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(54) Title: MACROCYCLIC RAS INHIBITORS

(57) Abstract: The disclosure features macrocyclic compounds, and pharmaceutical compositions and protein complexes thereof, capable of inhibiting Ras proteins, and their uses in the treatment of cancers.

MACROCYCLIC RAS INHIBITORS

Cross-Reference to Related Applications

The present application claims the benefit of priority to U.S. Application No. 63/351,146, filed on June 10, 2022, and U.S. Application No. 63/455,649, filed on March 30, 2023, each of which is hereby incorporated by reference in its entirety.

Background

The vast majority of small molecule drugs act by binding a functionally important pocket on a target protein, thereby modulating the activity of that protein. For example, cholesterol-lowering drugs known as statins bind the enzyme active site of HMG-CoA reductase, thus preventing the enzyme from engaging with its substrates. The fact that many such drug/target interacting pairs are known may have misled some into believing that a small molecule modulator could be discovered for most, if not all, proteins provided a reasonable amount of time, effort, and resources. This is far from the case. Current estimates are that only about 10% of all human proteins are targetable by small molecules. Bojadzic and Buchwald, Curr Top Med Chem 18: 674-699 (2019). The other 90% are currently considered refractory or intractable toward above-mentioned small molecule drug discovery. Such targets are commonly referred to as “undruggable.” These undruggable targets include a vast and largely untapped reservoir of medically important human proteins. Thus, there exists a great deal of interest in discovering new molecular modalities capable of modulating the function of such undruggable targets.

It has been well established in literature that Ras proteins (K-Ras, H-Ras and N-Ras) play an essential role in various human cancers and are therefore appropriate targets for anticancer therapy. Indeed, mutations in Ras proteins account for approximately 30% of all human cancers in the United States, many of which are fatal. Dysregulation of Ras proteins by activating mutations, overexpression or upstream activation is common in human tumors, and activating mutations in Ras are frequently found in human cancer. For example, activating mutations at codon 12 in Ras proteins function by inhibiting both GTPase-activating protein (GAP)-dependent and intrinsic hydrolysis rates of GTP, significantly skewing the population of Ras mutant proteins to the “on” (GTP-bound) state (Ras(ON)), leading to oncogenic MAPK signaling. Notably, Ras exhibits a picomolar affinity for GTP, enabling Ras to be activated even in the presence of low concentrations of this nucleotide. Mutations at codons 13 (e.g., G13D) and 61 (e.g., Q61K) of Ras are also responsible for oncogenic activity in some cancers.

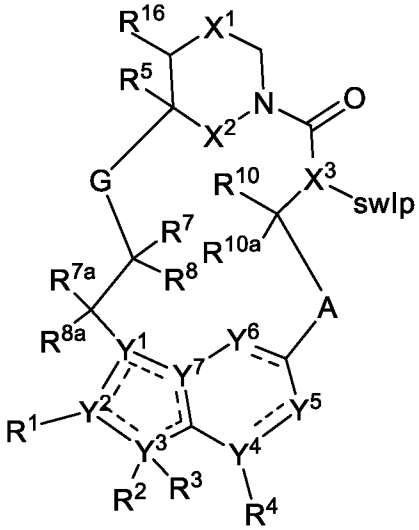
Despite extensive drug discovery efforts against Ras during the last several decades, a drug directly targeting the “on" form of Ras is still not approved. Additional efforts are needed to uncover additional medicines for cancers driven by the various Ras mutations.

Summary

Provided herein are Ras inhibitors. These Ras inhibitors target, that is, selectively bind to or inhibit, Ras(ON) (e.g., selective over the GDP-bound, inactive state of Ras). The approach described herein entails formation of a high affinity three-component complex between a synthetic ligand and two intracellular proteins which do not interact under normal physiological conditions: the target protein of interest (e.g., Ras), and a widely expressed cytosolic chaperone (presenter protein) in the cell (e.g., cyclophilin A). More specifically, in some embodiments, the inhibitors of Ras described herein induce a

new binding pocket in Ras by driving formation of a high affinity tri-complex between the Ras protein and the widely expressed cytosolic chaperone, cyclophilin A (CYPA). Without being bound by theory, the inventors believe that one way the inhibitory effect on Ras is affected by compounds of the invention and the complexes they form is by steric occlusion of the interaction site between Ras and downstream effector molecules, such as RAF and PI3K, which are required for propagating the oncogenic signal.

As such, in some embodiments, the disclosure features a compound, or pharmaceutically acceptable salt thereof, of structural Formula Ia:



Formula Ia

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is optionally substituted C_2-C_4 alkylene, optionally substituted C_1-C_4 heteroalkylene, or optionally substituted C_2-C_4 alkenylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

swlp (Switch I/P-loop) is an organic moiety that non-covalently binds to both the Switch I binding pocket and residues 12 or 13 of the P-loop of a Ras protein (see, e.g., Johnson et al., 292:12981-12993 (2017), incorporated herein by reference);

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally

substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

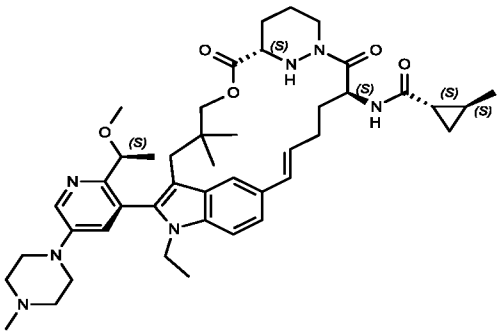
R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo;

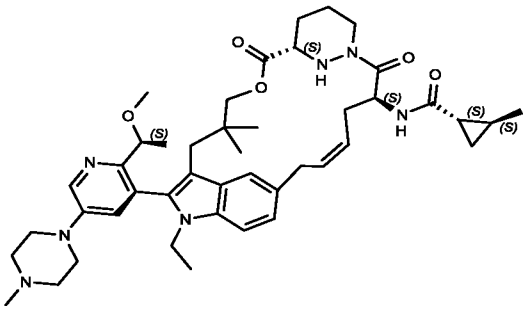
R^{16} is hydrogen or C_1-C_3 alkyl; and

wherein, in some embodiments,

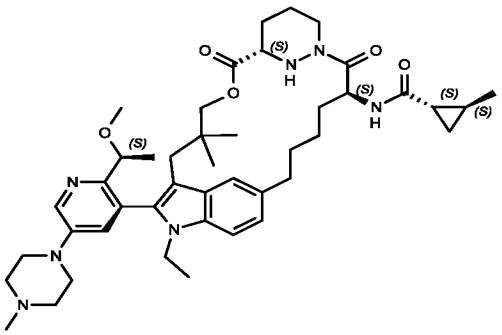
i. the compound is not



Example A,



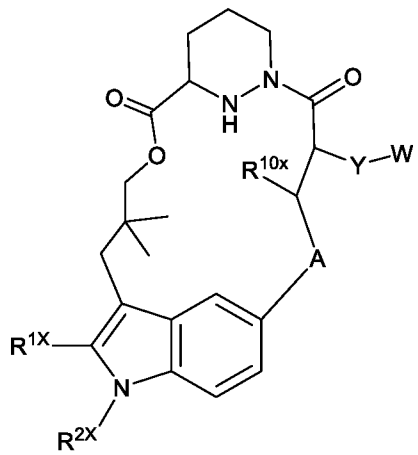
Example B, or



Example C;

or

ii. when W is cyclopropyl, then the compound is not of Formula X, wherein Formula X is:



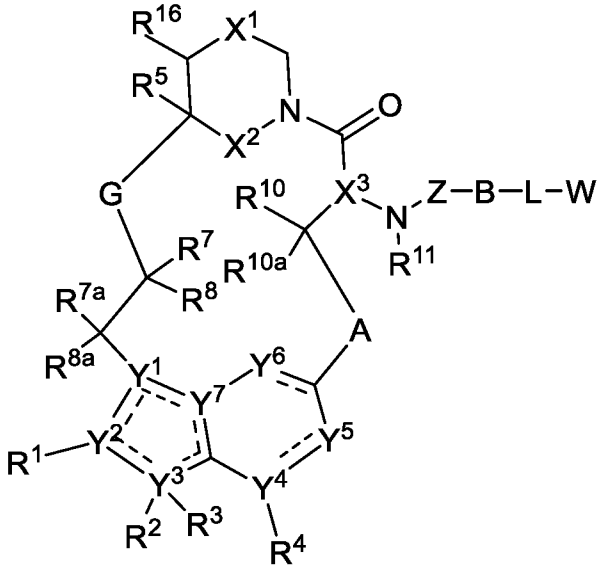
(Formula X)

wherein R^{1X} is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^{2X} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; and

Y is -NHC(O)-, -NHC(O)NH-, -NHC(O)NCH_3-, -NHC(O)O-, -NHS(O)-, -NHS(O)NH-, -$NHS(O)_2$, or -$NHS(O)_2$NH-.

In some embodiments, the disclosure features a compound, or a pharmaceutically acceptable salt thereof, of structural Formula Ib:



Formula Ib

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is optionally substituted C_2-C_4 alkylene, optionally substituted C_1-C_4 heteroalkylene, or optionally substituted C_2-C_4 alkenylene;

B is absent, -NH-, -$N(CH_3)$-, -O-, -$CH(R^9)$- or >$C=CR^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -$N(R^{11})C(O)$-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -$C(R^7R^8)$-, -C(O)NH-**C**H(R^6)- where **C** is bound to -$C(R^7R^8)$-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is hydrogen, cyano, optionally substituted amino, optionally substituted amido, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 3 to 10-membered heteroaryl;

Z is -C(O)- or -$S(O)_2$-;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent or R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), $C=N(O\text{-}C_1\text{-}C_3$ alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

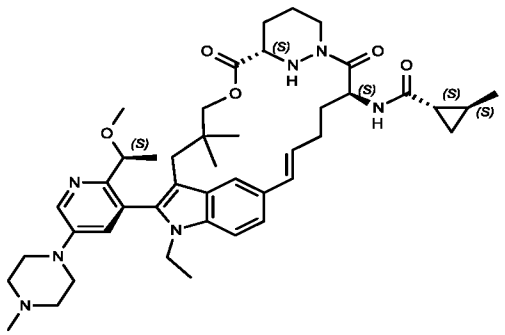
R^{10a} is hydrogen or halo;

R^{11} is hydrogen or C_1-C_3 alkyl;

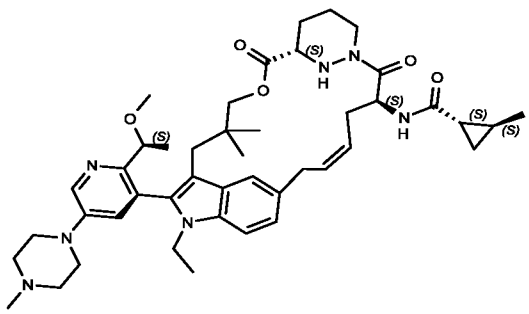
R^{16} is hydrogen or C_1-C_3 alkyl; and

wherein, in some embodiments:

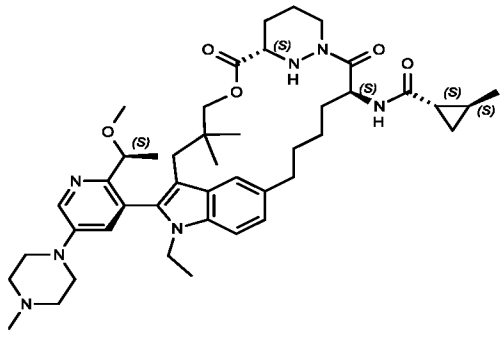
i. the compound is not



Example A,



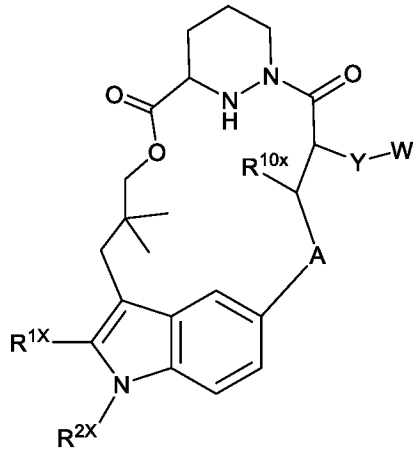
Example B, or



Example C;

or

ii. when W is cyclopropyl, then the compound is not of Formula X, wherein Formula X is:



(Formula X)

wherein R^{1X} is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^{2X} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; and

Y is -NHC(O)-, -NHC(O)NH-, -NHC(O)NCH_3-, -NHC(O)O-, -NHS(O)-, -NHS(O)NH-, -$NHS(O)_2$, or -$NHS(O)_2$NH-.

Also provided are pharmaceutical compositions comprising a compound of Formula Ia or Formula Ib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Also provided is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

In some embodiments, a method is provided of treating a Ras protein-related disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

Further provided is a method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

It is specifically contemplated that any limitation discussed with respect to one embodiment of the invention may apply to any other embodiment of the invention. Furthermore, any compound or composition of the invention may be used in any method of the invention, and any method of the invention may be used to produce or to utilize any compound or composition of the invention.

Definitions and Chemical Terms

In this application, unless otherwise clear from context, (i) the term “a” means “one or more”; (ii) the term "or" is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternative are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or"; (iii) the terms “comprising” and “including” are understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps; and (iv) where ranges are provided, endpoints are included.

As used herein, the term “about” is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value. In certain embodiments, the term “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of a stated value, unless otherwise stated or otherwise evident from the context (e.g., where such number would exceed 100% of a possible value).

As used herein, the term “adjacent” in the context of describing adjacent atoms refers to bivalent atoms that are directly connected by a covalent bond.

A “compound of the present invention” and similar terms as used herein, whether explicitly noted or not, refers to Ras inhibitors described herein, including compounds of Formula Ia or Formula Ib and subformulae thereof, and compounds of Table 1, as well as salts (e.g., pharmaceutically acceptable salts), solvates, hydrates, stereoisomers (including atropisomers), and tautomers thereof.

The term “wild-type” refers to an entity having a structure or activity as found in nature in a “normal” (as contrasted with mutant, diseased, altered, etc.) state or context. Those of ordinary skill in the art will appreciate that wild-type genes and polypeptides often exist in multiple different forms (e.g., alleles).

Those skilled in the art will appreciate that certain compounds described herein can exist in one or more different isomeric (e.g., stereoisomers, geometric isomers, atropisomers, tautomers) or isotopic (e.g., in which one or more atoms has been substituted with a different isotope of the atom, such as hydrogen substituted for deuterium) forms. Unless otherwise indicated or clear from context, a depicted structure can be understood to represent any such isomeric or isotopic form, individually or in combination.

Compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms.

In some embodiments, one or more compounds depicted herein may exist in different tautomeric forms. As will be clear from context, unless explicitly excluded, references to such compounds encompass all such tautomeric forms. In some embodiments, tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton. In certain embodiments, a tautomeric form may be a prototropic tautomer, which is an isomeric protonation state having the same empirical formula and total charge as a reference form. Examples of moieties with prototropic tautomeric

forms are ketone - enol pairs, amide - imidic acid pairs, lactam - lactim pairs, amide - imidic acid pairs, enamine - imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. In some embodiments, tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. In certain embodiments, tautomeric forms result from acetal interconversion.

Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Isotopically-labeled compounds (e.g., those labeled with ^{3}H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, one or more hydrogen atoms are replaced by ^{2}H or ^{3}H, or one or more carbon atoms are replaced by ^{13}C- or ^{14}C-enriched carbon. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Preparations of isotopically labelled compounds are known to those of skill in the art. For example, isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed for compounds of the present invention described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

As is known in the art, many chemical entities can adopt a variety of different solid forms such as, for example, amorphous forms or crystalline forms (e.g., polymorphs, hydrates, solvate). In some embodiments, compounds of the present invention may be utilized in any such form, including in any solid form. In some embodiments, compounds described or depicted herein may be provided or utilized in hydrate or solvate form.

At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_1-C_6 alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl. Furthermore, where a compound includes a plurality of positions at which substituents are disclosed in groups or in ranges, unless otherwise indicated, the present disclosure is intended to cover individual compounds and groups of compounds (e.g., genera and subgenera) containing each and every individual subcombination of members at each position.

The term "optionally substituted X" (e.g., "optionally substituted alkyl") is intended to be equivalent to "X, wherein X is optionally substituted" (e.g., "alkyl, wherein said alkyl is optionally substituted"). It is not intended to mean that the feature "X" (e.g., alkyl) *per se* is optional. As described herein, certain compounds of interest may contain one or more "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent, e.g., any of the substituents or groups described herein. Unless otherwise indicated, an "optionally substituted" group may have a suitable

substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. For example, in the term "optionally substituted C_1-C_6 alkyl-C_2-C_9 heteroaryl," the alkyl portion, the heteroaryl portion, or both, may be optionally substituted. Combinations of substituents envisioned by the present disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group may be, independently, deuterium; halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; 4-11 membered saturated or unsaturated heterocycloalkyl (e.g., 4-8 membered saturated or unsaturated heterocycloalkyl (e.g., pyridyl)) which may be further optionally substituted (e.g., with a methyl); 3-8 membered saturated or unsaturated cycloalkyl (e.g., cyclopropyl, cyclobutyl, or cyclopentyl); $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}$-$C(O)$-$N(R^o)_2$; $-(CH_2)_{0-4}$-$C(O)$-$N(R^o)$-$S(O)_2$-R^o; $-C(NCN)NR^\circ_2$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NOR^\circ)NR^\circ_2$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-P(O)(OR^\circ)_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; $-OP(O)(OR^\circ)R^\circ$, $-SiR^\circ_3$; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, $-C_{1-6}$ aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 3-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), may be, independently, halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered

saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, =NNR*$_2$, =NNHC(O)R*, =NNHC(O)OR*, =NNHS(O)$_2$R*, =NR*, =NOR*, -O(C(R*$_2$))$_{2-3}$O-, or -S(C(R*$_2$))$_{2-3}$S-, wherein each independent occurrence of R* is selected from hydrogen, C$_{1-6}$ aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: -O(CR*$_2$)$_{2-3}$O-, wherein each independent occurrence of R* is selected from hydrogen, C$_{1-6}$ aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of R* include halogen, -R•, -(haloR•), -OH, -OR•, -O(haloR•), -CN, -C(O)OH, -C(O)OR•, -NH$_2$, -NHR•, -NR•$_2$, or -NO$_2$, wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C$_{1-4}$ aliphatic, -CH$_2$Ph, -O(CH$_2$)$_{0-1}$Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include -R†, -NR†$_2$, -C(O)R†, -C(O)OR†, -C(O)C(O)R†, -C(O)CH$_2$C(O)R†, -S(O)$_2$R†, -S(O)$_2$NR†$_2$, -C(S)NR†$_2$, -C(NH)NR†$_2$, or -N(R†)S(O)$_2$R†; wherein each R† is independently hydrogen, C$_{1-6}$ aliphatic which may be substituted as defined below, unsubstituted -OPh, or an unsubstituted 3-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R†, taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on an aliphatic group of R† are independently halogen, -R•, -(haloR•), -OH, -OR•, -O(haloR•), -CN, -C(O)OH, -C(O)OR•, -NH$_2$, -NHR•, -NR•$_2$, or -NO$_2$, wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C$_{1-4}$ aliphatic, -CH$_2$Ph, -O(CH$_2$)$_{0-1}$Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R† include =O and =S.

The term "acetyl," as used herein, refers to the group -C(O)CH$_3$.

The term "alkoxy," as used herein, refers to a -O-C$_1$-C$_{20}$ alkyl group, wherein the alkoxy group is attached to the remainder of the compound through an oxygen atom.

The term "alkyl," as used herein, refers to a saturated, straight or branched monovalent hydrocarbon group containing from 1 to 20 (e.g., from 1 to 10 or from 1 to 6) carbons. In some embodiments, an alkyl group is unbranched (i.e., is linear); in some embodiments, an alkyl group is branched. Alkyl groups are exemplified by, but not limited to, methyl, ethyl, *n*- and *iso*-propyl, *n*-, *sec*-, *iso*- and *tert*-butyl, and neopentyl.

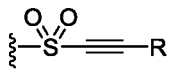
The term "alkylene," as used herein, represents a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, and is

exemplified by methylene, ethylene, isopropylene, and the like. The term "C_x-C_y alkylene" represents alkylene groups having between x and y carbons. Exemplary values for x are 1, 2, 3, 4, 5, and 6, and exemplary values for y are 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, or 20 (e.g., C_1-C_6, C_1-C_{10}, C_2-C_{20}, C_2-C_6, C_2-C_{10}, or C_2-C_{20} alkylene). In some embodiments, the alkylene can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein.

The term "alkenyl," as used herein, represents monovalent straight or branched chain groups of, unless otherwise specified, from 2 to 20 carbons (e.g., from 2 to 6 or from 2 to 10 carbons) containing one or more carbon-carbon double bonds and is exemplified by ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl. Alkenyls include both cis and trans isomers. The term "alkenylene," as used herein, represents a divalent straight or branched chain groups of, unless otherwise specified, from 2 to 20 carbons (e.g., from 2 to 6 or from 2 to 10 carbons) containing one or more carbon-carbon double bonds.

The term "alkynyl," as used herein, represents monovalent straight or branched chain groups from 2 to 20 carbon atoms (e.g., from 2 to 4, from 2 to 6, or from 2 to 10 carbons) containing a carbon-carbon triple bond and is exemplified by ethynyl, and 1-propynyl.

The term "alkynyl sulfone," as used herein, represents a group comprising the structure



, wherein R is any chemically feasible substituent described herein.

The term "amino," as used herein, represents $-N(R^{\dagger})_2$, e.g., $-NH_2$ and $-N(CH_3)_2$.

The term "aminoalkyl," as used herein, represents an alkyl moiety substituted on one or more carbon atoms with one or more amino moieties.

The term "amino acid," as described herein, refers to a molecule having a side chain, an amino group, and an acid group (e.g., $-CO_2H$ or $-SO_3H$), wherein the amino acid is attached to the parent molecular group by the side chain, amino group, or acid group (e.g., the side chain). As used herein, the term "amino acid" in its broadest sense, refers to any compound or substance that can be incorporated into a polypeptide chain, e.g., through formation of one or more peptide bonds. In some embodiments, an amino acid has the general structure H_2N-C(H)(R)-COOH. In some embodiments, an amino acid is a naturally-occurring amino acid. In some embodiments, an amino acid is a synthetic amino acid; in some embodiments, an amino acid is a D-amino acid; in some embodiments, an amino acid is an L-amino acid. "Standard amino acid" refers to any of the twenty standard L-amino acids commonly found in naturally occurring peptides. Exemplary amino acids include alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, optionally substituted hydroxylnorvaline, isoleucine, leucine, lysine, methionine, norvaline, ornithine, phenylalanine, proline, pyrrolysine, selenocysteine, serine, taurine, threonine, tryptophan, tyrosine, and valine.

