropyl, fluorocyclopropyl, difluorocyclopropyl, fluoromethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, vinyl, propylenyl, allyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl, hexadienyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, or hexoxy. In some preferred embodiments, ring A is pyridyl, benzothiazolyl, quinolinyl, isoquinolinyl, pyrazolopyridinyl, benzoimidazolyl, quinazolinyl, or quinazolinyl.

[0156] In one embodiment, ring A is

##STR00008## ##STR00009##

[0157] In one embodiment, ring A is

##STR00010##

[0158] In one embodiment, ring A is

##STR00011##

[0159] In one embodiment, ring A is

##STR00012##

[0160] In one embodiment, ring A is

##STR00013##

Aspect 3:
[0161] In one embodiment, moiety B is unsubstituted or substituted cycloalkyl or unsubstituted or substituted heterocyclyl. In one embodiment, the heterocyclyl comprises at least one oxygen as the ring member. In one embodiment, the heterocyclyl comprises at least one nitrogen as the ring member.
[0162] In one embodiment, moiety B is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 9-membered heterocylic ring comprising one or two or three nitrogen atoms as the ring members. In one embodiment, moiety B is oxazolidinyl, imidazolidinyl, thiazolidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, oxazinyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, phenyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, triazolyl, thiophenyl, furanyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl, tetrahydropyridinyl, azetidinyl, pyrrolidinyl, octahydroindolizinyl, octahydroquinolizinyl, hexahydro-1H-pyrrolizinyl, tetrahydroisoquinolinyl, or tetrahydropyridyl; and moiety B is optionally substituted. In one embodiment, moiety B is oxetanyl, tetrahydrofuryl, tetrahydro-2H-pyranyl, dihydro-2H-pyranyl, oxabicyclo[2.1.1]hexyl, oxabicyclo[2.2.1]heptyl, oxaspiro[3.3]heptyl, oxabicyclo[3.2.1]octyl, oxabicyclo[2.2.2]octyl, oxaspiro[3.5]nonyl, or oxaspiro[3.4]octyl; and moiety B is optionally substituted. In one embodiment, moiety B is optionally substituted with halogen, cyano, hydroxy, alkoxy, or alkyl optionally substituted with halogen, cyano, hydroxy, alkoxy, heterocyclyl, cycloalkyl or cycloalkyloxy.
[0163] In one embodiment, moiety B is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 9-membered heterocylic ring comprising one or two or three nitrogen atoms as the ring members, oxazolidinyl, imidazolidinyl, thiazolidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, oxazinyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, phenyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, triazolyl, thiophenyl, furanyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl or tetrahydropyridinyl optionally substituted with one or more substituent. In one embodiment, the substituent is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, —C.sub.2-8alkenyl, —C.sub.2-8alkynyl, C.sub.1-8alkoxy-C.sub.1-8alkyl-, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, oxazolidinyl, imidazolidinyl, thiazolidinyl, pyrazolidinyl, morpholinyl, piperidinyl, piperazinyl, oxazinyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, phenyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, triazolyl, thiophenyl, furanyl, pyridyl, pyrimidinyl, pyrazinyl or oxo; or two substituents together with the carbon atoms to which they are attached, form a 3- to 8-membered unsaturated or saturated ring, said ring comprising 0, 1, 2, or 3 heteroatoms independently selected from nitrogen oxygen or sulfur.
[0164] In one embodiment, moiety B is
##STR00014## ##STR00015## ##STR00016## ##STR00017##
In one embodiment, moiety B is
##STR00018## ##STR00019## ##STR00020##
In one embodiment, moiety B is
##STR00021##
[0165] In one embodiment moiety B is azetidyl pyridyl isoxazolyl oxazolyl dihydro-2H-pyranyl, tetrahydro-2H-pyranyl, pyrrolidinonyl, azaspiro[3.3]heptyl, azabicyclo[2.1.1]hexyl, pyrrolidyl, 1H-pyrazolyl; and moiety B is optionally substituted.
[0166] In one embodiment, moiety B is C.sub.2-5alkyl which is substituted with hydroxy and further substituted with halogen, haloalkyl or alkoxy.
[0167] In one embodiment, moiety B is optionally substituted with halogen, cyano, hydroxy, alkoxy, or alkyl optionally substituted with halogen, cyano, hydroxy, or alkoxy.
[0168] In one embodiment, moiety B is
##STR00022##
[0169] In one embodiment, moiety B is

##STR00023##
[0170] In one embodiment, moiety B is azetidyl, pyridyl, isoxazolyl, oxazolyl, dihydro-2H-pyranyl, tetrahydro-2H-pyranyl, pyrrolidinonyl, azaspiro[3.3]heptyl, azabicyclo[2.1.1]hexyl, pyrrolidyl, 1H-pyrazolyl; and moiety B is optionally substituted.
[0171] In one embodiment, moiety B is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or azetidyl; and moiety B is optionally substituted.
[0172] In one embodiment, moiety B is
##STR00024##
[0173] In one embodiment, moiety B is
##STR00025## ##STR00026## ##STR00027##
[0174] In one embodiment, moiety B is
##STR00028## ##STR00029## ##STR00030##
Aspect 4:
[0175] In one embodiment, ring A is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted benzo[b]thiophenyl, or substituted or unsubstituted benzo[d]thiazolyl.
[0176] In one embodiment, ring A is
##STR00031##
[0177] In one embodiment, ring A is
##STR00032##
Aspect 5:
[0178] In some embodiment, moiety B is
##STR00033## [0179] wherein each of R.sup.a and R.sup.b is, independently, substituted or unsubstituted C.sub.1-4 alkyl; substituted or unsubstituted C.sub.3-5 cycloalkyl; or R.sup.a and R.sup.b together with the N they are attached to form a substituted or unsubstituted heterocycle containing N, O or S; and [0180] R.sup.c is H, halogen, CN, substituted or unsubstituted C.sub.1-4 alkyl, substituted or unsubstituted C.sub.3-5 cycloalkyl, substituted or unsubstituted C.sub.1-4 alkoxyl, or C.sub.1-4 alkoxyl-C(O)—.
[0181] In one embodiment, moiety B is substituted or unsubstituted hexahydro-1H-pyrrolizinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted aminomethylcyclopropyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted oxabicyclo[2.1.1]hexanyl, substituted or unsubstituted oxabicyclo[2.2.1]heptanyl.
[0182] In one embodiment, moiety B is
##STR00034## [0183] wherein each of R.sup.a and R.sup.b is, independently, substituted or unsubstituted C.sub.1-4 alkyl; substituted or unsubstituted C.sub.3-5 cycloalkyl; or R.sup.a and R.sup.b together with the N they are attached to form a substituted or unsubstituted heterocycle containing N, O or S; and [0184] R.sup.c is H, halogen, CN, substituted or unsubstituted C.sub.1-4 alkyl, substituted or unsubstituted C.sub.3-5 cycloalkyl, substituted or unsubstituted C.sub.1-4 alkoxyl.
[0185] In one embodiment, moiety B is
##STR00035##
In one embodiment, moiety B is
##STR00036##
In one embodiment, moiety B is
##STR00037##
In one embodiment, moiety B is
##STR00038##
In one embodiment, moiety B is
##STR00039##
In one embodiment, moiety B is

##STR00040##
In one embodiment, moiety B is
##STR00041##
In one embodiment, moiety B is
##STR00042##
In one embodiment, moiety B is
##STR00043##
Aspect 6:
[0186] In one embodiment, W is O. In one embodiment, W is NH.
[0187] In one embodiment, the bridge formed by R.sup.6a, and R.sup.7a, or by R.sup.6a, and R.sup.8a, or by R.sup.5, and R.sup.7a, or by R.sup.5, and R.sup.8a is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
Aspect 7:
[0188] Group 1: In one embodiment, t is 0.
[0189] Group 1.1: In one embodiment, X is N.
[0190] In one embodiment, ring A is
##STR00044##
and moiety B is
##STR00045##
[0191] In one embodiment, R.sup.1 is methyl, or Cl. In one embodiment, R is —CF.sub.3. In one embodiment, R.sup.9 is —NH.sub.2.
[0192] Group 1.1.1: In one embodiment, ring A is
##STR00046##
[0193] In one embodiment, moiety B is
##STR00047##
[0194] Group 1.1.1.1: In one embodiment, moiety B is
##STR00048##
In one embodiment, moiety B is
##STR00049##
[0195] In one embodiment, W is O. In one embodiment, W is NH.
[0196] In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, OH, CN, amino, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, unsubstituted or substituted methyl, or unsubstituted or substituted ethyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6bR.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, methyl, or ethyl, optionally substituted by OH, CN, amino, or methylamino. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or methyl.
[0197] In one embodiment, the compound is
##STR00050## ##STR00051##
[0198] In one embodiment, R.sup.6a and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0199] In one embodiment, R.sup.5 and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —

(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0200] In one embodiment, the compound is
##STR00052##
[0201] Group 1.1.2: In one embodiment, ring A is
##STR00053##
[0202] In one embodiment, moiety B is
##STR00054##
[0203] Group 1.1.2.1: In one embodiment, moiety B is
##STR00055##
In one embodiment, moiety B is
##STR00056##
[0204] Group 1.1.3: In one embodiment, ring A is
##STR00057##
[0205] In one embodiment, moiety B is
##STR00058##
[0206] Group 1.1.3.1: In one embodiment, moiety B is
##STR00059##
In one embodiment, moiety B is
##STR00060##
[0207] In one embodiment, the compound is
##STR00061##
[0208] In one embodiment, the compound is
##STR00062##
[0209] Group 1.1.4: In one embodiment, W is O. In one embodiment, ring A is
##STR00063##
[0210] In one embodiment, moiety B is
##STR00064##
[0211] Group 1.1.4.1: In one embodiment, moiety B is
##STR00065##
In one embodiment, moiety B is
##STR00066##
[0212] In one embodiment, the compound is
##STR00067## ##STR00068##
[0213] In one embodiment, the compound is
##STR00069##
[0214] In one embodiment, the compound is
##STR00070##
[0215] In one embodiment, the compound is
##STR00071##
[0216] In one embodiment, the compound is
##STR00072##
[0217] In one embodiment, R.sup.6a and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0218] In one embodiment, R.sup.5 and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.

[0219] In one embodiment, the compound is
##STR00073##
[0220] In one embodiment, the compound is
##STR00074##
[0221] Group 1.1.4.2: In one embodiment, moiety B is
##STR00075##
[0222] In one embodiment, moiety B is
##STR00076##
[0223] In one embodiment, the compound is
##STR00077##
[0224] In one embodiment, the compound is
##STR00078##
[0225] Group 1.1.4.3: In one embodiment, moiety B is
##STR00079## [0226] wherein each of R.sup.a and R.sup.b is, independently, substituted or unsubstituted C.sub.1-4 alkyl; substituted or unsubstituted C.sub.3-5 cycloalkyl; or R.sup.a and R.sup.b together with the N they are attached to form a substituted or unsubstituted heterocycle containing N, O or S.
[0227] In one embodiment, moiety B is
##STR00080##
[0228] In one embodiment, the compound is
##STR00081##
[0229] In one embodiment, the compound is
##STR00082##
[0230] In one embodiment, the compound is
##STR00083##
[0231] In one embodiment, R.sup.6a and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0232] In one embodiment, R.sup.5 and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0233] In one embodiment, the compound is
##STR00084##
[0234] Group 1.1.5.1: In one embodiment, ring A is
##STR00085##
[0235] In one embodiment, moiety B is
##STR00086##
[0236] In one embodiment, moiety B is
##STR00087##
In one embodiment, moiety B is
##STR00088##
[0237] In one embodiment, the compound is
##STR00089##
[0238] In one embodiment, the compound is
##STR00090##
[0239] Group 1.2.4.1: In one embodiment X is CH. In one embodiment, W is O.
[0240] In one embodiment, ring A is
##STR00091##

[0241] In one embodiment, moiety B is
##STR00092##
In one embodiment, moiety B is
##STR00093##
[0242] In one embodiment, the compound is
##STR00094##
[0243] In one embodiment, the compound is OH
##STR00095##
[0244] In one embodiment, the compound is OH
##STR00096##
[0245] Group 1.2.4.3: In one embodiment, X is CH. In one embodiment, W is O.
[0246] In one embodiment, ring A is
##STR00097##
[0247] In one embodiment, moiety B is
##STR00098## [0248] wherein each of R.sup.a and R.sup.b is, independently, substituted or unsubstituted C.sub.1-4 alkyl; substituted or unsubstituted C.sub.3-5 cycloalkyl; or R.sup.a and R.sup.b together with the N they are attached to form a substituted or unsubstituted heterocycle containing N, O or S.
[0249] In one embodiment, moiety B is
##STR00099##
[0250] In one embodiment, the compound is
##STR00100##
[0251] Group 1.2.6.1: In one embodiment, X is CH. In one embodiment, W is O.
[0252] In one embodiment, ring A is
##STR00101##
[0253] In one embodiment, moiety B is
##STR00102##
In one embodiment, moiety B is
##STR00103##
[0254] In one embodiment, the compound is
##STR00104##
[0255] In one embodiment, the compound is
##STR00105##
[0256] In one embodiment, the compound is
##STR00106##
[0257] Group 1.2.6.3: In one embodiment, X is CH. In one embodiment, W is O.
[0258] In one embodiment, ring A is
##STR00107##
[0259] In one embodiment, moiety B is
##STR00108## [0260] wherein each of R.sup.a and R.sup.b is, independently, substituted or unsubstituted C.sub.1-4 alkyl; substituted or unsubstituted C.sub.3-5 cycloalkyl; or R.sup.a and R.sup.b together with the N they are attached to form a substituted or unsubstituted heterocycle containing N, O or S.
[0261] In one embodiment, moiety B is
##STR00109##
[0262] In one embodiment, the compound is
##STR00110##
[0263] Group 1.4.4.1: In one embodiment, X is C—Cl. In one embodiment, W is O.
[0264] In one embodiment, ring A is
##STR00111##

[0265] In one embodiment, moiety B is
##STR00112##
In one embodiment, moiety B is
##STR00113##
[0266] In one embodiment, the compound is
##STR00114##
[0267] In one embodiment, the compound is
##STR00115##
[0268] Group 1.4.4.3: In one embodiment, X is C—Cl. In one embodiment, W is O.
[0269] In one embodiment, ring A is
##STR00116##
[0270] In one embodiment, moiety B is
##STR00117## [0271] wherein each of R.sup.a and R.sup.b is, independently, substituted or unsubstituted C.sub.1-4 alkyl; substituted or unsubstituted C.sub.3-5 cycloalkyl; or R.sup.a and R.sup.b together with the N they are attached to form a substituted or unsubstituted heterocycle containing N, O or S
[0272] In one embodiment, moiety B is
##STR00118##
[0273] In one embodiment, the compound is
##STR00119##
[0274] Group 1.4.6.1: In one embodiment, X is C—Cl. In one embodiment, W is O.
[0275] In one embodiment, ring A is
##STR00120##
[0276] In one embodiment, moiety B is
##STR00121##
In one embodiment, moiety B is
##STR00122##
[0277] In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, OH, CN, amino, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, unsubstituted or substituted methyl, or unsubstituted or substituted ethyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, methyl, or ethyl, optionally substituted by OH, CN, amino, or methylamino. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or methyl.
[0278] In one embodiment, the compound is
##STR00123## ##STR00124##
[0279] In one embodiment, R.sup.6a and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0280] In one embodiment, R.sup.5 and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0281] In one embodiment, the compound is
##STR00125##

[0282] Group 1.4.6.3: In one embodiment X is C—Cl. In one embodiment, W is O.
[0283] In one embodiment, ring A is
##STR00126##
[0284] In one embodiment, moiety B is
##STR00127## [0285] wherein each of R.sup.a and R.sup.b is, independently, substituted or unsubstituted C.sub.1-4 alkyl; substituted or unsubstituted C.sub.3-5 cycloalkyl; or R.sup.a and R.sup.b together with the N they are attached to form a substituted or unsubstituted heterocycle containing N, O or S.
[0286] In one embodiment, moiety B is
##STR00128##
[0287] In one embodiment, the compound is
##STR00129##
[0288] In one embodiment, R.sup.6a and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0289] In one embodiment, R.sup.5 and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0290] In one embodiment, the compound is
##STR00130##
[0291] Group 1.4.6.6: In one embodiment, X is C—Cl. In one embodiment, W is O.
[0292] In one embodiment, ring A is
##STR00131##
[0293] In one embodiment, moiety B is
##STR00132## [0294] wherein R.sup.c is H, halogen, CN, substituted or unsubstituted C.sub.1-4 alkyl, substituted or unsubstituted C.sub.3-5 cycloalkyl, substituted or unsubstituted C.sub.1-4 alkoxyl.
[0295] In one embodiment, moiety B is
##STR00133##
[0296] In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, Rib, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, OH, CN, amino, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6aR.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, unsubstituted or substituted methyl, or unsubstituted or substituted ethyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, methyl, or ethyl, optionally substituted by OH, CN, amino, or methylamino. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or methyl.
[0297] In one embodiment, R.sup.6a and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0298] In one embodiment, R.sup.5 and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.

[0299] In one embodiment, the compound is
##STR00134##
Aspect 8:
[0300] Group 2: In one embodiment, t is 1.
[0301] Group 2.1: In one embodiment, X is N.
[0302] In one embodiment, moiety B is
##STR00135## [0303] wherein each of R.sup.a and R.sup.b is, independently, substituted or unsubstituted C.sub.1-4 alkyl; substituted or unsubstituted C.sub.3-5 cycloalkyl; or R.sup.a and R.sup.b together with the N they are attached to form a substituted or unsubstituted heterocycle containing N, O or S; and [0304] R.sup.c is H, halogen, CN, substituted or unsubstituted C.sub.1-4 alkyl, substituted or unsubstituted C.sub.3-5 cycloalkyl, substituted or unsubstituted C.sub.1-4 alkoxyl.
[0305] In one embodiment, ring A is
##STR00136##
and moiety B is
##STR00137##
[0306] In one embodiment, R.sup.1 is methyl, or Cl. In one embodiment, R.sup.2 is —CF.sub.3. In one embodiment, R.sup.9 is —NH.sub.2.
[0307] Group 2.1.1: In one embodiment, ring A is
##STR00138##
[0308] In one embodiment, moiety B is
##STR00139##
[0309] Group 2.1.1.1: In one embodiment, moiety B is
##STR00140##
In one embodiment, moiety B is
##STR00141##
[0310] In one embodiment, W is O. In one embodiment, W is NH.
[0311] In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, OH, CN, unsubstituted or substituted amino, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, unsubstituted or substituted methyl, or unsubstituted or substituted ethyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, methyl, or ethyl, optionally substituted by OH, CN, amino, or methylamino. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or methyl.
[0312] In one embodiment, the compound is
##STR00142##
[0313] In one embodiment, the compound is
##STR00143##
[0314] In one embodiment, R.sup.6a and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0315] In one embodiment, R.sup.5 and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment,

the bridge is —CH.sub.2—O—CH.sub.2—.
[0316] In one embodiment, the compound is
##STR00144##
[0317] Group 2.1.4: In one embodiment, W is O. In one embodiment, ring A is
##STR00145##
[0318] In one embodiment, moiety B is
##STR00146##
[0319] Group 2.1.4.1: In one embodiment, moiety B is
##STR00147##
In one embodiment, moiety B is
##STR00148##
[0320] In one embodiment, the compound is
##STR00149##
[0321] In one embodiment, R.sup.6a and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0322] In one embodiment, R.sup.5 and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0323] In one embodiment, the compound is
##STR00150##
[0324] Group 2.1.4.3: In one embodiment W is O.
[0325] In one embodiment, ring A is
##STR00151##
[0326] In one embodiment, moiety B is
##STR00152## [0327] wherein each of R.sup.a and R.sup.b is, independently, substituted or unsubstituted C.sub.1-4 alkyl; substituted or unsubstituted C.sub.3-5 cycloalkyl; or R.sup.a and R.sup.b together with the N they are attached to form a substituted or unsubstituted heterocycle containing N, O or S.
[0328] In one embodiment, moiety B is
##STR00153##
[0329] In one embodiment, the compound is
##STR00154##
[0330] In one embodiment, R.sup.6a and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0331] In one embodiment, R.sup.5 and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0332] In one embodiment, the compound is
##STR00155##
[0333] Group 2.1.4.6: In one embodiment. W is O.
[0334] In one embodiment, ring A is
##STR00156##
[0335] In one embodiment, moiety B is
##STR00157## [0336] wherein R.sup.c is H, halogen, CN, substituted or unsubstituted C.sub.1-4

alkyl, substituted or unsubstituted C.sub.3-5 cycloalkyl, substituted or unsubstituted C.sub.1-4 alkoxyl.
[0337] In one embodiment, moiety B is
##STR00158##
[0338] In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, OH, CN, unsubstituted or substituted amino, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, unsubstituted or substituted methyl, or unsubstituted or substituted ethyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, methyl, or ethyl, optionally substituted by OH, CN, amino, or methylamino. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or methyl.
[0339] In one embodiment, the compound is
##STR00159##
[0340] In one embodiment, R.sup.6a and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0341] In one embodiment, R.sup.5 and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge. In one embodiment, the bridge is —(CH.sub.2).sub.2—. In one embodiment, the bridge is —(CH.sub.2).sub.3—. In one embodiment, the bridge is —CH.sub.2—O—CH.sub.2—.
[0342] In one embodiment, the compound is
##STR00160##
[0343] Group 2.2.4.1: In one embodiment, X is CH. In one embodiment, W is O.
[0344] In one embodiment, ring A is
##STR00161##
[0345] In one embodiment, moiety B is
##STR00162##
In one embodiment, moiety B is
##STR00163##
[0346] In one embodiment, the compound is
##STR00164##
[0347] In one embodiment, the compound is
##STR00165##
[0348] Group 2.4.6.1: In one embodiment, X is C—Cl. In one embodiment, W is O.
[0349] In one embodiment, ring A is
##STR00166##
[0350] In one embodiment, moiety B is
##STR00167##
In one embodiment, moiety B is
##STR00168##
[0351] In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, OH, CN, unsubstituted or substituted amino, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a,

and R.sup.8b, independently, is H, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, unsubstituted or substituted methyl, or unsubstituted or substituted ethyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, methyl, or ethyl, optionally substituted by OH, CN, amino, or methylamino. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or methyl.

[0352] In one embodiment, the compound is

##STR00169##

[0353] Aspect 9: In some embodiments, the compounds provided herein have one of the following formulas:

##STR00170## [0354] and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, atropisomers, isotopologues, and prodrugs thereof, [0355] wherein: [0356] ring C is unsubstituted or substituted C.sub.3-6 cycloalkyl, or unsubstituted or substituted 3-membered to 6-membered heterocyclyl.

[0357] In some embodiments, the compounds provided herein have one of the following formulas:

##STR00171## [0358] and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, atropisomers, isotopologues, and prodrugs thereof, [0359] wherein: [0360] ring C is unsubstituted or substituted C.sub.3-6 cycloalkyl, or unsubstituted or substituted 3-membered to 6-membered heterocyclyl.

[0361] In one embodiment, ring C contains Y and is substituted with R.sup.a, wherein Y is CH.sub.2, 0, NH, N—R.sup.9, N—C(═O)—R.sup.10, or O═S═O; [0362] R.sup.9 is substituted or unsubstituted C.sub.1-4 alkyl, or unsubstituted or substituted C.sub.3-5 cycloalkyl; [0363] R.sup.10 is substituted or unsubstituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkoxy, unsubstituted or substituted C.sub.3-5 cycloalkyl, or unsubstituted or substituted 3-member to 5-member heterocyclyl; and [0364] R.sup.a is H, halogen, amino, —CN, —OH, unsubstituted or substituted C.sub.1-4alkyl, unsubstituted or substituted C.sub.1-4alkoxy, or unsubstituted or substituted C.sub.1-4alkylamino.

[0365] In one embodiment, Y is CH.sub.2. In one embodiment, Y is O. In one embodiment, Y is NH.

[0366] In one embodiment, R.sup.6a, and R.sup.7a together, form a bridge, wherein the bridge is —CH.sub.2—CH.sub.2—.

[0367] In one embodiment, R.sup.5, and R.sup.8a together, form a bridge, wherein the bridge is —CH.sub.2—CH.sub.2—.

[0368] In one embodiment, ring C is cyclopropyl. In one embodiment, ring C is cyclobutyl.

[0369] In one embodiment, ring C is oxetanyl.

[0370] Aspect 10: In some embodiments, the compounds provided herein have the following formula:

##STR00172## [0371] and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, atropisomers, isotopologues, and prodrugs thereof.

[0372] In one embodiment, X is N. In one embodiment, X is CH. In one embodiment, W is O. In one embodiment, W is NH.

[0373] In one embodiment, ring A is

##STR00173##

In one embodiment, ring A is

##STR00174##

[0374] In one embodiment, moiety B is

##STR00175##

In one embodiment, moiety B is

##STR00176##
[0375] In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.a, Rib, R.sup.7a, R.sup.7b, R.sup.8a1, R.sup.8b1, R.sup.8a2, and R.sup.8b2, independently, is H, OH, CN, unsubstituted or substituted amino, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a1, R.sup.8b1, R.sup.8a2, and R.sup.8b2, independently, is H, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a1, R.sup.8b1, R.sup.8a2, and R.sup.8b2, independently, is H, unsubstituted or substituted methyl, or unsubstituted or substituted ethyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, R.sup.8b1, R.sup.8a2, and R.sup.8b2, independently, is H, methyl, or ethyl, optionally substituted by OH, CN, amino, or methylamino. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a1, R.sup.8b1, R.sup.8a2, and R.sup.8b2, independently, is H, or methyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a1, R.sup.8b1, R.sup.8a2, and R.sup.8b2, independently, is H.
[0376] In one embodiment, the compound is
##STR00177##
[0377] Aspect 11: In some embodiments, the compounds provided herein have the following formula:
##STR00178## [0378] and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, atropisomers, isotopologues, and prodrugs thereof.
[0379] In one embodiment, X is N. In one embodiment, X is CH. In one embodiment, W is O. In one embodiment, W is NH.
[0380] In one embodiment, ring A is
##STR00179##
In one embodiment, ring A is
##STR00180##
[0381] In one embodiment, moiety B is
##STR00181##
In one embodiment, moiety B is
##STR00182##
[0382] In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a1, R.sup.6b1, R.sup.6a2, R.sup.6b2, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, OH, CN, unsubstituted or substituted amino, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a1, R.sup.6b1, R.sup.6a2, R.sup.6b2, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or unsubstituted or substituted C.sub.1-4alkyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a1, R.sup.6b1, R.sup.6a2, R.sup.6b2, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, unsubstituted or substituted methyl, or unsubstituted or substituted ethyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a1, R.sup.6b1, R.sup.6a2, R.sup.6b2, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, methyl, or ethyl, optionally substituted by OH, CN, amino, or methylamino. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a1, R.sup.6b1, R.sup.6a2, R.sup.6b2, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, or methyl. In one embodiment, each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a1, R.sup.6b1, R.sup.6a2, R.sup.6b2, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H.
[0383] In one embodiment, the compound is
##STR00183##
[0384] Aspect 12: In some embodiments, the compounds provided herein have the following

formula:
##STR00184##
[0385] And pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, atropisomers, isotopologues, and prodrugs thereof, wherein the variables are defined as in Formula (I) or (II).
[0386] In some embodiments, the compounds provided herein have the following formula:
##STR00185## [0387] and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, atropisomers, isotopologues, and prodrugs thereof, wherein the variables are defined as in Formula (I) or (II).
[0388] In one embodiment, R.sup.11 is halogen, deuterium, or substituted or unsubstituted C.sub.1-3 alkyl. In one embodiment, R.sup.11 is deuterium, or methyl. In one embodiment, R.sup.11 is methyl. In one embodiment, u is 0, 1, 2, 3, 4, or 5. In one embodiment, u is 0, 1, or 2. In one embodiment, u is 1. In one embodiment, u is 0.
[0389] In one embodiment, ring A is substituted or unsubstituted phenyl or substituted or unsubstituted pyridin-4-yl. In one embodiment, ring A is phenyl or pyridin-4-yl, wherein ring A is optionally substituted by one or more groups chosen from halogen, substituted or unsubstituted C.sub.1-3 alkyl, substituted or unsubstituted cyclopropyl, or substituted or unsubstituted amino. In one embodiment, ring A is a phenyl or pyridin-4-yl, wherein ring A is optionally substituted by one or more groups chosen from halogen CF.sub.3, CF.sub.2CH.sub.3, methyl, ethyl, or NH.sub.2. In one embodiment ring A is
##STR00186##
wherein R.sup.12 is H, halogen, substituted or unsubstituted C.sub.1-3 alkyl or cyclopropyl optionally substituted with F; and R.sup.12a is H, deuterium, F or Me. In one embodiment, ring A is
##STR00187##
wherein R.sup.12 is halogen, substituted or unsubstituted C.sub.1-3 alkyl or cyclopropyl optionally substituted with F. In one embodiment, ring A is
##STR00188##
wherein R.sup.12 is halogen, substituted or unsubstituted C.sub.1-3 alkyl or cyclopropyl optionally substituted with F. In one embodiment, R.sup.12 is F, Cl, methyl, or ethyl. In one embodiment, R.sup.12 is Cl, or methyl. In one embodiment, ring A is
##STR00189##
[0390] In one embodiment, ring A is
##STR00190##
[0391] In one embodiment, moiety B is unsubstituted or substituted heterocyclyl, wherein the heterocyclyl does not contain a secondary or tertiary amine. In one embodiment, the heterocyclyl comprises at least one oxygen as the ring member. In one embodiment, moiety B is
##STR00191## [0392] wherein each of R.sup.a and R.sup.b is, independently, substituted or unsubstituted C.sub.1-4 alkyl;
substituted or unsubstituted C.sub.3-5 cycloalkyl; or R.sup.a and R.sup.b together with the N they are attached to form a substituted or unsubstituted heterocycle containing N, O or S; and [0393] R.sup.c is H, halogen, CN, substituted or unsubstituted C.sub.1-4 alkyl, substituted or unsubstituted C.sub.3-5 cycloalkyl, substituted or unsubstituted C.sub.1-4 alkoxyl, or C.sub.1-4 alkoxyl-C(O)—.
In one embodiment, moiety B is
##STR00192## ##STR00193## ##STR00194## ##STR00195##
In one embodiment, moiety B is
##STR00196##
In one embodiment, moiety B is optionally substituted with halogen, cyano, hydroxy, C.sub.1-3 alkoxy, or C.sub.1-3 alkyl optionally substituted with halogen, cyano, hydroxy, or C.sub.1-3 alkoxy. In one embodiment, moiety B is substituted or unsubstituted oxabicyclo[2.1.1]hexanyl. In

one embodiment, moiety B is 2-oxabicyclo[2.1.1]hexan-4-yl, optionally substituted with halogen, cyano, hydroxy, C.sub.1-3 alkoxy, or C.sub.1-3 alkyl optionally substituted with halogen, cyano, hydroxy, or C.sub.1-3 alkoxy. In one embodiment, moiety B is 2-oxabicyclo[2.1.1]hexan-4-yl.

[0394] In one embodiment, the compound is

##STR00197##

In one embodiment, the compound is

##STR00198##

In one embodiment, the compound is

##STR00199##

In one embodiment, the compound is

##STR00200##

In one embodiment, the compound is

##STR00201##

In one embodiment, the compound is

##STR00202##

[0395] In one embodiment, moiety B is

##STR00203##

In one embodiment, moiety B is

##STR00204##

[0396] In one embodiment, the compound is

##STR00205##

In one embodiment, the compound is

##STR00206##

In one embodiment, the compound is

##STR00207##

In one embodiment, the compound is

##STR00208##

In one embodiment, the compound is

##STR00209##

In one embodiment, the compound is

##STR00210##

[0397] In one embodiment, the compound is

##STR00211##

[0398] In one embodiment, the compound is

##STR00212## ##STR00213## ##STR00214## ##STR00215## ##STR00216##

[0399] Aspect 13: Provided herein is a compound selected from the following table:

TABLE-US-00001 TABLE 1 [00217] [00218] [00219]
[00220] [00221] [00222]
[00223] [00224] [00225]
[00226] [00227] [00228]
[00229] [00230] [00231]
[00232] [00233] [00234]
[00235] [00236] [00237]
[00238] [00239] [00240]

[0400] Aspect 14: In one embodiment, the compound is selected from Table 1-Table 3.

[0401] Aspect 15: In one embodiment, provided herein is a pharmaceutical composition comprising an effective amount of a compound provided herein, or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer, enantiomer, atropisomer, or prodrug thereof, and a pharmaceutically acceptable carrier, excipient or vehicle.

[0402] Aspect 16: In one embodiment, provided herein is a method for inhibiting the activity of KRAS mutant protein in a cell, comprising contacting said cell with an effective amount of a compound provided herein, or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer, enantiomer, atropisomer, or prodrug thereof, optionally wherein the KRAS mutant protein is KRAS G12D and/or G12V mutant protein.
[0403] Aspect 17: In one embodiment, provided herein is a method for treatment or prevention of cancer, the method comprising administering to a subject in need thereof an effective amount of a compound provided herein, or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer, enantiomer, atropisomer, or prodrug thereof, optionally wherein the cancer is mediated by KRAS mutation; preferably KRAS G12D and/or G12V mutation. Provided here is a method for the treatment or prevention of a cancer, the methods comprising administering to a subject in need thereof an effective amount of a compound provided herein.
[0404] Aspect 18: Provided here is a method of modulating activity of KRAS G12D and/or G12V, comprising contacting said cell with an effective amount of a compound provided herein, or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer, enantiomer, atropisomer, or prodrug thereof.
[0405] Aspect 19: Provided herein is a kit for treating cancer, the kit comprising (a) a pharmaceutical composition comprising a compound provided herein; and (b) instructions for administration of an effective amount of the pharmaceutical composition comprising the KRAS G12D and/or G12V inhibitor provided herein to treat cancer in an individual.
[0406] The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

Methods for Making Compounds

[0407] The Compounds can be made using conventional organic syntheses and commercially available starting materials. By way of example and not limitation, Compounds of formula (I) can be prepared as outlined in Schemes 1-3 shown below as well as in the examples set forth herein. It should be noted that one skilled in the art would know how to modify the procedures set forth in the illustrative schemes and examples to arrive at the desired products. Common protecting groups may be used to prevent certain functional groups from undergoing undesired reaction. Exemplary protecting groups are described in “Protective Groups in Organic Synthesis”, 4.sup.th Edition, P. G. M. Wuts; T. W. Greene, John Wiley, 2007, and references cited therein.
##STR00241## ##STR00242##
[0408] As shown in Scheme 1, in some embodiments, provided herein are methods for preparing the compounds defined as formula (I). Halogen substituted compound 1-1 (X.sub.2 and X.sub.4 are halogen, X, is OH or Cl, and X.sub.3 could be methylthiolyl) is converted into compound 1-2 under substitution conditions (e.g., HATU, DIEA, if X, is OH; DIEA, DCM is X, is Cl); then compound 1-2 is converted to compound 1-3 under substitution conditions (e.g., NaH, THF); then compound 1-3 is converted to compound 1-4 under oxidation conditions (m-CPBA oxidation if LG is methyl sulfonyl or methyl sulfinyl); then compound 1-4 is converted to compound 1-5 followed by substitution or coupling reactions (e.g., NaH, THF); compound 1-5 further undergoes metal catalyzed cross-coupling reaction such as Suzuki, Negishi, or Stille coupling (e.g. Pd(dtbpf)Cl.sub.2, K.sub.3PO.sub.4, 1,4-dioxane, water for Suzuki coupling) to obtain compound 1-6, wherein M can be boronic acid, boronic ester, a metal (such as Zn), tributyltin, etc.; finally, protecting groups containing compound 1-6 is then deprotected (e.g., TFA and DCM to deprotect Boc group when PG.sub.1 and PG.sub.2 contains Boc group, CsF and DMF to deprotect TIPS group when PG.sub.1 and PG.sub.2 contains TIPS group) to yield the compound defined as formula (I).
##STR00243## ##STR00244##
[0409] As shown in Scheme 2, in some embodiments, provided herein are methods for preparing the compounds defined as formula (I). Halogen substituted compound 2-1 (X.sub.2 and X.sub.4 are

halogen, X.sub.1 is OH or Cl, and X.sub.3 could be methylthiolyl) is converted into compound 2-2 under substitution conditions (e.g., NaH, THF); then compound 2-2 is converted to compound 2-3 under substitution conditions (e.g., HATU, DIEA, if X, is OH; DIEA, DCM is X, is Cl); then compound 2-3 is converted to compound 2-4 under oxidation conditions (m-CPBA oxidation if LG is methyl sulfonyl or methyl sulfinyl); then compound 2-4 is converted to compound 2-5 followed by substitution or coupling reactions (e.g., NaH, THF); compound 2-5 further undergoes metal catalyzed cross-coupling reaction such as Suzuki, Negishi, or Stille coupling (e.g. Pd(dtbpf)Cl.sub.2, K.sub.3PO.sub.4, 1,4-dioxane, water for Suzuki coupling) to obtain compound 2-6, wherein M can be boronic acid, boronic ester, a metal (such as Zn), tributyltin, etc.; finally, protecting groups containing compound 2-6 is then deprotected (e.g., TFA and DCM to deprotect Boc group when PG.sub.1 and PG.sub.2 contains Boc group, CsF and DMF to deprotect TIPS group when PG.sub.1 and PG.sub.2 contains TIPS group) to yield the compound defined as formula (I).

##STR00245## ##STR00246##

[0410] As shown in Scheme 3, in some embodiments, provided herein are methods for preparing the compounds defined as formula (I). Halogen substituted compound 3-1 (X.sub.2 and X.sub.4 are halogen, X.sub.1 is OH or Cl, and X.sub.3 could be methylthiolyl) is converted into compound 3-2 under substitution conditions (e.g., NaH, THF); then compound 3-2 is converted to compound 3-3 under substitution conditions (e.g., HATU, DIEA, if X.sub.1 is OH; DIEA, DCM is X.sub.1 is Cl); then compound 3-3 is converted to compound 3-4 under oxidation conditions (m-CPBA oxidation if LG is methyl sulfonyl or methyl sulfinyl); then compound 3-4 is converted to compound 3-5 followed by substitution or coupling reactions (e.g., NaH, THF); compound 3-5 further undergoes metal catalyzed cross-coupling reaction such as Suzuki, Negishi, or Stille coupling (e.g. Pd(dtbpf)Cl.sub.2, K.sub.3PO.sub.4, 1,4-dioxane, water for Suzuki coupling) to obtain compound 3-6, wherein M can be boronic acid, boronic ester, a metal (such as Zn), tributyltin, etc.; finally, protecting groups containing compound 3-6 is then deprotected (e.g., TFA and DCM to deprotect Boc group when PG.sub.1 and PG.sub.2 contains Boc group, CsF and DMF to deprotect TIPS group when PG.sub.1 and PG.sub.2 contains TIPS group) to yield the compound defined as formula (II). The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

EXAMPLES

[0411] The examples below are intended to be purely exemplary and should not be considered to be limiting in any way. Unless otherwise specified, the experimental methods in the Examples described below are conventional methods. Unless otherwise specified, the reagents and materials are all commercially available. All solvents and chemicals employed are of analytical grade or chemical purity. Solvents are all redistilled before use. Anhydrous solvents are all prepared according to standard methods or reference methods. Silica gel (100-200 meshes) for column chromatography and silica gel (GF254) for thin-layer chromatography (TLC) are commercially available from Tsingdao Haiyang Chemical Co., Ltd. or Yantai Chemical Co., Ltd. of China; all were eluted with petroleum ether (60-90° C.)/ethyl acetate (v/v), and visualized by iodine or the solution of molybdphosphoric acid in ethanol unless otherwise specified. All extraction solvents, unless otherwise specified, were dried over anhydrous Na.sub.2SO.sub.4.

[0412] Unless otherwise indicated, the reactions set forth below were performed under a positive pressure of nitrogen or argon or with a drying tube in anhydrous solvents; the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe; and glassware was oven dried and/or heat dried.

[0413] Unless otherwise indicated, column chromatography purification was conducted on a Biotage system (Manufacturer: Dyax Corporation) having a silica gel column or on a silica SepPak cartridge (Waters), or was conducted on a Teledyne Isco Combiflash purification system using prepacked silica gel cartridges.

[0414] .sup.1H NMR spectra were recorded on a Varian instrument operating at 400 MHz or 500 MHz with TMS (tetramethylsilane) as the internal standard. .sup.1H-NMR spectra were obtained using CDCl.sub.3, CD.sub.2Cl.sub.2, CD.sub.3OD, D.sub.2O, d.sub.6-DMSO, d.sub.6-acetone or (CD.sub.3).sub.2CO as solvent and tetramethylsilane (0.00 ppm) or residual solvent (CDCl.sub.3: 7.25 ppm; CD.sub.3OD: 3.31 ppm; D.sub.2O: 4.79 ppm; d.sub.6-DMSO: 2.50 ppm; d.sub.6-acetone: 2.05; (CD.sub.3).sub.2CO: 2.05) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintuplet), sx (sextuplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).
[0415] LC/MS data was recorded by using Agilent 1100,1200 High Performance Liquid Chromatography-Ion Trap Mass Spectrometer (LC-MSD Trap) equipped with a diode array detector (DAD) detected at 214 nm and 254 nm, and an ion trap (ESI source). All compound names except the reagents were generated by ChemDraw® 19.1.
[0416] In the following examples, the following abbreviations are used: [0417] AcOH Acetic acid [0418] Aq. Aqueous [0419] BINAP 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene [0420] Brine Saturated aqueous sodium chloride solution [0421] Bn Benzyl [0422] BnBr Benzyl Bromide [0423] Boc Tert-butoxycarbonyl [0424] BOP Benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphonium hexa-fluorophosphate [0425] CH.sub.2Cl.sub.2 or DCM Dichloromethane [0426] CAN Cerium(IV) ammonium nitrate (cericammonium nitrate) [0427] Cs.sub.2CO.sub.3 Cesium carbonate [0428] DAST Diethylaminosulfur trifluoride [0429] DCM Dichloromethane [0430] DMF N,N-Dimethylformamide [0431] Dppf 1,1′-bis(diphenylphosphino)ferrocene [0432] DBU 1,8-diazabicyclo[5.4.0]undec-7-ene [0433] DHP 3,4-Dihydro-2H-pyran [0434] DIEA or DIPEA N,N-diisopropylethylamine [0435] DMAP 4-N,N-dimethylaminopyridine [0436] DMB (2,4-dimethoxyphenyl)methanamine [0437] Dess-Martin/DMP Dess-Martin Periodinane [0438] DMF N,N-dimethylformamide [0439] DMF-DMA N,N-Dimethylformamide dimethyl acetal purum [0440] DMSO Dimethyl sulfoxide [0441] DMEDA Dimethyl Ethylene Diamine [0442] EDCI 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride [0443] EtOAc or EA Ethyl acetate [0444] EtOH Ethanol [0445] Et.sub.3SiH Triethyl silhydride [0446] Et.sub.2O or ether Diethyl ether [0447] g Grams [0448] h or hr Hour [0449] HATU O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate [0450] Hex Hexane [0451] HCl Hydrochloric acid [0452] HMDS Hexamethyldisilazane [0453] HOBT 1-Hydroxybenzotriazole [0454] HPLC High-performance liquid chromatography [0455] IBX 2-Iodylbenzoic acid [0456] i-PrOH Isopropyl alcohol [0457] LCMS Liquid chromatography-mass spectrometry [0458] LDA Lithium diisopropylamide [0459] LiHMDS Lithium Bis(trimethylsilyl)amide [0460] K.sub.2OsO.sub.4.Math.H2O Potassium osmate(VI) dihydrate [0461] K.sub.3PO.sub.4 Tripotassium phosphate [0462] mg Milligrams [0463] mL Milliliters [0464] mmol Millimole [0465] MeCN Acetonitrile [0466] MeOH Methanol [0467] Min Minutes [0468] ms or MS Mass spectrum [0469] m-CPBA 2-chloranylbenzenecarboperoxoic acid [0470] MOM Methoxymethyl [0471] MPLC Medium Pressure Liquid Chromatography [0472] Na.sub.2SO.sub.4 Sodium sulfate [0473] NaBH(OAc).sub.3/STAB Sodium triacetyl borohydride [0474] NaH Sodium hydride [0475] NaHMDS Sodium bis(trimethylsilyl)amide [0476] NBS N-Bromosuccinimide [0477] NCS N-Chlorosuccinimide [0478] NMO 4-Methylmorpholine N-oxide [0479] NMP N-Methyl Pyrrolidone [0480] PD Pharmacodynamic(s) [0481] PE petroleum ether [0482] PK Pharmacokinetic(s) [0483] PMB (4-methoxyphenyl)methanamine [0484] POCl.sub.3 phosphorous oxychloride [0485] PyBOP Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate [0486] PddppfCl.sub.2 [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) [0487] Pd(dtbpf)Cl.sub.2 [1,1′-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) [0488] Pd.sub.2(dba).sub.3 Tris(dibenzylideneacetone)dipalladium [0489] Prep Preparative [0490] PTSA 4-Methylbenzenesulfonic acid [0491] Rt or rt Room temperature [0492] RuPhos 2-

Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl [0493] sat. Saturated [0494] SEMCI (2-(Chloromethoxy)ethyl)trimethylsilane [0495] TBSCI tert-Butyldimethylsilyl chloride [0496] TEA/Et3N triethylamine [0497] t-BuOK Potassium tert-butoxide [0498] t-BuONa Sodium tert-butoxide [0499] T.sub.3P n-Propylphosphonic cyclic anhydride [0500] TIPS Triisopropylsilyl [0501] TMSCN Trimethylsilyl cyanide [0502] TFA Trifluoroacetic acid [0503] TFAA Trifluoroacetic anhydride [0504] THF Tetrahydrofuran [0505] TLC thin layer chromatography [0506] tBuXPhospd-G3 Methanesulfonato(2-di-t-butylphosphino-2′,4′,6′-tri-i-propyl-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl)palladium(II) [0507] tBuXPhos 2-Di-tert-butylphosphino-2′,4′,6′-triisopropylbiphenyl [0508] UHP Urea hydrogen peroxide [0509] μL Microliters [0510] XantPhos 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene [0511] Xphos 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl [0512] 4CzIPN (4r,6r)-2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile

Compound Synthesis

Example 1: 2-amino-7-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-5-yl)benzo[b]thiophene-3-carbonitrile

##STR00247##

Step 1: 7-bromo-4-chloro-5,8-difluoro-2-(methylthio)quinazoline

##STR00248##

[0513] To a suspension of 7-bromo-5,8-difluoro-2-(methylthio)quinazolin-4(3H)-one (10 g, 32.6 mmol) in POCl.sub.3 (30 mL), DIPEA (15 mL) was added dropwise. The mixture was stirred at 100° C. overnight. Then, the mixture was cooled to rt, and concentrated in vacuo. The mixture was diluted with DCM, filtered off the solid to give crude product, and further purified by silica gel column chromatography (80 g, eluting with PE/EtOAc=100%:0%˜75%:25%) to give the title compound (6.9 g). MS (ESI, m/e) [M+H].sup.+ 324.4.

Step 2: (R)-(4-(7-bromo-5,8-difluoro-2-(methylthio)quinazolin-4-yl)morpholin-3-yl)methanol

##STR00249##

[0514] To a mixture of (R)-morpholin-3-ylmethanol (0.54 g, 4.6 mmol) and DIPEA (1.2 g, 9.3 mmol) in DCM (20 mL) was added 7-bromo-4-chloro-5,8-difluoro-2-(methylthio)quinazoline (1.5 g, 4.6 mmol) at 0° C. The mixture was stirred at r.t. overnight. The mixture was quenched with NH.sub.4Cl (10 mL, aq. sat.) solution, and extracted with DCM (20 mL*3). Combined organic layer was dried over Na.sub.2SO.sub.4, concentrated and purified with chromatography column on silica (eluting with PE/EtOAc=2/1) to give the title compound (0.93 g). MS (ESI, m/e) [M+H].sup.+ 406.2.

Step 3: (S)-10-bromo-9-fluoro-7-(methylthio)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline

##STR00250##

[0515] A mixture of (R)-(4-(7-bromo-5,8-difluoro-2-(methylthio)quinazolin-4-yl)morpholin-3-yl)methanol (0.93 g, 2.3 mmol) was placed in THF. NaH (0.28 g, 6.9 mmol) was added to the solution in portions at 0° C., and the mixture was stirred at r.t. overnight. The mixture was quenched with NH.sub.4Cl (10 mL, aq., sat), and extracted with DCM (20 mL*3). Combined organic layer was dried over Na.sub.2SO.sub.4, concentrated, and purified with chromatography column on silica (eluting with PE/EtOAc=1/1) to give the title compound (0.87 g). MS (ESI, m/e) [M+H].sup.+ 386.2.

Step 4: (13aS)-10-bromo-9-fluoro-7-(methylsulfinyl)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,17-de]quinazoline

##STR00251##

[0516] To a mixture of (S)-10-bromo-9-fluoro-7-(methylthio)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline (0.5 g, 1.3 mmol) in DCM (20 mL) was added m-CPBA (0.25 g, 1.43 mmol) in portions at 0° C. The mixture was stirred at 0° C. for 2 hrs. The mixture was diluted with DCM (20 mL), washed with aqueous NaHCO.sub.3 solution (2 M)

for 3 times. The resulting organic layer was dried over Na.sub.2SO.sub.4, concentrated to give the crude product (480 mg) which was used in the next step without further purification. MS (ESI, m/e) [M+H].sup.+ 402.2.
Step 5: (S)-10-bromo-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline
##STR00252##
[0517] ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (0.55 g, 1.4 mmol) was placed in THF (5 mL). LiHMDS (2.7 mL, 2.7 mmol, 1 M in THF) was added to the solution in dropwise at 0° C., and the mixture was stirred for another 0.5 h at 0° C. The resulting solution was added to the solution of (13aS)-10-bromo-9-fluoro-7-(methylsulfinyl)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline (0.55 g, 1.36 mmol) in THF (10 mL) dropwise at 0° C. The mixture was stirred at 0° C. for 30 min and then quenched with NH.sub.4Cl (aq., sat), extracted with DCM (20 mL*3). The combined organic layer was dried over Na.sub.2SO.sub.4, concentrated and purified with chromatography column on silica (eluting with DCM/MeOH=10/1) to give the title compound (480 mg). MS (ESI, m/e) [M+H].sup.+ 497.2.
Step 6: tert-butyl (3-cyano-7-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-5-yl)benzo[b]thiophen-2-yl)carbamate
##STR00253##
[0518] A mixture of(S)-10-bromo-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline (80 mg, 0.16 mmol), tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate (67 mg, 0.16 mmol), Bis(diphenylphosphinophenyl)ether palladium (II) dichloride (11.5 mg, 0.016 mmol), NaHCO.sub.3 (27 mg, 0.32 mmol) were placed in dioxane/water (5 mL, 9/1), and the mixture was stirred at 100° C. overnight. The reaction was cooled to room temperature, concentrated under vacuo, purified with chromatography column on silica (eluting with DCM/MeOH=9/1) to give the title compound (60 mg). MS (ESI, m/e) [M+H].sup.+ 709.2.
Step 7: 2-amino-7-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-5-yl)benzo[b]thiophene-3-carbonitrile
[0519] To a mixture of tert-butyl (3-cyano-7-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-5-yl)benzo[b]thiophen-2-yl)carbamate (60 mg, 0.084 mmol) in dioxane (2 mL), HCl (2 mL, 4M in dioxane) was added. The mixture was stirred at rt for 16 hrs. Solvents were concentrated via vacuo, and the residue was purified with HPLC to give the title product (30 mg). .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 8.05 (s, 2H), 7.29-7.20 (m, 1H), 7.12-7.03 (m, 1H), 6.77-6.70 (m, 1H), 5.38-5.20 (m, 1H), 4.84-4.76 (m, 1H), 4.46-4.26 (m, 2H), 4.19-3.91 (m, 4H), 3.65-3.45 (m, 2H), 3.27-3.17 (m, 1H), 3.16-3.00 (m, 3H), 2.27-2.24 (m, 1H), 2.15-1.96 (m, 3H), 1.95-1.70 (m, 3H). MS (ESI, m/e) [M+H].sup.+ 609.2.
Example 2: 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-5-yl)naphthalen-2-ol
##STR00254##
Step 1: (S)-4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline
##STR00255##
[0520] A mixture of (S)-10-bromo-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline

(80 mg, 0.16 mmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (82 mg, 0.16 mmol), Pd(dtbpf)Cl2 (10.4 mg, 0.016 mmol), NaHCO.sub.3 (27 mg, 0.32 mmol) were placed in dioxane/water (5 mL, 9/1), and the mixture was stirred at 100° C. overnight. The reaction mixture was cooled to room temperature, concentrated under vacuo, and purified with chromatography column on silica (eluting with DCM/MeOH=9/1) to give the title compound (60 mg, crude) which was used in the next step directly without further purification. MS (ESI, m/e) [M+H].sup.+ 803.4.