The term "aryl," as used herein, represents a monovalent monocyclic, bicyclic, or multicyclic ring system formed by carbon atoms, wherein the ring attached to the pendant group is aromatic. Examples of aryl groups are phenyl, naphthyl, phenanthrenyl, and anthracenyl. An aryl ring can be attached to its pendant group at any heteroatom or carbon ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified.

The term "C_0," as used herein, represents a bond. For example, part of the term -N(C(O)-(C_0-C_5 alkylene-H)- includes -N(C(O)-(C_0 alkylene-H)-, which is also represented by -N(C(O)-H)-.

The terms “carbocyclic” and “carbocyclyl,” as used herein, refer to a monovalent, optionally substituted C_3-C_{12} monocyclic, bicyclic, or tricyclic ring structure, which may be bridged, fused or spirocyclic, in which all the rings are formed by carbon atoms and at least one ring is non-aromatic. Carbocyclic structures include cycloalkyl, cycloalkenyl, and cycloalkynyl groups. Examples of carbocyclyl groups are cyclohexyl, cyclohexenyl, cyclooctynyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indenyl, indanyl, decalinyl, and the like. A carbocyclic ring can be attached to its pendant group at any ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified.

The term “carbonyl,” as used herein, represents a C(O) group, which can also be represented as C=O.

The term “carboxyl,” as used herein, means -CO_2H, (C=O)(OH), COOH, or C(O)OH or the unprotonated counterparts.

The term “cyano,” as used herein, represents a -CN group.

The term “cycloalkyl,” as used herein, represents a monovalent saturated cyclic hydrocarbon group, which may be bridged, fused or spirocyclic having from three to eight ring carbons, unless otherwise specified, and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cycloheptyl.

The term “cycloalkenyl,” as used herein, represents a monovalent, non-aromatic, saturated cyclic hydrocarbon group, which may be bridged, fused or spirocyclic having from three to eight ring carbons, unless otherwise specified, and containing one or more carbon-carbon double bonds.

The term “diastereomer,” as used herein, means stereoisomers that are not mirror images of one another and are non-superimposable on one another.

The term “enantiomer,” as used herein, means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e., at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

The term “haloacetyl,” as used herein, refers to an acetyl group wherein at least one of the hydrogens has been replaced by a halogen.

The term “haloalkyl,” as used herein, represents an alkyl moiety substituted on one or more carbon atoms with one or more of the same of different halogen moieties.

The term “halogen,” as used herein, represents a halogen selected from bromine, chlorine, iodine, or fluorine.

The term "heteroalkyl," as used herein, refers to an "alkyl" group, as defined herein, in which at least one carbon atom has been replaced with a heteroatom (e.g., an O, N, or S atom). The heteroatom may appear in the middle or at the end of the radical. The term “heteroalkylene,” as used herein, represents a divalent alkylene straight or branched chain groups of, unless otherwise specified, from 2 to 20 carbons (e.g., from 2 to 6 or from 2 to 10 carbons) in which at least one carbon atom has been replaced with a heteroatom (e.g., an O, N, or S atom). The heteroatom may appear in the middle or at the end of the radical.

The term “heteroaryl,” as used herein, represents a monovalent, monocyclic or polycyclic ring structure that contains at least one fully aromatic ring: i.e., they contain $4n$+2 pi electrons within the monocyclic or polycyclic ring system and contains at least one ring heteroatom selected from N, O, or S in

that aromatic ring. Exemplary unsubstituted heteroaryl groups are of 1 to 12 (e.g., 1 to 11, 1 to 10, 1 to 9, 2 to 12, 2 to 11, 2 to 10, or 2 to 9) carbons. The term "heteroaryl" includes bicyclic, tricyclic, and tetracyclic groups in which any of the above heteroaromatic rings is fused to one or more, aryl or carbocyclic rings, e.g., a phenyl ring, or a cyclohexane ring. Examples of heteroaryl groups include, but are not limited to, pyridyl, pyrazolyl, benzooxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, thiazolyl, quinolinyl, tetrahydroquinolinyl, and 4-azaindolyl. A heteroaryl ring can be attached to its pendant group at any ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified. In some embodiment, the heteroaryl is substituted with 1, 2, 3, or 4 substituents groups.

The term "heterocycloalkyl," as used herein, represents a monovalent monocyclic, bicyclic or polycyclic ring system, which may be bridged, fused or spirocyclic, wherein at least one ring is non-aromatic and wherein the non-aromatic ring contains one, two, three, or four heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The 5-membered ring has zero to two double bonds, and the 6- and 7-membered rings have zero to three double bonds. Exemplary unsubstituted heterocycloalkyl groups are of 1 to 12 (e.g., 1 to 11, 1 to 10, 1 to 9, 2 to 12, 2 to 11, 2 to 10, or 2 to 9) carbons. The term "heterocycloalkyl" also represents a heterocyclic compound having a bridged multicyclic structure in which one or more carbons or heteroatoms bridges two non-adjacent members of a monocyclic ring, e.g., a quinuclidinyl group. The term "heterocycloalkyl" includes bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one or more aromatic, carbocyclic, heteroaromatic, or heterocyclic rings, e.g., an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring, a pyridine ring, or a pyrrolidine ring. Examples of heterocycloalkyl groups are pyrrolidinyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, decahydroquinolinyl, dihydropyrrolopyridine, and decahydronapthyridinyl. A heterocycloalkyl ring can be attached to its pendant group at any ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified.

The term "hydroxy," as used herein, represents a -OH group.

The term "hydroxyalkyl," as used herein, represents an alkyl moiety substituted on one or more carbon atoms with one or more -OH moieties.

The term "isomer," as used herein, means any tautomer, stereoisomer, atropiosmer, enantiomer, or diastereomer of any compound of the invention. It is recognized that the compounds of the invention can have one or more chiral centers or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric E/Z isomers) or diastereomers (e.g., enantiomers (i.e., (+) or (-)) or cis/trans isomers). According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all the corresponding stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, e.g., racemates. Enantiomeric and stereoisomeric mixtures of compounds of the invention can typically be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically or enantiomerically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

As used herein, the term “linker” refers to a divalent organic moiety connecting a first moiety (e.g., a macrocyclic moiety) to a second moiety (e.g., a cross-linking group). In some embodiments, the linker results in a compound capable of achieving an IC50 of 2 μM or less in the Ras-RAF disruption assay protocol provided in the Examples below, and provided here:

The purpose of this biochemical assay is to measure the ability of test compounds to facilitate ternary complex formation between a nucleotide-loaded Ras isoform and cyclophilin A; the resulting ternary complex disrupts binding to a $BRAF^{RBD}$ construct, inhibiting Ras signaling through a RAF effector.

In assay buffer containing 25 mM HEPES pH 7.3, 0.002% Tween20, 0.1% BSA, 100 mM NaCl and 5 mM $MgCl_2$, tagless Cyclophilin A, His6-K-Ras-GMPPNP (or other Ras variant), and GST-$BRAF^{RBD}$ are combined in a 384-well assay plate at final concentrations of 25 μM, 12.5 nM and 50 nM, respectively. Compound is present in plate wells as a 10-point 3-fold dilution series starting at a final concentration of 30 μM. After incubation at 25°C for 3 hours, a mixture of Anti-His Eu-W1024 and anti-GST allophycocyanin is then added to assay sample wells at final concentrations of 10 nM and 50 nM, respectively, and the reaction incubated for an additional 1.5 hours. TR-FRET signal is read on a microplate reader (Ex 320 nm, Em 665/615 nm). Compounds that facilitate disruption of a Ras:RAF complex are identified as those eliciting a decrease in the TR-FRET ratio relative to DMSO control wells.

In some embodiments, the linker comprises 20 or fewer linear atoms. In some embodiments, the linker comprises 15 or fewer linear atoms. In some embodiments, the linker comprises 10 or fewer linear atoms. In some embodiments, the linker has a molecular weight of under 500 g/mol. In some embodiments, the linker has a molecular weight of under 400 g/mol. In some embodiments, the linker has a molecular weight of under 300 g/mol. In some embodiments, the linker has a molecular weight of under 200 g/mol. In some embodiments, the linker has a molecular weight of under 100 g/mol. In some embodiments, the linker has a molecular weight of under 50 g/mol.

The term “stereoisomer,” as used herein, refers to all possible different isomeric as well as conformational forms which a compound may possess (e.g., a compound of any formula described herein), in particular all possible stereochemically and conformationally isomeric forms, all diastereomers, enantiomers or conformers of the basic molecular structure, including atropisomers. Some compounds of the present invention may exist in different tautomeric forms, all of the latter being included within the scope of the present invention.

The term “sulfonyl,” as used herein, represents an $-S(O)_2-$ group.

The term “thiocarbonyl,” as used herein, refers to a -C(S)- group.

Those of ordinary skill in the art, reading the present disclosure, will appreciate that certain compounds described herein may be provided or utilized in any of a variety of forms such as, for example, salt forms, protected forms, pro-drug forms, ester forms, isomeric forms (e.g., optical or structural isomers), isotopic forms, etc. In some embodiments, reference to a particular compound may relate to a specific form of that compound. In some embodiments, reference to a particular compound may relate to that compound in any form. In some embodiments, for example, a preparation of a single stereoisomer of a compound may be considered to be a different form of the compound than a racemic mixture of the compound; a particular salt of a compound may be considered to be a different form from another salt form of the compound; a preparation containing one conformational isomer ((Z) or (E)) of a double bond may be

considered to be a different form from one containing the other conformational isomer ((E) or (Z)) of the double bond; a preparation in which one or more atoms is a different isotope than is present in a reference preparation may be considered to be a different form.

Detailed Description

Compounds

Provided herein are Ras inhibitors. These Ras inhibitors target, that is, selectively bind to or inhibit, Ras(ON) (e.g., selective over the GDP-bound, inactive state of Ras). As used herein, the term "RAS(ON) inhibitor" refers to an inhibitor that targets, that is, selectively binds to or inhibits, the GTP-bound, active state of RAS (e.g., selective over the GDP-bound, inactive state of RAS). Inhibition of the GTP-bound, active state of RAS includes, for example, the inhibition of oncogenic signaling from the GTP-bound, active state of RAS. In some embodiments, the RAS(ON) inhibitor is an inhibitor that selectively binds to and inhibits the GTP-bound, active state of RAS. In certain embodiments, RAS(ON) inhibitors may also bind to or inhibit the GDP-bound, inactive state of RAS (e.g., with a lower affinity or inhibition constant than for the GTP-bound, active state of RAS). In some embodiments, a RAS(ON) inhibitor has a molecular weight of between 800 and 1100 Da, inclusive. Accordingly, for example, the term "KRAS(ON) inhibitor" refers to any inhibitor that binds to KRAS in its GTP-bound "ON" position. A "$KRAS^{G12C}$(ON) inhibitor" is a KRAS inhibitor that selectively binds to or targets the G12C mutant form of KRAS. Non-limiting examples of RAS(ON) inhibitors, some of which are $KRAS^{G12C}$(ON) inhibitors, are provided in WO 2021091982, WO 2021091967, WO 2021091956, and WO 2020132597.

As used herein, the term "RAS(OFF) inhibitor" refers to an inhibitor that targets, that is, selectively binds to or inhibits the GDP-bound, inactive state of RAS (e.g., selective over the GTP-bound, active state of RAS). Inhibition of the GDP-bound, inactive state of RAS includes, for example, sequestering the inactive state by inhibiting the exchange of GDP for GTP, thereby inhibiting RAS from adopting the active conformation. In certain embodiments, RAS(OFF) inhibitors may also bind to or inhibit the GTP-bound, active state of RAS (e.g., with a lower affinity or inhibition constant than for the GDP-bound, inactive state of RAS). In some embodiments, a RAS(OFF) inhibitor has a molecular weight of under 700 Da. In some embodiments, a RAS(OFF) inhibitor has a molecular weight of under 700 Da. Accordingly, for example, the term "KRAS(OFF) inhibitor" refers to any inhibitor that binds to KRAS in its GDP-bound "OFF" position. A "$KRAS^{G12C}$(OFF) inhibitor" is a KRAS inhibitor that selectively binds to or targets the G12C mutant form of KRAS. $KRAS^{G12C}$(OFF) inhibitors are known in the art and non-limiting examples include adagrasib and sotorasib. Additional KRAS(OFF) inhibitors are provided herein.

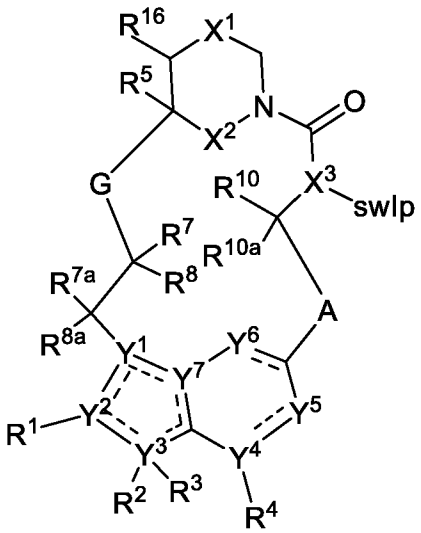
The term "inhibitor" means a compound or agent (e.g., peptide, antibody) that prevents a biomolecule, (e.g., a protein) from completing or initiating a reaction. An inhibitor can inhibit a reaction by competitive, uncompetitive, or non-competitive means.

The approach described herein entails formation of a high affinity three-component complex between a synthetic ligand and two intracellular proteins which do not interact under normal physiological conditions: the target protein of interest (e.g., Ras), and a widely expressed cytosolic chaperone (presenter protein) in the cell (e.g., cyclophilin A). More specifically, in some embodiments, the inhibitors of Ras described herein induce a new binding pocket in Ras by driving formation of a high affinity tri-complex between the Ras protein and the widely expressed cytosolic chaperone, cyclophilin A (CYPA). Without being bound by theory, the inventors believe that one way the inhibitory effect on Ras is effected by

compounds of the invention and the complexes they form is by steric occlusion of the interaction site between Ras and downstream effector molecules, such as RAF, which are required for propagating the oncogenic signal.

Without being bound by theory, the inventors postulate that non-covalent interactions of a compound of the present invention with Ras and the chaperone protein (e.g., cyclophilin A) may contribute to the inhibition of Ras activity. For example, van der Waals, hydrophobic, hydrophilic and hydrogen bond interactions, and combinations thereof, may contribute to the ability of the compounds of the present invention to form complexes and act as Ras inhibitors. Accordingly, a variety of Ras proteins may be inhibited by compounds of the present invention (e.g., a wild-type Ras or Ras^{amp}, or K-Ras, N-Ras, H-Ras, and mutants thereof at positions 12, 13 and 61, such as G12C, G12D, G12V, G12S, G13C, G13D, and Q61L, and others described herein, as well as combinations of Ras proteins).

Accordingly, provided herein are compounds, or pharmaceutically acceptable salts thereof, having the structure of Formula Ia:



Formula Ia

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is optionally substituted C_2-C_4 alkylene, optionally substituted C_1-C_4 heteroalkylene, or optionally substituted C_2-C_4 alkenylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

swlp (Switch I/P-loop) is an organic moiety that non-covalently binds to both the Switch I binding pocket and residues 12 or 13 of the P-loop of a Ras protein (see, e.g., Johnson et al., 292:12981-12993 (2017), incorporated herein by reference);

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

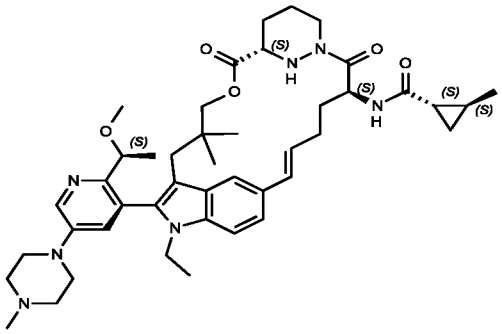
R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo;

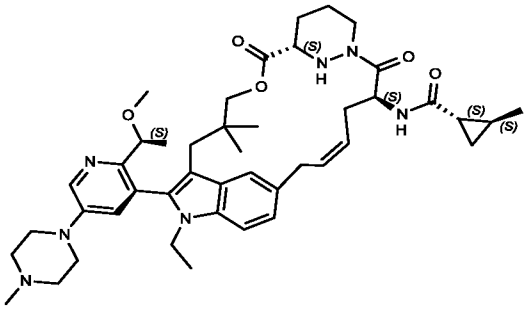
R^{16} is hydrogen or C_1-C_3 alkyl; and

wherein, in some embodiments,

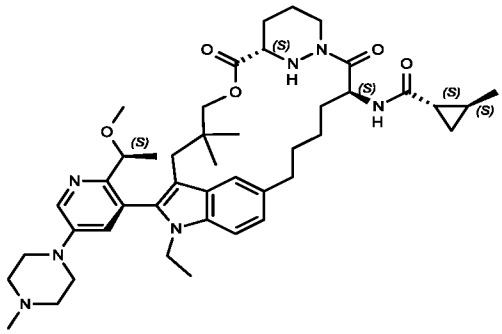
i. the compound is not



Example A,



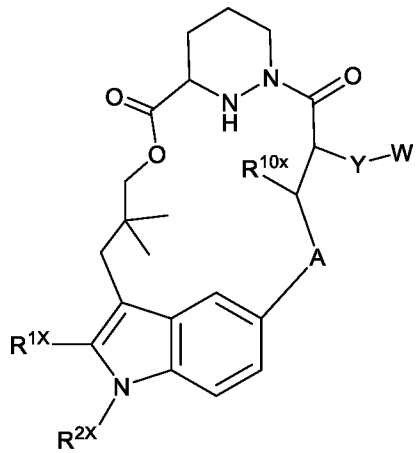
Example B, or



Example C;

or

ii. when W is cyclopropyl, then the compound is not of Formula X, wherein Formula X is:



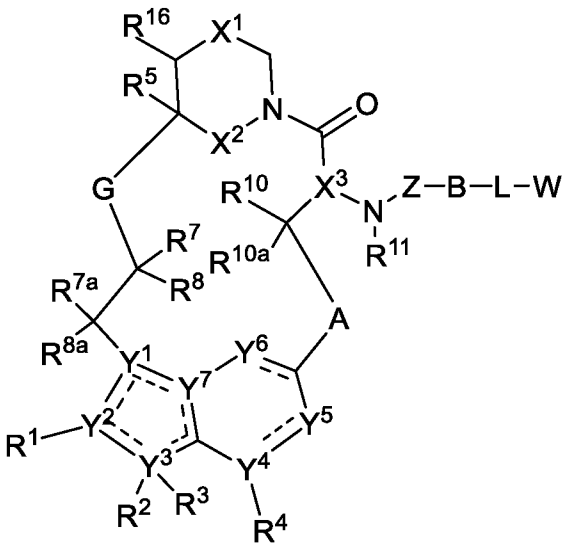
(Formula X)

wherein R^{1X} is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^{2X} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; and

Y is -NHC(O)-, -NHC(O)NH-, -NHC(O)NCH_3-, -NHC(O)O-, -NHS(O)-, -NHS(O)NH-, -$NHS(O)_2$, or -$NHS(O)_2$NH-.

In some embodiments, the compound, or a pharmaceutically acceptable salt thereof, has the structure of Formula Ib:



Formula Ib

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is optionally substituted C_2-C_4 alkylene, optionally substituted C_1-C_4 heteroalkylene, or optionally substituted C_2-C_4 alkenylene;

B is absent, -NH-, -$N(CH_3)$-, -O-, -$CH(R^9)$- or >$C=CR^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -$N(R^{11})C(O)$-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -$C(R^7R^8)$-, -C(O)NH-**C**H(R^6)- where **C** is bound to -$C(R^7R^8)$-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is hydrogen, cyano, optionally substituted amino, optionally substituted amido, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted

3 to 10-membered cycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 3 to 10-membered heteroaryl;

Z is -C(O)- or -$S(O)_2$-;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent or R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), $C=N(O\text{-}C_1\text{-}C_3$ alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

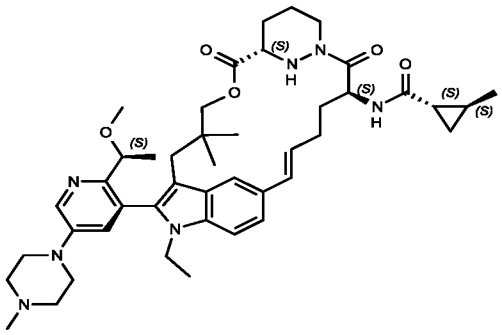
R^{10a} is hydrogen or halo;

R^{11} is hydrogen or C_1-C_3 alkyl;

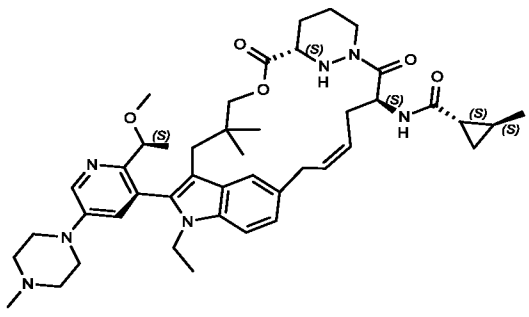
R^{16} is hydrogen or C_1-C_3 alkyl; and

wherein, in some embodiments:

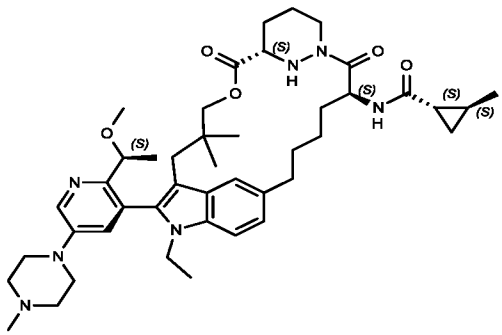
i. the compound is not



Example A,



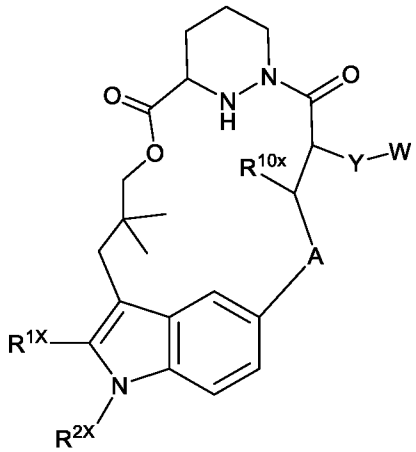
Example B, or



Example C;

or

ii. when W is cyclopropyl, then the compound is not of Formula X, wherein Formula X is:



(Formula X)

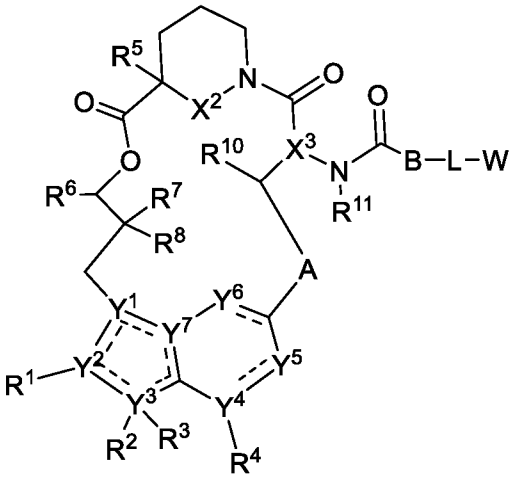
wherein R^{1X} is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^{2X} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; and

Y is -NHC(O)-, -NHC(O)NH-, -NHC(O)NCH_3-, -NHC(O)O-, -NHS(O)-, -NHS(O)NH-, -$NHS(O)_2$, or -$NHS(O)_2$NH-.

In some embodiments, Z is -C(O)-.

In some embodiments, the compound, or pharmaceutically acceptable salt thereof, has the structure of Formula Ic:



Formula Ic

wherein Y^5 and Y^6 are, independently, CH or N;

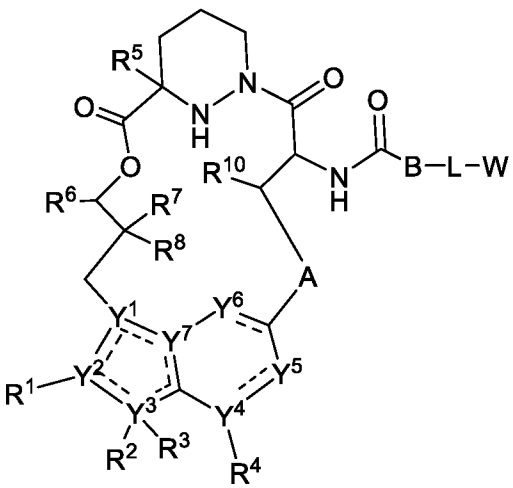
R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent or R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; and

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl.

In some embodiments, the compound, or pharmaceutically acceptable salt thereof, has the structure of Formula Id:



Formula Id

wherein B is absent, -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally susbtituted 3 to 8-membered heteroaryl;

Y^5 and Y^6 are, independently, CH or N;

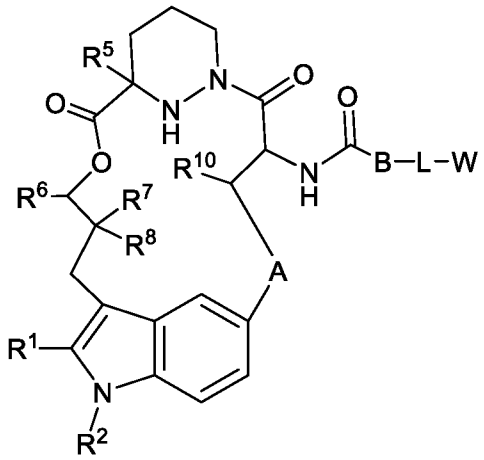
R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent or R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; and

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl.

In some embodiments, the compound, or pharmaceutically acceptable salt thereof, has the structure of Formula Ie:



Formula Ie

wherein B is absent, -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl

optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally susbtituted 3 to 8-membered heteroaryl;

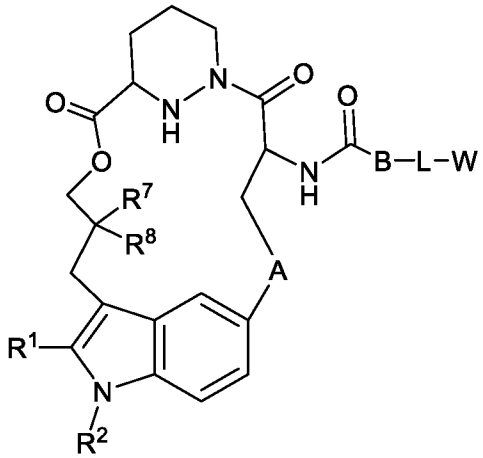
R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent or R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; and

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl.

In some embodiments, the compound, or pharmaceutically acceptable salt thereof, has the structure of Formula If:



Formula If

B is absent, -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally susbtituted 3 to 8-membered heteroaryl;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

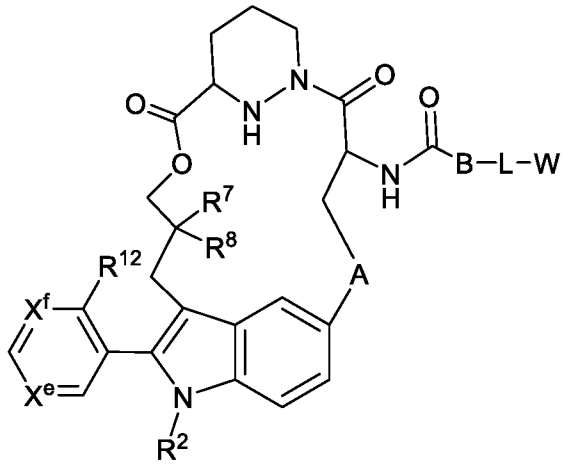
R^7 is C_1-C_3 alkyl;

R^8 is C_1-C_3 alkyl; and

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

In some embodiments, R^1 is optionally substituted 5 to 10-membered heteroaryl. In some embodiments, R^1 is optionally substituted 6-membered aryl or optionally substituted 6-membered heteroaryl.

In some embodiments, the compound, or pharmaceutically acceptable salt thereof, has the structure of Formula Ig:



Formula Ig

B is absent, -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally susbtituted 3 to 8-membered heteroaryl;

R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

R^7 is C_1-C_3 alkyl;

R^8 is C_1-C_3 alkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

X^e is N, CH, or CR^{17};

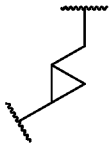
X^f is N or CH;

R^{12} is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl; and

R^{17} is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

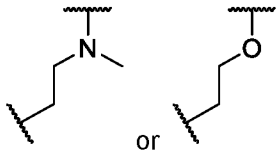
In some embodiments, R^7 is methyl. In some embodiments, R^8 is methyl.

In some embodiments, A is optionally substituted C_2-C_4 alkylene. In some embodiments, A is optionally substituted C_3 alkylene. In some embodiments, A is:



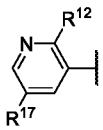
.

In some embodiments, A is optionally substituted C_2-C_4 alkenylene. In some embodiments, A is optionally substituted C_3 alkenylene. In some embodiments, A is optionally substituted C_1-C_4 heteroalkylene. In some embodiments, A is optionally substituted C_2 heteroalkylene. In some embodiments, A is:



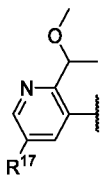
or .

In some embodiments, R^1 is



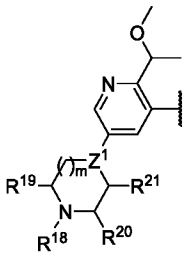
.

In some embodiments, R^1 is



.

In some embodiments, R^1 is



,

wherein Z^1 is N or CH;

m is 1 or 2;

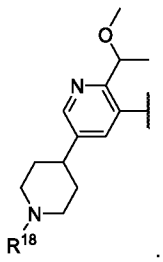
R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^{18} and R^{20} combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^{20} and R^{21} combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

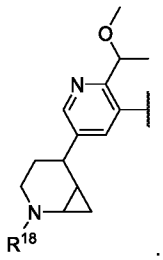
R^{19} and R^{20} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

In some embodiments, R^1 is



.

In some embodiments, R^1 is



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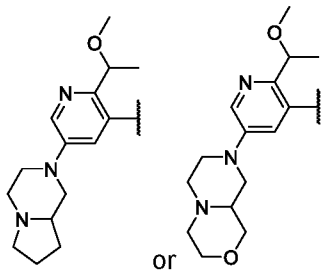
In some embodiments, R^{18} is methyl.

In some embodiments, R^1 is



or

.

In some embodiments, B is $-CHR^9-$. In some embodiments, R^9 is optionally substituted C_1-C_6 alkyl or optionally substituted 3 to 6-membered cycloalkyl. In some embodiments, B is optionally substituted 6-membered arylene. In some embodiments, B is absent.

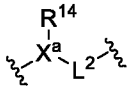
In some embodiments, the linker has the structure has the structure of Formula II:

$$A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h\text{-}(D^1)\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$$

Formula II

where A^1 is a bond between the linker and B; A^2 is a bond between W and the linker; B^1, B^2, B^3, and B^4 each, independently, is selected from optionally substituted C_1-C_2 alkylene, optionally substituted C_1-C_3 heteroalkylene, O, S, and NR^N; R^N is hydrogen, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_3 cycloalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted C_1-C_7 heteroalkyl; C^1 and C^2 are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; f, g, h, i, j, and k are each, independently, 0 or 1; and D^1 is optionally substituted C_1-C_{10} alkylene, optionally substituted C_2-C_{10} alkenylene, optionally substituted C_2-C_{10} alkynylene, optionally substituted 3 to 14-membered heterocycloalkylene, optionally substituted 5 to 10-membered heteroarylene, optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 6 to 10-membered arylene, optionally substituted C_2-C_{10} polyethylene glycolene, or optionally substituted C_1-C_{10} heteroalkylene, or a chemical bond linking $A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h$- to $\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$.

In some embodiments, the linker is acyclic. In some embodiments, the linker has the structure of Formula IIa:



Formula IIa

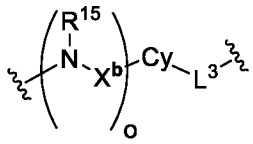
wherein X^a is absent or N;

R^{14} is absent, hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_3 cycloalkyl; and

L^2 is absent, -C(O)-, -SO_2-, optionally substituted C_1-C_4 alkylene or optionally substituted C_1-C_4 heteroalkylene,

wherein at least one of X^a, R^{14}, or L^2 is present.

In some embodiments, the linker is or comprises a cyclic group. In some embodiments, the linker has the structure of Formula IIb:



Formula IIb

wherein o is 0 or 1;

X^b is C(O) or SO_2;

R^{15} is hydrogen or optionally substituted C_1-C_6 alkyl;

Cy is optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 3 to 8-membered heterocycloalkylene, optionally substituted 6-10 membered arylene, or optionally substituted 5 to 10-membered heteroarylene; and

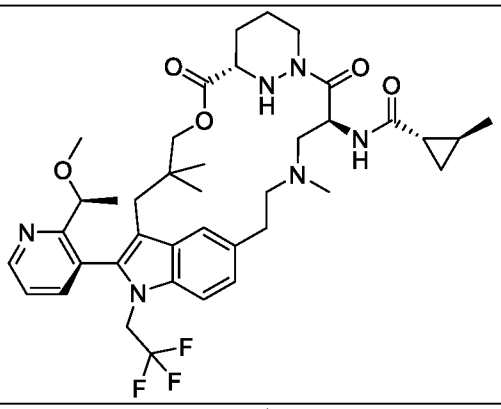
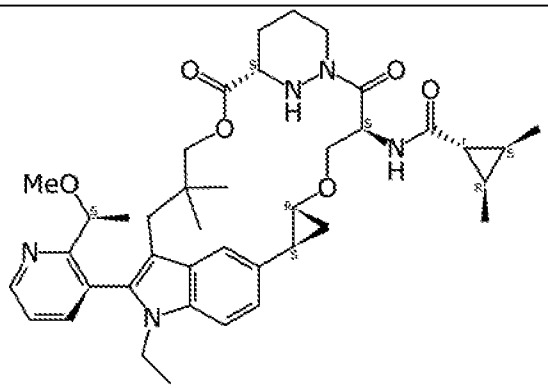
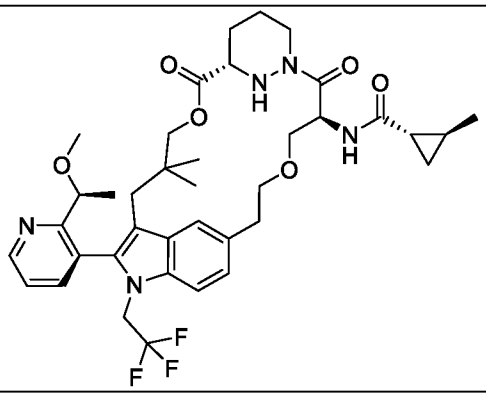
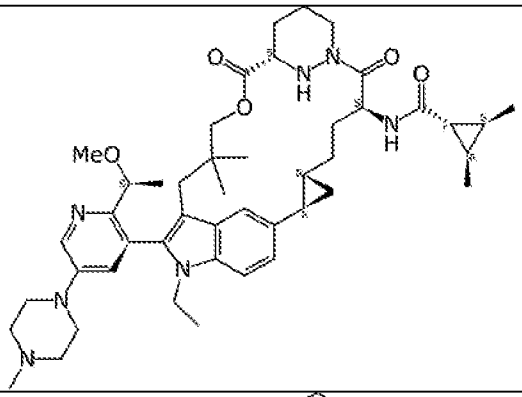
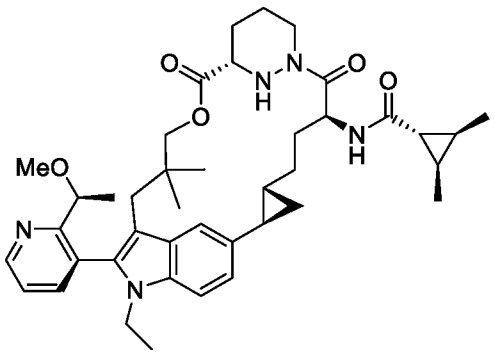
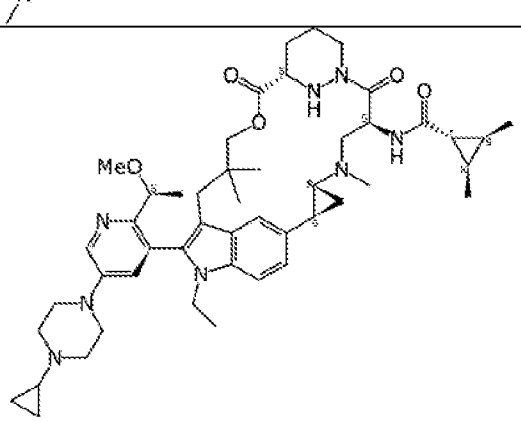
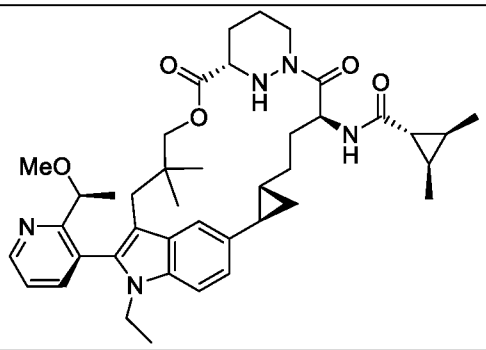
L^3 is absent, -C(O)-, -SO_2-, optionally substituted C_1-C_4 alkylene or optionally substituted C_1-C_4 heteroalkylene.

In some embodiments, the linker is absent.

In some embodiments, W is hydrogen. In some embodiments, W is optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclohexyl, optionally substituted piperidine, optionally substituted piperazine, optionally substituted pyridine, or optionally substituted phenyl. In some embodiments, W is optionally substituted amino. In some embodiments, W is optionally substituted amido. In some embodiments, W is optionally substituted C_1-C_4 alkoxy. In some embodiments, W is optionally substituted C_1-C_4 alkyl. In some embodiments, W is optionally substituted C_1-C_4 hydroxyalkyl. In some embodiments, W is optionally substituted C_1-C_4 aminoalkyl. In some embodiments, W is optionally substituted C_1-C_4 haloalkyl. In some embodiments, W is optionally substituted C_1-C_4 guanidinoalkyl. In some embodiments, W is C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl. In some embodiments, W is optionally substituted 3 to 10-membered cycloalkyl. In some embodiments, W is optionally substituted 3 to 10-membered heteroaryl. In some embodiments, W is optionally substituted 6- to 10-membered aryl.

In some embodiments, a compound of the present invention is selected from Table 1, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, a compound of the present invention is selected from Table 1, or a pharmaceutically acceptable salt or atropisomer thereof.

Table 1: Certain Compounds of the Present Invention

Ex #	Structure	Ex #	Structure
A1		A5	
A2		A6	
A3		A7	
A4			

Note that some compounds are shown with bonds as flat or wedged. In some instances, the relative stereochemistry of stereoisomers has been determined; in some instances, the absolute stereochemistry has been determined. All stereoisomers of the compounds of the foregoing table are contemplated by the present invention. In particular embodiments, an atropisomer of a compound of the foregoing table is contemplated.

In some embodiments, a compound of the present invention has improved oral bioavailability (%F) compared to what is known in the art. Methods of measuring oral bioavailability are known in the art, and one such method is provided below:

Oral bioavailability may be determined in BALB/c mice. Following intravenous (IV) bolus and oral gavage (PO) administration of a test compound, about 30 µL of whole blood samples are collected at designated time points into tubes containing K_2EDTA. The blood samples are centrifuged at 4600 rpm at 4 °C for about 5 minutes and plasma samples are stored at -80 °C prior to bioanalysis. Plasma samples are extracted by protein precipitation and analyzed by tandem mass spectrometry (LC MS/MS) on, for example, an API 5500 system using electrospray positive ionization.

All PK parameters may be derived from plasma concentration over time data with noncompartment analysis using WinNonlin. The bioavailability (F%, also %F) is estimated using the following equation:

$$F\% = \frac{AUC_{inf,PO}}{AUC_{inf,IV}} \cdot \frac{Dose_{IV}}{Dose_{PO}}$$

$AUC_{inf,PO}$ is the area under the plasma concentration over time from time zero to infinity following PO administration.

$AUC_{inf,IV}$ is the area under the plasma concentration over time from time zero to infinity following IV administration.

$Dose_{IV}$ is the total dose of IV administration

$Dose_{PO}$ is the total dose of PO administration

In general, F% (or %F) values of over 30% are preferred, with values over 50% being more preferred.

In some embodiments, a compound of the present invention is selective for one or more particular Ras mutants over other Ras mutants or wild-type compared to what is known in the art. Methods of measuring such selectivity are known in the art, such as the Ras-Raf binding assay, a protocol for which is provided in the Examples below. Accordingly, in some embodiments, compounds of the present invention are selective for $KRAS^{G12C}$ over other Ras mutants or over wild-type. In some embodiments, compounds of the present invention are selective for $KRAS^{G12D}$ over other Ras mutants or over wild-type. In some embodiments, compounds of the present invention are selective for $KRAS^{G12V}$ over other Ras mutants or over wild-type. In some embodiments, compounds of the present invention are selective for $KRAS^{G12D}$ over other Ras mutants or over wild-type. In some embodiments, compounds of the present invention are selective for $NRAS^{Q61K}$ over other Ras mutants or over wild-type. In some embodiments, compounds of the present invention are selective for $KRAS^{G12D}$ and $KRAS^{G12V}$ over other Ras mutants and wild-type. Compounds of the present invention may also exhibit greater selectivity with respect to other RAS mutants disclosed herein, or combinations thereof. In some embodiments, compounds of the present invention exhibit an IC50 value of less than 30 nm for one or more Ras mutants described herein in the Ras-Raf binding assay described above.

In some embodiments, a compound of the present invention is more potent for one or more particular Ras mutants over other Ras mutants or wild-type compared to what is known in the art. Methods of measuring such potency are known in the art, such as the pERK assay, a protocol for which is provided in the Examples below. Accordingly, in some embodiments, compounds of the present invention exhibit

greater potency with respect to $KRAS^{G12D}$ than what is known in the art. In some embodiments, compounds of the present invention exhibit greater potency with respect to $KRAS^{G12V}$ than what is known in the art. In some embodiments, compounds of the present invention exhibit greater potency with respect to $KRAS^{G12C}$ than what is known in the art. In some embodiments, compounds of the present invention exhibit greater potency with respect to both $KRAS^{G12D}$ and $KRAS^{G12V}$ than what is known in the art. Compounds of the present invention may also exhibit greater potency with respect to other RAS mutants disclosed herein, or combinations thereof.

In some embodiments, a compound of the present invention exhibits a greater detrimental effect on cell viability with respect to one or more particular Ras mutants over other Ras mutants or wild-type compared to what is known in the art. Methods of measuring cell viability are known in the art, such as the CellTiter-Glo® Cell Viability Assay assay, a protocol for which is provided in the Examples below. Accordingly, in some embodiments, compounds of the present invention exhibit a greater decrease in cell viability with respect to $KRAS^{G12D}$ compared to what is known in the art. In some embodiments, compounds of the present invention exhibit a greater decrease in cell viability with respect to $KRAS^{G12V}$ compared to what is known in the art. In some embodiments, compounds of the present invention exhibit a greater decrease in cell viability with respect to $KRAS^{G12C}$ compared to what is known in the art. In some embodiments, compounds of the present invention exhibit a greater decrease in cell viability with respect to both $KRAS^{G12D}$ and $KRAS^{G12V}$ compared to what is known in the art. Compounds of the present invention may also exhibit a greater decrease in cell viability respect to other RAS mutants disclosed herein, or combinations thereof.

In some embodiments, a compound of the present invention may exhibit greater metabolic stability, permeability, or solubility, or a combination thereof, versus what is known in the art. Methods for measuring such properties are known in the art. In some embodiments, a compound of the present invention may exhibit improvements with respect to any of the following properties, or a combination thereof, compared to what is known in the art: selectivity, potency, cell viability, metabolic stability, permeability, or solubility.

In some embodiments, a compound of the present invention is or acts as a prodrug, such as with respect to administration to a cell or to a subject in need thereof.

Also provided are pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Further provided is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof. The cancer may, for example, be pancreatic cancer, colorectal cancer, non-small cell lung cancer, acute myeloid leukemia, multiple myeloma, thyroid gland adenocarcinoma, a myelodysplastic syndrome, or squamous cell lung carcinoma. In some embodiments, the cancer comprises a Ras mutation, such as K-Ras G12C, K-Ras G12D, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G13D, K-Ras Q61H, K-Ras Q61R, K-Ras Q61K, or K-Ras Q61L, or a combination thereof. In some embodiments, the cancer comprises a Ras mutation, such as N-Ras G12D, N-Ras Q61R, N-Ras Q61K, N-Ras Q61L, N-Ras Q61H, or N-Ras Q61P, or a combination thereof. Other Ras mutations are described herein.

Further provided is a method of treating a Ras protein-related disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

Further provided is a method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof. For example, the Ras protein is K-Ras G12C, K-Ras G12D, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G13D, K-Ras Q61H, K-Ras Q61R, K-Ras Q61K, or K-Ras Q61L. The Ras protein may be, for example, N-Ras G12D, N-Ras Q61R, N-Ras Q61K, N-Ras Q61L, N-Ras Q61H, or N-Ras Q61P. Other Ras proteins are described herein. The cell may be a cancer cell, such as a pancreatic cancer cell, a colorectal cancer cell, a lung cancer (e.g., non-small cell lung cancer cell), an acute myeloid leukemia cell, a multiple myeloma cell, a thyroid gland adenocarcinoma cell, a myelodysplastic syndrome cell, a melanoma cell, or a squamous cell lung carcinoma cell. Other cancer types are described herein. The cell may be in vivo or in vitro.