Step 2: (S)-5-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline

##STR00256##

[0521] A mixture of (S)-4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline (60 mg, crude) and CsF (22 mg, 0.15 mmol) in DMF (5 mL) was stirred at rt for 2 hrs. The mixture was concentrated to give the crude product (60 mg, crude) which was used in the next step directly without further purification. MS (ESI, m/e) [M+H].sup.+ 647.2.

Step 3: 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-5-yl)naphthalen-2-ol

[0522] To a mixture of (S)-5-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline (60 mg, 0.093 mmol) in dioxane (3 mL) was added HCl (1 mL, 4M in dioxane) in portions. The mixture was stirred at rt for 16 hrs. The mixture was concentrated under vacuo, purified with HPLC to give the title product (6 mg). .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 10.11 (s, 1H), 7.96-7.93 (m, 1H), 7.48-7.41 (m, 1H), 7.37-7.30 (m, 1H), 7.10-7.00 (m, 1H), 6.77-6.69 (m, 1H), 5.37-5.18 (m, 1H), 4.87-4.76 (m, 1H), 4.47-4.34 (m, 2H), 4.13-4.04 (m, 2H), 4.04-3.91 (m, 6H), 3.66-3.40 (m, 2H), 3.14-3.04 (m, 2H), 2.88-2.79 (m, 1H), 2.18-1.96 (m, 3H), 1.88-1.70 (m, 3H). MS (ESI, m/e) [M+H].sup.+ 603.2.

Example 3: 3-chloro-5-((S)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)-4-(trifluoromethyl)aniline

##STR00257##

Step 1: (S)-7-chloro-8-fluoro-2-(methylthio)-5-(morpholin-3-ylmethoxy)pyrido[4,3-d]pyrimidin-4-ol

##STR00258##

[0523] To a stirred solution of 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol (200 mg, 0.72 mmol) and (R)-morpholin-3-ylmethanol (85 mg, 0.72 mmol) in THF (6 mL) was added NaH (100 mg, 2.5 mmol, 60%) at 0° C., and the resulting mixture was stirred for 2 hrs at room temperature. The reaction mixture was quenched with H.sub.2O, then adjusted pH to 6 with 1N aq HCl. The mixture was filtered and filter cake was directly used in the next step without further purification. MS (ESI, m/e) [M+H].sup.+ 361.2.

Step 2: (S)-2-chloro-1-fluoro-11-(methylthio)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene

##STR00259##

[0524] To a stirred solution of (S)-7-chloro-8-fluoro-2-(methylthio)-5-(morpholin-3-ylmethoxy)pyrido[4,3-d]pyrimidin-4-ol (0.72 mmol) in MeCN (50 mL) was added DIEA (186 mg, 1.4 mmol) and HATU (410 mg, 1.1 mmol) at room temperature, and the resulting mixture was stirred for 2 hrs at room temperature. The reaction mixture was concentrated and purified by flash chromatography (PE/EA=4:1 to 1:3) to afford the title product (220 mg). MS (ESI, m/e)

[M+H].sup.+ 343.0.
Step 3: (5aS)-2-chloro-1-fluoro-11-(methylsulfinyl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene
##STR00260##
[0525] To a stirred solution of (S)-2-chloro-1-fluoro-11-(methylthio)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (220 mg, 0.64 mmol) in DCM (15 mL) was added m-CPBA (156 mg, 0.77 mmol, 85%) at 0° C., and the resulting mixture was stirred at 0° C. for 10 min. The reaction was quenched with aq. Na.sub.2S.sub.2O.sub.3, then extracted with DCM. The organic layer was washed with Sat. aq NaHCO.sub.3 and brine, dried over anhydrous Na.sub.2SO.sub.4, and concentrated in vacuo. The residue was directly used in the next step without further purification. MS (ESI, m/e) [M+H].sup.+ 359.0.
Step 4: (S)-2-chloro-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene
##STR00261##
[0526] To a stirred solution of (5aS)-2-chloro-1-fluoro-11-(methylsulfinyl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (0.64 mmol) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (206 mg, 1.3 mmol) in THF (15 mL) was added LiHMDS (1.3 mL, 1.3 mmol, 1 M in THF) dropwise at 0° C., and the resulting mixture was stirred at 0° C. for 20 min. The reaction was quenched with Sat. aq NH.sub.4Cl, then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na.sub.2SO.sub.4, and concentrated in vacuo. The residue was purified by flash chromatography (DCM/MeOH=100:1 to 30:1) to afford the title product (78 mg). MS (ESI, m/e) [M+H].sup.+ 454.2.
Step 5: 3-chloro-5-((S)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)-4-(trifluoromethyl)aniline
[0527] A mixture of (S)-2-chloro-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (45 mg, 0.10 mmol), 3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (72 mg, 0.20 mmol, 89%), Pd(dtbpf)Cl.sub.2 (13 mg, 0.02 mmol), NaHCO.sub.3 (26 mg, 0.30 mmol), dioxane (5.0 mL), and H.sub.2O (1.0 mL) was stirred at 90° C. for 2 hrs. The reaction mixture was concentrated and purified by flash chromatography (DCM/MeOH=100:1 to 5:1), then prep-HPLC to give the title product (15.6 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 6.91-6.85 (m, 1H), 6.51-6.45 (m, 1H), 5.48-5.25 (m, 1H), 5.18-5.08 (m, 1H), 4.56-4.46 (m, 2H), 4.44-4.29 (m, 2H), 4.13-4.10 (m, 1H), 4.10-3.95 (m, 2H), 3.74-3.56 (m, 2H), 3.56-3.39 (m, 3H), 3.38-3.33 (m, 1H), 3.20-3.10 (m, 1H), 2.49-1.89 (m, 6H). MS (ESI, m/e) [M+H].sup.+ 613.4.
Example 4: 5-ethynyl-6-fluoro-4-((S)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol
##STR00262##
Step 1: (S)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-11-(((2R 7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene
##STR00263##
[0528] A mixture of (S)-2-chloro-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (30 mg, 0.07 mmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (72 mg, 0.14 mmol),

Pd(dtbpf)Cl.sub.2 (9.0 mg, 0.014 mmol), NaHCO.sub.3 (18 mg, 0.21 mmol), dioxane (4.0 mL), and H.sub.2O (0.8 mL) was stirred at 90° C. for 2 hrs. The reaction mixture was concentrated and purified by flash chromatography (DCM/MeOH=100:1 to 10:1) to give the title product (37 mg). MS (ESI, m/e) [M+H].sup.+ 804.6.

Step 2: (S)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene

##STR00264##

[0529] To a stirred solution of (S)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (37 mg, 0.046 mmol) in DMF (3 mL) was added CsF (70 mg, 0.46 mmol), and the resulting mixture was stirred for 2 hrs. The reaction mixture was diluted with EtOAc and H.sub.2O, then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na.sub.2SO.sub.4, and concentrated in vacuo. The crude was directly used in the next step without further purification. MS (ESI, m/e) [M+H].sup.+ 648.4.

Step 3: 5-ethynyl-6-fluoro-4-((S)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol

[0530] To a stirred solution of (S)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (0.046 mmol) in DCM (4.0 mL) was added 4N HCl (in dioxane) (0.8 mL) at 0° C., and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and basified with DIEA, and the residue was purified by flash chromatography (DCM/MeOH=100:1 to 10:1), then Prep-HPLC to afford the title product (10.2 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 7.87-7.79 (m, 1H), 7.37-7.14 (m, 3H), 5.44-5.24 (m, 1H), 5.23-7.12 (m, 1H), 4.63-4.46 (m, 2H), 4.42-4.24 (m, 2H), 4.23-4.14 (m, 1H), 4.10-3.99 (m, 2H), 3.75-3.60 (m, 2H), 3.55-3.50 (m, 1H), 3.46-3.33 (m, 3H), 3.14-3.03 (m, 1H), 2.43-1.85 (m, 6H). MS (ESI, m/e) [M+H].sup.+ 604.5.

Example 5: 5-ethyl-6-fluoro-4-((S)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol

##STR00265##

Step 1: (S)-2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene

##STR00266##

[0531] A mixture of (S)-2-chloro-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (35 mg, 0.08 mmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (56 mg, 0.16 mmol), Pd(dtbpf)Cl.sub.2 (10 mg, 0.02 mmol), NaHCO.sub.3 (20 mg, 0.24 mmol), dioxane (4.0 mL), and H.sub.2O (0.8 mL) was stirred at 90° C. for 2 hrs. The reaction mixture was concentrated and purified by flash chromatography (DCM/MeOH=100:1 to 10:1) to give the title product (31 mg). MS (ESI, m/e) [M+H].sup.+ 652.1.

Step 2: 5-ethyl-6-fluoro-4-((S)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol

[0532] To a stirred solution of (S)-2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (0.05 mmol) in DCM

(3.0 mL) was added 4N HCl (in dioxane) (0.5 mL) at 0° C., and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and basified with DIEA, and the residue was purified by flash chromatography (DCM/MeOH=100:1 to 10:1), then Prep-HPLC to afford the title product (8.3 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 7.71-7.60 (m, 1H), 7.33-7.02 (m, 3H), 5.47-5.26 (m, 1H), 5.24-5.10 (m, 1H), 4.62-4.47 (m, 2H), 4.45-4.28 (m, 2H), 4.26-4.12 (m, 1H), 4.10-3.98 (m, 2H), 3.76-3.56 (m, 2H), 3.54-3.34 (m, 4H), 3.20-3.06 (m, 1H), 2.57-1.87 (m, 8H), 0.92-0.78 (m, 3H). MS (ESI, m/e) [M+H].sup.+ 608.5.

Example 6: 3-chloro-4-cyclopropyl-5-((S)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)phenol

##STR00267##

Step 1: (S)-2-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene

##STR00268##

[0533] A mixture of (S)-2-chloro-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (35 mg, 0.08 mmol), 2-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (54 mg, 0.16 mmol), Pd(dtbpf)Cl.sub.2 (10 mg, 0.02 mmol), NaHCO.sub.3 (20 mg, 0.24 mmol), dioxane (4.0 mL), and H.sub.2O (0.8 mL) was stirred at 90° C. for 2 hrs. The reaction mixture was concentrated and purified by flash chromatography (DCM/MeOH=100:1 to 10:1) to give the title product (42 mg). MS (ESI, m/e) [M+H].sup.+ 630.1.

Step 2: 3-chloro-4-cyclopropyl-5-((S)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)phenol

[0534] To a stirred solution of (S)-2-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (30 mg, 0.05 mmol) in DCM (3.0 mL) was added TFA (1.0 mL) at 0° C., and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and basified with DIEA, and the residue was purified by flash chromatography (DCM/MeOH=100:1 to 10:1), then Prep-HPLC to afford the title product (5.2 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 6.97-6.90 (m, 1H), 6.78-6.70 (m, 1H), 5.47-5.25 (m, 1H), 5.22-5.10 (m, 1H), 4.56-4.45 (m, 2H), 4.40-4.27 (m, 2H), 4.23-4.13 (m, 1H), 4.10-3.94 (m, 2H), 3.73-3.57 (m, 2H), 3.55-3.32 (m, 4H), 3.18-3.06 (m, 1H), 2.47-1.77 (m, 7H), 0.75-0.55 (m, 2H), 0.23-0.05 (m, 2H). MS (ESI, m/e) [M+H].sup.+ 586.4.

Example 7: 5-ethynyl-6-fluoro-4-((S)-1-fluoro-11-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol

##STR00269##

Step 1: (5aS)-2-chloro-1-fluoro-11-(methylsulfinyl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene

##STR00270##

[0535] To a stirred solution of (S)-2-chloro-1-fluoro-11-(methylthio)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (68 mg, 0.20 mmol) in DCM (3.0 mL) was added m-CPBA (48 mg, 0.24 mmol, 85%) at 0° C., and the resulting mixture was stirred at 0° C. for 10 min. The reaction was quenched with aq. Na.sub.2S.sub.2O.sub.3, then extracted with DCM. The organic layer was washed with Sat. aq NaHCO.sub.3 and brine, dried over anhydrous Na.sub.2SO.sub.4, and concentrated in vacuo. The residue was directly used in the next step without further purification.

Step 2: (S)-2-chloro-1-fluoro-11-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene
##STR00271##
[0536] To a stirred solution of (5aS)-2-chloro-1-fluoro-11-(methylsulfinyl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (0.20 mmol) and ((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methanol (53 mg, 0.40 mmol) in THF (3.0 mL) was added LiHMDS (0.40 mL, 0.40 mmol, 1 M in THF) dropwise at 0° C., and the resulting mixture was stirred at 0° C. for 20 min. Solvents were evaporated and the residue was purified by flash chromatography (DCM/MeOH=100:1 to 30:1) to give the title product (32 mg). MS (ESI, m/e) [M+H].sup.+ 428.3.
Step 3: (S)-1-fluoro-11-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene
##STR00272##
[0537] A mixture of (S)-2-chloro-1-fluoro-11-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (32 mg, 0.075 mmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (77 mg, 0.15 mmol), Pd(dtbpf)Cl.sub.2 (10 mg, 0.015 mmol), NaHCO.sub.3 (19 mg, 0.23 mmol), dioxane (3.0 mL), and H.sub.2O (0.6 mL) was stirred at 100° C. for 2 hrs. The reaction mixture was concentrated and purified by flash chromatography (DCM/MeOH=100:1 to 20:1) to give the title product (46 mg). MS (ESI, m/e) [M+H].sup.+ 778.4.
Step 4: (S)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-11-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene
##STR00273##
[0538] To a stirred solution of (S)-1-fluoro-11-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (46 mg, 0.06 mmol) in DMF (3.0 mL) was added CsF (46 mg, 0.30 mmol), and the resulting mixture was stirred for 2 hrs. The reaction mixture was diluted with EtOAc and H.sub.2O, then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na.sub.2SO.sub.4, and concentrated in vacuo. The crude was directly used in the next step without further purification. MS (ESI, m/e) [M+H].sup.+ 622.4.
Step 5: 5-ethynyl-6-fluoro-4-((S)-1-fluoro-11-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol
[0539] To a stirred solution of (S)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-11-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (0.06 mmol) in DCM (5.0 mL) was added 4N HCl (in dioxane) (1.0 mL) at 0° C., and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and basified with DIEA, and the residue was purified by flash chromatography (DCM/MeOH=100:1 to 10:1), then Prep-HPLC to afford the title product (14.2 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 7.88-7.78 (m, 1H), 7.39-7.16 (m, 3H), 5.34-5.10 (m, 2H), 4.62-4.44 (m, 4H), 4.25-4.13 (m, 1H), 4.12-3.98 (m, 2H), 3.75-3.50 (m, 4H), 3.42-3.33 (m, 1H), 3.29-3.21 (m, 1H), 2.83-2.55 (m, 4H), 2.40-2.24 (m, 1H), 2.15-1.95 (m, 1H). MS (ESI, m/e) [M+H].sup.+ 578.5.
Example 8: (S)-5-ethynyl-6-fluoro-4-(1-fluoro-11-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol

##STR00274##
Step 1: (5aS)-2-chloro-1-fluoro-11-(methylsulfinyl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene
##STR00275##
[0540] To a stirred solution of (S)-2-chloro-1-fluoro-11-(methylthio)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (200 mg, 0.58 mmol) in DCM (8.0 mL) was added m-CPBA (142 mg, 0.70 mmol, 85%) at 0° C., and the resulting mixture was stirred at 0° C. for 10 min. The reaction was quenched with aq. Na.sub.2S.sub.2O.sub.3, then extracted with DCM. The organic layer was washed with Sat. aq NaHCO.sub.3 and brine, dried over anhydrous Na.sub.2SO.sub.4, and concentrated in vacuo. The residue was directly used in the next step without further purification.
Step 2: (S)-2-chloro-1-fluoro-11-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene
##STR00276##
[0541] To a stirred solution of (5aS)-2-chloro-1-fluoro-1-(methylsulfinyl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (0.58 mmol) and (1-(morpholinomethyl)cyclopropyl)methanol (205 mg, 1.2 mmol) in THF (8.0 mL) was added LiHMDS (1.2 mL, 1.2 mmol, 1 M in THF) dropwise at 0° C., and the resulting mixture was stirred at 0° C. for 20 min. The residue was purified by flash chromatography (DCM/MeOH=100:1 to 30:1) to give the title product (128 mg). MS (ESI, m/e) [M+H].sup.+ 466.5.
Step 3: (S)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-11-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene
##STR00277##
[0542] A mixture of (S)-2-chloro-1-fluoro-11-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (128 mg, 0.27 mmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (211 mg, 0.41 mmol), Pd(dtbpf)Cl.sub.2 (35 mg, 0.054 mmol), NaHCO.sub.3 (68 mg, 0.81 mmol), dioxane (10 mL), and H.sub.2O (2.0 mL) was stirred at 100° C. for 3 hrs. The reaction mixture was concentrated and purified by flash chromatography (DCM/MeOH=100:1 to 30:1) to give the title product (90 mg). MS (ESI, m/e) [M+H].sup.+ 816.6.
Step 4: (S)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-11-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene
##STR00278##
[0543] To a stirred solution of (S)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-11-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (90 mg, 0.11 mmol) in DMF (4.0 mL) was added CsF (167 mg, 1.1 mmol), and the resulting mixture was stirred for 2 hrs. The reaction mixture was diluted with EtOAc and H.sub.2O, then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na.sub.2SO.sub.4, and concentrated in vacuo. The crude was directly used in the next step without further purification. MS (ESI, m/e) [M+H].sup.+ 660.4.
Step 5: (S)-5-ethynyl-6-fluoro-4-(1-fluoro-11-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol
[0544] To a stirred solution of (S)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-11-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (0.11 mmol) in DCM (5.0 mL) was

added 4N HCl (in dioxane) (1.0 mL) at 0° C., and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and basified with DIEA, and the residue was purified by flash chromatography (DCM/MeOH=100:1 to 20:1), then Prep-HPLC to afford the title product (19.5 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 7.88-7.78 (m, 1H), 7.36-7.18 (m, 3H), 5.21-5.12 (m, 1H), 4.62-4.47 (m, 2H), 4.44-4.35 (m, 2H), 4.22-4.13 (m, 1H), 4.10-3.97 (m, 2H), 3.76-3.50 (m, 7H), 3.41-3.33 (m, 1H), 2.81-2.44 (m, 6H), 0.82-0.67 (m, 2H), 0.64-0.45 (m, 2H). MS (ESI, m/e) [M+H].sup.+ 616.4.

Example 9: (S)-4-(11-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-1-fluoro-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol

##STR00279##

Step 1: (5aS)-2-chloro-1-fluoro-11-(methylsulfinyl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene

##STR00280##

[0545] To a stirred solution of (S)-2-chloro-1-fluoro-11-(methylthio)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (68 mg, 0.20 mmol) in DCM (3.0 mL) was added m-CPBA (48 mg, 0.24 mmol, 85%) at 0° C., and the resulting mixture was stirred at 0° C. for 10 min. The reaction was quenched with aq. Na.sub.2S.sub.2O.sub.3, then extracted with DCM. The organic layer was washed with Sat. aq NaHCO.sub.3 and brine, dried over anhydrous Na.sub.2SO.sub.4, and concentrated in vacuo. The residue was directly used in the next step without further purification.

Step 2: (S)-11-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-chloro-1-fluoro-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[45]cyclohepta[1,2,3-de]naphthalene

##STR00281##

[0546] To a stirred solution of (5aS)-2-chloro-1-fluoro-11-(methylsulfinyl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (0.20 mmol) and (2-oxabicyclo[2.1.1]hexan-4-yl)methanol (46 mg, 0.40 mmol) in THF (3.0 mL) was added LiHMDS (0.40 mL, 0.40 mmol, 1 M in THF) dropwise at 0° C., and the resulting mixture was stirred at 0° C. for 20 min. Solvents were removed and the residue was purified by flash chromatography (DCM/MeOH=100:1 to 30:1) to give the title product (45 mg). MS (ESI, m/e) [M+H].sup.+ 409.2.

Step 3: (S)-11-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene

##STR00282##

[0547] A mixture of(S)-11-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-chloro-1-fluoro-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (45 mg, 0.11 mmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (113 mg, 0.22 mmol), Pd(dtbpf)Cl.sub.2 (13 mg, 0.02 mmol), NaHCO.sub.3 (28 mg, 0.33 mmol), dioxane (4.0 mL), and H.sub.2O (0.8 mL) was stirred at 100° C. for 2 hrs. The reaction mixture was concentrated and purified by flash chromatography (DCM/MeOH=100:1 to 30:1) to give the title product (60 mg). MS (ESI, m/e) [M+H].sup.+ 759.4.

Step 4: (S)-11-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene

##STR00283##

[0548] To a stirred solution of (S)-11-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (60 mg, 0.08 mmol) in DMF (3.0 mL) was added CsF (60 mg, 0.40 mmol), and the resulting mixture was stirred for 2 hrs. The reaction mixture was diluted with EtOAc and H.sub.2O, then extracted with EtOAc. The

organic layer was washed with brine, dried over anhydrous Na.sub.2SO.sub.4, and concentrated in vacuo. The crude was directly used in the next step without further purification. MS (ESI, m/e) [M+H].sup.+ 603.4.

Step 5: (S)-4-(11-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-1-fluoro-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol

[0549] To a stirred solution of (S)-11-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-5a,6,8,9-tetrahydro-5H-4,7-dioxa-3,9a,10,12-tetraazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene (0.08 mmol) in DCM (5.0 mL) was added 4N HCl (in dioxane) (1.0 mL) at 0° C., and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and basified with DIEA, and the residue was purified by flash chromatography (DCM/MeOH=100:1 to 20:1), then Prep-HPLC to afford the product (15.6 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 7.89-7.78 (m, 1H), 7.36-7.12 (m, 3H), 5.22-5.12 (m, 1H), 4.81-4.70 (m, 2H), 4.59-4.46 (m, 3H), 4.22-4.12 (m, 1H), 4.09-3.98 (m, 2H), 3.77-3.60 (m, 4H), 3.56-3.50 (m, 1H), 3.42-3.32 (m, 1H), 2.01-1.90 (m, 2H), 1.67-1.56 (m, 2H). MS (ESI, m/e) [M+H].sup.+ 559.4.

Example 10: 3-chloro-5-(1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline

##STR00284##

Step 1: tert-butyl 2-chloro-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

##STR00285##

[0550] To a solution of 4,5,7-trichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidine (1.5 g, crude) and DIPEA (1.49 g, 11.57 mmol) in DCM (15 mL) was added tert-butyl 2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 2.06 mmol) (Wuxi LabNetwork Catlog #QC50004035) at room temperature. The resulting mixture was stirred at room temperature for 3 hrs. After completion, the reaction mixture was diluted with EtOAc (50 mL), and washed with saturated NaCl (15 mL×3). The organic layer was dried over anhydrous Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to give the residue. The residue was purified by silica gel column chromatography, eluted with 0-100% ethyl acetate in petroleum ether to give the title product (400 mg). MS (ESI, m/e) [M+H].sup.+ 468.1.

Step 2: tert-butyl 2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

##STR00286##

[0551] To a solution of tert-butyl 2-chloro-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (250.0 mg, 0.53 mmol) in DCM (5 mL) was added m-CPBA (115.1 mg, 0.53 mmol, 80%) at room temperature, and the resulting mixture was stirred at room temperature for 1 hrs to get mixture 1. To another mixture of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (253.0 mg, 1.59 mmol) in THF (5 mL) was added LiHMDS (2.0 mL, 2.0 mmol)) at room temperature. The resulting mixture was stirred for 1 h at room temperature. Then, to the above reaction mixture was added mixture 1. The resulting mixture was stirred for 1 h at room temperature. After completion, the reaction mixture was diluted with EtOAc (30 mL), and washed with saturated NaCl (15 mL×3). The organic layer was dried over anhydrous Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to give the residue. The residue was purified by silica gel column chromatography, eluted with 0-100% ethyl acetate in petroleum ether to give the title product (60 mg). MS (ESI, m/e) [M+H].sup.+ 579.2.