With respect to compounds of the present invention, one stereoisomer may exhibit better inhibition than another stereoisomer. For example, one atropisomer may exhibit inhibition, whereas the other atropisomer may exhibit little or no inhibition.

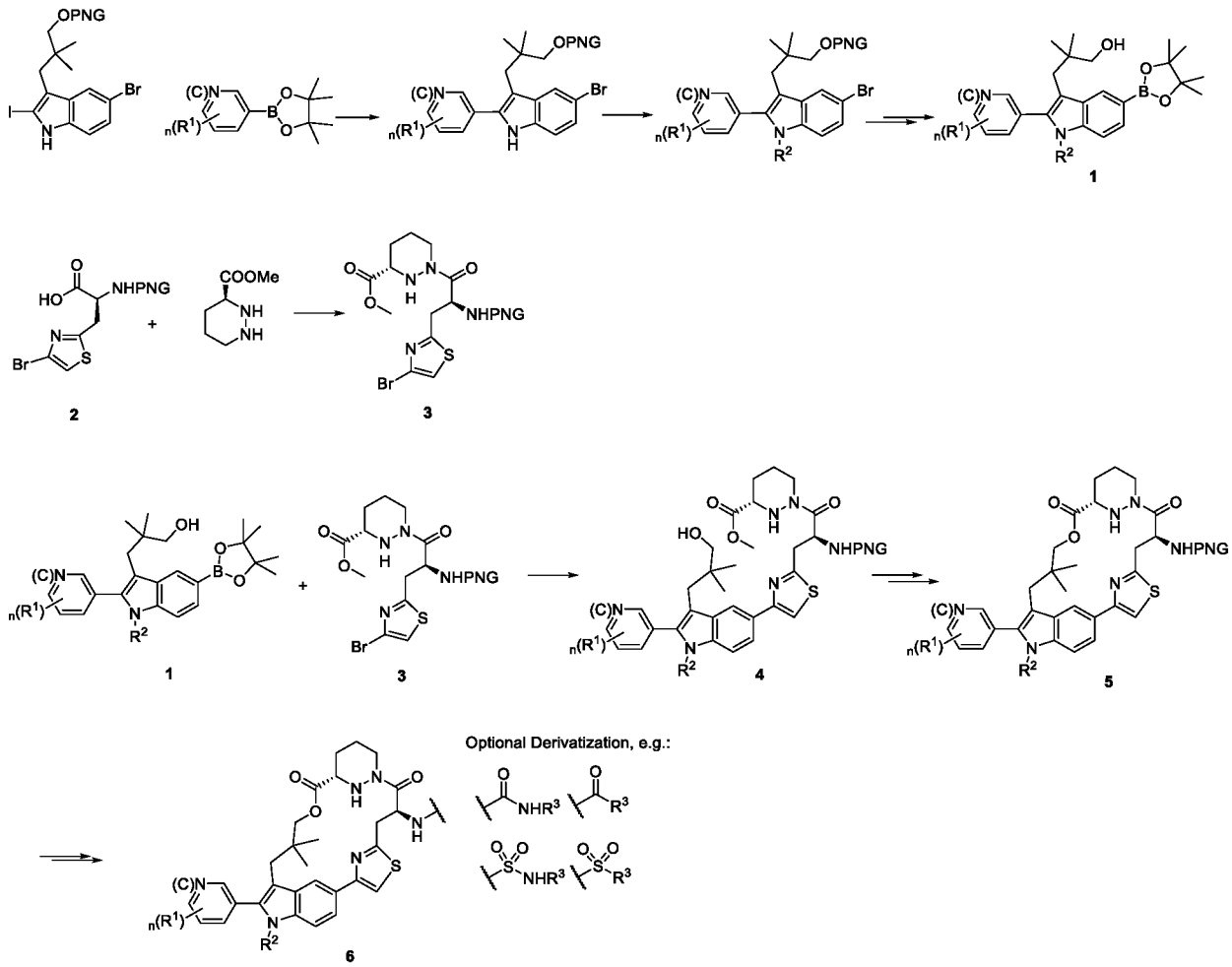
In some embodiments, a method or use described herein further comprises administering an additional anti-cancer therapy. In some embodiments, the additional anti-cancer therapy is a HER2 inhibitor, an EGFR inhibitor, a second Ras inhibitor, a SHP2 inhibitor, a SOS1 inhibitor, a Raf inhibitor, a MEK inhibitor, an ERK inhibitor, a PI3K inhibitor, a PTEN inhibitor, an AKT inhibitor, an mTORC1 inhibitor, a BRAF inhibitor, a PD-L1 inhibitor, a PD-1 inhibitor, a CDK4/6 inhibitor, or a combination thereof. In some embodiments, the additional anticancer therapy is a SHP2 inhibitor. Other additional anti-cancer therapies are described herein.

Methods of Synthesis

The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, or enzymatic processes.

The compounds of the present invention can be prepared by methods known to those of skill in the art, such as those disclosed in WO 2021/091956 and WO 2022/060836 in combination with known synthetic organic chemistry techniques, the disclosure of each of which is incorporated herein by reference. By way of example, compounds of the present invention can be synthesized using the methods described in the Schemes below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. These methods include but are not limited to those methods described in the Schemes below.

Scheme 1. General synthesis of macrocyclic esters



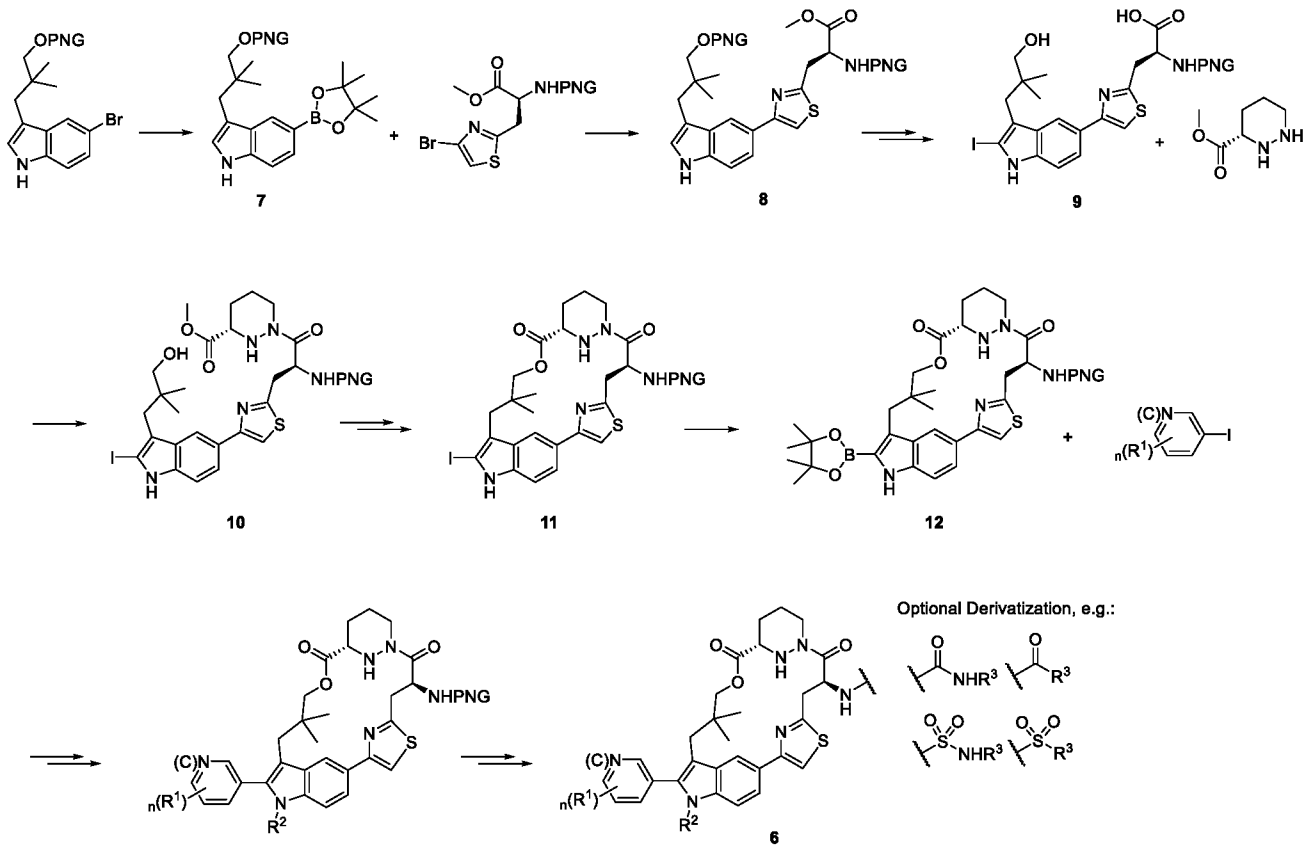
A general synthesis of macrocyclic esters is outlined in Scheme 1. An appropriately substituted indolyl boronic ester (**1**) can be prepared in four steps starting from protected 3-(5-bromo-2-iodo-1H-indol-3-yl)-2,2-dimethylpropan-1-ol and appropriately substituted boronic acid, including palladium mediated coupling, alkylation, de-protection, and palladium mediated borylation reactions.

Methyl-amino-3-(4-bromothiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (**3**) can be prepared via coupling of (S)-2-amino-3-(4-bromothiazol-2-yl)propanoic acid (**2**) with methyl (*S*)-hexahydropyridazine-3-carboxylate.

The final macrocyclic esters can be made by coupling of methyl-amino-3-(4-bromothiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (**3**) and an appropriately substituted indolyl boronic ester (**1**) in the presence of Pd catalyst followed by hydrolysis and macrolactonization steps to result in an appropriately protected macrocyclic intermediate (**5**). Deprotection and coupling with an appropriately substituted carboxylic acid (or other coupling partner) can result in a macrocyclic product. Additional deprotection or functionalization steps could be required to produce a final compound **6**.

Further, with respect to Scheme 1, the thiazole may be replaced with an alternative optionally substituted 5 to 6-membered heteroarylene, or an optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene (e.g., morpholino), or optionally substituted 6-membered arylene (e.g., phenyl).

Scheme 2. Alternative general synthesis of macrocyclic esters



Alternatively, macrocyclic esters can be prepared as described in Scheme 2. An appropriately substituted and protected indolyl boronic ester (**7**) can be coupled in the presence of Pd catalyst with (S)-2-amino-3-(4-bromothiazol-2-yl)propanoic acid, followed by iodination, deprotection, and ester hydrolysis. Subsequent coupling with methyl (*S*)-hexahydropyridazine-3-carboxylate, followed by hydrolysis and macrolactonization can result in iodo intermediate (**11**). Subsequent palladium mediated borylation and coupling in the presence of Pd catalyst with an appropriately substituted iodo aryl or iodo heteroaryl intermediate can yield an appropriately protected macrocyclic intermediate. Alkylation, deprotection and coupling with an appropriately substituted carboxylic acid carboxylic acid (or other coupling partner) results in a macrocyclic product. Additional deprotection or functionalization steps could be required to produce a final compound **6**.

Further, with respect to Scheme 2, the thiazole may be replaced with an alternative optionally substituted 5 to 6-membered heteroarylene, or an optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene (e.g., morpholino), or optionally substituted 6-membered arylene (e.g., phenyl).

Compounds of Table 1 herein were prepared using methods disclosed herein or were prepared using methods described herein combined with the knowledge of one of skill in the art.

Pharmaceutical Compositions and Methods of Use

Pharmaceutical Compositions and Methods of Administration

The compounds with which the invention is concerned are Ras inhibitors, and are useful in the treatment of cancer. Accordingly, one embodiment of the present invention provides pharmaceutical compositions containing a compound of the invention or a pharmaceutically acceptable salt thereof, and a

pharmaceutically acceptable excipient, as well as methods of using the compounds of the invention to prepare such compositions.

As used herein, the term “pharmaceutical composition” refers to a compound, such as a compound of the present invention, or a pharmaceutically acceptable salt thereof, formulated together with a pharmaceutically acceptable excipient.

In some embodiments, a compound is present in a pharmaceutical composition in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

A “pharmaceutically acceptable excipient,” as used herein, refers any inactive ingredient (for example, a vehicle capable of suspending or dissolving the active compound) having the properties of being nontoxic and non-inflammatory in a subject. Typical excipients include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, or waters of hydration. Excipients include, but are not limited to: butylated optionally substituted hydroxyltoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, optionally substituted hydroxylpropyl cellulose, optionally substituted hydroxylpropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol. Those of ordinary skill in the art are familiar with a variety of agents and materials useful as excipients. See, e.g., e.g., Ansel, et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, et al., Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. In some embodiments, a composition includes at least two different pharmaceutically acceptable excipients.

Compounds described herein, whether expressly stated or not, may be provided or utilized in salt form, e.g., a pharmaceutically acceptable salt form, unless expressly stated to the contrary. The term “pharmaceutically acceptable salt,” as use herein, refers to those salts of the compounds described herein that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other animals without undue toxicity, irritation, allergic response and the like, and are commensurate

with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting the free base group with a suitable organic acid.

The compounds of the invention may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention, be prepared from inorganic or organic bases. In some embodiments, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulfuric, hydrobromic, acetic, lactic, citric, or tartaric acids for forming acid addition salts, and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, various amines, and the like for forming basic salts. Methods for preparation of the appropriate salts are well-established in the art.

Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-optionally substituted hydroxyl-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like.

As used herein, the term “subject” refers to any member of the animal kingdom. In some embodiments, “subject” refers to humans, at any stage of development. In some embodiments, “subject” refers to a human patient. In some embodiments, “subject” refers to non-human animals. In some embodiments, the non-human animal is a mammal (e.g., a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, subjects include, but are not limited to, mammals, birds, reptiles, amphibians, fish, or worms. In some embodiments, a subject may be a transgenic animal, genetically-engineered animal, or a clone.

As used herein, the term “dosage form” refers to a physically discrete unit of a compound (e.g., a compound of the present invention) for administration to a subject. Each unit contains a predetermined quantity of compound. In some embodiments, such quantity is a unit dosage amount (or a whole fraction thereof) appropriate for administration in accordance with a dosing regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population (i.e., with a therapeutic dosing regimen). Those of ordinary skill in the art appreciate that the total amount of a therapeutic composition or compound administered to a particular subject is determined by one or more attending physicians and may involve administration of multiple dosage forms. As used herein, the term “dosing regimen” refers to a set of unit doses (typically more than one) that are administered individually to

a subject, typically separated by periods of time. In some embodiments, a given therapeutic compound (e.g., a compound of the present invention) has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount. In some embodiments, a dosing regimen is correlated with a desired or beneficial outcome when administered across a relevant population (i.e., is a therapeutic dosing regimen).

A “therapeutic regimen” refers to a dosing regimen whose administration across a relevant population is correlated with a desired or beneficial therapeutic outcome.

The term “treatment” (also “treat” or “treating”), in its broadest sense, refers to any administration of a substance (e.g., a compound of the present invention) that partially or completely alleviates, ameliorates, relieves, inhibits, delays onset of, reduces severity of, or reduces incidence of one or more symptoms, features, or causes of a particular disease, disorder, or condition. In some embodiments, such treatment may be administered to a subject who does not exhibit signs of the relevant disease, disorder or condition or of a subject who exhibits only early signs of the disease, disorder, or condition. Alternatively, or additionally, in some embodiments, treatment may be administered to a subject who exhibits one or more established signs of the relevant disease, disorder or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, or condition.

The term “therapeutically effective amount” means an amount that is sufficient, when administered to a population suffering from or susceptible to a disease, disorder, or condition in accordance with a therapeutic dosing regimen, to treat the disease, disorder, or condition. In some embodiments, a therapeutically effective amount is one that reduces the incidence or severity of, or delays onset of, one or more symptoms of the disease, disorder, or condition. Those of ordinary skill in the art will appreciate that the term “therapeutically effective amount” does not in fact require successful treatment be achieved in a particular individual. Rather, a therapeutically effective amount may be that amount that provides a particular desired pharmacological response in a significant number of subjects when administered to patients in need of such treatment. It is specifically understood that particular subjects may, in fact, be “refractory” to a “therapeutically effective amount.” In some embodiments, reference to a therapeutically effective amount may be a reference to an amount as measured in one or more specific tissues (e.g., a tissue affected by the disease, disorder or condition) or fluids (e.g., blood, saliva, serum, sweat, tears, urine). Those of ordinary skill in the art will appreciate that, in some embodiments, a therapeutically effective amount may be formulated or administered in a single dose. In some embodiments, a therapeutically effective amount may be formulated or administered in a plurality of doses, for example, as part of a dosing regimen.

For use as treatment of subjects, the compounds of the invention, or a pharmaceutically acceptable salt thereof, can be formulated as pharmaceutical or veterinary compositions. Depending on the subject to be treated, the mode of administration, and the type of treatment desired, e.g., prevention, prophylaxis, or therapy, the compounds, or a pharmaceutically acceptable salt thereof, are formulated in ways consonant with these parameters. A summary of such techniques may be found in *Remington: The Science and Practice of Pharmacy*, *21st Edition*, Lippincott Williams & Wilkins, (2005); and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, each of which is incorporated herein by reference.

Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1% to about 99%, from about 5% to about 90%, or from about 1% to about 20% of a compound of the present invention, or pharmaceutically acceptable salt thereof, by weight or volume. In some embodiments, compounds, or a pharmaceutically acceptable salt thereof, described herein may be present in amounts totaling 1-95% by weight of the total weight of a composition, such as a pharmaceutical composition.

The composition may be provided in a dosage form that is suitable for intraarticular, oral, parenteral (e.g., intravenous, intramuscular), rectal, cutaneous, subcutaneous, topical, transdermal, sublingual, nasal, vaginal, intravesicular, intraurethral, intrathecal, epidural, aural, or ocular administration, or by injection, inhalation, or direct contact with the nasal, genitourinary, reproductive or oral mucosa. Thus, the pharmaceutical composition may be in the form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, sprays, preparations suitable for iontophoretic delivery, or aerosols. The compositions may be formulated according to conventional pharmaceutical practice.

As used herein, the term “administration” refers to the administration of a composition (e.g., a compound, or a preparation that includes a compound as described herein) to a subject or system. Administration to an animal subject (e.g., to a human) may be by any appropriate route. For example, in some embodiments, administration may be bronchial (including by bronchial instillation), buccal, enteral, interdermal, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (including by intratracheal instillation), transdermal, vaginal or vitreal.

Formulations may be prepared in a manner suitable for systemic administration or topical or local administration. Systemic formulations include those designed for injection (e.g., intramuscular, intravenous or subcutaneous injection) or may be prepared for transdermal, transmucosal, or oral administration. A formulation will generally include a diluent as well as, in some cases, adjuvants, buffers, preservatives and the like. Compounds, or a pharmaceutically acceptable salt thereof, can be administered also in liposomal compositions or as microemulsions.

For injection, formulations can be prepared in conventional forms as liquid solutions or suspensions or as solid forms suitable for solution or suspension in liquid prior to injection or as emulsions. Suitable excipients include, for example, water, saline, dextrose, glycerol and the like. Such compositions may also contain amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as, for example, sodium acetate, sorbitan monolaurate, and so forth.

Various sustained release systems for drugs have also been devised. See, for example, U.S. Patent No. 5,624,677.

Systemic administration may also include relatively noninvasive methods such as the use of suppositories, transdermal patches, transmucosal delivery and intranasal administration. Oral administration is also suitable for compounds of the invention, or a pharmaceutically acceptable salt thereof. Suitable forms include syrups, capsules, and tablets, as is understood in the art.

Each compound, or a pharmaceutically acceptable salt thereof, as described herein, may be formulated in a variety of ways that are known in the art. For example, the first and second agents of the combination therapy may be formulated together or separately. Other modalities of combination therapy are described herein.

The individually or separately formulated agents can be packaged together as a kit. Non-limiting examples include, but are not limited to, kits that contain, e.g., two pills, a pill and a powder, a suppository and a liquid in a vial, two topical creams, etc. The kit can include optional components that aid in the administration of the unit dose to subjects, such as vials for reconstituting powder forms, syringes for injection, customized IV delivery systems, inhalers, etc. Additionally, the unit dose kit can contain instructions for preparation and administration of the compositions. The kit may be manufactured as a single use unit dose for one subject, multiple uses for a particular subject (at a constant dose or in which the individual compounds, or a pharmaceutically acceptable salt thereof, may vary in potency as therapy progresses); or the kit may contain multiple doses suitable for administration to multiple subjects ("bulk packaging"). The kit components may be assembled in cartons, blister packs, bottles, tubes, and the like.

Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, optionally substituted hydroxylpropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.

Two or more compounds may be mixed together in a tablet, capsule, or other vehicle, or may be partitioned. In one example, the first compound is contained on the inside of the tablet, and the second compound is on the outside, such that a substantial portion of the second compound is released prior to the release of the first compound.

Formulations for oral use may also be provided as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (e.g., potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders, granulates, and pellets may be prepared using the ingredients mentioned above

under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment.

Dissolution or diffusion-controlled release can be achieved by appropriate coating of a tablet, capsule, pellet, or granulate formulation of compounds, or by incorporating the compound, or a pharmaceutically acceptable salt thereof, into an appropriate matrix. A controlled release coating may include one or more of the coating substances mentioned above or, e.g., shellac, beeswax, glycowax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitostearate, ethylcellulose, acrylic resins, dl-polylactic acid, cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylmethacrylate, 2-optionally substituted hydroxylmethacrylate, methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol methacrylate, or polyethylene glycols. In a controlled release matrix formulation, the matrix material may also include, e.g., hydrated methylcellulose, carnauba wax and stearyl alcohol, carbopol 934, silicone, glyceryl tristearate, methyl acrylate-methyl methacrylate, polyvinyl chloride, polyethylene, or halogenated fluorocarbon.

The liquid forms in which the compounds, or a pharmaceutically acceptable salt thereof, and compositions of the present invention can be incorporated for administration orally include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Generally, when administered to a human, the oral dosage of any of the compounds of the invention, or a pharmaceutically acceptable salt thereof, will depend on the nature of the compound, and can readily be determined by one skilled in the art. A dosage may be, for example, about 0.001 mg to about 2000 mg per day, about 1 mg to about 1000 mg per day, about 5 mg to about 500 mg per day, about 100 mg to about 1500 mg per day, about 500 mg to about 1500 mg per day, about 500 mg to about 2000 mg per day, or any range derivable therein. In some embodiments, the daily dose range for oral administration, for example, may lie within the range of from about 0.001 mg to about 2000 mg per kg body weight of a human, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

In some embodiments, the pharmaceutical composition may further comprise an additional compound having antiproliferative activity. Depending on the mode of administration, compounds, or a pharmaceutically acceptable salt thereof, will be formulated into suitable compositions to permit facile delivery. Each compound, or a pharmaceutically acceptable salt thereof, of a combination therapy may be formulated in a variety of ways that are known in the art. For example, the first and second agents of the combination therapy may be formulated together or separately. Desirably, the first and second agents are formulated together for the simultaneous or near simultaneous administration of the agents.

It will be appreciated that the compounds and pharmaceutical compositions of the present invention can be formulated and employed in combination therapies, that is, the compounds and pharmaceutical compositions can be formulated with or administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics or procedures and the desired therapeutic effect to be achieved. It

will also be appreciated that the therapies employed may achieve a desired effect for the same disorder, or they may achieve different effects (e.g., control of any adverse effects).

Administration of each drug in a combination therapy, as described herein, can, independently, be one to four times daily for one day to one year, and may even be for the life of the subject. Chronic, long-term administration may be indicated.

Methods of Use

In some embodiments, the invention discloses a method of treating a disease or disorder that is characterized by aberrant Ras activity due to a Ras mutant. In some embodiments, the disease or disorder is a cancer.

Accordingly, also provided is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising such a compound or salt. In some embodiments, the cancer is colorectal cancer, non-small cell lung cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, melanoma, acute myeloid leukemia, small bowel cancer, ampullary cancer, germ cell cancer, cervical cancer, cancer of unknown primary origin, endometrial cancer, esophagogastric cancer, GI neuroendocrine cancer, ovarian cancer, sex cord stromal tumor cancer, hepatobiliary cancer, or bladder cancer. In some embodiments, the cancer is appendiceal, endometrial or melanoma. Also provided is a method of treating a Ras protein-related disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising such a compound or salt.

In some embodiments, the compounds of the present invention or pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising such compounds or salts, and methods provided herein may be used for the treatment of a wide variety of cancers including tumors such as lung, prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compounds or salts thereof, pharmaceutical compositions comprising such compounds or salts, and methods of the invention include, but are not limited to tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas. Other cancers include, for example:

Cardiac, for example: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma;

Lung, for example: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma;

Gastrointestinal, for example: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma);

Genitourinary tract, for example: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma);

Liver, for example: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma;

Biliary tract, for example: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma;

Bone, for example: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors;

Nervous system, for example: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, neurofibromatosis type 1, meningioma, glioma, sarcoma);

Gynecological, for example: uterus (endometrial carcinoma, uterine carcinoma, uterine corpus endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma);

Hematologic, for example: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases (e.g., myelofibrosis and myeloproliferative neoplasms, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma);

Skin, for example: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and

Adrenal glands, for example: neuroblastoma.

In some embodiments, the Ras protein is wild-type. (Ras^{WT}). Accordingly, in some embodiments, a compound of the present invention is employed in a method of treating a patient having a cancer comprising a Ras^{WT} (e.g., K-Ras^{WT}, H-Ras^{WT} or N-Ras^{WT}). In some embodiments, the Ras protein is Ras amplification (e.g., K-Ras^{amp}). Accordingly, in some embodiments, a compound of the present invention is employed in a method of treating a patient having a cancer comprising a Ras^{amp} (K-Ras^{amp}, H-Ras^{amp} or N-Ras^{amp}). In some embodiments, the cancer comprises a Ras mutation, such as a Ras mutation described herein. In some embodiments, a mutation is selected from:

(a) the following K-Ras mutants: G12D, G12V, G12C, G13D, G12R, G12A, Q61H, G12S, A146T, G13C, Q61L, Q61R, K117N, A146V, G12F, Q61K, L19F, Q22K, V14I, A59T, A146P, G13R, G12L, or G13V, and combinations thereof;

(b) the following H-Ras mutants: Q61R, G13R, Q61K, G12S, Q61L, G12D, G13V, G13D, G12C, K117N, A59T, G12V, G13C, Q61H, G13S, A18V, D119N, G13N, A146T, A66T, G12A, A146V, G12N, or G12R, and combinations thereof; and

(c) the following N-Ras mutants: Q61R, Q61K, G12D, Q61L, Q61H, G13R, G13D, G12S, G12C, G12V, G12A, G13V, G12R, P185S, G13C, A146T, G60E, Q61P, A59D, E132K, E49K, T50I, A146V, or A59T, and combinations thereof;

or a combination of any of the foregoing. In some embodiments, the cancer comprises a Ras mutation selected from the group consisting of G12C, G13C, G12A, G12D, G13D, G12S, G13S, G12V and G13V. In some embodiments, the cancer comprises at least two Ras mutations selected from the group consisting of G12C, G13C, G12A, G12D, G13D, G12S, G13S, G12V and G13V. In some embodiments, a compound of the present invention inhibits more than one Ras mutant. For example, a compound may inhibit both K-Ras G12D and K-Ras G12C. In some embodiments, a compound may inhibit both K-Ras G12V and K-Ras G12C. In some embodiments, a compound may inhibit both K-Ras G12C and K-Ras G13C. In some embodiments, a compound may inhibit both K-Ras G12D and K-Ras G12V. In some embodiments, a compound may inhibit both K-Ras G12V and K-Ras G12S. In some embodiments, the mutation is selected from the group consisting of G12A, G12C, G12D, G12E, G12F, G12H, G12I, G12K, G12L, G12M, G12N, G12P, G12Q, G12R, G12S, G12T, G12V, G12W and G12Y, or a combination thereof, of K-Ras, N-Ras or H-Ras. In some embodiments, the mutation is selected from the group consisting of G12H, G12I, G12K, G12M, G12N, G12P, G12Q, G12T, G12W, and G12Y, or a combination thereof, of K-Ras, N-Ras or H-Ras. In some embodiments, the compound inhibits wild-type K-Ras, wild-type H-Ras or wild-type N-Ras, and optionally further inhibits a mutated Ras protein containing a mutation as described herein. In some embodiments, the cancer is non-small cell lung cancer and the Ras mutation comprises a K-Ras mutation, such as K-Ras G12C. In some embodiments, the cancer is colorectal cancer and the Ras mutation comprises a K-Ras mutation, such as K-Ras G12C. In some embodiments, the cancer is pancreatic cancer and the Ras mutation comprises an N-Ras mutation, such as N-Ras G12D. In some embodiments, the cancer is non-small cell lung cancer and the Ras protein is K-Ras^{amp}.

Additionally, in some embodiments, the cancer comprises a K-Ras mutation selected from the group consisting of G12C, G12D, G13C, G12V, G13D, G12R, G12S, Q61H, Q61K and Q61L. In some embodiments, the cancer comprises an N-Ras mutation selected from the group consisting of G12C, Q61H, Q61K, Q61L, Q61P and Q61R. In some embodiments, the cancer comprises an H-Ras mutation selected from the group consisting of Q61H and Q61L. In some embodiments, the cancer comprises a Ras mutation selected from the group consisting of G12C, G13C, G12A, G12D, G13D, G12S, G13S, G12V and G13V. In some embodiments, the cancer comprises at least two Ras mutations selected from the group consisting of G12C, G13C, G12A, G12D, G13D, G12S, G13S, G12V and G13V. In some embodiments, a compound of the present invention inhibits more than one Ras mutant. For example, a compound may inhibit both K-Ras G12C and K-Ras G13C. A compound may inhibit both N-Ras G12C and K-Ras G12C. In some embodiments, a compound may inhibit both K-Ras G12C and K-Ras G12D. In some embodiments, a compound may inhibit both K-Ras G12V and K-Ras G12C. In some embodiments, a compound may inhibit both K-Ras G12V and K-Ras G12S. In some embodiments, a compound of the present invention inhibits Ras^{WT} in addition to one or more additional Ras mutations (e.g., K-, H- or N-Ras^{WT} and K-Ras G12D, G12V, G12C, G13D, G12R, G12A, Q61H, G12S, A146T, G13C, Q61L, Q61R, K117N, A146V, G12F, Q61K, L19F, Q22K, V14I, A59T, A146P, G13R, G12L, or G13V; K-, H- or N-Ras^{WT}

and H-Ras Q61R, G13R, Q61K, G12S, Q61L, G12D, G13V, G13D, G12C, K117N, A59T, G12V, G13C, Q61H, G13S, A18V, D119N, G13N, A146T, A66T, G12A, A146V, G12N, or G12R; or K-, H- or N-Ras^{WT} and N-Ras Q61R, Q61K, G12D, Q61L, Q61H, G13R, G13D, G12S, G12C, G12V, G12A, G13V, G12R, P185S, G13C, A146T, G60E, Q61P, A59D, E132K, E49K, T50I, A146V, or A59T). In some embodiments, a compound of the present invention inhibits Ras^{amp} in addition to one or more additional Ras mutations (e.g., K-, H- or N-Ras^{amp} and K-Ras G12D, G12V, G12C, G13D, G12R, G12A, Q61H, G12S, A146T, G13C, Q61L, Q61R, K117N, A146V, G12F, Q61K, L19F, Q22K, V14I, A59T, A146P, G13R, G12L, or G13V; K-, H- or N-Ras^{amp} and H-Ras Q61R, G13R, Q61K, G12S, Q61L, G12D, G13V, G13D, G12C, K117N, A59T, G12V, G13C, Q61H, G13S, A18V, D119N, G13N, A146T, A66T, G12A, A146V, G12N, or G12R; or K-, H- or N-Ras^{amp} and N-Ras Q61R, Q61K, G12D, Q61L, Q61H, G13R, G13D, G12S, G12C, G12V, G12A, G13V, G12R, P185S, G13C, A146T, G60E, Q61P, A59D, E132K, E49K, T50I, A146V, or A59T).

Methods of detecting Ras mutations are known in the art. Such means include, but are not limited to direct sequencing, and utilization of a high-sensitivity diagnostic assay (with CE-IVD mark), e.g., as described in Domagala, et al., Pol J Pathol 3: 145-164 (2012), incorporated herein by reference in its entirety, including TheraScreen PCR; AmoyDx; PNAClamp; RealQuality; EntroGen; LightMix; StripAssay; Hybcell plexA; Devyser; Surveyor; Cobas; and TheraScreen Pyro. See, also, e.g., WO 2020/106640.

In some embodiments, the cancer is non-small cell lung cancer and the Ras mutation comprises a K-Ras mutation, such as K-Ras G12C, K-Ras G12V or K-Ras G12D. In some embodiments, the cancer is colorectal cancer and the Ras mutation comprises a K-Ras mutation, such as K-Ras G12C, K-Ras G12V or K-Ras G12D. In some embodiments, the cancer is pancreatic cancer and the Ras mutation comprises an K-Ras mutation, such as K-Ras G12D or K-Ras G12V. In some embodiments, the cancer is pancreatic cancer and the Ras mutation comprises an N-Ras mutation, such as N-Ras G12D. In some embodiments, the cancer is melanoma and the Ras mutation comprises an N-Ras mutation, such as N-Ras Q61R or N-Ras Q61K. In some embodiments, the cancer is non-small cell lung cancer and the Ras protein is K-Ras^{amp}. In any of the foregoing if not already specified, a compound may inhibit Ras^{WT} (e.g., K-, H- or N-Ras^{WT}) or Ras^{amp} (e.g., K-, H- or N-Ras^{amp}) as well.

In some embodiments, a cancer comprises a Ras mutation and an STK11^{LOF}, a KEAP1, an EPHA5 or an NF1 mutation, or a combination thereof. In some embodiments, the cancer is non-small cell lung cancer and comprises a K-Ras G12C mutation. In some embodiments, the cancer is non-small cell lung cancer and comprises a K-Ras G12C mutation, an STK11^{LOF} mutation, and a KEAP1 mutation. In some embodiments, the cancer is non-small cell lung cancer and comprises a K-Ras G12C mutation and an STK11^{LOF} mutation. In some embodiments, the cancer is non-small cell lung cancer and comprises a K-Ras G12C mutation and an STK11^{LOF} mutation. In some embodiments, a cancer comprises a K-Ras G13C Ras mutation and an STK11^{LOF}, a KEAP1, an EPHA5 or an NF1 mutation. In some embodiments, the cancer is non-small cell lung cancer and comprises a K-Ras G12D mutation. In some embodiments, the cancer is non-small cell lung cancer and comprises a K-Ras G12V mutation. In some embodiments, the cancer is colorectal cancer and comprises a K-Ras G12C mutation. In some embodiments, the cancer is pancreatic cancer and comprises a K-Ras G12D mutation. In some embodiments, the cancer is pancreatic cancer and comprises a K-Ras G12V mutation. In some embodiments, the cancer is endometrial cancer and comprises a K-Ras G12C mutation. In some embodiments, the cancer is gastric

cancer and comprises a K-Ras G12C mutation. In any of the foregoing, a compound may inhibit Ras^{WT} (e.g., K-, H- or N-Ras^{WT}) or Ras^{amp} (e.g., K-, H- or N-Ras^{amp}) as well.

Also provided is a method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof. A compound, or a pharmaceutically acceptable salt thereof, may inhibit more than one type of Ras protein in a cell. A method of inhibiting RAF-Ras binding, the method comprising contacting the cell with an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, is also provided. The cell may be a cancer cell. The cancer cell may be of any type of cancer described herein. The cell may be in vivo or in vitro.

Combination Therapy

The methods of the invention may include a compound of the invention used alone or in combination with one or more additional therapies (e.g., non-drug treatments or therapeutic agents). The dosages of one or more of the additional therapies (e.g., non-drug treatments or therapeutic agents) may be reduced from standard dosages when administered alone. For example, doses may be determined empirically from drug combinations and permutations or may be deduced by isobolographic analysis (e.g., Black et al., *Neurology* 65:S3-S6 (2005)).

A compound of the present invention may be administered before, after, or concurrently with one or more of such additional therapies. When combined, dosages of a compound of the invention and dosages of the one or more additional therapies (e.g., non-drug treatment or therapeutic agent) provide a therapeutic effect (e.g., synergistic or additive therapeutic effect). A compound of the present invention and an additional therapy, such as an anti-cancer agent, may be administered together, such as in a unitary pharmaceutical composition, or separately and, when administered separately, this may occur simultaneously or sequentially. Such sequential administration may be close or remote in time.

In some embodiments, the additional therapy is the administration of side-effect limiting agents (e.g., agents intended to lessen the occurrence or severity of side effects of treatment. For example, in some embodiments, the compounds of the present invention can also be used in combination with a therapeutic agent that treats nausea. Examples of agents that can be used to treat nausea include: dronabinol, granisetron, metoclopramide, ondansetron, and prochlorperazine, or pharmaceutically acceptable salts thereof.

In some embodiments, the one or more additional therapies includes a non-drug treatment (e.g., surgery or radiation therapy). In some embodiments, the one or more additional therapies includes a therapeutic agent (e.g., a compound or biologic that is an anti-angiogenic agent, signal transduction inhibitor, antiproliferative agent, glycolysis inhibitor, or autophagy inhibitor). In some embodiments, the one or more additional therapies includes a non-drug treatment (e.g., surgery or radiation therapy) and a therapeutic agent (e.g., a compound or biologic that is an anti-angiogenic agent, signal transduction inhibitor, antiproliferative agent, glycolysis inhibitor, or autophagy inhibitor). In other embodiments, the one or more additional therapies includes two therapeutic agents. In still other embodiments, the one or more additional therapies includes three therapeutic agents. In some embodiments, the one or more additional therapies includes four or more therapeutic agents.

In this Combination Therapy section, all references are incorporated by reference for the agents described, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof, whether explicitly stated as such or not.

Non-drug therapies

Examples of non-drug treatments include, but are not limited to, radiation therapy, cryotherapy, hyperthermia, surgery (e.g., surgical excision of tumor tissue), and T cell adoptive transfer (ACT) therapy.

In some embodiments, the compounds of the invention may be used as an adjuvant therapy after surgery. In some embodiments, the compounds of the invention may be used as a neo-adjuvant therapy prior to surgery.

Radiation therapy may be used for inhibiting abnormal cell growth or treating a hyperproliferative disorder, such as cancer, in a subject (e.g., mammal (e.g., human)). Techniques for administering radiation therapy are known in the art. Radiation therapy can be administered through one of several methods, or a combination of methods, including, without limitation, external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachy therapy. The term "brachy therapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended, without limitation, to include exposure to radioactive isotopes (e.g., At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm-153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner of the present invention include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, or Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

In some embodiments, the compounds of the present invention can render abnormal cells more sensitive to treatment with radiation for purposes of killing or inhibiting the growth of such cells. Accordingly, this invention further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of a compound of the present invention, which amount is effective to sensitize abnormal cells to treatment with radiation. The amount of the compound in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein. In some embodiments, the compounds of the present invention may be used as an adjuvant therapy after radiation therapy or as a neo-adjuvant therapy prior to radiation therapy.

In some embodiments, the non-drug treatment is a T cell adoptive transfer (ACT) therapy. In some embodiments, the T cell is an activated T cell. The T cell may be modified to express a chimeric antigen receptor (CAR). CAR modified T (CAR-T) cells can be generated by any method known in the art. For example, the CAR-T cells can be generated by introducing a suitable expression vector encoding the CAR to a T cell. Prior to expansion and genetic modification of the T cells, a source of T cells is obtained from a subject. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural

effusion, spleen tissue, and tumors. In certain embodiments of the present invention, any number of T cell lines available in the art may be used. In some embodiments, the T cell is an autologous T cell. Whether prior to or after genetic modification of the T cells to express a desirable protein (e.g., a CAR), the T cells can be activated and expanded generally using methods as described, for example, in U.S. Patents 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 7,572,631; 5,883,223; 6,905,874; 6,797,514; and 6,867,041.

Therapeutic agents

A therapeutic agent may be a compound used in the treatment of cancer or symptoms associated therewith.

For example, a therapeutic agent may be a steroid. Accordingly, in some embodiments, the one or more additional therapies includes a steroid. Suitable steroids may include, but are not limited to, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difuprednate, enoxolone, fluazacort, fiucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and salts or derivatives thereof.

Further examples of therapeutic agents that may be used in combination therapy with a compound of the present invention include compounds described in the following patents: U.S. Patent Nos. 6,258,812, 6,630,500, 6,515,004, 6,713,485, 5,521,184, 5,770,599, 5,747,498, 5,990,141, 6,235,764, and 8,623,885, and International Patent Applications WO01/37820, WO01/32651, WO02/68406, WO02/66470, WO02/55501, WO04/05279, WO04/07481, WO04/07458, WO04/09784, WO02/59110, WO99/45009, WO00/59509, WO99/61422, WO00/12089, and WO00/02871.

A therapeutic agent may be a biologic (e.g., cytokine (e.g., interferon or an interleukin such as IL-2)) used in treatment of cancer or symptoms associated therewith. In some embodiments, the biologic is an immunoglobulin-based biologic, e.g., a monoclonal antibody (e.g., a humanized antibody, a fully human antibody, an Fc fusion protein, or a functional fragment thereof) that agonizes a target to stimulate an anti-cancer response or antagonizes an antigen important for cancer. Also included are antibody-drug conjugates.

A therapeutic agent may be a T-cell checkpoint inhibitor. In one embodiment, the checkpoint inhibitor is an inhibitory antibody (e.g., a monospecific antibody such as a monoclonal antibody). The antibody may be, e.g., humanized or fully human. In some embodiments, the checkpoint inhibitor is a fusion protein, e.g., an Fc-receptor fusion protein. In some embodiments, the checkpoint inhibitor is an agent, such as an antibody, that interacts with a checkpoint protein. In some embodiments, the checkpoint inhibitor is an agent, such as an antibody, that interacts with the ligand of a checkpoint protein. In some embodiments, the checkpoint inhibitor is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor)

of CTLA-4 (e.g., an anti-CTLA-4 antibody or fusion a protein). In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or small molecule inhibitor) of PD-1. In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or small molecule inhibitor) of PD-L1. In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or Fc fusion or small molecule inhibitor) of PD-L2 (e.g., a PD-L2/Ig fusion protein). In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or small molecule inhibitor) of B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands, or a combination thereof. In some embodiments, the checkpoint inhibitor is pembrolizumab, nivolumab, PDR001 (NVS), REGN2810 (Sanofi/Regeneron), a PD-L1 antibody such as, *e.g.,* avelumab, durvalumab, atezolizumab, pidilizumab, JNJ-63723283 (JNJ), BGB-A317 (BeiGene & Celgene) or a checkpoint inhibitor disclosed in Preusser, M. et al. (2015) Nat. Rev. Neurol., including, without limitation, ipilimumab, tremelimumab, nivolumab, pembrolizumab, AMP224, AMP514/ MEDI0680, BMS936559, MEDI4736, MPDL3280A, MSB0010718C, BMS986016, IMP321, lirilumab, IPH2101, 1-7F9, and KW-6002.

A therapeutic agent may be an anti-TIGIT antibody, such as MBSA43, BMS-986207, MK-7684, COM902, AB154, MTIG7192A or OMP-313M32 (etigilimab).

A therapeutic agent may be an agent that treats cancer or symptoms associated therewith (e.g., a cytotoxic agent, non-peptide small molecules, or other compound useful in the treatment of cancer or symptoms associated therewith, collectively, an “anti-cancer agent”). Anti-cancer agents can be, e.g., chemotherapeutics or targeted therapy agents.

Anti-cancer agents include mitotic inhibitors, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitors, interferons, platinum coordination complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog. Further anti-cancer agents include leucovorin (LV), irenotecan, oxaliplatin, capecitabine, paclitaxel, and doxetaxel. In some embodiments, the one or more additional therapies includes two or more anti-cancer agents. The two or more anti-cancer agents can be used in a cocktail to be administered in combination or administered separately. Suitable dosing regimens of combination anti-cancer agents are known in the art and described in, for example, Saltz et al., *Proc. Am. Soc. Clin. Oncol.* 18:233a (1999), and Douillard et al., *Lancet* 355(9209):1041-1047 (2000).

Other non-limiting examples of anti-cancer agents include Gleevec® (Imatinib Mesylate); Kyprolis® (carfilzomib); Velcade® (bortezomib); Casodex (bicalutamide); Iressa® (gefitinib); alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; sarcodictyin A; spongistatin; nitrogen mustards such as

chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, such as calicheamicin gammall and calicheamicin omegall (see, e.g., *Agnew, Chem. Intl. Ed Engl.* 33:183-186 (1994)); dynemicin such as dynemicin A; bisphosphonates such as clodronate; an esperamicin; neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, caminomycin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo- 5-oxo-L-norleucine, adriamycin (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenishers such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone such as epothilone B; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes such as T- 2 toxin, verracurin A, roridin A and anguidine; urethane; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., Taxol® (paclitaxel), Abraxane® (cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel), and Taxotere® (doxetaxel); chloranbucil; tamoxifen (Nolvadex™); raloxifene; aromatase inhibiting 4(5)-imidazoles; 4-hydroxytamoxifen; trioxifene; keoxifene; LY 117018; onapristone; toremifene (Fareston®); flutamide, nilutamide, bicalutamide, leuprolide, goserelin; chlorambucil; Gemzar® gemcitabine; 6-thioguanine; mercaptopurine; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; Navelbine® (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; ibandronate; irinotecan (e.g., CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; esperamicins; capecitabine (e.g., Xeloda®); and pharmaceutically acceptable salts of any of the above.