Step 3: tert-butyl 2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2R,7aS)-2-

fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate
##STR00287##
[0552] A mixture of tert-butyl 2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (60 mg, 0.10 mmol), (5-amino-3-chloro-2-(trifluoromethyl)phenyl)boronic acid (71.7 mg, 0.30 mmol), NaHCO.sub.3 (25.2 mg, 0.30 mmol), Pd(dppf)Cl.sub.2(36.5 mg, 0.05 mmol), dioxane (5 mL), and water (1 mL) was stirred at 100° C. for 4 hrs. After completion, the reaction mixture was diluted with DCM (20 mL), and washed with saturated NaCl (10 mL×3). The organic layer was dried over anhydrous Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to give the residue. The residue was purified by Prep-TLC (DCM:MeOH=10:1) to give the title product (30 mg). MS (ESI, m/e) [M+H].sup.+ 738.4.
Step 4: 3-chloro-5-(1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline
[0553] To a solution of tert-butyl 2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (30.0 mg, 0.04 mmol) in DCM (2 mL) was added TFA (2 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 hrs. After completion, the reaction mixture was concentrated to give the residue. The residue was purified by prep-HPLC to give the title product (1.48 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 6.94-6.86 (m, 1H), 6.53-6.40 (m-1H), 5.44-5.20 (m, 1H), 5.05-4.99 (m, 1H), 4.69-4.00 (m-4H), 3.80-3.60 (m-2H), 3.32-3.00 (m-5H), 2.72-2.03 (m, 10H). MS (ESI, m/e) [M+H].sup.+ 638.1.
Example 11: 5-ethynyl-6-fluoro-4-(1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
##STR00288##
Step 1: tert-butyl 1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate
##STR00289##
[0554] A mixture of tert-butyl 2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (60 mg, 0.10 mmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (153.7 mg, 0.30 mmol), NaHCO.sub.3 (25.2 mg, 0.30 mmol), Pd(dtbpf)Cl.sub.2(32.6 mg, 0.05 mmol), dioxane (5 mL), and water (1 mL) was stirred at 100° C. for 4 hrs. After completion, the reaction mixture was diluted with DCM (20 mL), and washed with saturated NaCl (10 mL×3). The organic layer was dried over anhydrous Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to give the residue. The residue was purified by Prep-TLC (DCM:MeOH=10:1) to give the title product (25 mg). MS (ESI, m/e) [M+H].sup.+ 929.5.
Step 2: tert-butyl 2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate
##STR00290##
[0555] To a solution of tert-butyl 1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-

methanonaphtho[1,8-ab]heptalene-14-carboxylate (25.0 mg, 0.03 mmol) in DMF (2 mL) was added CsF (45.6 mg, 0.3 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 hrs. After completion, the reaction mixture was diluted with EtOAc (20 mL), and washed with saturated NaCl (10 mL×3). The organic layer was dried over anhydrous Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to give the crude product (25 mg). MS (ESI, m/e) [M+H].sup.+ 773.3.

Step 3: 5-ethynyl-6-fluoro-4-(1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

[0556] To tert-butyl 2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (25 mg crude) was added HCl in EtOAc (1 M, 2 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 hrs. After completion, the reaction mixture was concentrated to give the residue. The residue was purified by prep-HPLC to give the title product (3.3 mg). .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 10.15 (s-1H), 7.97-7.94 (m-1H), 7.50-7.40 (m, 1H), 7.37 (s-1H), 7.25-7.05 (m, 1H), 5.42-5.20 (m-1H), 4.87-4.78 (m-1H), 4.54-4.49 (m-1H), 4.38-3.95 (m, 4H), 3.32-3.00 (m, 5H), 2.20-1.57 (m, 10H). MS (ESI, m/e) [M+H].sup.+ 629.5.

Example 12: 3-chloro-5-((S)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)-4-(trifluoromethyl)aniline

##STR00291##

Step 1: tert-butyl (S)-4-(5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-yl)-3-(hydroxymethyl)piperazine-1-carboxylate

##STR00292##

[0557] To a solution of 4,5,7-trichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidine (1.5 g crude) and DIPEA (1.49 g, 11.57 mmol) in DCM (15 mL) was added tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (648.3 mg, 3.0 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 hrs. After completion, the reaction mixture was diluted with EtOAc (50 mL), and washed with saturated NaCl (15 mL×3). The organic layer was dried over anhydrous Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to give the residue. The residue was purified by silica gel column chromatography, eluted with 0-60% ethyl acetate in petroleum ether to give the title product (500 mg). MS (ESI, m/e) [M+H].sup.+ 478.1.

Step 2: tert-butyl (S)-2-chloro-1-fluoro-11-(methylthio)-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene-7(5H)-carboxylate

##STR00293##

[0558] To a solution of tert-butyl (S)-4-(5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (500 mg, 1.05 mmol) in THF (15 mL) was added LiHMDS (1.05 mL, 1.05 mmol, 1M) at room temperature. The resulting mixture was stirred at room temperature for 0.5 hrs. After completion. The reaction mixture was directly concentrated to give the residue. The residue was purified by silica gel column chromatography, eluted with 0-100% ethyl acetate in petroleum ether to give the title product (300 mg). MS (ESI, m/e) [M+H].sup.+ 442.1.

Step 3: tert-butyl (S)-2-chloro-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene-7(5H)-carboxylate

##STR00294##

[0559] To a solution of tert-butyl (S)-2-chloro-1-fluoro-11-(methylthio)-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene-7(5H)-carboxylate (234.0 mg, 0.53 mmol) in DCM (5 mL) was added m-CPBA (115.1 mg, 0.53 mmol, 80%) at room

temperature, The resulting mixture was stirred at room temperature for 1 hrs to get mixture 1. To another mixture of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (253.0 mg, 1.59 mmol) in THF (5 mL) was added LiHMDS (2.0 mL, 2.0 mmol)) at room temperature. The resulting mixture was stirred for 1 h at room temperature. Then, to the reaction mixture was added mixture 1 and the resulting mixture was stirred for 1 h at room temperature. After completion, the reaction mixture was diluted with EtOAc (30 mL), and washed with saturated NaCl (15 mL×3). The organic layer was dried over anhydrous Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to give the residue. The residue was purified by silica gel column chromatography, eluted with 0-100% ethyl acetate in petroleum ether to give the title product (100 mg). MS (ESI, m/e) [M+H].sup.+ 553.2.

Step 4: tert-butyl (S)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene-7(5H)-carboxylate

##STR00295##

[0560] A mixture of tert-butyl (S)-2-chloro-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene-7(5H)-carboxylate (55.2 mg, 0.10 mmol), (5-amino-3-chloro-2-(trifluoromethyl)phenyl)boronic acid (71.7 mg, 0.30 mmol), Pd(dppf)Cl.sub.2(36.5 mg, 0.05 mmol), NaHCO.sub.3 (25.2 mg, 0.30 mmol), dioxane (5 mL), and water (1 mL) was stirred at 100° C. for 4 hrs. After completion, the reaction mixture was diluted with DCM (20 mL), and washed with saturated NaCl (10 mL×3). The organic layer was dried over anhydrous Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to give the residue. The residue was purified by Prep-TLC (DCM:MeOH=10:1) to give the title product (35 mg). MS (ESI, m/e) [M+H].sup.+ 712.2.

Step 5: 3-chloro-5-((S)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-2-yl)-4-(trifluoromethyl)aniline

[0561] To a solution of tert-butyl (S)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-11-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-de]naphthalene-7(5H)-carboxylate (35.0 mg, 0.05 mmol) in DCM (4 mL) was added TFA (2 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 hrs. After completion, the reaction mixture was concentrated to give the residue. The residue was purified by prep-HPLC to give the title product (6.6 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 6.94-6.85 (m, 1H), 6.53-6.43 (m, 1H), 5.59-5.40 (m, 1H), 5.35-5.26 (m, 1H), 4.65-4.50 (m, 4H), 4.18-4.10 (m, 1H), 3.80-3.65 (m, 3H), 3.43-3.33 (m, 3H), 3.30-2.88 (m, 3H), 2.64-2.05 (m, 6H). MS (ESI, m/e) [M+H].sup.+ 612.4.

Example 13: 3-chloro-5-(1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,6a,7,8,9,10-hexahydro-5H-4-oxa-3,8,10a,11,13-pentaazabenzo[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-4-(trifluoromethyl)aniline

##STR00296##

Step 1: tert-butyl 3-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)piperazine-1-carboxylate

##STR00297##

[0562] To a solution of tert-butyl 3-(2-hydroxyethyl)piperazine-1-carboxylate (460.4 mg, 2.0 mmol) in THF (15 mL) was added NaH (200 mg, 5 mmol, 60%) at room temperature. The resulting mixture was stirred at room temperature for 1 h. Then, 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one (500 mg, 1.79 mmol) was added to the reaction mixture and the mixture was stirred at 60° C. for 16 hrs. After completion, the reaction mixture was quenched with water (50 mL), and extracted with EtOAc (40 mL×3). The organic layer was dried over anhydrous Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to give the residue.

The residue was purified by silica gel column chromatography, eluted with 0-100% ethyl acetate in petroleum ether to give the title product (350 mg). MS (ESI, m/e) [M+H].sup.+ 474.1.
Step 2: tert-butyl 2-chloro-1-fluoro-12-(methylthio)-5,6,6a,7,9,10-hexahydro-8H-4-oxa-3,8,10a,11,13-pentaazabenzo[4,5]cycloocta[1,2,3-de]naphthalene-8-carboxylate
##STR00298##
[0563] To a solution of tert-butyl 3-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)piperazine-1-carboxylate (350 mg, 0.74 mmol) and DIPEA (193.8 mg, 1.5 mmol) in DMF (150 mL) was added HATU (570.4 mg, 1.5 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 hrs. After completion, the reaction mixture was diluted with EtOAc (150 mL), and washed with saturated NaCl (50 mL×5). The organic layer was dried over anhydrous Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to give the residue. The residue was purified by silica gel column chromatography, eluted with 0-100% ethyl acetate in petroleum ether to give the title product (100 mg). MS (ESI, m/e) [M+H].sup.+ 456.1.
[0564] The following steps of Example 13 was following similar procedures as the synthesis of Example 12. .sup.1H NMR (500 MHz, CD.sub.3OD) δ 6.94-6.85 (m, 1H), 6.58-6.37 (m, 1H), 5.55-5.37 (m, 1H), 5.30-5.20 (m, 1H), 4.65-4.40 (m, 3H), 4.30-4.22 (m, 1H), 4.07-3.96 (m, 1H), 3.77-3.55 (m, 3H), 3.30-2.98 (m, 4H), 2.91-2.80 (m, 1H), 2.64-2.02 (m, 8H). MS (ESI, m/e) [M+H].sup.+ 626.5.
Example 14: 2-amino-4-((S)-6-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-5-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile
##STR00299##
Step 1: (R)-(4-(7-bromo-6-chloro-5,8-difluoro-2-(methylthio)quinazolin-4-yl)morpholin-3-yl)methanol
##STR00300##
[0565] To a mixture of (R)-morpholin-3-ylmethanol (3 g, 8.4 mmol) and DIPEA (2.2 g, 17.1 mmol) in DCM (30 mL) was added 7-bromo-4,6-dichloro-5,8-difluoro-2-(methylthio)quinazoline (1.0 g, 8.4 mmol) at 0° C. The mixture was stirred at r.t. overnight. NH.sub.4Cl (10 mL, aq. sat.) solution was added to the mixture, and the aqueous phase extracted with DCM (20 mL*3). The combined organic layer was dried over Na.sub.2SO.sub.4, concentrated and purified with chromatography column on silica (eluting with PE/EtOAc=2/1) to give the title compound (1.4 g). MS (ESI, m/e) [M+H].sup.+ 440.2.
Step 2: (S)-10-bromo-11-chloro-9-fluoro-7-(methylthio)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline
##STR00301##
[0566] A mixture of (R)-(4-(7-bromo-6-chloro-5,8-difluoro-2-(methylthio)quinazolin-4-yl)morpholin-3-yl)methanol (1.4 g, 3.16 mmol) was placed in THF. NaH (0.38 g, 9.5 mmol) was added to the solution in portions at 0° C., the mixture was stirred at RT overnight. Quenched with NH.sub.4Cl (10 mL, aq, sat.), extracted with DCM (20 mL*3). The combined organic layer was dried over Na.sub.2SO.sub.4, concentrated and purified with chromatography column on silica (eluting with PE/EtOAc=1/1) to give the title compound (1.2 g). MS (ESI, m/e) [M+H].sup.+ 420.2.
Step 3: (13aS)-10-bromo-11-chloro-9-fluoro-7-(methylsulfinyl)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline
##STR00302##
[0567] To a mixture of(S)-10-bromo-11-chloro-9-fluoro-7-(methylthio)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline (0.6 g, 1.41 mmol) in DCM (20 mL) was added m-CPBA (0.26 g, 1.5 mmol) at 0° C. The mixture was stirred at 0° C. for 2 hrs. The mixture was diluted with DCM (20 mL), washed with aqueous NaHCO.sub.3 solution (2 M) for 3 times. The resulting organic layer was dried over Na.sub.2SO.sub.4, concentrated to give the crude

product (0.5 g) which was used for next step without further purification. MS (ESI, m/e) [M+H].sup.+ 435.9.
Step 4: (S)-10-bromo-11-chloro-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline
##STR00303##
[0568] To a stirred solution of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (0.33 g, 0.66 mmol) in THF (10 mL). LiHMDS (1.4 ml, 1.38 mmol) was added to the solution of (13aS)-10-bromo-11-chloro-9-fluoro-7-(methylsulfinyl)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline (0.3 g, 0.69 mmol) in THF (10 mL) in portions at 0° C. The mixture was stirred at RT for 30 min. Quenched with NH.sub.4Cl (aq., sat), extracted with DCM (20 mL*3), the combined organic layer was dried over Na.sub.2SO.sub.4, concentrated and purified with chromatography column on silica (eluting with DCM/MeOH=10/1) to give the title compound (200 mg). MS (ESI, m/e) [M+H].sup.+ 531.2.
Step 5: tert-butyl (4-((S)-6-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-5-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate
##STR00304##
[0569] A mixture of (S)-10-bromo-11-chloro-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3,4,13,13a-tetrahydro-1H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazoline (70 mg, 0.132 mmol), tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate (130 mg, 0.132 mmol), Pd(dtbpf)Cl.sub.2 (42 mg, 0.066 mmol), K.sub.3PO.sub.4 (84 mg, 0.396 mmol) were placed in dioxane/water (5 mL, 9/1), the mixture was stirred at 100° C. overnight. Cooling the reaction to room temperature, concentrated under vacuo, purified with chromatography column on silica (eluting with DCM/MeOH=9/1) to give the title compound (50 mg). MS (ESI, m/e) [M+H].sup.+ 744.2.
Step 6: 2-amino-4-((S)-6-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-5-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile
[0570] To a mixture of tert-butyl (4-((S)-6-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-8H-[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-5-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (50 mg, 0.067 mmol) in dioxane (2 mL) was added HCl (2 mL, 4M in dioxane). The mixture was stirred at rt for 16 hrs. Concentrated via vacuo, purified with Prep-HPLC to give the title product (Isomer 1=4 mg, Isomer 2=5 mg). Isomer 1: .sup.1H NMR (500 MHz, DMSO-d6) δ 8.09 (s, 2H), 7.24-7.21 (m, 1H), 7.18-7.10 (m, 1H), 5.38-5.18 (m, 1H), 4.80-4.70 (m, 1H), 4.57-4.49 (m, 1H), 4.43-4.34 (m, 1H), 4.16-4.03 (m, 2H), 4.02-3.94 (m, 2H), 3.64-3.53 (m, 2H), 3.31-3.23 (m, 4H), 3.15-3.07 (m, 1H), 3.05-2.99 (m, 1H), 2.85-2.79 (m, 1H), 2.16-2.09 (m, 1H), 2.08-1.96 (m, 1H), 1.91-1.71 (m, 3H). MS (ESI, m/e) [M+H].sup.+ 643.3. Isomer 2: .sup.1H NMR (500 MHz, DMSO-d6) δ 8.09 (s, 2H), 7.22-7.21 (m, 1H), 7.16-7.12 (m, 1H), 5.37-5.17 (m, 1H), 4.80-4.70 (m, 1H), 4.50-4.37 (m, 2H), 4.14-4.07 (m, 2H), 4.01-3.94 (m, 3H), 3.61-3.52 (m, 2H), 3.29-3.19 (m, 2H), 3.12-3.05 (m, 2H), 3.04-3.00 (m, 1H), 2.88-2.78 (m, 1H), 2.16-1.95 (m, 2H), 1.89-1.70 (m, 3H). MS (ESI, m/e) [M+H].sup.+ 643.3.
Example 15: 2-amino-4-(11-chloro-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3,4-dihydro-1H,13H-4,13a-ethano[1,4]oxazino[3′,4′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-10-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile
##STR00305##
[0571] Example 15 was prepared by similar procedure as described in Example 14 by replacing (R)-morpholin-3-ylmethanol with (3-oxa-8-azabicyclo[3.2.1]octan-1-yl)methanol to give the title product (16 mg). .sup.1H NMR (500 MHz, DMSO-d6) δ 8.09 (s, 2H), 7.26-7.12 (m, 2H), 5.50-5.30

(m, 1H), 4.82-4.70 (m, 1H), 4.19-4.16 (m, 1H), 3.96-3.83 (m, 2H), 3.82-3.75 (m, 1H), 3.72-3.65 (m, 1H), 3.33-3.30 (m, 4H), 2.55-2.50 (m, 3H), 2.27-2.13 (m, 2H), 2.08-1.97 (m, 4H), 1.92-1.78 (m, 3H), 1.20-1.06 (m, 1H). MS (ESI, m/e) [M+H].sup.+ 669.4.

Example 16: 3-chloro-5-((S)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,9,10-hexahydro-4,8-dioxa-3,10a,11,13-tetraazabenzo[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-4-(trifluoromethyl)aniline

##STR00306##

[0572] Example 16 was prepared by similar procedure as described in Example 3 by replacing (R)-morpholin-3-ylmethanol with tert-butyl (S)-3-(2-hydroxyethyl)morpholine-4-carboxylate to give the title product (0.4 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 6.89-6.87 (m, 1H), 6.60-6.34 (m, 1H), 5.44-5.39 (m, 1H), 5.18-5.12 (m, 1H), 4.62-4.54 (m, 2H), 4.43-4.37 (m, 1H), 4.32-4.21 (m, 2H), 4.10-4.04 (m, 1H), 3.94-3.82 (m, 2H), 3.79-3.71 (m, 1H), 3.65-3.56 (m, 1H), 3.49-3.33 (m, 4H), 3.18-3.08 (m, 1H), 2.65-2.56 (m, 1H), 2.46-1.89 (m, 6H). MS (ESI, m/e) [M+H].sup.+ 627.4.

Example 17: 3-chloro-5-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline

##STR00307##

Step 1: methyl (R)-5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate

##STR00308##

[0573] To a solution of methyl (R)-5-oxopyrrolidine-2-carboxylate (24.6 g, 0.20 mol) in DCM (300 mL) was added Me.sub.3OBF.sub.4 (32.6 g, 0.44 mol) at room temperature. The resulting mixture was stirred at room temperature for 16 hrs. After completion, the reaction mixture was quenched with saturated NaHCO.sub.3 aqueous solution (200 mL), extracted with DCM (150 mL×3). The organic layer was dried over anhydrous Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to give the residue. The residue was purified by silica gel column chromatography, eluted with 0-10% MeOH in DCM to give the title product (16.0 g). MS (ESI, m/e) [M+H].sup.+ 158.1.

Step 2: methyl (R)-5-(2-ethoxy-1-nitro-2-oxoethylidene)pyrrolidine-2-carboxylate

##STR00309##

[0574] To methyl (R)-5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (8.5 g, 0.05 mol) was added ethyl 2-nitroacetate (21.6 g, 0.16 mmol) at room temperature. The resulting mixture was stirred at 60° C. for 16 hrs. The reaction mixture was concentrated to give the residue. The residue was purified by silica gel column chromatography, eluted with 0-100% ethyl acetate in petroleum ether to give the title product (6.0 g). MS (ESI, m/e) [M+H].sup.+ 259.2.

Step 3: ethyl (1S,2S,5R)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2-carboxylate

##STR00310##

[0575] To a mixture of methyl (R)-5-(2-ethoxy-1-nitro-2-oxoethylidene)pyrrolidine-2-carboxylate (6.0 g, 23.2 mmol) in ethanol (600 mL) was added wet palladium carbon (6 g) at room temperature. The resulting mixture was stirred at rt for 72 hours under (0.4 MPa) H.sub.2 atmosphere. After completion, the reaction mixture was filtered and the filtrate was concentrated to give the residue. The residue was purified by silica gel column chromatography, eluted with 0-10% MeOH in DCM to give the title product (2.3 g). MS (ESI, m/e) [M+H].sup.+ 199.1.

Step 4: 8-(tert-butyl) 2-ethyl (1S,2S,5R)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate

##STR00311##

[0576] To a solution of ethyl (1S,2S,5R)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2-carboxylate (2.3 g, 11.6 mmol) in DCM (50 mL) were added di-tert-butyl decarbonate (2.52 g, 11.6 mmol) and triethylamine (2.34 g, 23.2 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 hrs. After completion, the reaction mixture was concentrated to give the residue. The residue was purified by silica gel column chromatography, eluted with 0-100% EtOAc in petroleum ether to give the title product (2.8 g). MS (ESI, m/e) [M+H].sup.+ 299.2.

Step 5: tert-butyl (1S,2S,5R)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
##STR00312##
[0577] To a solution of 8-(tert-butyl) 2-ethyl (1S,2S,5R)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate (1.4 g, 7.1 mmol) in THF (30 mL) were added LiAlH.sub.4 (760 mg, 20 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 hrs. After completion, the reaction mixture was quenched with NaSO.sub.4.Math.10H.sub.2O, filtered and the filtrate was concentrated to give the crude product (900 mg). MS (ESI, m/e) [M+H].sup.+ 243.2.
Step 6: 3-chloro-5-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline
[0578] Example 17 was prepared by similar procedure as described in Example 10 by replacing tert-butyl (1S,5R)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate with tert-butyl (1S,2S,5R)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate to give the title product (2.8 mg). .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 6.90-6.85 (m, 1H), 6.55-6.25 (m, 3H), 5.41-5.20 (m, 1H), 4.98-4.78 (m, 1H), 4.60-4.35 (m, 2H), 4.20-3.98 (m, 3H), 3.85-3.70 (m, 2H), 3.24-3.00 (m, 4H), 2.90-2.80 (m, 1H), 2.22-1.98 (m, 3H), 1.97-1.55 (m, 7H). MS (ESI, m/e) [M+H].sup.+ 638.4.
Example 18: 2-amino-4-((S)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,12,12a-tetrahydro-1H-pyrrolo[2′,1′:3,4][1,4]oxazepino[5,6,7-de]quinazolin-9-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile
##STR00313##
Step 1: tert-butyl (S)-3-(2-((7-bromo-6-chloro-8-fluoro-4-hydroxy-2-(methylthio)quinazolin-5-yl)oxy)ethyl)morpholine-4-carboxylate
##STR00314##
[0579] To a solution of 7-bromo-6-chloro-5,8-difluoro-2-(methylthio)quinazolin-4-ol (500 mg, 1.47 mmol) in THF (10 mL), tert-butyl (S)-3-(2-hydroxyethyl)morpholine-4-carboxylate (509 mg, 2.20 mmol) and NaH (60%, 176 mg, 4.41 mmol) was added. The mixture was stirred at 50° C. for 3 hours. The mixture was allow to cooled to rt, and quenched by MeOH (5 mL). The mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (12 g, PE:EtOAc=100%:0%˜0%:100%) to give title compound (441 mg). MS (ESI, m/e) [M+H].sup.+ 552.2.
Step 2: (S)-7-bromo-6-chloro-8-fluoro-2-(methylthio)-5-(2-(morpholin-3-yl)ethoxy)quinazolin-4-ol
##STR00315##
[0580] A mixture of tert-butyl (S)-3-(2-((7-bromo-6-chloro-8-fluoro-4-hydroxy-2-(methylthio)quinazolin-5-yl)oxy)ethyl)morpholine-4-carboxylate (440 mg, 0.673 mmol) in HCl (4M)/dioxane (10 mL) was stirred at rt for 2 hours. Then the mixture was concentrated in vacuo to give crude product (493 mg, crude). MS (ESI, m/e) [M+H].sup.+ 452.2.
Step 3: (S)-10-bromo-11-chloro-9-fluoro-7-(methylthio)-1,3,4,13,14,14a-hexahydro-[1,4]oxazino[4′,3′:5,6][1,5]oxazocino[4,3,2-de]quinazoline
##STR00316##
[0581] To a solution of (S)-7-bromo-6-chloro-8-fluoro-2-(methylthio)-5-(2-(morpholin-3-yl)ethoxy)quinazolin-4-ol (490 mg, 1.08 mmol) in DMF (10 mL), HATU (1.23 g, 3.24 mmol) and DIEA (700 mg, 5.4 mmol) was added. Then the mixture was stirred at rt overnight. The mixture was extracted with EtOAc (20 mL*2), washed with brine (20 mL), dried over Na.sub.2SO.sub.4, and the combined organic phase was concentrated in vacuo. The residue was purified by silica gel column chromatography (12 g, eluting with PE/EtOAc=100%:0%˜0%:100%) to give the title compound (300 mg). MS (ESI, m/e) [M+H].sup.+ 434.1.
Step 4: (S)-10-bromo-11-chloro-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,4,13,14,14a-hexahydro-[1,4]oxazino[4′,3′:5,6][1,5]oxazocino[4,3,2-