Additional non-limiting examples of anti-cancer agents include trastuzumab (Herceptin®), bevacizumab (Avastin®), cetuximab (Erbitux®), rituximab (Rituxan®), Taxol®, Arimidex®, ABVD, avicine, abagovomab, acridine carboxamide, adecatumumab, 17-N-allylamino-17-demethoxygeldanamycin, alpharadin, alvocidib, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone, amonafide, anthracenedione, anti-CD22 immunotoxins, antineoplastics (e.g., cell-cycle nonspecific antineoplastic agents, and other

antineoplastics described herein), antitumorigenic herbs, apaziquone, atiprimod, azathioprine, belotecan, bendamustine, BIBW 2992, biricodar, brostallicin, bryostatin, buthionine sulfoximine, CBV (chemotherapy), calyculin, dichloroacetic acid, discodermolide, elsamitrucin, enocitabine, eribulin, exatecan, exisulind, ferruginol, forodesine, fosfestrol, ICE chemotherapy regimen, IT-101, imexon, imiquimod, indolocarbazole, irofulven, laniquidar, larotaxel, lenalidomide, lucanthone, lurtotecan, mafosfamide, mitozolomide, nafoxidine, nedaplatin, olaparib, ortataxel, PAC-1, pawpaw, pixantrone, proteasome inhibitors, rebeccamycin, resiquimod, rubitecan, SN-38, salinosporamide A, sapacitabine, Stanford V, swainsonine, talaporfin, tariquidar, tegafur-uracil, temodar, tesetaxel, triplatin tetranitrate, tris(2-chloroethyl)amine, troxacitabine, uramustine, vadimezan, vinflunine, ZD6126, and zosuquidar.

Further non-limiting examples of anti-cancer agents include natural products such as vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine), epidipodophyllotoxins (e.g., etoposide and teniposide), antibiotics (e.g., dactinomycin (actinomycin D), daunorubicin, and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin), mitomycin, enzymes (e.g., L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine), antiplatelet agents, antiproliferative/antimitotic alkylating agents such as nitrogen mustards (e.g., mechlorethamine, cyclophosphamide and analogs, melphalan, and chlorambucil), ethylenimines and methylmelamines (e.g., hexamethylmelamine and thiotepa), CDK inhibitors (e.g., a CDK4/6 inhibitor such as abemaciclib, ribociclib, palbociclib; seliciclib, UCN-01, P1446A-05, PD-0332991, dinaciclib, P27-00, AT-7519, RGB286638, and SCH727965), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine (BCNU) and analogs, and streptozocin), trazenes-dacarbazinine (DTIC), antiproliferative/antimitotic antimetabolites such as folic acid analogs, pyrimidine analogs (e.g., fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (e.g., mercaptopurine, thioguanine, pentostatin, and 2-chlorodeoxyadenosine), aromatase inhibitors (e.g., anastrozole, exemestane, and letrozole), and platinum coordination complexes (e.g., cisplatin and carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide, histone deacetylase (HDAC) inhibitors (e.g., trichostatin, sodium butyrate, apicidan, suberoyl anilide hydroamic acid, vorinostat, LBH 589, romidepsin, ACY-1215, and panobinostat), mTOR inhibitors (e.g., vistusertib, temsirolimus, everolimus, ridaforolimus, and sirolimus), KSP(Eg5) inhibitors (e.g., Array 520), DNA binding agents (e.g., Zalypsis®), PI3K inhibitors such as PI3K delta inhibitor (e.g., GS-1101 and TGR-1202), PI3K delta and gamma inhibitor (e.g., CAL-130), copanlisib, alpelisib and idelalisib; multi-kinase inhibitor (e.g., TG02 and sorafenib), hormones (e.g., estrogen) and hormone agonists such as leutinizing hormone releasing hormone (LHRH) agonists (e.g., goserelin, leuprolide and triptorelin), BAFF-neutralizing antibody (e.g., LY2127399), IKK inhibitors, p38MAPK inhibitors, anti-IL-6 (e.g., CNT0328), telomerase inhibitors (e.g., GRN 163L), aurora kinase inhibitors (e.g., MLN8237), cell surface monoclonal antibodies (e.g., anti-CD38 (HUMAX-CD38), anti-CSI (e.g., elotuzumab), HSP90 inhibitors (e.g., 17 AAG and KOS 953), P13K / Akt inhibitors (e.g., perifosine), Akt inhibitors (e.g., GSK-2141795), PKC inhibitors (e.g., enzastaurin), FTIs (e.g., Zarnestra™), anti-CD138 (e.g., BT062), Torcl/2 specific kinase inhibitors (e.g., INK128), ER/UPR targeting agents (e.g., MKC-3946), cFMS inhibitors (e.g., ARRY-382), JAK1/2 inhibitors (e.g., CYT387), PARP inhibitors (e.g., olaparib and veliparib (ABT-888)), and BCL-2 antagonists.

In some embodiments, an anti-cancer agent is selected from mechlorethamine, camptothecin, ifosfamide, tamoxifen, raloxifene, gemcitabine, Navelbine®, sorafenib, or any analog or derivative variant of the foregoing.

In some embodiments, the anti-cancer agent is a HER2 inhibitor. Non-limiting examples of HER2 inhibitors include monoclonal antibodies such as trastuzumab (Herceptin®) and pertuzumab (Perjeta®); small molecule tyrosine kinase inhibitors such as gefitinib (Iressa®), erlotinib (Tarceva®), pilitinib, CP-654577, CP-724714, canertinib (CI 1033), HKI-272, lapatinib (GW-572016; Tykerb®), PKI-166, AEE788, BMS-599626, HKI-357, BIBW 2992, ARRY-334543, and JNJ-26483327.

In some embodiments, an anti-cancer agent is an ALK inhibitor. Non-limiting examples of ALK inhibitors include ceritinib, TAE-684 (NVP-TAE694), PF02341066 (crizotinib or 1066), alectinib; brigatinib; entrectinib; ensartinib (X-396); lorlatinib; ASP3026; CEP-37440; 4SC-203; TL-398; PLB1003; TSR-011; CT-707; TPX-0005, and AP26113. Additional examples of ALK kinase inhibitors are described in examples 3-39 of WO 05016894.

In some embodiments, an anti-cancer agent is an inhibitor of a member downstream of a Receptor Tyrosine Kinase (RTK)/Growth Factor Receptor (e.g., a SHP2 inhibitor (e.g., SHP099, TNO155, RMC-4550, RMC-4630, JAB-3068, JAB-3312, RLY-1971, ERAS-601, SH3809, PF-07284892, or BBP-398, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof), a SOS1 inhibitor (e.g., BI-1701963, BI-3406, SDR5, BAY-293, or RMC-5845, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof), a Raf inhibitor, a MEK inhibitor, an ERK inhibitor, a PI3K inhibitor, a PTEN inhibitor, an AKT inhibitor, or an mTOR inhibitor (e.g., mTORC1 inhibitor or mTORC2 inhibitor). In some embodiments, the anti-cancer agent is JAB-3312.

In some embodiments, an anti-cancer agent is a SOS1 inhibitor. In some embodiments, the SOS1 inhibitor is selected from those disclosed in WO 2021173524, WO 2021130731, WO 2021127429, WO 2021092115, WO 2021105960, WO 2021074227, WO 2020180768, WO 2020180770, WO 2020173935, WO 2020146470, WO 2019201848, WO 2019122129, WO 2018172250, and WO 2018115380, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof.

In some embodiments, an anti-cancer agent is an additional Ras inhibitor or a Ras vaccine, or another therapeutic modality designed to directly or indirectly decrease the oncogenic activity of Ras. In some embodiments, an anti-cancer agent is an additional Ras inhibitor. In some embodiments, the Ras inhibitor targets Ras in its active, or GTP-bound state. In some embodiments, the Ras inhibitor targets Ras in its inactive, or GDP-bound state. In some embodiments, the Ras inhibitor is, such as an inhibitor of K-Ras G12C, such as AMG 510 (sotorasib), MRTX1257, MRTX849 (adagrasib), JNJ-74699157, LY3499446, ARS-1620, ARS-853, BPI-421286, LY3537982, JDQ443, JAB-3312, JAB-21000, JAB-21822, ERAS-3490, BI 1823911, D-1553, D3S-001, HBI-2438, HS-10370, MK-1084, YL-15293, GFH925 (IBI351), RMC-6291 or GDC-6036, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof. In some embodiments, the Ras inhibitor is an inhibitor of K-Ras G12D, such as MRTX1133, MRTX282, JAB-22000, ERAS-4, HRS-4642, BI-2852, ASP3082, TH-Z827, TH-7835 or KD-8, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof. In some embodiments, the Ras inhibitor is a K-Ras G12V inhibitor, such as JAB-23000, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof. In some embodiments, the KRAS(OFF) inhibitor is a pan-RAS(OFF) inhibitor. In specific embodiments, the pan-RAS(OFF) inhibitor is JAB-23400. In some embodiments, the Ras inhibitor is RMC-6236, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof. In some embodiments, the Ras inhibitor is selected from a Ras(ON) inhibitor disclosed in the following, incorporated herein by reference in their entireties, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer),

prodrug, or tautomer thereof: WO 2023060253, WO 2022/060836, WO 2022/235864, WO 2022/235/870, WO 2021091982, WO 2021091967, WO 2021091956 and WO 2020132597. Other examples of Ras inhibitors that may be combined with a Ras inhibitor of the present invention are provided in the following, incorporated herein by reference in their entireties: WO 2023287896, WO 2023287730, WO 2023284881, WO 2023284730, WO 2023284537, WO 2023283933, WO 2023283213, WO 2023280280, WO 2023280136, WO 2023280026, WO 2023278600, WO 2023274383, WO 2023327324, WO 2023040989, WO 2023039240, WO 2023039020, WO 2023036282, WO 2023034290, WO 2023030517, WO 2023030495, WO 2023030385, WO 2023025116, WO 2023020523, WO 2023020521, WO 2023020519, WO 2023020518, WO 2023020347, WO 2023018812, WO 2023018810, WO 2023018809, WO 2023018699, WO 2023014979, WO 2023014006, WO 2023004102, WO 2023003417, WO 2023001141, WO 2023001123, WO 2022271658, WO 2022269508, WO 2022266167, WO 2022266069, WO 2022266015, WO 2022265974, WO 2022261154, WO 2022261154, WO 2022251576, WO 2022251296, WO 2022237815, WO 2022232332, WO 2022232331, WO 2022232320, WO 2022232318, WO 2022223037, WO 2022221739, WO 2022221528, WO 2022221386, WO 2022216762 (e.g., Compound 44 or Compound 66a), WO 2022192794, WO 2022192790, WO 2022188729, WO 2022187411, WO 2022184178, WO 2022173870, WO 2022173678, WO 2022135346, WO 2022133731, WO 2022133038, WO 2022133345, WO 2022132200, WO 2022119748, WO 2022109485, WO 2022109487, WO 2022066805, WO 2022002102, WO 2022002018, WO 2021259331, WO 2021257828, WO 2021252339, WO 2021248095, WO 2021248090, WO 2021248083, WO 2021248082, WO 2021248079, WO 2021248055, WO 2021245051, WO 2021244603, WO 2021239058, WO 2021231526, WO 2021228161, WO 2021219090, WO 2021219090, WO 2021219072, WO 2021218939, WO 2021217019, WO 2021216770, WO 2021215545, WO 2021215544, WO 2021211864, WO 2021190467, WO 2021185233, WO 2021180181, WO 2021175199, WO 2021173923, WO 2021169990, WO 2021169963, WO 2021168193, WO 2021158071, WO 2021155716, WO 2021152149, WO 2021150613, WO 2021147967, WO 2021147965, WO 2021143693, WO 2021142252, WO 2021141628, WO 2021139748, WO 2021139678, WO 2021129824, WO 2021129820, WO 2021127404, WO 2021126816, WO 2021126799, WO 2021124222, WO 2021121371, WO 2021121367, WO 2021121330, WO 2020050890, WO 2020047192, WO 2020035031, WO 2020028706, WO 2019241157, WO 2019232419, WO 2019217691, WO 2019217307, WO 2019215203, WO 2019213526, WO 2019213516, WO 2019155399, WO 2019150305, WO 2019110751, WO 2019099524, WO 2019051291, WO 2018218070, WO 2018217651, WO 2018218071, WO 2018218069, WO 2018206539, WO 2018143315, WO 2018140600, WO 2018140599, WO 2018140598, WO 2018140514, WO 2018140513, WO 2018140512, WO 2018119183, WO 2018112420, WO 2018068017, WO 2018064510, WO 2017201161, WO 2017172979, WO 2017100546, WO 2017087528, WO 2017058807, WO 2017058805, WO 2017058728, WO 2017058902, WO 2017058792, WO 2017058768, WO 2017058915, WO 2017015562, WO 2016168540, WO 2016164675, WO 2016049568, WO 2016049524, WO 2015054572, WO 2014152588, WO 2014143659, and WO 2013155223, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof.

In some embodiments, a therapeutic agent that may be combined with a compound of the present invention is an inhibitor of the MAP kinase (MAPK) pathway (or “MAPK inhibitor”). MAPK inhibitors include, but are not limited to, one or more MAPK inhibitor described in Cancers (Basel) 2015 Sep; 7(3): 1758–1784. For example, the MAPK inhibitor may be selected from one or more of trametinib, binimetinib,

selumetinib, cobimetinib, LErafAON (NeoPharm), ISIS 5132; vemurafenib, pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901; CH5126766; MAP855; AZD6244; refametinib (RDEA 119/BAY 86-9766); GDC-0973/XL581; AZD8330 (ARRY-424704/ARRY-704); RO5126766 (Roche, described in PLoS One. 2014 Nov 25;9(11)); and GSK1120212 (or JTP-74057, described in Clin Cancer Res. 2011 Mar 1;17(5):989-1000). The MAPK inhibitor may be PLX8394, LXH254, GDC-5573, or LY3009120.

In some embodiments, an anti-cancer agent is a disrupter or inhibitor of the RAS-RAF-ERK or PI3K-AKT-TOR or PI3K-AKT signaling pathways. The PI3K/AKT inhibitor may include, but is not limited to, one or more PI3K/AKT inhibitor described in Cancers (Basel) 2015 Sep; 7(3): 1758–1784. For example, the PI3K/AKT inhibitor may be selected from one or more of NVP-BEZ235; BGT226; XL765/SAR245409; SF1126; GDC-0980; PI-103; PF-04691502; PKI-587; GSK2126458.

In some embodiments, an anti-cancer agent is a PD-1 or PD-L1 antagonist.

In some embodiments, additional therapeutic agents include ALK inhibitors, HER2 inhibitors, EGFR inhibitors, IGF-1R inhibitors, MEK inhibitors, PI3K inhibitors, AKT inhibitors, TOR inhibitors, MCL-1 inhibitors, BCL-2 inhibitors, SHP2 inhibitors, proteasome inhibitors, and immune therapies. In some embodiments, a therapeutic agent may be a pan-RTK inhibitor, such as afatinib.

IGF-1R inhibitors include linsitinib, or a pharmaceutically acceptable salt thereof.

EGFR inhibitors include, but are not limited to, small molecule antagonists, antibody inhibitors, or specific antisense nucleotide or siRNA. Useful antibody inhibitors of EGFR include cetuximab (Erbitux®), panitumumab (Vectibix®), zalutumumab, nimotuzumab, and matuzumab. Further antibody-based EGFR inhibitors include any anti-EGFR antibody or antibody fragment that can partially or completely block EGFR activation by its natural ligand. Non-limiting examples of antibody-based EGFR inhibitors include those described in Modjtahedi et al., Br. J. Cancer 1993, 67:247-253; Teramoto et al., Cancer 1996, 77:639-645; Goldstein et al., Clin. Cancer Res. 1995, 1:1311-1318; Huang et al., 1999, Cancer Res. 15:59(8):1935-40; and Yang et al., Cancer Res.1999, 59:1236-1243. The EGFR inhibitor can be monoclonal antibody Mab E7.6.3 (Yang, 1999 supra), or Mab C225 (ATCC Accession No. HB-8508), or an antibody or antibody fragment having the binding specificity thereof.

Small molecule antagonists of EGFR include gefitinib (Iressa®), erlotinib (Tarceva®), and lapatinib (TykerB®). See, e.g., Yan et al., Pharmacogenetics and Pharmacogenomics In Oncology Therapeutic Antibody Development, BioTechniques 2005, 39(4):565-8; and Paez et al., EGFR Mutations In Lung Cancer Correlation With Clinical Response To Gefitinib Therapy, Science 2004, 304(5676):1497-500. In some embodiments, the EGFR inhibitor is osimertinib (Tagrisso®). Further non-limiting examples of small molecule EGFR inhibitors include any of the EGFR inhibitors described in the following patent publications, and all pharmaceutically acceptable salts of such EGFR inhibitors: EP 0520722; EP 0566226; WO96/33980; U.S. Pat. No. 5,747,498; WO96/30347; EP 0787772; WO97/30034; WO97/30044; WO97/38994; WO97/49688; EP 837063; WO98/02434; WO97/38983; WO95/19774; WO95/19970; WO97/13771; WO98/02437; WO98/02438; WO97/32881; DE 19629652; WO98/33798; WO97/32880; WO97/32880; EP 682027; WO97/02266; WO97/27199; WO98/07726; WO97/34895; WO96/31510; WO98/14449; WO98/14450; WO98/14451; WO95/09847; WO97/19065; WO98/17662; U.S. Pat. No. 5,789,427; U.S. Pat. No. 5,650,415; U.S. Pat. No. 5,656,643; WO99/35146; WO99/35132; WO99/07701; and WO92/20642. Additional non-limiting examples of small molecule EGFR inhibitors include any of the EGFR inhibitors described in Traxler et al., Exp. Opin. Ther. Patents 1998, 8(12):1599-1625. In some

embodiments, an EGFR inhibitor is an ERBB inhibitor. In humans, the ERBB family contains HER1 (EGFR, ERBB1), HER2 (NEU, ERBB2), HER3 (ERBB3), and HER (ERBB4).

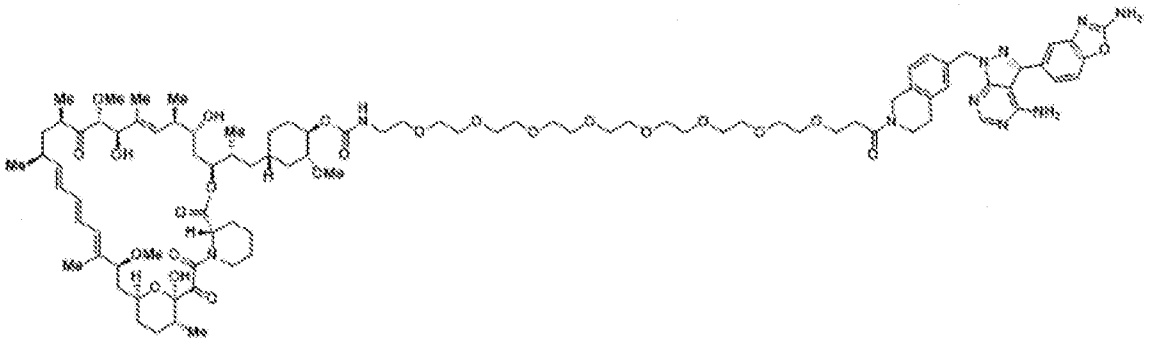
MEK inhibitors include, but are not limited to, pimasertib, selumetinib, cobimetinib (Cotellic®), trametinib (Mekinist®), and binimetinib (Mektovi®). In some embodiments, a MEK inhibitor targets a MEK mutation that is a Class I MEK1 mutation selected from D67N; P124L; P124S; and L177V. In some embodiments, the MEK mutation is a Class II MEK1 mutation selected from ΔE51-Q58; ΔF53-Q58; E203K; L177M; C121S; F53L; K57E; Q56P; and K57N.

PI3K inhibitors include, but are not limited to, wortmannin; 17-hydroxywortmannin analogs described in WO06/044453; 4-[2-(1H-Indazol-4-yl)-6-[[4-(methylsulfonyl)piperazin-1-yl]methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine (also known as pictilisib or GDC-0941 and described in WO09/036082 and WO09/055730); 2-methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydroimidazo[4,5-c]quinolin-1-yl]phenyl]propionitrile (also known as BEZ 235 or NVP-BEZ 235, and described in WO06/122806); (S)-l-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholinothieno[3,2-d]pyrimidin-6-yl)methyl)piperazin-1-yl)-2-hydroxypropan-1-one (described in WO08/070740); LY294002 (2-(4-morpholinyl)-8-phenyl-4H-l-benzopyran-4-one (available from Axon Medchem); PI 103 hydrochloride (3-[4-(4-morpholinylpyrido-[3',2':4,5]furo[3,2-d]pyrimidin-2-yl] phenol hydrochloride (available from Axon Medchem); PIK 75 (2-methyl-5-nitro-2-[(6-bromoimidazo[1,2-a]pyridin-3-yl)methylene]-1-methylhydrazide-benzenesulfonic acid, monohydrochloride) (available from Axon Medchem); PIK 90 (N-(7,8-dimethoxy-2,3-dihydro-imidazo[l,2-c]quinazolin-5-yl)-nicotinamide (available from Axon Medchem); AS-252424 (5-[l-[5-(4-fluoro-2-hydroxy-phenyl)-furan-2-yl]-meth-(Z)-ylidene]-thiazolidine-2,4-dione (available from Axon Medchem); TGX-221 (7-methyl-2-(4-morpholinyl)-9-[1-(phenylamino)ethyl]-4H-pyrido-[1,2-a]pyrirnidin-4-one (available from Axon Medchem); XL-765; and XL-147. Other PI3K inhibitors include demethoxyviridin, perifosine, CAL101, PX-866, BEZ235, SF1126, INK1117, IPI-145, BKM120, XL147, XL765, Palomid 529, GSK1059615, ZSTK474, PWT33597, IC87114, TGI 00-115, CAL263, PI-103, GNE-477, CUDC-907, and AEZS-136.