de]quinazoline
##STR00317##
[0582] To a mixture of (S)-9-bromo-10-chloro-8-fluoro-6-(methylthio)-2,3,12,12a-tetrahydro-1H-pyrrolo[2′,1′:3,4][1,4]oxazepino[5,6,7-de]quinazoline (100 mg, 0.231 mmol) in DCM (10 mL) was added m-CPBA (45 mg, 0.266 mmol) in portions at 0° C. The mixture was stirred at 0° C. for 2 hrs. ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (110 mg, 0.693 mmol) was placed in THF (10 mL). LiHMDS (0.46 mL, 0.46 mmol) was added to the solution in portions at 0° C. The mixture was stirred at rt for 30 mins, and the mixture was added into DCM solution above. The mixture was stirred at rt overnight, quenched with MeOH (5 mL), and concentrated in vacuo. The residue was purified with chromatography column on silica (12 g, eluting with DCM/MeOH=90%:10%) to give the title compound (100 mg). MS (ESI, m/e) [M+H].sup.+ 545.3.
Step 5: tert-butyl (4-((S)-11-chloro-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,4,13,14,14a-hexahydro-[1,4]oxazino[4′,3′:5,6][1,5]oxazocino[4,3,2-de]quinazolin-10-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate
##STR00318##
[0583] A solution of K.sub.3PO.sub.4 (97 mg, 0.46 mmoL) in dioxane/water (10 mL/2 mL) was stirred at 80° C. for 10 mins. (S)-10-bromo-11-chloro-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,4,13,14,14a-hexahydro-[1,4]oxazino[4′,3′:5,6][1,5]oxazocino[4,3,2-de]quinazoline (100 mg, 0.184 mmol), tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)benzo[b]thiophen-2-yl)carbamate (153 mg, 0.367 mmol) and 1,1′-Bis (di-t-butylphosphino)ferrocene palladium dichloride (60 mg, 0.092 mmol) was added. The mixture was stirred at 80° C. for 1 hours, then cooling the reaction to room temperature, concentrated under vacuo, purified with chromatography column on silica (12 g, eluting with DCM/MeOH=90%:10%) to give the crude product (70 mg, crude). MS (ESI, m/e) [M+H].sup.+ 757.4.
Step 6: 2-amino-4-((S)-11-chloro-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,4,13,14,14a-hexahydro-[1,4]oxazino[4′,3′:5,6][1,5]oxazocino[4,3,2-de]quinazolin-10-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile
[0584] To a solution of tert-butyl (4-((S)-11-chloro-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,4,13,14,14a-hexahydro-[1,4]oxazino[4′,3′:5,6][1,5]oxazocino[4,3,2-de]quinazolin-10-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (70 mg, 0.092 mmol) in dioxane (5 mL) was added HCl (4M)/dioxane (5 mL). The mixture was stirred at rt overnight. Then, the mixture was concentrated in vacuo and purified by prep-HPLC to give the title compound (8.33 mg). .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 8.08 (s, 2H), 7.34-7.07 (m, 2H), 5.37-5.20 (m, 1H), 4.58-4.36 (m, 2H), 4.35-4.18 (m, 1H), 4.10-3.91 (m, 3H), 3.85-3.75 (m, 1H), 3.71-3.48 (m, 4H), 3.14-2.98 (m, 3H), 2.84-2.81 (m, 1H), 2.37-2.25 (m, 1H), 2.17-1.95 (m, 4H), 1.94-1.70 (m, 3H). MS (ESI, m/e) [M+H].sup.+ 657.4.
Example 19: 3-chloro-5-((S)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,9,10-tetrahydro-5H,8H-4,7-dioxa-3,10a,11,13-tetraazanaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline
##STR00319##
Step 1: tert-butyl (R)-3-(hydroxymethyl)-1,4-oxazepane-4-carboxylate
##STR00320##
[0585] To a stirred solution of (S)-4-(tert-butoxycarbonyl)-1,4-oxazepane-3-carboxylic acid (245 mg, 1 mmol) in THF (10 mL) was added BH.sub.3.Math.THF (3.5 mL, 3.5 mmol, 1 M in THF) dropwise at 0° C., the resulting mixture was stirred overnight at room temperature. The reaction was quenched with water at 0° C., then concentrated in vacuo. The crude was purified by flash chromatography (CH.sub.2Cl.sub.2/EA=1:1) to afford the desired product (217 mg).
Step 2: (R)-(1,4-oxazepan-3-yl)methanol
##STR00321##

[0586] To a stirred solution of tert-butyl tert-butyl (R)-3-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (217 mg, 0.9 mmol) in CH.sub.2Cl.sub.2 (5 mL) was added HCl (5 mL, 4 M in dioxane), the resulting mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and used in the next step without further purification.
[0587] Example 19 was prepared by similar procedure as described in Example 3 by replacing (R)-morpholin-3-ylmethanol with (R)-(1,4-oxazepan-3-yl)methanol to give the title product (3.5 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 6.90-6.86 (m, 1H), 6.55-6.41 (m, 1H), 5.41-5.24 (m, 1H), 5.23-5.15 (m, 1H), 4.76-4.65 (m, 1H), 4.63-4.47 (m, 4H), 4.39-4.24 (m, 3H), 4.22-4.12 (m, 1H), 4.04-3.91 (m, 1H), 3.82-3.70 (m, 1H), 3.59-3.49 (m, 1H), 3.48-3.36 (m, 3H), 3.14-3.03 (m, 1H), 2.43-2.10 (m, 4H), 2.09-1.87 (m, 4H). [M+H].sup.+ 627.3.
Example 20: 5-ethynyl-6-fluoro-4-((S)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,9,10-tetrahydro-5H,8H-4,7-dioxa-3,10a,11,13-tetraazanaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
##STR00322##
[0588] Example 20 was prepared by similar procedure as described in Example 3/4 by replacing (R)-morpholin-3-ylmethanol with (R)-(1,4-oxazepan-3-yl)methanol to give the title product (38 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 7.90-7.78 (m, 1H), 7.40-7.15 (m, 3H), 5.60-5.40 (m, 1H), 5.30-5.15 (m, 1H), 4.77-4.51 (m, 4H), 4.48-4.29 (m, 1H), 4.24-4.05 (m, 1H), 4.00-3.64 (m, 6H), 3.63-3.46 (m, 1H), 3.45-3.34 (m, 2H), 2.74-2.46 (m, 2H), 2.43-2.22 (m, 3H), 2.22-1.87 (m, 3H). MS (ESI, m/e) [M+H].sup.+ 618.5.
Example 21: 3-chloro-5-(1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,9,10-hexahydro-4,8-dioxa-3,10a,11,13-tetraazanaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline
##STR00323##
[0589] Example 21 was prepared by similar procedure as described in Example 19 by replacing tert-butyl (R)-3-(hydroxymethyl)-1,4-oxazepane-4-carboxylate with tert-butyl 5-(hydroxymethyl)-1,4-oxazepane-4-carboxylate to give the title product (6.3 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 6.90-6.86 (m, 1H), 6.59-6.40 (m, 1H), 5.44-5.15 (m, 2H), 4.73-4.64 (m, 1H), 4.63-4.47 (m, 1H), 4.40-4.21 (m, 3H), 4.05-3.82 (m, 3H), 3.66-3.54 (m, 1H), 3.54-3.42 (m, 2H), 3.42-3.32 (m, 3H), 3.16-3.05 (m, 1H), 2.46-1.87 (m, 8H). [M+H].sup.+ 627.3.
Example 22: 5-ethynyl-6-fluoro-4-(1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,9,10-hexahydro-4,8-dioxa-3,10a,11,13-tetraazanaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
##STR00324##
[0590] Example 22 was prepared by similar procedure as described in Example 20 by replacing tert-butyl (R)-3-(hydroxymethyl)-1,4-oxazepane-4-carboxylate with tert-butyl 5-(hydroxymethyl)-1,4-oxazepane-4-carboxylate to give the title product (18 mg). .sup.1H NMR (500 MHz, CD.sub.3OD) δ 7.88-7.78 (m, 1H), 7.41-7.12 (m, 3H), 5.49-5.15 (m, 2H), 4.73-4.63 (m, 1H), 4.63-4.50 (m, 1H), 4.47-4.24 (m, 3H), 4.05-3.86 (m, 3H), 3.73-3.36 (m, 7H), 3.22-3.09 (m, 1H), 2.54-1.88 (m, 8H). MS (ESI, m/e) [M+H].sup.+ 618.5.
Example 23: 3-((7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-5-chloro-4-(trifluoromethyl)aniline
##STR00325##
[0591] From a synthetic perspective, Example 23 is different from Example 17 with a 8-member ring. The synthesis of Example 23 with a 8-member ring requires key intermediate tert-butyl (1S,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate. The synthesis of Example 23 requires particular synthetic procedures, and sophisticated functional group transformations to avoid stereochemistry epimerization.
[0592] Intermediate 23-0 (tert-butyl (1S,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-

carboxylate) was prepared by the following synthetic routes (Scheme 4).
##STR00326## ##STR00327## ##STR00328##
[0593] As described in scheme 4, three different synthetic routes could be used to generate intermediate 23-0 (tert-butyl (1S,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate) from commercial available starting materials. In route 1, amine 23-1 undergoes protecting group manipulation and ester hydrolysis to generate carboxylic acid 23-3, which is further converted to diazoketone 23-5 via mixed anhydride 23-4, followed by Wolff rearrangement to generate ester 23-6. Ester reduction followed by deprotection yield the desired intermediate alcohol 23-0. Alternatively, in route 2, alcohol 23-11 is converted to mesylate 23-13 after amine protection, which is further transformed to corresponding cyanide 23-14 via S.sub.N2 reaction. Cyanide 23-14 is hydrolyzed into ester 23-15, which is further reduced to alcohol 23-16 and yield desired intermediate alcohol 23-0 after deprotection. Alternatively, in route 3, alcohol 23-21 is oxidized into corresponding aldehyde 23-22 via common methods known to the field, which undergo Wittig reaction to yield alkene 23-23. Alkene 23-23 undergoes hydroboration reaction to generate alcohol 23-24, which is further converted to the desired intermediate 23-0 after deprotection.
Step 1: 3-benzyl 8-(tert-butyl) 2-ethyl (1S,5R)-3,8-diazabicyclo[3.2.1]octane-2,3,8-tricarboxylate
##STR00329##
[0594] A mixture of 8-(tert-butyl) 2-ethyl (1S,5R)-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate (6.5 g, 22.89 mmol) and TEA (11.66 g, 114.44 mmol) and Cbz-Cl (7.8 g, 45.88 mmol) in DCM (65 mL) as stirred at 0° C. for 12 h under nitrogen. The reaction mixture was quenched by addition of water 5 mL, and then diluted with water (100 mL) and extracted with EA. The combined organic layers were washed with solvent brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (PE:EA=100:1 to 5:1) to give the title product (7.5 g, 78% yield) as a colorless oil. MS (ESI, m/e) [M+H+22].sup.+=441.
Step 2: (1S,5R)-3-((benzyloxy)carbonyl)-8-(tert-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octane-2-carboxylic acid
##STR00330##
[0595] Into a 25 mL sealed tube were added 3-benzyl 8-(tert-butyl) 2-ethyl (1S,5R)-3,8-diazabicyclo[3.2.1]octane-2,3,8-tricarboxylate (7 g, 16.74 mmol), EtOH (6 mL) and H.sub.2O (1.5 mL) and LiOH (1.93 g, 83.70 mmol). After stirring for 3 h at 50° C., the mixture was adjusted to PH=5 with 1M HCl, and then diluted with water (25 mL) and extracted with EtOAc. The combined organic layers were concentrated. The crude product (5.5 g) was used in the next step directly without further purification. (ESI, m/e) [M+H].sup.+=391.
Step 3: (1S,5R)-3-((benzyloxy)carbonyl)-8-(tert-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octane-2-carboxylic_(isobutyl carbonic) anhydride
##STR00331##
[0596] A mixture of (1S,5R)-3-((benzyloxy)carbonyl)-8-(tert-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octane-2-carboxylic acid (2 g, 5.13 mmol,) and DIPEA (3.3 g, 25.60 mmol) in THF (20 mL) was stirred at −50° C. for 10 min under nitrogen. and then add isobutyl carbonochloridate (3.50 g, 25.60 mmol), the reaction mixture stirred at −50° C. for 1 h, the resulting mixture was used in the next step directly without further purification.
Step 4: 3-benzyl 8-(tert-butyl) (1S,5R)-2-(2-diazoacetyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate
##STR00332##
[0597] Into the crude mixture of step 3 was added CH.sub.2N.sub.2(25.60 mmol in Et.sub.2O 250 mL) at 0° C. After stirring for 12 h at rt, the mixture was concentrated. The residue was purified by silica gel chromatography (PE:EA=100:1 to 5:1) to give the title product (1.2 g). MS (ESI, m/e) [M+Na].sup.+=437.

Step 5: 3-benzyl 8-(tert-butyl) (1S,5R)-2-(2-methoxy-2-oxoethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate

##STR00333##

[0598] To a solution of 3-benzyl 8-(tert-butyl) (1R,5S)-2-(2-diazoacetyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (1.2 g, 2.9 mmol) and TEA (178 mg, 1.77 mmol) in MeOH (15 mL) were added AgOAc (47 mg, 0.29 mmol) at 0° C. After stirring for 30 min at 60° C., the mixture was concentrated and purified by silica gel chromatography (PE:EA=100:0 to 50:50) to give the title product (800 mg). (ESI, m/e) [M+H].sup.+=419.

Step 6: 3-benzyl 8-(tert-butyl) (1S,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate

##STR00334##

[0599] To a solution of 3-benzyl 8-(tert-butyl) (1S,5R)-2-(2-methoxy-2-oxoethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (750 mg, 1.86 mmol) in THF (15 mL) were added LiBH.sub.4 (164.2 mg, 7.46 mmol) at 0° C. After stirring overnight at room temperature, the mixture was quenched by NH.sub.4Cl(aq) at 0° C. and extracted with EA. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (PE:EA=100:0 to 50:50) to give the title product (480 mg). (ESI, m/e) [M+H].sup.+=392.

Step 7: tert-butyl (1S,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

##STR00335##

[0600] To a solution of 3-benzyl 8-(tert-butyl) (1S,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (400 mg, 1.03 mmol) in MeOH (10 mL) were added Pd/C (400 mg, 10% w) at room temperature. After stirring for 3 h at room temperature under H.sub.2(g) atmosphere, the resulting mixture was filtered, the filter cake was washed with DCM/MeOH (3:1). The filtrate was concentrated to give the title product (187 mg) designated as Isomer 1 of intermediate 23-0: .sup.1H NMR (400 MHz, CDCl.sub.3) δ 4.27-3.94 (m, 2H), 3.89-3.74 (m, 2H), 3.46-3.14 (m, 1H), 2.99-2.72 (m, 1H), 2.46-2.41 (m, 1H), 2.10-2.08 (m, 1H), 2.07-1.87 (m, 2H), 1.86-1.62 (m, 3H), 1.47 (s, 9H). MS (ESI, m/e) [M+H].sup.+=257.15.

[0601] Intermediate 23-0 was also generated from route 3 in Scheme 4 and is designated as Isomer 2: .sup.1H NMR (500 MHz, CDCl.sub.3) δ 4.16-3.94 (m, 2H), 3.83-3.74 (m, 2H), 3.11-2.97 (m, 2H), 2.73-2.46 (m, 2H), 2.00-1.93 (m, 1H), 1.84-1.79 (m, 2H), 1.70-1.64 (m, 1H), 1.60-1.59 (m, 1H), 1.48 (s, 9H). MS (ESI, m/e) [M+H].sup.+ 257.3.

Step 8: tert-butyl (1S,5R)-2-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

##STR00336##

[0602] To a mixture of tert-butyl (1S,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (737 mg, 2.9 mmol, isomer 2 of intermediate 23-0) and 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol (803 mg, 2.9 mmol) in THF (75 mL) was added NaH (576 mg, 14.4 mmol, 60% w/w) at room temperature. The resulting mixture was stirred at room temperature for 16 hours. Saturated ammonium chloride aqueous solution (50 mL) was then added to the mixture, followed by addition of H.sub.2O (50 mL). The aqueous phase was extracted by EtOAc (50 mL×3 times). The organic phase was combined, dried over Na.sub.2SO.sub.4 and concentrated in vacuo, affording the title product as crude (1.8 g). MS (ESI, m/e) [M+H].sup.+ 500.3.

Step 9: tert-butyl (7S,10R)-2-chloro-1-fluoro-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate

##STR00337##

[0603] To a solution of tert-butyl (1S,5R)-2-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

(1.27 g, 2.5 mmol) in MeCN (70 mL) was added BOP—Cl (1.29 g, 5.1 mmol) and DIPEA (980 mg, 7.6 mmol). The resulting mixture was stirred at 70° C. for 1 hour. The mixture was then cooled to room temperature and concentrated in vacuo. The crude was purified by flash chromatography (DCM/EtOAc=5/1) to give the title product (630 mg). MS (ESI, m/e) [M+H].sup.+ 482.2.

Step 10: tert-butyl (7S,10R)-2-chloro-1-fluoro-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate

##STR00338##

[0604] To a solution of tert-butyl (7S,10R)-2-chloro-1-fluoro-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (392 mg, 0.8 mmol) in DCM (40 mL) was added mCPBA (140 mg, 0.8 mmol). The resulting mixture was stirred at room temperature for 1 hour. The mixture was then concentrated in vacuo. The crude was used directly in the next step without further purification. MS (ESI, m/e) [M+H].sup.+ 498.2.

Step 11: tert-butyl (7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-chloro-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate

##STR00339##

[0605] To a solution of (2-oxabicyclo[2.1.1]hexan-4-yl)methanol (137 mg, 1.2 mmol) in THF (15 mL) was added LiHMDS (1M in THF, 1.12 mL, 1.12 mmol). The resulting mixture was stirred at 0° C. for 30 minutes. Tert-butyl (7S,10R)-2-chloro-1-fluoro-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (crude, 0.4 mmol) was then added to the reaction mixture at 0° C., which was further stirred at room temperature for 1 hour. The mixture was concentrated in vacuo. The crude was purified by Prep-TLC (DCM/MeOH=10/1) to give the title product (78 mg). MS (ESI, m/e) [M+H].sup.+ 548.3.

Step 12: tert-butyl (7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate

##STR00340##

[0606] A mixture of tert-butyl (7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-chloro-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (78 mg, 0.14 mmol), 3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (114 mg, 0.36 mmol), Pd(dppf)Cl.sub.2 (52 mg, 0.07 mmol) and NaHCO.sub.3 (36 mg, 0.43 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was degassed by vacuum and refilling with nitrogen for 3 times. The mixture was stirred at 95° C. for 2 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude was purified by pre-TLC (DCM/MeOH/NH.sub.4OH=12/1/0.1) to give the title product (99 mg). MS (ESI, m/e) [M+H].sup.+ 707.4.

Step 13: 3-((7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-5-chloro-4-(trifluoromethyl)aniline

[0607] To a solution of tert-butyl (7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (99 mg, 0.14 mmol) in DCM (10 mL) was added TFA (5 mL). The resulting mixture was stirred at room temperature for 30 minutes. The mixture was then concentrated in vacuo. The crude was purified by prep-HPLC to give the title product (30 mg, formic acid salt). MS (ESI, m/e) [M+H].sup.+ 607.6. .sup.1H NMR (500 MHz, CD.sub.3OD) δ 8.49 (s, 1H), 6.89 (s, 1H), 6.54-6.51

(m, 1H), 4.86-4.78 (m, 2H), 4.58 (s, 1H), 4.40-4.23 (m, 3H), 4.19-4.06 (m, 1H), 4.04-3.98 (m, 1H), 3.95-3.81 (m, 2H), 3.74 (s, 2H), 2.47-1.75 (m, 8H), 1.64-1.60 (m, 2H).
Example 24: 3-chloro-5-((7S,10R)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-4-(trifluoromethyl)aniline
##STR00341##
[0608] Example 24 was prepared by similar procedure as described in Example 23 by replacing (2-oxabicyclo[2.1.1]hexan-4-yl)methanol with ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol. Tert-butyl (1S,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (isomer 2 of intermediate 23-0) was used.
[0609] MS (ESI, m/e) [M+H].sup.+: 652.4
[0610] .sup.1H NMR (500 MHz, CD.sub.3OD) δ 6.91 (s, 1H), 6.52 (s, 1H), 5.59-5.48 (m, 1H), 4.63 (s, 2H), 4.46-4.29 (m, 2H), 4.27-4.01 (m, 3H), 3.92-3.75 (m, 4H), 3.44-3.38 (m, 1H), 3.31 (s, 1H), 2.68-2.53 (m, 2H), 2.51-2.21 (m, 5H), 2.20-1.93 (m, 5H).
Example 25: 3-chloro-5-((7S,10R)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-4-(trifluoromethyl)aniline
##STR00342##
[0611] Example 25 was prepared by similar procedure as described in Example 23 by replacing (2-oxabicyclo[2.1.1]hexan-4-yl)methanol with ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol. Tert-butyl (1S,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (isomer 1 of intermediate 23-0) was used.
[0612] MS (ESI, m/e) [M+H].sup.+: 652.7
[0613] .sup.1H NMR (500 MHz, CD.sub.3OD) δ 6.90 (s, 1H), 6.60-6.38 (m, 1H), 5.62-5.52 (m, 1H), 5.42-5.39 (m, 1H), 4.69-4.59 (m, 4H), 4.32-4.28 (m, 1H), 4.14-4.00 (m, 3H), 3.95-3.82 (m, 2H), 3.50-3.43 (m, 2H), 2.76-2.54 (m, 2H), 2.50-2.45 (m, 1H), 2.41-2.25 (m, 4H), 2.20-2.00 (m, 3H), 1.85-1.72 (m, 2H).
Intermediate 26-0: tert-butyl (1S,2R,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
##STR00343##
Synthetic Route
##STR00344##
Step 1: tert-butyl (1S,2S,5R)-3-benzyl-2-formyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
##STR00345##
[0614] To a 250-mL round-bottom flask was added tert-butyl (1S,2S,5R)-3-benzyl-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.55 g, 4.65 mmol), DMP (2.37 g, 5.58 mmol), and DCM (50 mL). The reaction mixture was stirred at rt for 2 h, which was then concentrated in vacuo. The crude was purified by column chromatography (PE/EA=0-12%), affording the title product (1.02 g, 68% yield) as a colorless oil.
Step 2: tert-butyl (1S,2R,5R)-3-benzyl-2-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
##STR00346##
[0615] To a 50-mL round-bottom flask was added PPh.sub.3MeBr (748 mg, 2.11 mmol), THF (6 mL), and KHMDS (1 M, 1.76 mL, 1.76 mmol). The reaction mixture was stirred at rt for 30 min, followed by addition of tert-butyl (1S,2S,5R)-3-benzyl-2-formyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (580 mg, 1.76 mmol) in THF (6 mL) dropwise at rt. The resulting mixture was stirred at rt for 2 h. The reaction was then quenched by addition of sat. NH.sub.4Cl (50 mL). The mixture was extracted by EtOAc (20 mL) for 3 times. The organic phase was combined, dried with Na.sub.2SO.sub.4, and filtered through Celite. The mixture was concentrated in vacuo. The resulting crude was purified by column chromatography (PE/EA=0-12%), affording the title compound (400 mg, 69% yield) as a white solid.