AKT inhibitors include, but are not limited to, Akt-1-1 (inhibits Aktl) (Barnett et al., Biochem. J. 2005, 385(Pt. 2): 399-408); Akt-1-1,2 (inhibits Akl and 2) (Barnett et al., Biochem. J. 2005, 385(Pt. 2): 399-408); API-59CJ-Ome (e.g., Jin et al., Br. J. Cancer 2004, 91:1808-12); 1-H-imidazo[4,5-c]pyridinyl compounds (e.g., WO 05/011700); indole-3-carbinol and derivatives thereof (e.g., U.S. Pat. No. 6,656,963; Sarkar and Li J Nutr. 2004, 134(12 Suppl):3493S-3498S); perifosine (e.g., interferes with Akt membrane localization; Dasmahapatra et al. Clin. Cancer Res. 2004, 10(15):5242-52); phosphatidylinositol ether lipid analogues (e.g., Gills and Dennis Expert. Opin. Investig. Drugs 2004, 13:787-97); and triciribine (TCN or API-2 or NCI identifier: NSC 154020; Yang et al., Cancer Res. 2004, 64:4394-9).

mTOR inhibitors include, but are not limited to, ATP-competitive mTORC1/mTORC2 inhibitors, e.g., PI-103, PP242, PP30; Torin 1; FKBP12 enhancers; 4H-1-benzopyran-4-one derivatives; and rapamycin (also known as sirolimus) and derivatives thereof, including: temsirolimus (Torisel®); everolimus (Afinitor®; WO94/09010); ridaforolimus (also known as deforolimus or AP23573); rapalogs, e.g., as disclosed in WO98/02441 and WO01/14387, e.g. AP23464 and AP23841; 40-(2-hydroxyethyl)rapamycin; 40-[3-hydroxy(hydroxymethyl)methylpropanoate]-rapamycin (also known as CC1779); 40-epi-(tetrazolyt)-rapamycin (also called ABT578); 32-deoxorapamycin; 16-pentynyloxy-32(S)-dihydrorapanycin; derivatives disclosed in WO05/005434; derivatives disclosed in U.S. Patent Nos. 5,258,389, 5,118,677, 5,118,678, 5,100,883, 5,151,413, 5,120,842, and 5,256,790, and in WO94/090101, WO92/05179, WO93/111130, WO94/02136, WO94/02485, WO95/14023, WO94/02136, WO95/16691, WO96/41807, WO96/41807, and

WO2018204416; and phosphorus-containing rapamycin derivatives (e.g., WO05/016252). In some embodiments, the mTOR inhibitor is a bisteric inhibitor (see, e.g., WO2018204416, WO2019212990 and WO2019212991), such as RMC-5552, having the structure



BRAF inhibitors that may be used in combination with compounds of the invention include, for example, vemurafenib, dabrafenib, and encorafenib. A BRAF may comprise a Class 3 BRAF mutation. In some embodiments, the Class 3 BRAF mutation is selected from one or more of the following amino acid substitutions in human BRAF: D287H; P367R; V459L; G466V; G466E; G466A; S467L; G469E; N581S; N581I; D594N; D594G; D594A; D594H; F595L; G596D; G596R and A762E.

MCL-1 inhibitors include, but are not limited to, AMG-176, MIK665, and S63845. The myeloid cell leukemia-1 (MCL-1) protein is one of the key anti-apoptotic members of the B-cell lymphoma-2 (BCL-2) protein family. Over-expression of MCL-1 has been closely related to tumor progression as well as to resistance, not only to traditional chemotherapies but also to targeted therapeutics including BCL-2 inhibitors such as ABT-263.

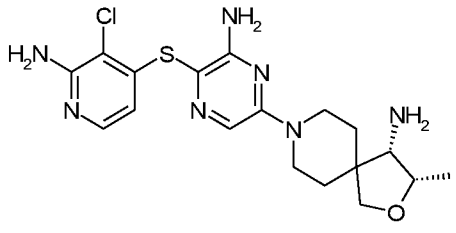
In some embodiments, the additional therapeutic agent is a SHP2 inhibitor. SHP2 is a non-receptor protein tyrosine phosphatase encoded by the PTPN11 gene that contributes to multiple cellular functions including proliferation, differentiation, cell cycle maintenance and migration. SHP2 has two N-terminal Src homology 2 domains (N-SH2 and C-SH2), a catalytic domain (PTP), and a C-terminal tail. The two SH2 domains control the subcellular localization and functional regulation of SHP2. The molecule exists in an inactive, self-inhibited conformation stabilized by a binding network involving residues from both the N-SH2 and PTP domains. Stimulation by, for example, cytokines or growth factors acting through receptor tyrosine kinases (RTKs) leads to exposure of the catalytic site resulting in enzymatic activation of SHP2.

SHP2 is involved in signaling through the RAS-mitogen-activated protein kinase (MAPK), the JAK-STAT or the phosphoinositol 3-kinase-AKT pathways. Mutations in the PTPN11 gene and subsequently in SHP2 have been identified in several human developmental diseases, such as Noonan Syndrome and Leopard Syndrome, as well as human cancers, such as juvenile myelomonocytic leukemia, neuroblastoma, melanoma, acute myeloid leukemia and cancers of the breast, lung and colon. Some of these mutations destabilize the auto-inhibited conformation of SHP2 and promote autoactivation or enhanced growth factor driven activation of SHP2. SHP2, therefore, represents a highly attractive target for the development of novel therapies for the treatment of various diseases including cancer. A SHP2 inhibitor (e.g., RMC-4550 or SHP099) in combination with a RAS pathway inhibitor (e.g., a MEK inhibitor) have been shown to inhibit the proliferation of multiple cancer cell lines in vitro (e.g., pancreas, lung, ovarian and breast cancer). Thus,

combination therapy involving a SHP2 inhibitor with a RAS pathway inhibitor could be a general strategy for preventing tumor resistance in a wide range of malignancies.

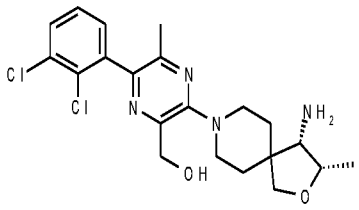
Non-limiting examples of such SHP2 inhibitors that are known in the art, include: Chen *et al. Mol Pharmacol*. 2006, *70*, 562; Sarver *et al.*, *J. Med. Chem.* 2017, 62, 1793; Xie *et al.*, *J. Med. Chem.* 2017, 60, 113734; and Igbe *et al.*, *Oncotarget*, 2017, 8, 113734; and PCT applications: WO 2023282702, WO 2023280283, WO 2023280237, WO 2023018155, WO 2023011513, WO 2022271966, WO 2022271964, WO 2022271911, WO 2022259157, WO 2022242767, WO 2022241975, WO 2022237676, WO 2022237367, WO 2022237178, WO 2022235822, WO 20222084008, WO 2022135568, WO 2021176072, WO 2021171261, WO 2021149817, WO 2021148010, WO 2021147879, WO 2021143823, WO 2021143701, WO 2021143680, WO 2021121397, WO 2021119525, WO 2021115286, WO 2021110796, WO 2021088945, WO 2021073439, WO 2021061706, WO 2021061515, WO 2021043077, WO 2021033153, WO 2021028362, WO 2021033153, WO 2021028362, WO 2021018287, WO 2020259679, WO 2020249079, WO 2020210384, WO 2020201991, WO 2020181283, WO 2020177653, WO 2020165734, WO 2020165733, WO 2020165732, WO 2020156243, WO 2020156242, WO 2020108590, WO 2020104635, WO 2020094104, WO 2020094018, WO 2020081848, WO 2020073949, WO 2020073945, WO 2020072656, WO 2020065453, WO 2020065452, WO 2020063760, WO 2020061103, WO 2020061101, WO 2020033828, WO 2020033286, WO 2020022323, WO 2019233810, WO 2019213318, WO 2019183367, WO 2019183364, WO 2019182960, WO 2019167000, WO 2019165073, WO 2019158019, WO 2019152454, WO 2019051469, WO 2019051084, WO 2018218133, WO 2018172984, WO 2018160731, WO 2018136265, WO 2018136264, WO 2018130928, WO 2018129402, WO 2018081091, WO 2018057884, WO 2018013597, WO 2017216706, WO 2017211303, WO 2017210134, WO 2017156397, WO 2017100279, WO 2017079723, WO 2017078499, WO 2016203406, WO 2016203405, WO 2016203404, WO 2016196591, WO 2016191328, WO 2015107495, WO 2015107494, WO 2015107493, WO 2014176488, WO 2014113584, CN 115677661, CN 115677660, CN 115611869, CN 115521305, CN 115490697, CN 115466273, CN 115394612, CN 115304613, CN 115304612, CN 115300513, CN 115197225, CN 114957162, CN 114920759, CN 114716448, CN 114671879, CN 114539223, CN 114524772, CN 114213417, CN 114195799, CN 114163457, CN 113896710, CN 113248521, CN 113248449, CN 113135924, CN 113024508, CN 112920131, CN 112823796, CN 112409334, CN 112402385, CN 112174935, 111848599, CN 111704611, CN 111393459, CN 111265529, CN 110143949, CN 108113848, US 11179397, US 20210085677, US 10858359, US 10934302, US 10954243, US 10988466, US 11001561, US 11033547, US 11034705, or US 11044675, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof, each of which is incorporated herein by reference.

In some embodiments, a SHP2 inhibitor binds in the active site. In some embodiments, a SHP2 inhibitor is a mixed-type irreversible inhibitor. In some embodiments, a SHP2 inhibitor binds an allosteric site e.g., a non-covalent allosteric inhibitor. In some embodiments, a SHP2 inhibitor is a covalent SHP2 inhibitor, such as an inhibitor that targets the cysteine residue (C333) that lies outside the phosphatase's active site. In some embodiments a SHP2 inhibitor is a reversible inhibitor. In some embodiments, a SHP2 inhibitor is an irreversible inhibitor. In some embodiments, the SHP2 inhibitor is SHP099. In some embodiments, the SHP2 inhibitor is TNO155, having the structure

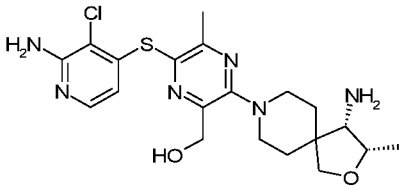


,or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof.

In some embodiments, the SHP2 inhibitor is RMC-4550, having the structure



or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof. In some embodiments, the SHP2 inhibitor is RMC-4630, having the structure:



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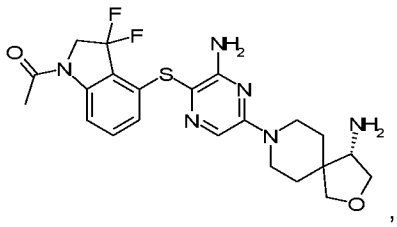
or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof.

In some embodiments, the SHP2 inhibitor is JAB-3068, having the structure



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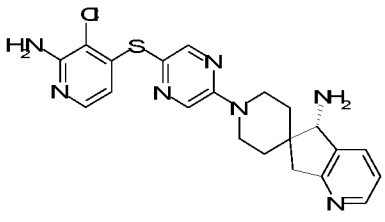
or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof. In some embodiments, the SHP2 inhibitor is JAB-3312. In some ebodiments, the SHP2 inhibitor is the following compound,



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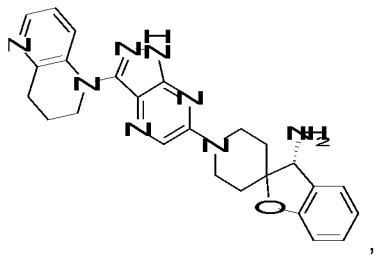
or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof. In some embodiments, the SHP2 inhibitor is RLY-1971, having the structure



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or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof. In some embodiments, the SHP2 inhibitor is ERAS-601, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof. In some embodiments, the SHP2 inhibitor is BBP-398, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof. In some embodiments, the SHP2 inhibitor is SH3809. In some embodiments, the SHP2 inhibitor is PF-07284892, or a pharmaceutically acceptable salt, solvate, isomer (e.g., stereoisomer), prodrug, or tautomer thereof.

In some embodiments, the additional therapeutic agent is selected from the group consisting of a MEK inhibitor, HER2 inhibitor, a SHP2 inhibitor, CDK4/6 inhibitor, an mTOR inhibitor, a SOS1 inhibitor, and a PD-L1 inhibitor. In some embodiments, the additional therapeutic agent is selected from the group consisting of a MEK inhibitor, a SHP2 inhibitor, and a PD-L1 inhibitor. See, e.g., Hallin et al., Cancer Discovery, DOI: 10.1158/2159-8290 (October 28, 2019) and Canon et al., Nature, 575:217 (2019). In some embodiments, a Ras inhibitor of the present invention is used in combination with a MEK inhibitor and a SOS1 inhibitor. In some embodiments, a Ras inhibitor of the present invention is used in combination with a PD-L1 inhibitor and a SOS1 inhibitor. In some embodiments, a Ras inhibitor of the present invention is used in combination with a PD-L1 inhibitor and a SHP2 inhibitor. In some embodiments, a Ras inhibitor of the present invention is used in combination with a MEK inhibitor and a SHP2 inhibitor. In some embodiments, the cancer is colorectal cancer and the treatment comprises administration of a Ras inhibitor of the present invention in combination with a second or third therapeutic agent.

Proteasome inhibitors include, but are not limited to, carfilzomib (Kyprolis®), bortezomib (Velcade®), and oprozomib.

Immune therapies include, but are not limited to, monoclonal antibodies, immunomodulatory imides (IMiDs), GITR agonists, genetically engineered T-cells (e.g., CAR-T cells), bispecific antibodies (e.g., BiTEs), and anti-PD-1, anti-PD-L1, anti-CTLA4, anti-LAGl, and anti-OX40 agents).

Immunomodulatory agents (IMiDs) are a class of immunomodulatory drugs (drugs that adjust immune responses) containing an imide group. The IMiD class includes thalidomide and its analogues (lenalidomide, pomalidomide, and apremilast).

Exemplary anti-PD-1 antibodies and methods for their use are described by Goldberg et al., Blood 2007, 110(1):186-192; Thompson et al., Clin. Cancer Res. 2007, 13(6):1757-1761; and WO06/121168 A1), as well as described elsewhere herein.

GITR agonists include, but are not limited to, GITR fusion proteins and anti-GITR antibodies (e.g., bivalent anti-GITR antibodies), such as, a GITR fusion protein described in U.S. Pat. No. 6,111,090, , U.S. Pat. No. 8,586,023, WO2010/003118 and WO2011/090754; or an anti-GITR antibody described, e.g., in U.S. Pat. No. 7,025,962, EP 1947183, U.S. Pat. No. 7,812,135, U.S. Pat. No. 8,388,967, U.S. Pat. No. 8,591,886, U.S. Pat. No. 7,618,632, EP 1866339, and WO2011/028683, WO2013/039954, WO05/007190,

WO07/133822, WO05/055808, WO99/40196, WO01/03720, WO99/20758, WO06/083289, WO05/115451, and WO2011/051726.

Another example of a therapeutic agent that may be used in combination with the compounds of the invention is an anti-angiogenic agent. Anti-angiogenic agents are inclusive of, but not limited to, in vitro synthetically prepared chemical compositions, antibodies, antigen binding regions, radionuclides, and combinations and conjugates thereof. An anti-angiogenic agent can be an agonist, antagonist, allosteric modulator, toxin or, more generally, may act to inhibit or stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote cell death or arrest cell growth. In some embodiments, the one or more additional therapies include an anti-angiogenic agent.

Anti-angiogenic agents can be MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-II (cyclooxygenase 11) inhibitors. Non-limiting examples of anti-angiogenic agents include rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Examples of useful COX-II inhibitors include alecoxib, valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO96/33172, WO96/27583, WO98/07697, WO98/03516, WO98/34918, WO98/34915, WO98/33768, WO98/30566, WO90/05719, WO99/52910, WO99/52889, WO99/29667, WO99007675, EP0606046, EP0780386, EP1786785, EP1181017, EP0818442, EP1004578, and US20090012085, and U.S. Patent Nos. 5,863,949 and 5,861,510. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 or AMP-9 relative to the other matrix-metalloproteinases (i.e., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP- 8, MMP-10, MMP-11, MMP-12, and MMP-13). Some specific examples of MMP inhibitors are AG-3340, RO 32-3555, and RS 13-0830.

Further exemplary anti-angiogenic agents include KDR (kinase domain receptor) inhibitory agents (e.g., antibodies and antigen binding regions that specifically bind to the kinase domain receptor), anti-VEGF agents (e.g., antibodies or antigen binding regions that specifically bind VEGF (e.g., bevacizumab), or soluble VEGF receptors or a ligand binding region thereof) such as VEGF-TRAP™, and anti-VEGF receptor agents (e.g., antibodies or antigen binding regions that specifically bind thereto), EGFR inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto) such as Vectibix® (panitumumab), erlotinib (Tarceva®), anti-Angl and anti-Ang2 agents (e.g., antibodies or antigen binding regions specifically binding thereto or to their receptors, e.g., Tie2/Tek), and anti-Tie2 kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto). Other anti-angiogenic agents include Campath, IL-8, B-FGF, Tek antagonists (US2003/0162712; US6,413,932), anti-TWEAK agents (e.g., specifically binding antibodies or antigen binding regions, or soluble TWEAK receptor antagonists; see US6,727,225), ADAM distintegrin domain to antagonize the binding of integrin to its ligands (US 2002/0042368), specifically binding anti-eph receptor or anti-ephrin antibodies or antigen binding regions (U.S. Patent Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124 and patent family members thereof), and anti-PDGF-BB antagonists (e.g., specifically binding antibodies or antigen binding regions) as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands, and PDGFR kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto). Additional anti-angiogenic agents include: SD-7784 (Pfizer, USA); cilengitide (Merck KGaA, Germany, EPO 0770622); pegaptanib octasodium, (Gilead Sciences, USA); Alphastatin, (BioActa, UK); M-PGA, (Celgene, USA, US 5712291); ilomastat, (Arriva, USA, US5892112); emaxanib, (Pfizer, USA, US

5792783); vatalanib, (Novartis, Switzerland); 2-methoxyestradiol (EntreMed, USA); TLC ELL-12 (Elan, Ireland); anecortave acetate (Alcon, USA); alpha-D148 Mab (Amgen, USA); CEP-7055 (Cephalon, USA); anti-Vn Mab (Crucell, Netherlands), DACantiangiogenic (ConjuChem, Canada); Angiocidin (InKine Pharmaceutical, USA); KM-2550 (Kyowa Hakko, Japan); SU-0879 (Pfizer, USA); CGP-79787 (Novartis, Switzerland, EP 0970070); ARGENT technology (Ariad, USA); YIGSR-Stealth (Johnson & Johnson, USA); fibrinogen-E fragment (BioActa, UK); angiogenic inhibitor (Trigen, UK); TBC-1635 (Encysive Pharmaceuticals, USA); SC-236 (Pfizer, USA); ABT-567 (Abbott, USA); Metastatin (EntreMed, USA); maspin (Sosei, Japan); 2-methoxyestradiol (Oncology Sciences Corporation, USA); ER-68203-00 (IV AX, USA); BeneFin (Lane Labs, USA); Tz-93 (Tsumura, Japan); TAN-1120 (Takeda, Japan); FR-111142 (Fujisawa, Japan, JP 02233610); platelet factor 4 (RepliGen, USA, EP 407122); vascular endothelial growth factor antagonist (Borean, Denmark); bevacizumab (pINN) (Genentech, USA); angiogenic inhibitors (SUGEN, USA); XL 784 (Exelixis, USA); XL 647 (Exelixis, USA); MAb, alpha5beta3 integrin, second generation (Applied Molecular Evolution, USA and MedImmune, USA); enzastaurin hydrochloride (Lilly, USA); CEP 7055 (Cephalon, USA and Sanofi-Synthelabo, France); BC 1 (Genoa Institute of Cancer Research, Italy); rBPI 21 and BPI-derived antiangiogenic (XOMA, USA); PI 88 (Progen, Australia); cilengitide (Merck KGaA, German; Munich Technical University, Germany, Scripps Clinic and Research Foundation, USA); AVE 8062 (Ajinomoto, Japan); AS 1404 (Cancer Research Laboratory, New Zealand); SG 292, (Telios, USA); Endostatin (Boston Childrens Hospital, USA); ATN 161 (Attenuon, USA); 2-methoxyestradiol (Boston Childrens Hospital, USA); ZD 6474, (AstraZeneca, UK); ZD 6126, (Angiogene Pharmaceuticals, UK); PPI 2458, (Praecis, USA); AZD 9935, (AstraZeneca, UK); AZD 2171, (AstraZeneca, UK); vatalanib (pINN), (Novartis, Switzerland and Schering AG, Germany); tissue factor pathway inhibitors, (EntreMed, USA); pegaptanib (Pinn), (Gilead Sciences, USA); xanthorrhizol, (Yonsei University, South Korea); vaccine, gene-based, VEGF-2, (Scripps Clinic and Research Foundation, USA); SPV5.2, (Supratek, Canada); SDX 103, (University of California at San Diego, USA); PX 478, (ProlX, USA); METASTATIN, (EntreMed, USA); troponin I, (Harvard University, USA); SU 6668, (SUGEN, USA); OXI 4503, (OXiGENE, USA); o-guanidines, (Dimensional Pharmaceuticals, USA); motuporamine C, (British Columbia University, Canada); CDP 791, (Celltech Group, UK); atiprimod (pINN), (GlaxoSmithKline, UK); E 7820, (Eisai, Japan); CYC 381, (Harvard University, USA); AE 941, (Aeterna, Canada); vaccine, angiogenic, (EntreMed, USA); urokinase plasminogen activator inhibitor, (Dendreon, USA); oglufanide (pINN), (Melmotte, USA); HIF-lalfa inhibitors, (Xenova, UK); CEP 5214, (Cephalon, USA); BAY RES 2622, (Bayer, Germany); Angiocidin, (InKine, USA); A6, (Angstrom, USA); KR 31372, (Korea Research Institute of Chemical Technology, South Korea); GW 2286, (GlaxoSmithKline, UK); EHT 0101, (ExonHit, France); CP 868596, (Pfizer, USA); CP 564959, (OSI, USA); CP 547632, (Pfizer, USA); 786034, (GlaxoSmithKline, UK); KRN 633, (Kirin Brewery, Japan); drug delivery system, intraocular, 2-methoxyestradiol; anginex (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510 (Abbott, USA); AAL 993 (Novartis, Switzerland); VEGI (ProteomTech, USA); tumor necrosis factor-alpha inhibitors; SU 11248 (Pfizer, USA and SUGEN USA); ABT 518, (Abbott, USA); YH16 (Yantai Rongchang, China); S-3APG (Boston Childrens Hospital, USA and EntreMed, USA); MAb, KDR (ImClone Systems, USA); MAb, alpha5 beta (Protein Design, USA); KDR kinase inhibitor (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116 (South Florida University, USA and Yale University, USA); CS 706 (Sankyo, Japan); combretastatin A4 prodrug (Arizona State University, USA); chondroitinase AC (IBEX, Canada); BAY RES 2690 (Bayer, Germany); AGM 1470 (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925

(Agouron, USA); Tetrathiomolybdate (University of Michigan, USA); GCS 100 (Wayne State University, USA) CV 247 (Ivy Medical, UK); CKD 732 (Chong Kun Dang, South Korea); irsogladine, (Nippon Shinyaku, Japan); RG 13577 (Aventis, France); WX 360 (Wilex, Germany); squalamine, (Genaera, USA); RPI 4610 (Sirna, USA); heparanase inhibitors (InSight, Israel); KL 3106 (Kolon, South Korea); Honokiol (Emory University, USA); ZK CDK (Schering AG, Germany); ZK Angio (Schering AG, Germany); ZK 229561 (Novartis, Switzerland, and Schering AG, Germany); XMP 300 (XOMA, USA); VGA 1102 (Taisho, Japan); VE-cadherin-2 antagonists(ImClone Systems, USA); Vasostatin (National Institutes of Health, USA); Flk-1 (ImClone Systems, USA); TZ 93 (Tsumura, Japan); TumStatin (Beth Israel Hospital, USA); truncated soluble FLT 1 (vascular endothelial growth factor receptor 1) (Merck & Co, USA); Tie-2 ligands (Regeneron, USA); and thrombospondin 1 inhibitor (Allegheny Health, Education and Research Foundation, USA).