Step 3: tert-butyl (1S,2R,5R)-3-benzyl-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
##STR00347##
[0616] To a 100-mL round-bottom flask was added tert-butyl (1S,2R,5R)-3-benzyl-2-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1 g, 0.0030 mol), 9-BBN (0.5 M, 36.5 mL, 0.018 mol), and THF (10 mL). The reaction mixture was stirred at 50° C. for 2 h under N.sub.2 atmosphere. After the reaction is complete as indicated by LCMS, aq. NaOH (3 M, 7 ml) and H.sub.2O.sub.2(7 mL) was added dropwise at 0° C. The resulting mixture was stirred at rt for 2 h. The mixture was diluted with H.sub.2O (50 mL) and extracted by EtOAc (30 mL) for 3 times. The organic phase was combined, dried over Na.sub.2SO.sub.4, and concentrated in vacuo. The crude was purified by column chromatography (PE/EA=0-23%), affording the title compound (900 mg, 85% yield) as a colorless oil.
Step 4: tert-butyl (1S,2R,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
##STR00348##
[0617] To a 100-mL round bottom flask was added tert-butyl (1S,2R,5R)-3-benzyl-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.7 g, 4.91 mmol), Pd/C (10 wt %, 1.7 g), and MeOH (15 mL). The reaction was stirred at rt for 3 h under H.sub.2 atmosphere. The reaction mixture was then filtered through Celite, and concentrated in vacuo, affording the title compound (1.1 g, 91% yield) as a colorless oil. MS (ESI, m/e) [M+H].sup.+=257.10. .sup.1H NMR (300 MHz, DMSO-d6) δ 4.45 (d, J=4.8 Hz, 1H), 4.06-3.80 (m, 1H), 3.73 (d, J=6.6 Hz, 1H), 3.42 (q, J=11.1, 8.8 Hz, 2H), 3.06-2.63 (m, 2H), 2.09 (t, J=33.2 Hz, 1H), 1.87-1.48 (m, 4H), 1.39 (s, 9H).
Example 26: 3-((6aR,7S,10R)-13-((3-(difluoromethyl)oxetan-3-yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
##STR00349##
Synthetic Route
##STR00350##
Step 1: tert-butyl (1S,2R,5R)-2-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
##STR00351##
[0618] To a mixture of tert-butyl (1S,2R,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.53 g, 6 mmol) and 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol (1.68 g, 6 mmol) in THF (150 mL) was added NaH (1.2 g, 30 mmol). The mixture was stirred at room temperature for 20 hours. The reaction was then quenched by addition of saturated ammonium chloride aqueous solution (50 mL) and water (50 mL). The resulting mixture was extracted by EtOAc (50 mL) for 3 times. The organic phase was combined, dried over Na.sub.2SO.sub.4, and concentrated in vacuo to give the crude title product (4 g). MS (ESI, m/e) [M+H].sup.+ 499.8.
Step 2: tert-butyl (6aR,7S,10R)-2-chloro-1-fluoro-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate
##STR00352##
[0619] To a solution of tert-butyl (1S,2R,5R)-2-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4 g, 8 mmol) in MeCN (220 mL) was added BOP—Cl (4.1 g, 5.1 mmol) and DIPEA (980 mg, 7.6 mmol). The resulting mixture was stirred at 70° C. for 1 hour. The mixture was cooled to room temperature and concentrated in vacuo. The crude was purified by column chromatography (DCM/EtOAc=5/1) to give the title product (1.6 g). MS (ESI, m/e) [M+H].sup.+ 481.9.
Step 3: tert-butyl (6aR,7S,10R)-2-chloro-1-fluoro-13-(methylsulfonyl)-5,6,6a,7,8,9,10,11-

octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate
##STR00353##
[0620] A solution of tert-butyl (6aR,7S,10R)-2-chloro-1-fluoro-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (378 mg, 0.8 mmol) in THF (28 mL) and water (7 mL) was added NaIO.sub.4 (505 mg, 2.4 mmol) and RuCl.sub.3 (16 mg, 0.08 mmol). The resulting mixture was stirred at 0° C. for 1 hour. The mixture was diluted by addition of water (20 mL), extracted by EtOAc (20 mL) for 3 times. The organic phase was combined and concentrated in vacuo to give the crude title compound (335 mg), which was used as is in next step. MS (ESI, m/e) [M+H].sup.+ 514.2.
Step 4: tert-butyl (6aR,7S,10R)-2-chloro-13-((3-(difluoromethyl)oxetan-3-yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate
##STR00354##
[0621] To a solution of (3-(difluoromethyl)oxetan-3-yl)methanol (27.6 mg, 0.2 mmol) in THF (5 mL) was added LiHMDS (1M in THF, 0.2 mL, 0.2 mmol), the resulting solution was stirred for 0.5 hours at room temperature. Then tert-butyl (6aR,7S,10R)-2-chloro-1-fluoro-13-(methylsulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (100 mg, 0.2 mmol) was added to the reaction mixture, which was stirred for additional 1 h at room temperature. After the reaction was complete as indicated by LCMS, the reaction mixture was concentrated and purified by column chromatography (DCM/MeOH=10/1) to give the title product (85.7 mg, 0.15 mmol). MS (ESI, m/e) [M+H].sup.+ 572.2.
Step 5: tert-butyl (6aR,7S,10R)-2-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-13-((3-(difluoromethyl)oxetan-3-yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oexamplexa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate
##STR00355##
[0622] A mixture of tert-butyl (6aR,7S,10R)-2-chloro-13-((3-(difluoromethyl)oxetan-3-yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (85.7 mg, 0.15 mmol), 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (135.5 mg, 0.45 mmol), Pd(dtbpf)Cl.sub.2 (19.5 mg, 0.03 mmol) and K.sub.3PO.sub.4 (127.1 mg, 0.60 mmol) in 1,4-dioxane (15 mL) and water (3 mL) was degassed by bubbling nitrogen through for 5 min, and then stirred at 95° C. for 4 hours. The resulting mixture was cooled to room temperature, concentrated in vacuo, and purified by prep-TLC (DCM/MeOH=15/1) to give the title product (71.0 mg, 0.10 mmol). MS (ESI, m/e) [M+H].sup.+ 711.3.
Step 6: 3-((6aR,7S,10R)-13-((3-(difluoromethyl)oxetan-3-yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
##STR00356##
[0623] To a solution of tert-butyl (6aR,7S,10R)-2-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-13-((3-(difluoromethyl)oxetan-3-yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (71.0 mg, 0.10 mmol) in DCM (14 mL) was added TFA (7 mL). The reaction mixture was stirred at room temperature for 1 hour and concentrated in vacuo. The crude was purified by prep-HPLC to give the title product (22 mg). MS (ESI, m/e) [M+H].sup.+ 611.3. .sup.1H NMR (500 MHz, DMSO) δ 6.61 (s, 1H), 6.52-6.30 (m, 2H), 5.87 (s, 2H), 4.73-4.58 (m, 6H), 4.30-3.94 (m, 5H), 3.55-3.32 (m, 2H), 2.36 (s, 3H), 2.13-1.57 (m, 6H).

[0624] Examples 27-68: The following compounds were prepared in similar manners as described in Example 26:

TABLE-US-00002 MS (ESI, m/e) Example Structure Compound Name [M + H].sup.+ .sup.1H NMR 27 [00357]  embedded image 3-((6aR,7S,10R)-13-((2- oxabicyclo[2.1.1]hexan-4-yl)methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10-methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 5-methyl-4- (trifluoromethyl)aniline 587.4 (500 MHz, MeOD) δ 6.70 (s, 1H), 6.45 (s, 1H), 4.80 (q, J = 11.7 Hz, 2H), 4.58 (s, 1H), 4.53-4.21(m, 3H), 4.21-3.81 (m, 4H), 3.74 (s, 2H), 2.43 (d, J = 1.8 Hz, 3H), 2.38-2.09 (m, 3H), 2.09-1.81 (m, 5H), 1.62 (dd, J = 4.8, 1.5 Hz, 2H). 28 [00358]embedded image 3-((6aR,7S,10R)-1-fluoro-13- ((1-methyl-2- oxabicyclo[2.1.1]hexan-4- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)-5-methyl-4- (trifluoromethyl)aniline 601.4 (500 MHz, MeOD) δ 6.69 (s, 1H), 6.43 (s, 1H), 4.74 (dd, J = 28.0, 11.7 Hz, 3H), 4.58 (s, 1H), 4.36 (s, 1H), 4.28 (s, 1H), 4.19-3.94 (m, 2H), 3.80 (s, 3H), 2.43 (s, 3H), 2.32-1.96 (m, 3H), 1.96-1.85 (m, 2H), 1.82 (d, J = 6.0 Hz, 3H), 1.62 (d, J = 4.7 Hz, 2H), 1.44 (s, 3H). 29 [00359]embedded image 3-((6aR,7S,10R)-13-((1- (difluoromethyl)-2-oxabicyclo[2.1.1]hexan-4- yl)methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 5-methyl-4- (trifluoromethyl)aniline 637.5 (500 MHz, MeOD) δ 6.69 (s, 1H), 6.44 (d, J = 27.4 Hz, 1H), 6.03 (t, J = 55.1 Hz, 1H), 4.78 (dd, J = 29.8, 11.7 Hz, 2H), 4.32 (d, J = 47.9 Hz, 3H), 4.19-3.92 (m, 2H), 3.88 (s, 2H), 3.80- 3.69 (m, 1H), 3.68- 3.53 (m, 1H), 2.42 (s, 3H), 2.18-2.02 (m, 4H), 2.02-1.78 (m, 4H), 1.78-1.73 (m, 2H). 30 [00360]embedded image 3-((6aR,7S,10R)-1-fluoro-13-((5-fluoro-3- oxabicyclo[3.1.1]heptan-1- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 5-methyl-4- (trifluoromethyl)aniline 619.5 (500 MHz, MeOD) δ 6.70 (s, 1H), 6.46 (s, 1H), 4.44 (dd, J = 25.3, 11.2 Hz, 2H), 4.39- 4.33 (m, 1H), 4.32- 4.24 (m, 1H), 4.21- 4.00 (m, 2H), 4.00- 3.81 (m, 4H), 3.80- 3.51 (m, 3H), 2.43 (d, J = 1.9 Hz, 3H), 2.33- 2.26 (m, 2H), 2.20- 2.06 (m, 5H), 2.00-1.74 (m, 3H). 31 [00361]embedded image 5-((6aR,7S,10R)-13-((3- (difluoromethyl)oxetan-3-yl)methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10-methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 2-fluoro-3-methyl-4-(trifluoromethyl)aniline 637.5 (500 MHz, MeOD) δ 6.63 (d, J = 25.5 Hz, 1H), 6.27 (t, J = 56.0 Hz, 1H), 4.79-4.75 (m, 5H), 4.67 (d, J = 6.7 Hz, 2H), 4.52-4.20 (m, 3H), 4.15-4.08 (m, 1H), 3.76-3.66 (m, 1H), 3.66-3.51 (m, 1H), 2.39 (s, 3H), 2.19-1.69 (m, 6H). 32 [00362]embedded image 3-chloro-5-((6aR,7S,10R)-13- ((3-(difluoromethyl)oxetan-3- yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo-octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 631.3 (500 MHz, MeOD) δ 6.89 (s, 1H), 6.52 (d, J = 26.8 Hz, 1H), 6.27 (t, J = 56.0 Hz, 1H), 4.85- 4.73 (m, 4H), 4.67 (d, J = 6.7 Hz, 2H), 4.34 (m, 3H), 4.11 (s, 2H), 3.87 (s, 1H), 3.78 (s, 1H), 2.35-1.71 (m, 6H). 33 [00363]embedded image ethyl 3-((((6aR,7S,10R)-2-(5- amino-3-chloro-2- (trifluoromethyl)phenyl)-1-fluoro-5,6,6a,7,8,9,10,11- octahydro-4-oxa- 3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-13- yl)oxy)methyl)-3- methylazetidine-1-carboxylate 666.5 (500 MHz, MeOD) δ 6.89 (d, J = 2.0 Hz, 1H), 6.52 (d, J = 32.6 Hz, 1H), 4.60-4.24 (m, 6H), 4.10 (q, J = 7.1 Hz, 3H), 4.05-3.80 (m, 3H), 3.76-3.67 (m, 3H), 2.14-1.79 (m, 6H), 1.43 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). 34 [00364]embedded image 3-chloro-5-((6aR,7S,10R)-1-fluoro-13-((1-methyl-2- oxabicyclo[2.1.1]hexan-4- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)-4-(trifluoromethyl)aniline 621.4 (500 MHz, MeOD) δ 6.89 (d, J = 1.7 Hz, 1H), 6.52 (d, J = 37.0 Hz, 1H), 4.73 (dd, J = 31.7, 11.6 Hz, 2H), 4.53- 3.92 (m, 5H), 3.79 (s, 2H), 3.75-3.67 (m, 1H), 3.65-3.53 (m, 1H), 2.20-1.72 (m, 8H), 1.63 (t, J = 6.7 Hz, 2H), 1.43 (s, 3H). 35 [00365]embedded image 3-chloro-5-((6aR,7S,10R)-13- ((1-(difluoromethyl)-2- oxabicyclo[2.1.1]hexan-4- yl)methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10-

methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 657.4 (500 MHz, MeOD) δ 6.89 (s, 1H), 6.52 (d, J = 37.2 Hz, 1H), 6.03 (t, J = 55.1 Hz, 1H), 4.78 (dd, J = 30.9, 11.8 Hz, 2H), 4.53-4.35 (m, 2H), 4.34-4.19 (m, 2H), 4.13-4.07 (m, 1H), 3.87 (s, 2H), 3.78-3.67 (m, 1H), 3.64- 3.55 (m, 1H), 2.13- 1.74 (m, 10H). 36 [00366]embedded image 3-chloro-5-((6aR,7S,10R)-1- fluoro-13-((1-methyl-2- oxabicyclo[2.2.1]heptan-4- yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo-octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 635.4 (500 MHz, MeOD) δ 6.89 (d, J = 1.5 Hz, 1H), 6.52 (d, J = 36.7 Hz, 1H), 4.68-4.55 (m, 2H), 4.47-4.18 (m, 3H), 4.16-3.81 (m, 3H), 3.78-3.72 (m, 1H), 3.72-3.65 (m, 1H), 3.64-3.51 (m, 1H), 2.15-1.70 (m, 10H), 1.69-1.61 (m, 2H), 1.40 (s, 3H). 37 [00367]embedded image 3-chloro-5-((6aR,7S,10R)-1- fluoro-13-((5-fluoro-3-oxabicyclo[3.1.1]heptan-1- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15-pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 639.4 (500 MHz, MeOD) δ 6.89 (s, 1H), 6.52 (d, J = 37.4 Hz, 1H), 4.49-4.35 (m, 3H), 4.33- 4.01 (m, 3H), 3.96- 3.80 (m, 3H), 3.80- 3.73 (m, 2H), 3.73- 3.65 (m, 1H), 3.64-3.50 (m, 1H), 2.35- 2.25 (m, 2H), 2.16- 1.73 (m, 8H). 38 [00368]embedded image 3-((6aR,7S,10R)-13-((2- oxabicyclo[2.1.1]hexan-4- yl)methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 5-chloro-4-cyclopropylphenol 580.3 (500 MHz, MeOD) δ 6.95 (d, J = 2.5 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 4.80-4.76 (m, 3H), 4.46-4.34 (m, 4H), 3.96 (d, J = 53.5 Hz, 3H), 3.74 (s, 2H), 2.21 (d, J = 50.0 Hz, 2H), 1.99-1.94 (m, 5H), 1.91-1.80 (m, 1H), 1.66-1.55 (m, 2H), 0.66 (d, J = 4.5 Hz, 2H), 0.10 (d, J = 5.6 Hz, 2H). 39 [00369]embedded image 3-chloro-5-((6aR,7S,10R)-1- fluoro-13-((1- (methoxymethyl)-2- oxabicyclo[2.1.1]hexan-4- yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo-octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 651.4 (500 MHz, MeOD) δ 6.89 (d, J = 2.0 Hz, 1H), 6.52 (d, J = 14.5 Hz, 1H), 4.77 (q, J = 11.7 Hz, 3H), 4.33 (s, 2H), 4.00 (s, 1H), 3.81 (s, 2H), 3.64 (s, 2H), 3.39 (s, 3H), 2.43-1.86 (m, 8H), 1.72- 1.63 (m, 2H), 1.30 (s, 3H). 40 [00370]embedded image 3-((6aR,7S,10R)-13-((2- oxabicyclo[2.2.2]octan-4- yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo-octa[1,2,3-de]naphthalen-2-yl)- 5-chloro-4- (trifluoromethyl)aniline 635.4 NMR (500 MHz, MeOD) δ 6.90 (d, J = 1.9 Hz, 1H), 6.52 (s, 1H), 4.42-4.09 (m, 7H), 3.84 (d, J = 28.8 Hz, 4H), 2.45-1.92 (m, 7H), 1.88- 1.57 (m, 7H). 41 [00371]embedded image 3-((6aR,7S,10R)-13-((2-oxabicyclo[2.2.1]heptan-4- yl)methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 5-chloro-4- (trifluoromethyl)aniline 621.3 NMR (500 MHz, MeOD) δ 6.89 (d, J = 2.0 Hz, 1H), 6.52 (d, J = 21.1 Hz, 1H), 4.69 (dd, J = 24.4, 11.3 Hz, 2H), 4.47-3.76 (m, 9H), 3.68 (d, J = 6.6 Hz, 1H), 2.30-1.75 (m, 10H), 1.72 (d, J = 9.5 Hz, 1H), 1.62 (d, J = 9.6 Hz, 1H). 42 [00372]embedded image 4-((6aR,7R,10S)-13-((2- oxabicyclo[2.1.1]hexan-4- yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo-octa[1,2,3-de]naphthalen-2-yl)- 6-methyl-5- (trifluoromethyl)pyridin-2- amine 588.4 .sup.1H NMR (500 MHz, DMSO) δ 6.82 (s, 2 H), 6.26 (s, 1 H), 4.71-4.50 (m, 3 H), 4.30-3.92 (m, 5 H), 3.60-3.32 (m, 4 H), 2.07-1.99 (m, 1 H), 1.83-1.47(m, 9 H). 43 [00373]embedded image methyl 3-((((6aR,7S,10R)-2- (5-amino-3-methyl-2- (trifluoromethyl)phenyl)-1- fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa- 3,11a,12,14,15-pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-13- yl)oxy)methyl)-3- methylazetidine-1-carboxylate 632.4 NMR (500 MHz, MeOD) δ 6.69 (s, 1H), 6.46 (s, 1H), 4.48 (dd, J = 25.7, 10.9 Hz, 2H), 4.40-3.64 (m, 14H), 2.42 (d, J = 1.9 Hz, 3H), 2.00 (d, J = 113.1 Hz, 6H), 1.43 (s, 3H). 44 [00374]embedded image (S)-3-(((6aR,7S,10R)-2-(5- amino-3-chloro-2- (trifluoromethyl)phenyl)-1- fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa- 3,11a,12,14,15-pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-13- yl)oxy)-1,1,1-trifluoro-2- methylpropan-2-ol 637.38 NMR (500 MHz, MeOD) δ 6.89 (d, J = 2.0 Hz, 1H), 6.52 (d, J = 24.9 Hz, 1H), 4.68-4.49 (m, 2H), 4.43-4.00 (m, 4H), 3.79 (d, J

= 47.2 Hz, 2H), 2.26-2.05 (m, 2H), 1.92 (s, 3H), 1.50 (s, 3H), 1.40-1.22 (m, 2H). 45 [00375] embedded image 3-((6aR,7S,10R)-13-((3- oxabicyclo[3.2.1]octan-1- yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo-octa[1,2,3-de]naphthalen-2-yl)- 5-chloro-4- (trifluoromethyl)aniline 635.2 NMR (500 MHz, MeOD) δ 6.88 (s, 1H), 6.51 (d, J = 35.6 Hz, 1H), 4.36-4.27 (m, 6H), 4.08 (s, 2H), 3.78-3.67 (m, 2H), 3.66-3.55 (m, 4H), 2.06 (d, J = 25.6 Hz, 2H), 2.01-1.68 (m, 9H), 1.66- 1.55 (m, 1H). 46 [00376] embedded image 5-((((6aR,7S,10R)-2-(5-amino- 3-chloro-2- (trifluoromethyl)phenyl)-1-fluoro-5,6,6a,7,8,9,10,11- octahydro-4-oxa- 3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-13- yl)oxy)methyl)-4-methyl-2- oxa-4-azabicyclo[3.1.1]heptan- 3-one 650.4 NMR (500 MHz, MeOD) 8 6.89 (d, J = 2.1 Hz, 1H), 6.51 (d, J = 36.8 Hz, 1H), 4.99 (t, J = 3.3 Hz, 2H), 4.81-4.68 (m, 2H), 4.47-4.20 (m, 3H), 4.02 (d, J = 85.8 Hz, 2H), 3.72 (s, 1H), 3.61 (d, J = 24.9 Hz, 1H), 3.20- 3.07 (m, 3H), 2.50 (s, 2H), 2.19-1.72 (m, 9H). 47 [00377] embedded image 5-((((6aR,7S,10R)-2-(5-amino- 3-chloro-2-(trifluoromethyl)phenyl)-1- fluoro-5,6,6a,7,8,9,10,11- octahydro-4-oxa- 3,11a,12,14,15-pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-13- yl)oxy)methyl)-1,4-dimethyl- 2-oxa-4- azabicyclo[3.1.1]heptan-3-one 664.4 NMR (500 MHz, MeOD) δ 6.89 (d, J = 2.0 Hz, 1H), 6.51 (d, J = 37.1 Hz, 1H), 4.78 (m, 2H), 4.50-4.20 (m, 3H), 4.11 (s, 2H), 3.71 (s, 1H), 3.60 (d, J = 24.6 Hz, 1H), 3.11 (s, 3H), 2.41-2.26 (m, 2H), 2.18-1.74 (m, 8H), 1.51 (s, 3H). 48 [00378] embedded image 3-chloro-5-((6aR,7S,10R)-1- fluoro-13-((5-methyl-3- oxabicyclo[3.1.1]heptan-1- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10-methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 635.4 NMR (500 MHz, MeOD) δ 6.90 (d, J = 2.0 Hz, 1H), 6.53 (s, 1H), 4.32 (m, 7H), 3.89 (s, 2H), 3.69 (s, 3H), 2.11 (s, 5H), 1.76 (m, 4H), 1.01 (s, 3H). 49 [00379] embedded image 3-((6aR,7S,10R)-1-fluoro-13- ((1-(fluoromethyl)-2- oxabicyclo[2.1.1]hexan-4- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 5-methyl-4- (trifluoromethyl)aniline 619.4 NMR (500 MHz, MeOD) δ 6.69 (s, 1H), 6.44 (d, J = 26.7 Hz, 1H), 4.73 (d, J = 11.7 Hz, 2H), 4.65 (s, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.18-4.09 (m, 4H), 3.85 (s, 2H), 3.71 (s, 1H), 3.61 (s, 1H), 2.42 (d, J = 1.9 Hz, 3H), 2.17-1.66 (m, 10H). 50 [00380] embedded image 3-chloro-5-((6aR,7S,10R)-1- fluoro-13-((1-(fluoromethyl)- 2-oxabicyclo[2.1.1]hexan-4- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15-pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 639.4 .sup.1H NMR (500 MHz, DMSO) δ 6.87 (s, 1H), 6.54-6.51 (m, 1 H), 6.35 (s, 2 H), 4.73-4.58 (m, 4 H), 4.30-3.92 (m, 7 H), 3.72-3.71 (m, 2 H), 2.17- 1.72 (m, 8 H), 1.63- 1.61(m, 2 H). 51 [00381] embedded image 3-((6aR,7S,10R)-1-fluoro-13- ((1-methyl-2-oxabicyclo[2.2.1]heptan-4- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15-pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 5-methyl-4-(trifluoromethyl)aniline 615.5 .sup.1H NMR (500 MHz, MeOD) δ 6.68 (s, 1H), 6.46-6.41 (m, 1 H), 4.63- 4.58 (m, 2 H), 4.36- 3.98 (m, 4 H), 3.85-3.57 (m, 4 H), 2.42 (s, 3 H), 2.09-1.64 (m, 12 H), 1.40 (s, 3 H). 52 [00382] embedded image 4-((6aR,7S,10R)-13-((1- (difluoromethyl)-2-oxabicyclo[2.1.1]hexan-4- yl)methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 5-ethynyl-6-fluoronaphthalen- 2-ol 648.4 .sup.1H NMR (500 MHz, MeOD) 7.87-7.83 (m, 1 H), 7.34-7.19 (m, 3 H), 6.14-5.92 (m, 1 H), 4.59- 4.58 (m, 2 H), 4.36- 3.58 (m, 8 H), 2.29-1.76 (m, 10 H). 53 [00383] embedded image 3-chloro-5-((6aR,7S,10R)-1- fluoro-13-((1- (trifluoromethyl)-2-oxabicyclo[2.1.1]hexan-4- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15-pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 675.4 .sup.1H NMR (500 MHz, DMSO) δ 6.86 (s, 1H), 6.54-6.45 (m, 1H), 6.30 (s, 2 H), 4.75-4.66 (m, 2 H), 4.30-3.87 (m, 7 H), 3.55-3.45 (m, 2 H), 2.17- 1.99 (m,3 H),1.82-1.27(m, 7 H). 54 [00384] embedded image 3-((6aR,7S,10R)-13-((3- (difluoromethyl)oxetan-3-yl)methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10-

methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 2-fluoro-5-methyl-4-(trifluoromethyl)aniline 629.5 .sup.1H NMR (500 MHz, MeOD) δ 6.67-6.85 (m, 1H), 6.38-6.16 (m, 1 H), 4.85-4.67 (m, 6 H), 4.40- 4.11 (m, 4 H), 3.70-3.56 (m, 2 H), 2.40 (s, 3 H), 2.13-1.81 (m, 6 H). 55 [00385]embedded image 3-((6aR,7S,10R)-13-((7- oxabicyclo[2.2.1]heptan-1-yl)methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10-methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 5-chloro-4- (trifluoromethyl)aniline 621.45 .sup.1H NMR (500 MHz, MeOD) δ 6.88 (s, 1H), 6.50 (d, J = 61.1 Hz, 1H), 4.82-4.65 (m, 3H), 4.62- 4.52 (m, 1H), 4.46- 4.06 (m, 4H), 3.75-3.65 (m, 1H), 3.62-3.51 (m, 1H), 2.16-1.94 (m, 3H), 1.91-1.75 (m, 7H), 1.73- 1.62 (m, 4H). 56 [00386]embedded image 3-((6aR,7S,10R)-13-((1- (difluoromethyl)-2- oxabicyclo[2.2.1]heptan-4- yl)methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 5-methyl-4- (trifluoromethyl)aniline 651.4 .sup.1H NMR (500 MHz, MeOD) δ 6.68 (s, 1 H), 6.40-6.39 (m, 1H), 6.14- 5.92(m, 1 H), 4.69- 4.60 (m, 2 H), 4.36-4.08 (m, 4 H), 3.93-3.54 (m, 4 H), 2.42 (s, 3 H), 2.08- 1.78 (m, 12 H). 57 [00387]embedded image 3-chloro-5-((6aR,7S,10R)-13- ((3,3-difluoro-1- methylcyclobutyl)methoxy)-1- fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa- 3,11a,12,14,15-pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 629.4 .sup.1H NMR (500 MHz, MeOD) 6.89-6.88 (m, 1 H), 6.55-6.48 (m, 1 H), 4.44-4.09 (m, 6 H), 3.65- 3.54 (m, 2 H), 2.79-2.69 (m, 2 H), 2.39-2.31 (m, 2 H), 2.10-1.80 (m, 6 H), 1.39 (s, 3 H). 58 [00388]embedded image 3-chloro-5-((6aR,7S,10R)-13- ((1- (difluoromethyl)cyclobutyl) methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 629.4 .sup.1H NMR (500 MHz, MeOD) 6.89-6.88 (m, 1 H), 6.55-6.48 (m, 1 H), 6.14-5.91 (m, 1 H), 4.55- 4.09 (m, 6 H), 3.69- 3.54 (m, 2 H), 2.32-2.27 (m, 2 H), 2.10-1.80 (m, 10 H). 59 [00389]embedded image (1-((((6aR,7S,10R)-2-(5- amino-3-chloro-2- (trifluoromethyl)phenyl)-1- fluoro-5,6,6a,7,8,9,10,11- octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-13-yl)oxy)methyl)-2,2- difluorocyclopropyl)methanol 631.4 .sup.1H NMR (500 MHz, MeOD) 6.89-6.88 (m, 1 H), 6.55-6.48 (m, 1 H), 4.73-4.10 (m, 6 H), 3.79- 3.54 (m, 4 H), 2.16- 1.75 (m, 6 H), 1.59-1.46 (m, 2 H). 60 [00390]embedded image 3-chloro-5-((6aR,7S,10R)-1- fluoro-13-((3-methyltetrahydrofuran-3- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15-pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 609.4 NMR (500 MHz, MeOD) & 6.90 (d, J = 2.1 Hz, 1H), 6.53 (s, 1H), 4.55-4.04 (m, 6H), 4.01- 3.65 (m, 4H), 3.49 (dd, J = 8.7, 1.6 Hz, 1H), 2.54- 1.67 (m, 7H), 1.28 (s, 3H). 61 [00391]embedded image 3-chloro-5-((6aR,7S,10R)-1- fluoro-13-((3-methoxyoxetan- 3-yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10-methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 611.4 .sup.1H NMR (500 MHz, MeOD) δ 6.80 (s, 1 H), 6.54-6.50(m, 1 H), 4.75- 4.61 (m, 4 H), 4.36-4.08 (m, 4 H),3.91-3.82 (m, 2 H), 3.44-3.41 (m,5 H), 2.18-1.93(m, 6 H). 62 [00392]
embedded image 3-chloro-5-((6aR,7S,10R)-1- fluoro-13-((3- (methoxymethyl)oxetan-3-yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10-methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 625.4 .sup.1H NMR (500 MHz, DMSO) δ 6.86 (s, 1H), 6.53-6.45 (m, 1H), 6.30 (s, 2 H), 4.57-4.41 (m, 6 H), 4.30-3.92 (m, 5 H), 3.64-3.44 (m, 6 H), 2.07- 2.01 (m, 1 H),1.80- 1.57(m, 5 H). 63 [00393]
embedded image 3-chloro-5-((6aR,7S,10R)-13- ((3- (difluoromethyl)tetrahydrofuran- 3-yl)methoxy)-1-fluoro- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10-methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 645.3 (500 MHz, MeOD) δ 6.89 (d, J = 2.0 Hz, 1H), 6.52 (d, J = 29.2 Hz, 1H), 6.18 (t, J = 56.4 Hz, 1H), 4.60-4.50 (m, 3H), 4.33 (d, J = 39.7 Hz, 3H), 4.11- 3.76 (m, 8H), 2.23- 1.93 (m, 8H) 64 [00394]
embedded image 4-((((6aR,7S,10R)-2-(5-amino- 3-chloro-2- (trifluoromethyl)phenyl)-1- fluoro-5,6,6a,7,8,9,10,11- octahydro-4-oxa- 3,11a,12,14,15-pentaaza-7,10- methanocyclohepta[4,5]cyclo-

octa[1,2,3-de]naphthalen-13- yl)oxy)methyl)tetrahydro-2H- pyran-4-carbonitrile 634.44 .sup.1H NMR (500 MHz, MeOD) δ 6.89 (d, J = 1.9 Hz, 1H), 6.52 (d, J = 37.9 Hz, 1H), 4.57 (dd, J = 33.6, 10.8 Hz, 2H), 4.21-4.47 (m, 3H), 4.20- 3.93 (m, 4H), 3.81-3.89 (m, 1H), 3.72 (t, J = 11.4 Hz, 3H), 2.27-1.99 (m, 5H), 1.99-1.76 (m, 5H). 65 [00395]embedded image 3-chloro-5-((6aR,7S,10R)-1-fluoro-13-((4- methyltetrahydro-2H-pyran-4- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 623.41 .sup.1H NMR (500 MHz, MeOD) δ 6.89 (d, J = 2.0 Hz, 1H), 6.52 (d, J = 28.8 Hz, 1H), 4.51-4.19 (m, 5H), 4.19-3.91 (m, 2H), 3.84-3.75 (m, 3H), 3.74-3.62 (m, 3H), 2.23- 2.00 (m, 3H), 1.99-1.82 (m, 3H), 1.76 (ddd, J = 13.7, 9.4, 4.3 Hz, 2H), 1.47 (d, J = 13.7 Hz, 2H), 1.20 (s, 3H). 66 [00396]embedded image 3-chloro-5-((6aR,7S,10R)-1- fluoro-13-((3-methyloxetan-3- yl)methoxy)- 5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10-methanocyclohepta[4,5]cyclo- octa[1,2,3-de]naphthalen-2-yl)- 4-(trifluoromethyl)aniline 595.34 .sup.1H NMR (500 MHz, MeOD) 8 6.89 (d, J = 1.9 Hz, 1H), 6.52 (d, J = 36.7 Hz, 1H), 4.68 (d, J = 5.4 Hz, 2H), 4.57 (dd, J = 26.6, 10.8 Hz, 2H), 4.46 (d, J = 6.0 Hz, 2H), 4.41-4.19 (m, 3H), 4.19-3.84 (m, 2H), 3.76- 3.65 (m, 1H), 3.65-3.49 (m, 1H), 2.19-1.73 (m, 6H), 1.46 (s, 3H). 67 [00397]embedded image 3-((6aR,7S,10R)-13-((3- oxabicyclo[3.1.1]heptan-1- yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro- 4-oxa-3,11a,12,14,15- pentaaza-7,10- methanocyclohepta[4,5]cyclo-octa[1,2,3-de]naphthalen-2-yl)- 5-chloro-4- (trifluoromethyl)aniline 621.43 .sup.1H NMR (500 MHz, MeOD) δ 6.89 (d, J = 2.0 Hz, 1H), 6.52 (d, J = 33.4 Hz, 1H), 4.44-4.20 (m, 5H), 4.12-4.08 (m, 1H), 4.04-3.91 (m, 5H), 3.77-3.67 (m, 1H), 3.67- 3.52 (m, 1H), 2.46-2.33 (m, 1H), 2.23-2.04 (m, 4H), 2.04-2.00 (m, 1H), 1.95-1.79 (m, 3H), 1.75- 1.68 (m, 2H).

Example 68: 3-((6aR,7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-5-ethyl-4-(trifluoromethyl)aniline

Synthetic Route

##STR00398##

##STR00399##

Step 1: tert-butyl (6aR,7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-(5-amino-2-(trifluoromethyl)-3-vinylphenyl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate

##STR00400##

[0625] A mixture of tert-butyl (6aR,7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (56 mg, 0.08 mmol), Potassium vinyltrifluoroborate (54 mg, 0.4 mmol), Pd(dppf)Cl.sub.2 (29 mg, 0.04 mmol) and NaHCO.sub.3 (20 mg, 0.24 mmol) in 1,4-dioxane (12.5 mL) and water (2.5 mL) was degassed by vacuum and refilled with N.sub.2 for 3 times. The resulting mixture was stirred at 95° C. for 2 hours. The resulting cooled mixture was concentrated in vacuo and dissolved in DCM (20 mL). After filtering, the filtrate was concentrated to give the title product which was used in next step without further purification. MS (ESI, m/e) [M+H].sup.+ 700.1.

Step 2: tert-butyl (6aR,7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-(5-amino-3-ethyl-2-(trifluoromethyl)phenyl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate

##STR00401##

[0626] To a solution of tert-butyl (6aR,7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-(5-amino-2-(trifluoromethyl)-3-vinylphenyl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (crude, 0.08 mmol) in MeOH (30 mL) was added Pd/C (10% w/w, 100 mg). The reaction mixture was stirred at 25° C. for 1 hour under a H.sub.2 balloon. The resulting mixture

was filtered, and the filtrate was concentrated to give the title product which was used in next step without further purification. MS (ESI, m/e) [M+H].sup.+ 701.4.
Step 3: 3-((6aR,7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-5-ethyl-4-(trifluoromethyl)aniline
##STR00402##
[0627] To a solution of tert-butyl (6aR,7S,10R)-13-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-2-(5-amino-3-ethyl-2-(trifluoromethyl)phenyl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (crude, 0.08 mmol) in DCM (15 mL) was added TFA (5 mL). The reaction mixture was stirred at room temperature for 0.5 hour, which was then concentrated and further purified by prep-HPLC to give the title product (14 mg, FA salt). MS (ESI, m/e) [M+H].sup.+ 601.45. .sup.1H NMR (500 MHz, CD.sub.3OD) δ 8.48 (s, 1H), 6.89-6.76 (m, 1H), 6.47-6.44 (m, 1H), 4.82-4.75 (m, 2H), 4.58 (s, 1H), 4.50-3.80 (m, 7H), 3.74 (s, 2H), 2.76 (q, J=7.1 Hz, 2H), 2.35-1.90 (m, 8H), 1.65-1.60 (m, 2H), 1.26 (t, J=7.5 Hz, 3H).
Assays
KRAS WT and KRAS G12V Probe Displacement Assay
[0628] This assay was used to identify compounds which bind to GDP-loaded KRAS protein and are able to displace a biotinylated probe occupying the KRAS binding site. GST-tagged GDP-loaded WT KRAS (amino acids 1-169) and GST-tagged GDP-loaded KRAS G12V (amino acids 1-169) were expressed in *E. coli* and purified in house. All protein and reaction solutions were prepared in assay buffer containing 50 mM HEPES pH7.5, 50 mM NaCl, 1 mM MgCl.sub.2, 1 mM TCEP, 0.01% BSA, and 0.008% Brij-35. Purified WT KRAS (3 nM final concentration) or KRAS G12V protein (2 nM final concentration) was incubated with a 3-fold serially diluted compound in the assay plate (384 well microplate, black, Corning). Plates are incubated at 24° C. for 1 hr. Following the incubation, biotinylated probe 1 (60 nM final assay concentration) for WT KRAS and biotinylated probe 2 (2.5 nM final assay concentration) for KRAS G12V was added to the assay plate, respectively. After 1 hr incubation at 24° C., Mab Anti-GST-Tb cryptate (Cisbio) and Streptavidin-XL665 (Cisbio) were added and further incubated at 24° C. for another 1 hr. The TR-FRET signals (ex337 nm, em665 nm/620 nm) were read on BMG PHERAstar FSX instrument. The inhibition percentage of KRAS protein binding with biotinylated probe in presence of increasing concentrations of compounds was calculated based on the ratio of fluorescence at 665 nm to that at 620 nm. The IC.sub.50 value of each compound was calculated from fitting the data to the four-parameter logistic model by Dotmatics.
KRAS WT and KRAS G12D Probe Displacement Assay
[0629] This assay was used to identify compounds which bind to GDP-loaded KRAS protein and are able to displace a biotinylated probe occupying the KRAS binding site. GST-tagged GDP-loaded WT KRAS (amino acids 1-188) and GST-tagged GDP-loaded KRAS G12D (amino acids 1-188) were expressed in *E. coli* and purified in house. All protein and reaction solutions were prepared in assay buffer containing 50 mM HEPES pH7.5, 50 mM NaCl, 1 mM MgCl.sub.2, 1 mM TCEP, 0.01% BSA, and 0.008% Brij-35. Purified WT KRAS (3 nM final concentration) or KRAS G12D protein (0.5 nM final concentration) was incubated with a 3-fold serially diluted compound in the assay plate (384 well microplate, black, Corning). Plates are incubated at 24° C. for 1 hr. Following the incubation, biotinylated probe 1 (60 nM final assay concentration) for WT KRAS and biotinylated probe 2 (4 nM final assay concentration) for KRAS G12D was added to the assay plate, respectively. After 1 hr incubation at 24° C., Mab Anti-GST-Tb cryptate (Cisbio) and Streptavidin-XL665 (Cisbio) were added and further incubated at 24° C. for another 1 hr. The TR-FRET signals (ex337 nm, em665 nm/620 nm) were read on BMG PHERAstar FSX instrument. The inhibition percentage of KRAS protein binding with biotinylated probe in presence of increasing concentrations of compounds was calculated based on the ratio of fluorescence at 665

nm to that at 620 nm. The IC.sub.50 value of each compound was calculated from fitting the data to the four-parameter logistic model by Dotmatics.

KRAS G12V pERK Assay

[0630] SW620 cell line was used in this study. Cells were maintained in RPMI 1640 supplemented with 10% fetal bovine serum (Thermo Fisher), 50 units/mL penicillin and streptomycin (Thermo Fisher) and kept at 37° C. in a humidified atmosphere of 5% CO2 in air. Cells were reinstated from frozen stocks that were laid down within 30 passages from the original cells purchased. 40000 cells per well were seeded into a 96-well plate and incubated overnight. Cells were treated with a 10-point dilution series. The final compound concentration is from 0 to 10 μM. After 2 hrs compound treatment, cells were lysed, and the pERK1/2(THR202/TYR204) level in the cell lysates was detected by HTRF kit (Cisbio). In brief, a total of 16 μL of cell lysate from each well of a 96-well plate was transferred to a 384-well white assay plate. Lysate from each well was incubated with 2 μL of Eu3+-cryptate (donor) labeled anti-phospho-ERK1/2 and 2 μL of D2 (acceptor) labeled anti-phospho-ERK1/2 antibodies (Cisbio) overnight in dark at room temperature. When donor and acceptor are in close proximity, excitation of the donor with laser triggers a Fluorescence Resonance Energy Transfer (FRET) towards the acceptor, which in turn fluoresces at 655 nm wavelength. FRET signals were measured using a PHERAstar FSX reader (BMG Labtech). IC50 determination was performed by fitting the curve of percent inhibition versus the log of the inhibitor concentration using Dotmatics.

KRAS G12D pERK Assay

[0631] AsPC-1 cell line was used in this study. Cells were maintained in RPMI-1640 supplemented with 10% fetal bovine serum (Thermo Fisher), 50 units/mL penicillin and streptomycin (Thermo Fisher) and kept at 37° C. in a humidified atmosphere of 5% CO.sub.2 in air. Cells were reinstated from frozen stocks that were laid down within 30 passages from the original cells purchased. 30000 cells per well were seeded into a 96-well plate and incubated overnight. Cells were treated with a 10-point dilution series. The final compound concentration is from 0 to 10 μM. After 2 h compound treatment, cells were lysed, and the pERK1/2(THR202/TYR204) level in the cell lysates was detected by HTRF kit (Cisbio). In brief, a total of 16 μL of cell lysate from each well of a 96-well plate was transferred to a 384-well white assay plate. Lysate from each well was incubated with 2 μL of Eu3+-cryptate (donor) labeled anti-phospho-ERK1/2 and 2 μL of D2 (acceptor) labeled anti-phospho-ERK1/2 antibodies (Cisbio) overnight in dark at room temperature. When donor and acceptor are in close proximity, excitation of the donor with laser triggers a Fluorescence Resonance Energy Transfer (FRET) towards the acceptor, which in turn fluoresces at 655 nm wavelength. FRET signals were measured using a PHERAstar FSX reader (BMG Labtech). IC.sub.50 determination was performed by fitting the curve of percent inhibition versus the log of the inhibitor concentration using Dotmatics.

KRAS G12D Protein Preparation and Crystallization

KRAS G12D Protein Purification

[0632] KRAS G12D 1-169aa was cloned into the pET28a vector. Gene was placed in-frame with an N-terminal 6×his-tag and a Sumo tag. The construct was transformed into BL21(DE3) cells. Protein expression was induced when cells reached an OD.sub.600 of 0.6, by addition of 1-thio-β-D-galactopyranoside (IPTG) to a final concentration of 200 uM followed by overnight incubation at 16° C. Bacteria were harvested by centrifugation (4000 rpm, 20 mins, 4° C.), 1 liter cell paste was resuspended in 30 ml of 50 mM Tris pH 8.0, 300 mM NaCl, 20 mM imidazole, 5 mM $MgCl_2$ supplied with 2 piles of EDTA-free protease inhibitor cocktail table (Roche Diagnostics). Protein was purified with His-trap HP column (Cytiva) following standard protocols. The N-terminal His-sumo tag was cleaved by overnight digestion with ULP1 proteas, and UPL1, His-sumo tag were removed by reload into His-trap HP column (Cytiva). Protein was further purified by gel filtration using HiLoad 16/600 Superdex 75 pg (Cytiva) equilibrated with 20 mM Tris pH 8.0, 100 mM NaCl, 5 mM $MgCl_2$. Protein solution was concentrated to 30-40 mg/ml

for crystallization trials.

KRAS G12D Crystallization

[0633] KRAS G12D with small molecule inhibitor co-crystals were grown at 20° C. by mixing 1 ul of protein (40 mg/ml) with an equal volume of crystallization buffer using sitting drop vapor diffusion. Crystals appeared in drops containing 1.0 M LiCl, 0.1 M Citric acid pH 5.0, 20% PEG 6000. Diffraction data were collected at beamlines BL10U2 at Shanghai Synchrotron Radiation Facility.

Metabolic Stability in Different Species of Liver Microsome

[0634] Liver microsomes were first mixed with NADPH to obtain final concentrations of microsomes and NADPH of 0.5 mg/mL and 1 mM, respectively. Test compounds was added to incubation system at final concentration of 1 μM and incubated at 37° C. The incubation was initiated by the addition of NADPH into the system. Aliquots of 20 μL were taken from the incubation system at 0, 15, 30, 45 and 60 min after the initiation of incubation. The reaction solutions were stopped by the addition of cold acetonitrile with analytical IS. Samples were centrifuged at 4000 rpm for 5 minutes and were then analyzed on LC-MS/MS.

[0635] Peak areas of samples from various timepoints were determined from extracted ion chromatograms; and were then plotted to calculate metabolic stability. The slope value, k, was determined by linear regression of the natural logarithm of the remaining percentage of the parent drug vs. incubation time curve. The in vitro half-life (in vitro t.sub.1/2) was determined from the slope value:

[00001]invitro$t_{1/2}$ = -(0.693 / k)

Conversion of the in vitro t.sub.1/2 (in min) into the in vitro intrinsic clearance (in vitro CL.sub.int, in μL/min/mg proteins) was done using the following equation (mean of duplicate determinations):

[00002]invitro$\mathrm{CL_{int}} = \frac{0.693}{t_{1/2}} \times \frac{\mathrm{volumeofincubation(\mu L)}}{\mathrm{amountofproteins(mg)}}$

[0636] The control compound (verapamil) was included in the assay to ensure the data consistency. The negative control (identical experimental set-up but no NADPH in the incubation system) was used to exclude the misleading factor that resulted from instability of chemical itself.

CYP (Cytochrome P450) Enzymes Inhibition Assay in Human Liver Microsome

[0637] The incubation was carried out in 96-well plates. 1 μL of test compound working solution or vehicle was added into 179 μL of human liver microsomes fortified with substrates of CYP1A2 (40 M phenacetin), 2C9 (6 μM diclofenac), 2C19 (50 μM (S)-mephenytoin), 2D6 (10 μM dextromethorphan) and 3A4 (1 μM midazolam or 50 μM testosterone). The incubation plate was pre-warmed at 37° C. for 5 min in water bath before the reactions are started by the addition of 20 μL of 10 mM NADPH solution. The reaction was carried out in the 37° C. -water bath.

[0638] At the predetermined time points, the reaction was stopped by adding 300 μL of quenching solution (acetonitrile with internal standards) to each well. The sample plate was vortexed for 1 min and centrifuged at 3000 g for 10 min. 100 μL of the supernatant was transferred to a new 96-well plate then mixed with 100 μL water for analysis by LC-MS/MS followed by data processing (i.e., percent inhibition at 10 uM or IC50 determination).

Time Dependent Cytochrome P450 (CYP) Enzymes Inhibition Assay (TDI) in Human Liver Microsome

[0639] The TDI assay involves pre-incubation (“inactivation incubation”) of 0.1 mg.Math.mL-1 human liver microsome with 10 uM test compounds and Positive Control in the presence or absence of 1 mM NADPH at 37° C. for 30 min. Following the pre-incubation period, remaining CYP activity was determined by subsequently adding substrates (1A2, 40 μM phenacetin; CYP2B6, 50 μM bupropion; CYP2C8, 5 μM paclitaxel; CYP2C9, 6 μM diclofenac; CYP2C19, 50 μM (S)-mephenytoin; CYP2D6, 10 M dextromethorphan, CYP3A, 1 μM Midazolam or 50 μM Testosterone) and NADPH to the pre-incubation mixtures and an “activity incubation” was done for another 20 min for CYP1A2, 2B6, 2C19, 2D6, 10 min for CYP2C8, CYP3A (testosterone), 6 min for CYP2C9 and 5 min for 3A (midazolam). All reactions are terminated by the addition of ice-

cold acetonitrile with internal standard and then centrifuge for LC-MS/MS analysis.

Bidirectional Permeability Assay in MDCKII-MDR1 Cell Monolayer

[0640] MDCKII-MDR1 cells were first prepared in cell seeding medium. 50 μL of cultured cell suspension was added to each well of a previously prepared Transwell plate. Incubate the plate for 4-8 days. Replace the medium every other day. The integrity of cell monolayer was assessed via electrical resistance method prior to permeability measurement.

[0641] To determine the rate of drug transport in the apical to basolateral direction. 125 μL of test compound working solution were added to the Transwell insert (apical compartment), and transferred 50 L sample (DO sample) immediately from the apical compartment to a new 96-well plate. To determine the rate of drug transport in the basolateral to apical direction. 285 μL of working solution of compounds are added to the receiver plate wells (basolateral compartment), and transfer 50 μL sample (DO sample) immediately from the basolateral compartment to a new 96-well plate. The plates are incubated at 37° C. for 2 hours. At the end of the transport period, transfer 50 μL directly from the apical and basolateral wells and transfer to a new plate. Then add 200 μL of cold acetonitrile containing internal standards (IS: 2 μM ketoprofen, 200 nM labetalol, 200 nM caffeine and 100 nM alprazolam) into the plate. Vortex for 5 minutes. Samples are centrifuged at 3,220 g for 20 minutes. Aliquot of 100 μL of the supernatant is diluted by 100 μL ultra-pure H2O, and the mixture is used for LC/MS/MS analysis. All incubations are performed in duplicate. The apparent permeability (Papp), in units of centimeter per second, can be calculated for MDCKII-MDR1 drug transport assays using the following equation:

[00003] $$P_{\text{app}} = \frac{V_A}{\text{Area} \times \text{time}} \times \frac{[\text{drug}]_{\text{acceptor}}}{[\text{drug}]_{\text{initial, donor}}}$$

Where VA is the volume (in mL) in the acceptor well (0.235 mL for Ap.fwdarw.Bl flux and 0.075 mL for Bl.fwdarw.Ap flux), Area is the surface area of the membrane (0.143 cm.sup.2 for Transwell-96 Well Permeable Supports), and time is the total transport time in seconds.

[0642] The efflux ratio can be determined using the following equation:

[00004] $$\text{EffluxRatio} = \frac{\text{app}(B\text{-}A)}{\text{app}(A\text{-}B)}$$

Where P.sub.app(B-A) indicates the apparent permeability coefficient in basolateral to apical direction, and P.sub.app(A-B) indicates the apparent permeability coefficient in apical to basolateral direction.

[0643] The recovery can be determined using the following equation:

[00005] $$\text{Recovery\%} = \frac{[\text{drug}]_{\text{acceptor}} \times V_A + [\text{drug}]_{\text{donor}} \times V_D}{[\text{drug}]_{\text{initial, donor}} \times V_D} \times 100$$

[0644] Where V.sub.A is the volume (in mL) in the acceptor well (0.235 mL for Ap.fwdarw.Bl flux, and 0.075 mL for Bl.fwdarw.Ap), V.sub.D is the volume (in mL) in the donor well (0.075 mL for Ap.fwdarw.Bl flux, and 0.235 mL for Bl.fwdarw.Ap).

Intrinsic Clearances in Different Species of Hepatocytes

[0645] Prepare 10 mM stock solutions of test compounds and positive control in appropriate solvent (DMSO). Place incubation medium (William's E Medium supplemented with GlutaMAX) in a 37° C. water bath, and allow warming for at least 15 minutes prior to use. In separate conical tubes, dilute the 10 mM test compound and the positive control to 100 μM by combining 198 μL of 50% acetonitrile/50% water and 2 μL of 10 mM stock. Pipette 198 μL of cryopreserved hepatocytes (0.5×10.sup.6 viable cells/mL) into each wells of a 96-well non-coated plate. Pipette 2 μL of the 100 μM test compounds or positive control into respective wells of the 96-well non-coated plate to start the reaction. The final concentration of test compound or control compounds is 1 μM. Return the plate to the incubator and place on an orbital shaker. Remove well contents in 25 μL aliquots at time points of 0, 15, 30, 60, 90 and 120 minutes. The aliquots are then mixed with 6 volumes (150 μL) of cold acetonitrile with IS (2 M ketoprofen, 200 nM labetalol, 200 nM caffeine and 100 nM alprazolam) to terminate the reaction. Centrifuge for 30 minutes at 3,220 g. Aliquots of 100 μL of the supernatants will be used for LC/MS/MS analysis. The supernatant may be diluted with

ultrapure water according to the LC-MS signal response and peak shape. All incubations will be performed in duplicate.

[0646] All calculations are carried out using Microsoft Excel. Peak areas are determined from extracted ion chromatograms. Determine the in vitro half-life (t.sub.1/2) of parent compound by regression analysis of the percent parent disappearance vs. time curve.

[0647] The in vitro half-life (in vitro t.sub.1/2) is determined from the slope value:

[00006]invitro$t_{1/2}$ = 0.693 / k

[0648] Conversion of the in vitro t.sub.1/2 (in min) into the in vitro intrinsic clearance (in vitro CL.sub.int, in L/min/10.sup.6 cells) is done using the following equation:

[00007]invitroCL_{int} = kV / N

[0649] V=incubation volume (0.2 mL); N=number of hepatocytes per well (0.1×10.sup.6 cells).

Mouse and Rat PK Study

[0650] The pharmacokinetics of compounds were evaluated in male CD-1 mice or SD-JVC rats via intravenous and oral administration. For intravenous administration study, test compounds were dissolved in DMA:30% Solutol HS 15(w/v): Saline (20:20:60, by volume) and injected with a 1 mg/kg dose via tail vein. For oral administration study, test compounds were dissolved in 0.5% MC or PEG400/Phosal 50 PG/EtOH (30/60/10, by volume) and administrated to mice at 10 mg/kg or 30 mg/kg by gavage. Animals will be grouped and treated according to body weight. At the time points after dosing (5 (IV only), 15, and 30 min and 1, 2, 4, 8 and 24 h after administration), Rat blood samples will be collected from JVC, Mice will be anesthetized by isoflurane and blood samples will be collected from orbital bleeding. Blood samples will be collected into 1.5 mL EDTA.K2 coated EP tube. Approximately 50 μL blood (Mouse) and 150 μL blood (Rat) were collected at each time point and placed on ice, then centrifuge at 5600 rpm 7 min at 4° C. to obtain plasma. Plasma will be transferred into new tube and stored at −20° C. or dry ice temporary. The samples will be stored at −80° C. until ex vivo PK assay.

[0651] Plasma concentrations were determined via the following sample processing method and measurement conditions. An aliquot of 10 μL sample was added with 200 μL IS (Terfenadine, 5 ng/mL) in ACN. The mixture was vortexed for 1 min, and centrifuged at 4000 rpm for 10 min at 4° C. An aliquot of 80 μL supernatant was diluted with 80 μL water, and the mixed sample was injected to liquid chromatography-tandem mass spectrometry (LC-MS/MS, Triple Quad 5500) for analysis. Injected sample amount: 2 μL. Monitor: MRM; Column: Advanced Materials Technology, HALO AQ-C18 2.7 μm 90A, 50*2.1 mm; Column temperature: 40° C.; Mobile phase A: H2O-0.1% FA, Mobile phase B: ACN-0.1% FA, Gradient program: 15% B-15% B (0 min-0.3 min), 15% B-90% B (0.3 min-1.0 min), 90% B-90% B (1.0 min-1.8 min), 90% B-30% B (1.8 min-2.0 min), 30% B-30% B (2.0 min-2.5 min).

SW1990 PD Studies:

[0652] Female NCG mice were subcutaneously implanted with 5×10.sup.6 SW1990 cells per 200 μL PBS/matrigel in the right flank. After inoculation, when tumors reached a mean volume of approximately 350-450 mm.sup.3 in size, mice were randomized into treatment groups. Randomized mice would receive a single dose of vehicle consisting of 0.5% MC or test compounds at various dose (e.g. 30, 50, or 100 mg/kg) by oral administration. Plasma was collected at 0.5, 2, 4, and 7 hours, and tumor was collected at 7 hours after dosing to determine exposure levels. Tumor fragments were snap frozen in homogenization tubes with liquid nitrogen and homogenized with T-PER Tissue Protein Extraction Buffer with protease and phosphatase inhibitors added fresh before use. Tumor lysates were then analyzed for ERK1/2 phosphorylation.

SW1990 Efficacy Studies:

[0653] Female NCG mice were subcutaneously implanted with 5×10.sup.6 SW1990 cells per 200 μL PBS/matrigel in the right flank. After inoculation, when tumors reached a mean volume of approximately 150-250 mm.sup.3 in size, mice were randomized into treatment groups. Randomized mice would receive vehicle consisting of 0.5% MC or test compounds at various dose

(e.g. 30, 50, or 100 mg/kg BID) by oral administration. Animals were monitored daily, tumor volumes were determined twice weekly in two dimensions using a caliper, and were expressed in mm.sup.3 using the formula: V=0.5(a×b.sup.2) where a and b are the long and short diameters of the tumor, respectively. Partial regression (PR) was defined as tumor volume smaller than 50% of the starting tumor volume on the first day of dosing in three consecutive measurements and complete regression (CR) was defined as tumor volume less than 14 mm.sup.3 in three consecutive measurements. Data is presented as mean tumor volume±standard error of the mean (SEM). Tumor growth inhibition (TGI) is calculated using the following formula:

[00008]$\%\text{growthinhibition} = 100 \times (1 - (\frac{(\text{treated}t) - (\text{treatedto})}{(\text{placebo}t) - (\text{placeboto})}))\text{treated}t = \text{treatedtumorvolumeattime}t$ $\text{treated}t_0 = \text{treatedtumorvolumeattime0}\text{placebo}t = \text{placebotumorvolumeattime}t$ $\text{placebo}t_0 = \text{placebotumorvolumeattime0}$

[0654] It has been found that Example 23 as a mono-basic G12D inhibitor shows improved KRas WT selectivity, enhanced oral exposure, reduced gastrointestinal accumulation and reduced toxicity compared to dibasic G12D inhibitors (e.g., Example 17). It is also found that Examples 26, 27, 29, 32, 35, 40, 41 and other show enhanced oral pharmacodynamic effects.

SW620 PD Studies:

[0655] Female NOD/SCID mice were subcutaneously implanted with 5×10.sup.6 SW620 cells per 200 L PBS/matrigel in the right flank. After inoculation, when tumors reached a mean volume of approximately 350-450 mm.sup.3 in size, mice were randomized into treatment groups. Randomized mice would receive a single dose of vehicle consisting of 0.5% MC or test compounds at various dose (e.g. 30, 50, or 100 mg/kg) by oral administration. Plasma was collected at 0.5, 2, 4, and 8 hours, and tumor was collected at 4 and 8 hours after dosing to determine exposure levels. Tumor fragments were snap frozen in homogenization tubes with liquid nitrogen and homogenized with T-PER Tissue Protein Extraction Buffer with protease and phosphatase inhibitors added fresh before use. Tumor lysates were then analyzed for ERK1/2 phosphorylation.

SW620 Efficacy Studies:

[0656] Female NOD/SCID mice were subcutaneously implanted with 5×10.sup.6 SW620 cells per 200 L PBS/matrigel in the right flank. After inoculation, when tumors reached a mean volume of approximately 150-250 mm.sup.3 in size, mice were randomized into treatment groups. Randomized mice would receive vehicle consisting of 0.5% MC or test compounds at various dose (e.g. 30, 50, or 100 mg/kg BID) by oral administration. Animals were monitored daily, tumor volumes were determined twice weekly in two dimensions using a caliper, and were expressed in mm.sup.3 using the formula: V=0.5(a×b.sup.2) where a and b are the long and short diameters of the tumor, respectively. Partial regression (PR) was defined as tumor volume smaller than 50% of the starting tumor volume on the first day of dosing in three consecutive measurements and complete regression (CR) was defined as tumor volume less than 14 mm.sup.3 in three consecutive measurements. Data is presented as mean tumor volume±standard error of the mean (SEM). Tumor growth inhibition (TGI) is calculated using the following formula:

[00009]$\%\text{growthinhibition} = 100 \times (1 - (\frac{(\text{treated}t) - (\text{treatedto})}{(\text{placebo}t) - (\text{placeboto})}))\text{treated}t = \text{treatedtumorvolumeattime}t$ $\text{treated}t_0 = \text{treatedtumorvolumeattime0}\text{placebo}t = \text{placebotumorvolumeattime}t$ $\text{placebo}t_0 = \text{placebotumorvolumeattime0}$

RKN PD Studies:

[0657] Female NOD/SCID mice were subcutaneously implanted with 5×10.sup.6 RKN cells per 200 μL PBS/matrigel in the right flank. After inoculation, when tumors reached a mean volume of approximately 350-450 mm.sup.3 in size, mice were randomized into treatment groups. Randomized mice would receive a single dose of vehicle consisting of 0.5% MC or test compounds at various dose (e.g. 30, 50, or 100 mg/kg) by oral administration. Plasma was collected at 0.5, 2, 4, and 8 hours, and tumor was collected at 4 and 8 hours after dosing to determine exposure levels. Tumor fragments were snap frozen in homogenization tubes with liquid nitrogen and homogenized

with T-PER Tissue Protein Extraction Buffer with protease and phosphatase inhibitors added fresh before use. Tumor lysates were then analyzed for ERK1/2 phosphorylation.

SW620 Efficacy Studies:

[0658] Female NOD/SCID mice were subcutaneously implanted with 5×10.sup.6 RKN cells per 200 μL PBS/matrigel in the right flank. After inoculation, when tumors reached a mean volume of approximately 150-250 mm.sup.3 in size, mice were randomized into treatment groups. Randomized mice would receive vehicle consisting of 0.5% MC or test compounds at various dose (e.g. 30, 50, or 100 mg/kg BID) by oral administration. Animals were monitored daily, tumor volumes were determined twice weekly in two dimensions using a caliper, and were expressed in mm.sup.3 using the formula: V=0.5(a×b.sup.2) where a and b are the long and short diameters of the tumor, respectively. Partial regression (PR) was defined as tumor volume smaller than 50% of the starting tumor volume on the first day of dosing in three consecutive measurements and complete regression (CR) was defined as tumor volume less than 14 mm.sup.3 in three consecutive measurements. Data is presented as mean tumor volume±standard error of the mean (SEM). Tumor growth inhibition (TGI) is calculated using the following formula:

[00010]%growthinhibition = $100 \times (1 - (\frac{(\text{treated}t) - (\text{treated}to)}{(\text{placebo}t) - (\text{placebo}to)}))$treated$t$ = treatedtumorvolumeattime$t$ treatedt_0 = treatedtumorvolumeattime0placebo$t$ = placebotumorvolumeattime$t$ placebot_0 = placebotumorvolumeattime0

AsPC-1 PD Studies:

[0659] Female BALB/c Nude mice were subcutaneously implanted with 3×10.sup.6 AsPC-1 cells per 200 μL PBS/matrigel in the right flank. After inoculation, when tumors reached a mean volume of approximately 350-450 mm.sup.3 in size, mice were randomized into treatment groups. Randomized mice would receive a single dose of vehicle consisting of 0.5% MC or test compounds at various dose (e.g. 30, 50, or 100 mg/kg) by oral administration. Plasma was collected at 0.5, 2, 4, and 8 hours, and tumor was collected at 4 and 8 hours after dosing to determine exposure levels. Tumor fragments were snap frozen in homogenization tubes with liquid nitrogen and homogenized with T-PER Tissue Protein Extraction Buffer with protease and phosphatase inhibitors added fresh before use. Tumor lysates were then analyzed for ERK1/2 phosphorylation.

AsC-1 Efficacy Studies:

[0660] Female BALB/c Nude mice were subcutaneously implanted with 3×10.sup.6 AsPC-1 cells per 200 μL PBS/matrigel in the right flank. After inoculation, when tumors reached a mean volume of approximately 150-250 mm.sup.3 in size, mice were randomized into treatment groups. Randomized mice would receive vehicle consisting of 0.5% MC or test compounds at various dose (e.g. 30, 50, or 100 mg/kg BID) by oral administration. Animals were monitored daily, tumor volumes were determined twice weekly in two dimensions using a caliper, and were expressed in mm.sup.3 using the formula: V=0.5(a×b.sup.2) where a and b are the long and short diameters of the tumor, respectively. Partial regression (PR) was defined as tumor volume smaller than 50% of the starting tumor volume on the first day of dosing in three consecutive measurements and complete regression (CR) was defined as tumor volume less than 14 mm.sup.3 in three consecutive measurements. Data is presented as mean tumor volume±standard error of the mean (SEM). Tumor growth inhibition (TGI) is calculated using the following formula:

[00011]%growthinhibition = $100 \times (1 - (\frac{(\text{treated}t) - (\text{treated}to)}{(\text{placebo}t) - (\text{placebo}to)}))$treated$t$ = treatedtumorvolumeattime$t$ treatedt_0 = treatedtumorvolumeattime0placebo$t$ = placebotumorvolumeattime$t$ placebot_0 = placebotumorvolumeattime0

hERG Assay

[0661] hERG (the human Ether-à-go-go-Related Gene) encodes the rapidly activating potassium channel (I.sub.Kr) contributing to the repolarization of the cardiac action potential. The blockade of hERG channel can lead to a QT prolongation in the electrocardiogram known as long QT syndrome. Drug-induced delayed ventricular repolarization in some cases may trigger a fatal

arrhythmias-torsional apical ventricular tachycardia. About 25-40% of the leading drug compounds show varied extent of hERG dependent potential risks, and many drugs are withdrawn from the market due to the risk of the QT interval prolongation.

[0662] Before testing hERG current, the blank control will be diluted with appropriate volume of extracellular solution to make control working solution. The positive control and test article stock solutions will be taken from −20° C., thawed, and diluted with an appropriate volume of extracellular solution to make the working solution.

[0663] The working solution for test article at highest concentration will be diluted with extracellular solution from the stock solution or the stock solution should be diluted with DMSO firstly. For other test concentrations of the test article, serial dilutions will be made using DMSO and then be prepared to the working solutions with extracellular solution. The DMSO concentration in the final working solutions will be 0.3%. The specific preparation information will be recorded in the compound working-solution preparation form. Finally, all the working solutions of test article will be ultrasonicated for 20 minutes before performing the patch clamp experiment.

[0664] The blank control (DMSO) stock solution will be kept at room temperature. The blank control working solution will be prepared on the test day and kept at room temperature. The positive control stock solution and the test article stock solution will be kept at −20° C. The positive control and the test article working solutions will be prepared on the test day and kept at room temperature.

[0665] The test articles concentrations will be automatically set for 30, 10, 3, 1 and 0.3 μM. The blank control will be 0.3 DMSO, and the positive control (Cisapride) concentrations will be 1000, 100, 10, 1, 0.1 nM.

[0666] Automated Patch Clamp system QPatch 48X (Sophion) will be used for electrophysiological recording in this study.

[0667] Place the prepared cells on the centrifuge of the Qpatch work plane, wash the cells with multiple centrifugation/suspension times, and replace the cell culture medium with extracellular solution. Take out an MTP-96 plate and place it on the MTP source position. A QPlate chip will be took out and put in the Qplate source position. The barcode reader scans the barcode of MTP-96 board and QPlate chip and the gripper arm grab them to the measurement position. The intracellular and extracellular solution from the saline reservoir will be added to the intracellular saline well, cell and compound well of the QPlate chip. For the measuring, all the measuring points of QPlate will be under the initial quality control. The quality control process includes sucking the cell suspension from the cell container of the centrifuge, positioning the cells on the chip hole by the pressure controller, establishing a high-resistance seal, and forming a whole-cell recording mode. Once a stable control current baseline is obtained, the test article will be applied to the cells by sequential aspiration from the MTP-96 plate in order of concentration. The hERG current will be recorded using the whole-cell patch clamp technique at a holding potential of −80 mV and then depolarized to −50 mV for 0.5 seconds to test the leak current. Then the voltage will be depolarized to 30 mV for 2.5 seconds. The peak tail current will be induced by a repolarizing pulse to −50 mV for 4 seconds. This protocol will be repeated at 10 s intervals to observe the effect of test article on hERG tail current. The data will be collected by QPatch screening station and stored in QPatch database server.

[0668] In the experiment, each drug concentration will be applied twice recording period of at least 5 min. The control and test solutions will be applied to the cells sequentially from low to high concentration. The current of each cell detected in the extracellular solution without compound will be used as its own blank control.

[0669] IC.sub.50 value will be calculated, and dose-response curve will be fitted using non-linear regression equation above, where IC.sub.50 is the half maximal inhibitory concentration. IC.sub.50 calculation and curve-fitting will be performed using GraphPad Prism software.

Activity Tables

[0670] Each of the compounds in Tables 2 and 3 was tested in one or more of the biochemical assays provided herein and was found to have activity therein.
TABLE-US-00003 TABLE 2 KRAS.sup.WT Probe KRAS.sup.G12V Probe Displacement Displacement SW620 pERK Example No. Assay IC50 (nM) Assay IC50 (nM) IC.sub.50 (nM) Example 1 1.3 0.93 161 Example 2 4.3 1.7 178 Example 3 8.0 3.0 133 Example 4 0.63 0.58 6.7 Example 5 1.0 0.51 22 Example 6 3.7 2.7 118 Example 7 1.9 1.1 72 Example 8 1.1 0.89 43 Example 9 18 24 Example 14- 14 15 Isomer 1 Example 14- 0.51 0.61 33 Isomer 2 Example 15 2.1 2.3 83 Example 16 1.8 1.2 24 Example 18 0.98 0.91 30 Example 19 0.65 0.88 40 Example 20 0.48 0.51 1.3 Example 21 2.2 1.8 74 Example 22 0.67 0.91 13
TABLE-US-00004 TABLE 3 KRASWT Probe KRASG12D Probe Displacement Displacement AsPC-1 pERK Example No. Assay IC50 (nM) Assay IC50 (nM) IC50 (nM) Example 4 0.63 0.61 76 Example 10 8.1 0.9 58 Example 11 0.96 0.16 30 Example 12 22 2.8 Example 13 21 59 Example 17 1.7 0.17 11 Example 23 181 0.53 114 Example 24 2 0.16 4.4 Example 25 68 4.4 504 Example 26 272 0.52 142 Example 27 465 1.2 203 Example 28 379 1.1 152 Example 29 313 0.74 92 Example 30 259 1.2 198 Example 31 366 0.92 162 Example 32 116 0.23 117 Example 33 253 0.91 286 Example 34 148 0.36 82 Example 35 100 0.25 61 Example 36 166 0.81 106 Example 37 205 0.53 97 Example 38 >1000 3.6 1866 Example 39 292 0.47 409 Example 40 430 1.1 303 Example 41 125 0.51 112 Example 42 >1000 8.2 1849 Example 43 585 2.5 584 Example 44 >1000 5.2 2215 Example 45 298 0.63 221 Example 46 246 0.84 4861 Example 47 154 0.26 1928 Example 48 649 2.5 296 Example 49 444 2.1 172 Example 50 160 0.34 109 Example 51 >1000 2.9 272 Example 52 13 0.22 Example 53 255 0.81 211 Example 54 >1000 15 Example 55 684 4.2 Example 56 563 2.4 Example 58 >1000 15 Example 59 85 0.44 Example 61 354 0.46 332 Example 62 307 0.74 346 Example 63 257 0.48 151 Example 64 113 1.1 Example 65 688 2.0 Example 66 204 0.69 145 Example 67 276 1.3 169 Example 68 >1000 5.5 548
[0671] As demonstrated by the data in Tables 2-3, the inventors surprisingly and unexpectedly discovered that the exemplary compounds in Tables 2-3 modulate or inhibit the activity of KRAS G12D and/or G12V.
[0672] A number of references have been cited, the disclosures of which are incorporated herein by reference in their entirety.

Claims

1-**38**. (canceled)
39. A compound having Formula (II): ##STR00403## or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer, enantiomer, atropisomer, or prodrug thereof, wherein ring A is unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; moiety B is unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocyclyl, or unsubstituted or substituted C.sub.2-5alkyl; X is N, or C—R.sup.8; W is O, NH, N—R.sup.9, N—C(═O)—R.sup.10, or O═S═O; each of R.sup.0 is, independently, H, halogen, amino, —CN, —OH, unsubstituted or substituted C.sub.1-4alkyl, unsubstituted or substituted C.sub.1-4 alkenyl, unsubstituted or substituted C.sub.1-4 alkynyl, unsubstituted or substituted C.sub.1-4alkoxy, unsubstituted or substituted C.sub.3-5cycloalkyl, unsubstituted or substituted 3-member to 5-member heterocyclyl, unsubstituted or substituted C.sub.1-4alkylamino, carboxy, nitro, thiol, or thioether; or one or more pairs of the R.sup.0 groups, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, is, independently, H, halogen, amino, —CN, —OH, unsubstituted or substituted C.sub.1-4alkyl, unsubstituted or substituted C.sub.1-4alkoxy, unsubstituted or substituted C.sub.3-5cycloalkyl, unsubstituted or substituted 3-member to 5-member heterocyclyl, unsubstituted or

substituted C.sub.1-4alkylamino, carboxy, nitro, thiol, or thioether; optionally, R.sup.3a, and R.sup.3b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or R.sup.4a, and R.sup.4b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or R.sup.6a, and R.sup.6b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or R.sup.7a, and R.sup.7b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or R.sup.8a, and R.sup.8b, together with the atom to which they are attached to, form unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl; or R.sup.6a, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or R.sup.6a, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or R.sup.5, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or R.sup.5, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; R.sup.8 is H, halogen, unsubstituted or substituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkenyl, unsubstituted or substituted C.sub.3-5 cycloalkyl, unsubstituted or substituted C.sub.1-4 alkoxyl, unsubstituted or substituted C.sub.1-4 halogenated alkyl, unsubstituted or substituted C.sub.3-5 halogenated cycloalkyl, unsubstituted or substituted C.sub.1-4 halogenated alkoxyl, CN, OH, or amino; R.sup.9 is substituted or unsubstituted C.sub.1-4 alkyl, or unsubstituted or substituted C.sub.3-5 cycloalkyl; R.sup.10 is substituted or unsubstituted C.sub.1-4 alkyl, unsubstituted or substituted C.sub.1-4 alkoxy, unsubstituted or substituted C.sub.3-5 cycloalkyl, or unsubstituted or substituted 3-member to 5-member heterocyclyl; t is 0, or 1; each of s and r, is independently, is 1, or 2; and each of m, and q is, independently, an integer between 0 and the maximum number of the substituent groups allowed on rings A, and B, respectively.

40. The compound of claim 39, wherein the compound has formula (IIf): ##STR00404## or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer, enantiomer, atropisomer, or prodrug thereof, wherein X is N, or CH; W is O, or NH; ring A is ##STR00405## moiety B is ##STR00406## and each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a, R.sup.6b, R.sup.7a, R.sup.7b, R.sup.8a1, R.sup.8b1, R.sup.8a2, and R.sup.8b2, independently, is H, OH, CN, unsubstituted or substituted amino, or unsubstituted or substituted C.sub.1-4alkyl.

41. The compound of claim 39, wherein the compound has formula (IIg): ##STR00407## or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer, enantiomer, atropisomer, or prodrug thereof, wherein X is N, or CH; W is O, or NH; ring A is ##STR00408## moiety B is ##STR00409## and each of R.sup.3a, R.sup.3b, R.sup.4a, R.sup.4b, R.sup.5, R.sup.6a1, R.sup.6b1, R.sup.6a2, R.sup.6b2, R.sup.7a, R.sup.7b, R.sup.8a, and R.sup.8b, independently, is H, OH, CN, unsubstituted or substituted amino, or unsubstituted or substituted C.sub.1-4alkyl.

42. The compound of claim 39, wherein the compound has formula (IIh): ##STR00410## or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, atropisomer, isotopologue, or prodrug thereof, wherein R.sup.11 is deuterium, or substituted or unsubstituted C.sub.1-3 alkyl; and u is 0, 1, 2, 3, 4, or 5.

43. (canceled)

44. The compound of claim 39, wherein ring A is ##STR00411## wherein R.sup.12 is H, halogen, substituted or unsubstituted C.sub.1-3 alkyl or cyclopropyl optionally substituted with F; and R.sup.12a is H, deuterium, F or Me.

45. The compound of claim 39, wherein ring A is ##STR00412##

46. (canceled)

47. The compound of claim 39, wherein moiety B is ##STR00413## wherein each of R.sup.a and R.sup.b is, independently, substituted or unsubstituted C.sub.1-4 alkyl; substituted or unsubstituted C.sub.3-5 cycloalkyl; or R.sup.a and R.sup.b together with the N they are attached to form a

substituted or unsubstituted heterocycle containing N, O or S; and R.sup.c is H, halogen, CN, substituted or unsubstituted C.sub.1-4 alkyl, substituted or unsubstituted C.sub.3-5 cycloalkyl, substituted or unsubstituted C.sub.1-4 alkoxyl, or C.sub.1-4 alkoxyl-C(O)—.

48. The compound of claim 39, wherein moiety B is ##STR00414## ##STR00415## ##STR00416## ##STR00417##

49. The compound of claim 39, wherein moiety B is oxabicyclo[2.1.1]hexanyl, optionally substituted with halogen, cyano, hydroxy, C.sub.1-3 alkoxy, or C.sub.1-3 alkyl optionally substituted with halogen, cyano, hydroxy, or C.sub.1-3 alkoxy.

50. The compound of claim 39, wherein moiety B is ##STR00418## or 2-oxabicyclo[2.1.1]hexan-4-yl.

51. The compound of claim 39, wherein moiety B is ##STR00419##

52. The compound of claim 39, wherein the compound is selected from: ##STR00420## ##STR00421## ##STR00422## ##STR00423## ##STR00424## ##STR00425## ##STR00426## ##STR00427## ##STR00428## ##STR00429## ##STR00430## ##STR00431## ##STR00432## ##STR00433## or a pharmaceutically acceptable salt thereof.

53. A pharmaceutical composition comprising an effective amount of a compound of claim 39, or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer, enantiomer, atropisomer, or prodrug thereof, and a pharmaceutically acceptable carrier, excipient or vehicle.

54. (canceled)

55. A method for treatment or prevention of cancer, the method comprising administering to a subject in need thereof an effective amount of a compound of claim 39, or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer, enantiomer, atropisomer, or prodrug thereof, optionally wherein the cancer is mediated by KRAS mutation; preferably KRAS G12D and/or G12V mutation.

56. The compound of claim 39, wherein the compound has one of the following formulas: ##STR00434## or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, atropisomer, isotopologue, or prodrug thereof, wherein: ring C is unsubstituted or substituted C.sub.3-6 cycloalkyl, or unsubstituted or substituted 3-membered to 6-membered heterocyclyl.

57. The compound of claim 56, wherein ring C is cyclopropyl, cyclobutyl, or oxetanyl.

58. The compound of claim 39, wherein R.sup.6a, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or R.sup.6a, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or R.sup.5, and R.sup.7a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; or R.sup.5, and R.sup.8a, together with the atom to which they are attached to, form an unsubstituted or substituted bridge; and the bridge is —(CH.sub.2).sub.2—, —(CH.sub.2).sub.3—, or —CH.sub.2—O—CH.sub.2—.

59. The compound of claim 39, wherein X is N, C—H, C—Cl, or C—CF.sub.3.

60. The compound of claim 39, wherein W is O, or NH.