Further examples of therapeutic agents that may be used in combination with compounds of the invention include agents (e.g., antibodies, antigen binding regions, or soluble receptors) that specifically bind and inhibit the activity of growth factors, such as antagonists of hepatocyte growth factor (HGF, also known as Scatter Factor), and antibodies or antigen binding regions that specifically bind its receptor, c-Met.

Another example of a therapeutic agent that may be used in combination with compounds of the invention is an autophagy inhibitor. Autophagy inhibitors include, but are not limited to chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4-imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNA that inhibits expression of proteins including but not limited to ATG5 (which are implicated in autophagy), may also be used. In some embodiments, the one or more additional therapies include an autophagy inhibitor.

Another example of a therapeutic agent that may be used in combination with compounds of the invention is an anti-neoplastic agent. In some embodiments, the one or more additional therapies include an anti-neoplastic agent. Non-limiting examples of anti-neoplastic agents include acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ancer, ancestim, arglabin, arsenic trioxide, BAM-002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetrorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-NI, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-la, interferon beta-lb, interferon gamma, natural interferon gamma- la, interferon gamma-lb, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine,

lovastatin, masoprocol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, nartograstim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburiembodiment, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, virulizin, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), decitabine, dexaminoglutethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techni clone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

Additional examples of therapeutic agents that may be used in combination with compounds of the invention include ipilimumab (Yervoy®); tremelimumab; galiximab; nivolumab, also known as BMS-936558 (Opdivo®); pembrolizumab (Keytruda®); avelumab (Bavencio®); AMP224; BMS-936559; MPDL3280A, also known as RG7446; MEDI-570; AMG557; MGA271; IMP321; BMS-663513; PF-05082566; CDX-1127; anti-OX40 (Providence Health Services); huMAbOX40L; atacicept; CP-870893; lucatumumab; dacetuzumab; muromonab-CD3; ipilumumab; MEDI4736 (Imfinzi®); MSB0010718C; AMP 224; adalimumab (Humira®); ado-trastuzumab emtansine (Kadcyla®); aflibercept (Eylea®); alemtuzumab (Campath®); basiliximab (Simulect®); belimumab (Benlysta®); basiliximab (Simulect®); belimumab (Benlysta®); brentuximab vedotin (Adcetris®); canakinumab (Ilaris®); certolizumab pegol (Cimzia®); daclizumab (Zenapax®); daratumumab (Darzalex®); denosumab (Prolia®); eculizumab (Soliris®); efalizumab (Raptiva®); gemtuzumab ozogamicin (Mylotarg®); golimumab (Simponi®); ibritumomab tiuxetan (Zevalin®); infliximab (Remicade®); motavizumab (Numax®); natalizumab (Tysabri®); obinutuzumab (Gazyva®); ofatumumab (Arzerra®); omalizumab (Xolair®); palivizumab (Synagis®); pertuzumab (Perjeta®); pertuzumab (Perjeta®); ranibizumab (Lucentis®); raxibacumab (Abthrax®);

tocilizumab (Actemra®); tositumomab; tositumomab-i-131; tositumomab and tositumomab-i-131 (Bexxar®); ustekinumab (Stelara®); AMG 102; AMG 386; AMG 479; AMG 655; AMG 706; AMG 745; and AMG 951.

The compounds described herein can be used in combination with the agents disclosed herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments the one or more compounds of the disclosure will be co-administered with other therapies as described herein. When used in combination therapy, the compounds described herein may be administered with the second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described herein can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of the invention and any of the therapies described herein can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound of the present disclosure can be administered and followed by any of the therapies described herein, or vice versa. In some embodiments of the separate administration protocol, a compound of the invention and any of the therapies described herein are administered a few minutes apart, or a few hours apart, or a few days apart.

In some embodiments of any of the methods described herein, the first therapy (e.g., a compound of the invention) and one or more additional therapies are administered simultaneously or sequentially, in either order. The first therapeutic agent may be administered immediately, up to 1 hour, up to 2 hours, up to 3 hours, up to 4 hours, up to 5 hours, up to 6 hours, up to 7 hours, up to, 8 hours, up to 9 hours, up to 10 hours, up to 11 hours, up to 12 hours, up to 13 hours, 14 hours, up to hours 16, up to 17 hours, up 18 hours, up to 19 hours up to 20 hours, up to 21 hours, up to 22 hours, up to 23 hours, up to 24 hours, or up to 1-7, 1-14, 1-21 or 1-30 days before or after the one or more additional therapies.

The invention also features kits including (a) a pharmaceutical composition including an agent (e.g., a compound of the invention) described herein, and (b) a package insert with instructions to perform any of the methods described herein. In some embodiments, the kit includes (a) a pharmaceutical composition including an agent (e.g., a compound of the invention) described herein, (b) one or more additional therapies (e.g., non-drug treatment or therapeutic agent), and (c) a package insert with instructions to perform any of the methods described herein.

As one aspect of the present invention contemplates the treatment of the disease or symptoms associated therewith with a combination of pharmaceutically active compounds that may be administered separately, the invention further relates to combining separate pharmaceutical compositions in kit form. The kit may comprise two separate pharmaceutical compositions: a compound of the present invention, and one or more additional therapies. The kit may comprise a container for containing the separate compositions such as a divided bottle or a divided foil packet. Additional examples of containers include syringes, boxes, and bags. In some embodiments, the kit may comprise directions for the use of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing health care professional.

Examples

The disclosure is further illustrated by the following examples and synthesis examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure or scope of the appended claims.

Chemical Syntheses

Definitions used in the following examples and elsewhere herein are:

B_2pin_2	Bis(pinacolato)diboron
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
CH_2Cl_2, DCM	Methylene chloride, Dichloromethane
CH_3CN, MeCN	Acetonitrile
CuI	Copper (I) iodide
DIPEA, DIEA	Diisopropylethyl amine
DMF	N,N-Dimethylformamide
EA	Ethyl acetate
EDCI	N-Ethyl-N'-carbodiimide hydrochloride
EtOAc	Ethyl acetate
h	hour
H_2O	Water
HCl	Hydrochloric acid
HOBt	Hydroxybenzotriazole
K_3PO_4	Potassium phosphate (tribasic)
MeOH	Methanol
Na_2SO_4	Sodium sulfate
NMM	N-methylmorpholine
NMP	N-methyl pyrrolidone
$Pd(dppf)Cl_2$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PE	Petroleum ether
rt	Room temperature
TFA	Trifluoroacetic acid

Instrumentation

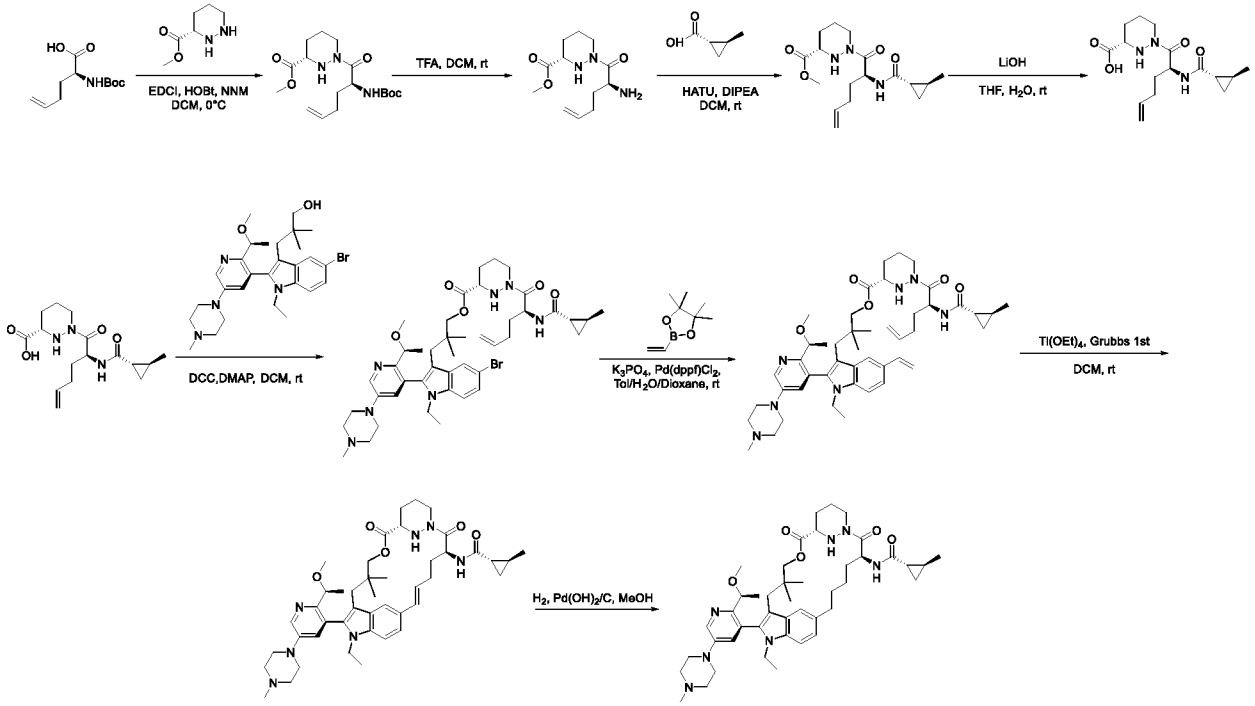
Mass spectrometry data collection took place with a Shimadzu LCMS-2020, an Agilent 1260LC-6120/6125MSD, a Shimadzu LCMS-2010EV, or a Waters Acquity UPLC, with either a QDa detector or SQ Detector 2. Samples were injected in their liquid phase onto a C-18 reverse phase. The compounds were eluted from the column using an acetonitrile gradient and fed into the mass analyzer. Initial data analysis took place with either Agilent ChemStation, Shimadzu LabSolutions, or Waters MassLynx. NMR data was

collected with either a Bruker AVANCE III HD 400MHz, a Bruker Ascend 500MHz instrument, or a Varian 400MHz, and the raw data was analyzed with either TopSpin or Mestrelab Mnova.

Example 1. Synthesis of Compounds

Compounds of Table 1, and intermediates in the synthesis thereto, can be prepared by those skilled in the art of synthetic organic chemistry, such as combining known techniques with experimental procedures detailed in the Example sections of WO 2021/091956 and WO 2022/060836, which are each incorporated herein by reference in their entirety. Additional synthetic preparations are provided below.

Example C: Synthesis of (1*S*,2*S*)-*N*-((7^3*S*,9*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-3,3-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^{1}H-5-oxa-1(3,5)-indola-7(3,1)-pyridazinacyclotridecaphane-9-yl)-2-methylcyclopropane-1-carboxamide



Step 1. To a stirred solution of methyl (*S*)-hexahydropyridazine-3-carboxylate (1.47 g, 4.36 mmol) and NMM (43.6mmol) in 20 mL DCM were added (*S*)-2-((*tert*-butoxycarbonyl)amino)hex-5-enoic acid (1 g, 4.36 mmol) and EDCI (1.67 g, 8.72 mmol)/HOBT (0.87 mmol) in portions at 0 °C under air atmosphere. The resulting mixture was stirred for 2 h at 25 °C under air atmosphere. The resulting mixture was washed with H_2O (3 x 20 mL). The aqueous layer was extracted with DCM (3 x 20 mL). The organic phase was concentrated under reduced pressure. The residue was purified by preparative-HPLC to afford methyl (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)hex-5-enoyl)hexahydropyridazine-3-carboxylate (782 mg, 50.44%) as yellow oil. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{17}H_{30}N_3O_5$ 356.2; found 356.0.

Step 2. To a stirred solution/mixture of (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)hex-5-enoyl)hexahydropyridazine-3-carboxylate (500 mg) and DCM (10 mL) was added TFA (10 mL) at room temperature. The resulting mixture was concentrated under reduced pressure and used directly for next step without further purification.

Step 3. To a stirred solution of methyl (*S*)-1-((*S*)-2-aminohex-5-enoyl)hexahydropyridazine-3-carboxylate (500 mg, 1.96 mmol) and (1*S*,2*S*)-2-methylcyclopropane-1-carboxylic acid (196.06 mg, 1.96 mmol) in 10 mL DCM were added HATU (744.62 mg, 1.96 mmol) and DIPEA (2531.02 mg, 19.56 mmol) at room temperature. The resulting mixture was washed with H_2O (3 x 100 mL). The residue was purified by silica gel column chromatography to afford methyl (*S*)-1-((*S*)-2-((1*S*,2*S*)-2-methylcyclopropane-1-carboxamido)hex-5-enoyl)hexahydropyridazine-3-carboxylate (500 mg, 75.67%) as a white solid.

Step 4. To a stirred solution of methyl (3*S*)-1-[(2*S*)-2-{[(1*S*,2*S*)-2-methylcyclopropyl]formamido}hex-5-enoyl]-1,2-diazinane-3-carboxylate (500 mg, 1.48 mmol) in THF (10 mL) and H_2O (10 mL) was added LiOH (177.43 mg, 7.41 mmol) at room temperature. The mixture was acidified to pH 5 with 1 M HCl (aq.). The aqueous layer was extracted with DCM (3 x 100mL). The organic mixture was concentrated under reduced pressure to afford 420 mg crude product which used directly without further purification. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{16}H_{26}N_3O_4$ 324.2; found 324.3.

Step 5. To a stirred solution of (*S*)-1-((*S*)-2-((1*S*,2*S*)-2-methylcyclopropane-1-carboxamido)hex-5-enoyl)hexahydropyridazine-3-carboxylic acid (320 mg, 0.99 mmol) and (*S*)-3-(5-bromo-1-ethyl-2-(2-(1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-indol-3-yl)-2,2-dimethylpropan-1-ol (537.85 mg, 0.99 mmol) in 10 mL DCM were added DCC (408.32 mg, 1.98 mmol) and DMAP (24.18 mg, 0.20 mmol) at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-(5-bromo-1-ethyl-2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-indol-3-yl)-2,2-dimethylpropyl (*S*)-1-((*S*)-2-((1*S*,2*S*)-2-methylcyclopropane-1-carboxamido)hex-5-enoyl)hexahydropyridazine-3-carboxylate (720 mg, 85.71%) as a white solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{44}H_{63}BrN_7O_5$ 848.4; found 848.5.

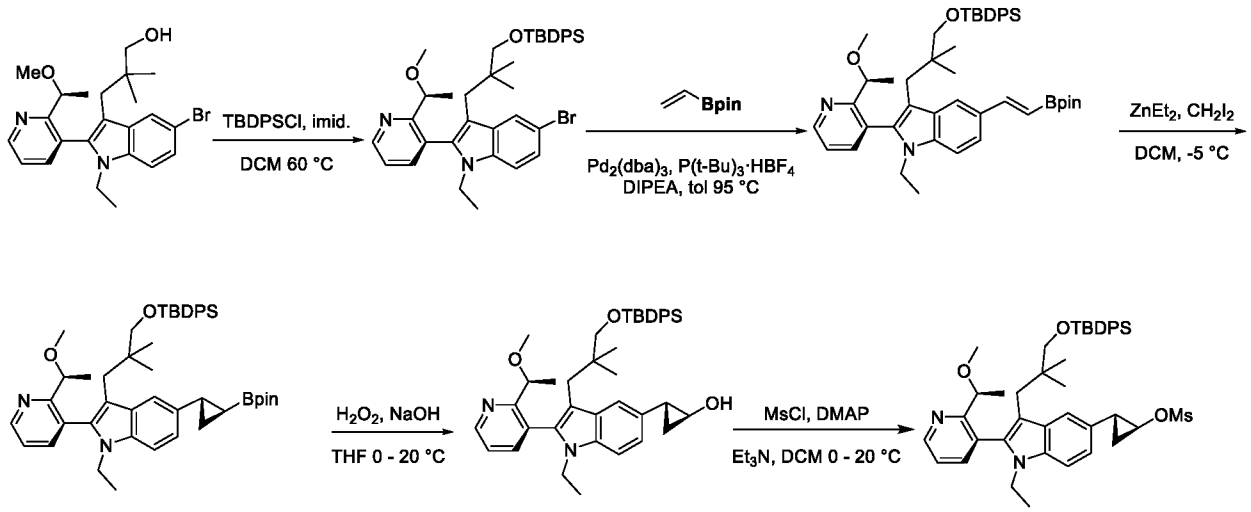
Step 6. To a stirred solution of 3-(5-bromo-1-ethyl-2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-indol-3-yl)-2,2-dimethylpropyl (*S*)-1-((*S*)-2-((1*S*,2*S*)-2-methylcyclopropane-1-carboxamido)hex-5-enoyl)hexahydropyridazine-3-carboxylate (640 mg, 0.75 mmol) and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1161.14 mg, 7.54 mmol) in toluene (9 mL), dioxane (3mL) and H_2O (3mL) was added K_3PO_4 (400 mg, 1.88 mmol) and $Pd(dppf)Cl_2$ (122 mg, 0.15 mmol) at room temperature under a nitrogen atmosphere. The reaction was stirred for overnight at 70 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-(1-ethyl-2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-5-vinyl-1*H*-indol-3-yl)-2,2-dimethylpropyl (*S*)-1-((*S*)-2-((1*S*,2*S*)-2-methylcyclopropane-1-carboxamido)hex-5-enoyl)hexahydropyridazine-3-carboxylate (500 mg, 83.31%) as a white solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{46}H_{66}N_7O_5$ 796.5; found 796.5.

Step 7. To a stirred solution of 3-(1-ethyl-2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-5-vinyl-1*H*-indol-3-yl)-2,2-dimethylpropyl (*S*)-1-((*S*)-2-((1*S*,2*S*)-2-methylcyclopropane-1-carboxamido)hex-5-enoyl)hexahydropyridazine-3-carboxylate (800 mg, 1.01 mmol) and Titanium tetraisopropanolate (142.81 mg, 0.50 mmol) in 100 mL DCM was added Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (0.17 g, 0.20 mmol) in portions at 25 °C under an air atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Preperatory-HPLC to afford (1*S*,2*S*)-N-

((7^3*S*,9*S*,*E*)-11-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-3,3-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-5-oxa-1(3,5)-indola-7(3,1)-pyridazinacyclotridecaphan-12-en-9-yl)-2-methylcyclopropane-1-carboxamide (17 mg, 2.17%) as a white solid. LCMS (ESI): m/z [M+H]$^+$ calc'd for $C_{44}H_{62}N_7O_5$ 768.5; found 768.5.

Step 8. To a solution of (1*S*,2*S*)-N-((7^3*S*,9*S*, *E*)-11-ethyl-12-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-3,3-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-5-oxa-1(3,5)-indola-7(3,1)-pyridazinacyclotridecaphan-12-en-9-yl)-2-methylcyclopropane-1-carboxamide (260 mg, 0.13 mmol) in 3 mL MeOH was added $Pd(OH)_2$/C (20%, 0.26 g) in a pressure tank. The mixture was hydrogenated at room temperature under 30 psi of H_2 for 1 h, filtered through a sand core funnel and concentrated under reduced pressure. The residue was purified by Preparatory-HPLC to afford (1*S*,2*S*)-N-((7^3*S*,9*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-3,3-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-5-oxa-1(3,5)-indola-7(3,1)-pyridazinacyclotridecaphane-9-yl)-2-methylcyclopropane-1-carboxamide (30 mg, 29.08%) as a white solid. LCMS (ESI): m/z [M+H]$^+$ calc'd for $C_{44}H_{64}N_7O_5$ 770.5; found 770.6. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.51 – 8.43 (d, 1H), 8.01 – 7.93 (m, 1H), 7.43 – 7.34 (m, 1H), 7.28 (s, 1H), 7.24 – 7.18 (m, 1H), 7.03 – 6.95 (m, 1H), 5.48 – 5.38 (m, 1H), 5.34 – 5.23 (m, 1H), 4.40 – 4.28 (m, 1H), 4.16 – 3.97 (m, 2H), 3.95 – 3.81 (m, 1H), 3.71 – 3.47(m, 3H), 3.28 – 3.21 (m, 4H), 3.00 – 2.79 (m, 4H), 2.66 – 2.58 (m, 1H), 2.48 – 2.43 (m, 4H), 2.28 – 2.21 (m, 4H), 1.92 – 1.76 (m, 3H), 1.69 – 1.41 (m, 7H), 1.40 – 1.32 (m, 5H), 1.18 – 1.06 (m, 3H), 1.04 – 0.95 (m, 4H), 0.88 – 0.72 (m, 4H), (s, 4H), 0.57 (s, 3H), 0.47 – 0.36 (m, 1H).

Synthesis of (1*S*,2*R*)-2-(3-(3-((*tert*-butyldiphenylsilyl)oxy)-2,2-dimethylpropyl)-1-ethyl-2-(2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-1*H*-indol-5-yl)cyclopropyl methanesulfonate



Step 1. To a stirred solution of 3-(5-bromo-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-3-yl)-2,2-dimethylpropan-1-ol (15 g, 33.7 mol) in DCM (150 mL) and DMF (30 mL) was added Imidazole (6.88 g, 101.1 mol) and TBDPSCl (13.89 g, 50.5 mol) at 20 °C. The resulting solution was stirred for 2 h at 60 °C. The solution was diluted with DCM (300 mL) and H_2O (300 mL). Layers were separated and the organic layer was washed with H_2O (100 mL × 3), brine (300 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure to give a residue. The residue was purified by silica

gel chromatography to give 5-bromo-3-{3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-dimethylpropyl}-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indole (19.8 g, 81% yield) as a colorless oil. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{39}H_{47}BrN_2O_2Si$ 683.3; found 683.2.

Step 2. To a solution of the Pinacol vinylboronate (10.4 g, 67.5 mmol), 5-bromo-3-{3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-dimethylpropyl}-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indole (42 g, 61.4 mmol), DIPEA (15.87 g, 122.8 mmol), $Pd_2(dba)_3$ (5.62 g, 6.1 mmol) and $P(t\text{-}Bu)_3 \cdot HBF_4$ (3.56 g, 12.2 mmol) in dry toluene (320 mL) was stirred at 95 °C for 2 h under N_2 atmosphere. The solution was cooled down, and the precipitate was filtrated. The filtrate was evaporated under reduced pressure to give a residue. The residue was purified by silica gel chromatography to give 3-{3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-dimethylpropyl}-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}-5-[(1*E*)-prop-1-en-1-yl]indole (37 g, 84% yield) as a green semi-oil. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{47}H_{61}BN_2O_4Si$ 757.5; found 757.5.

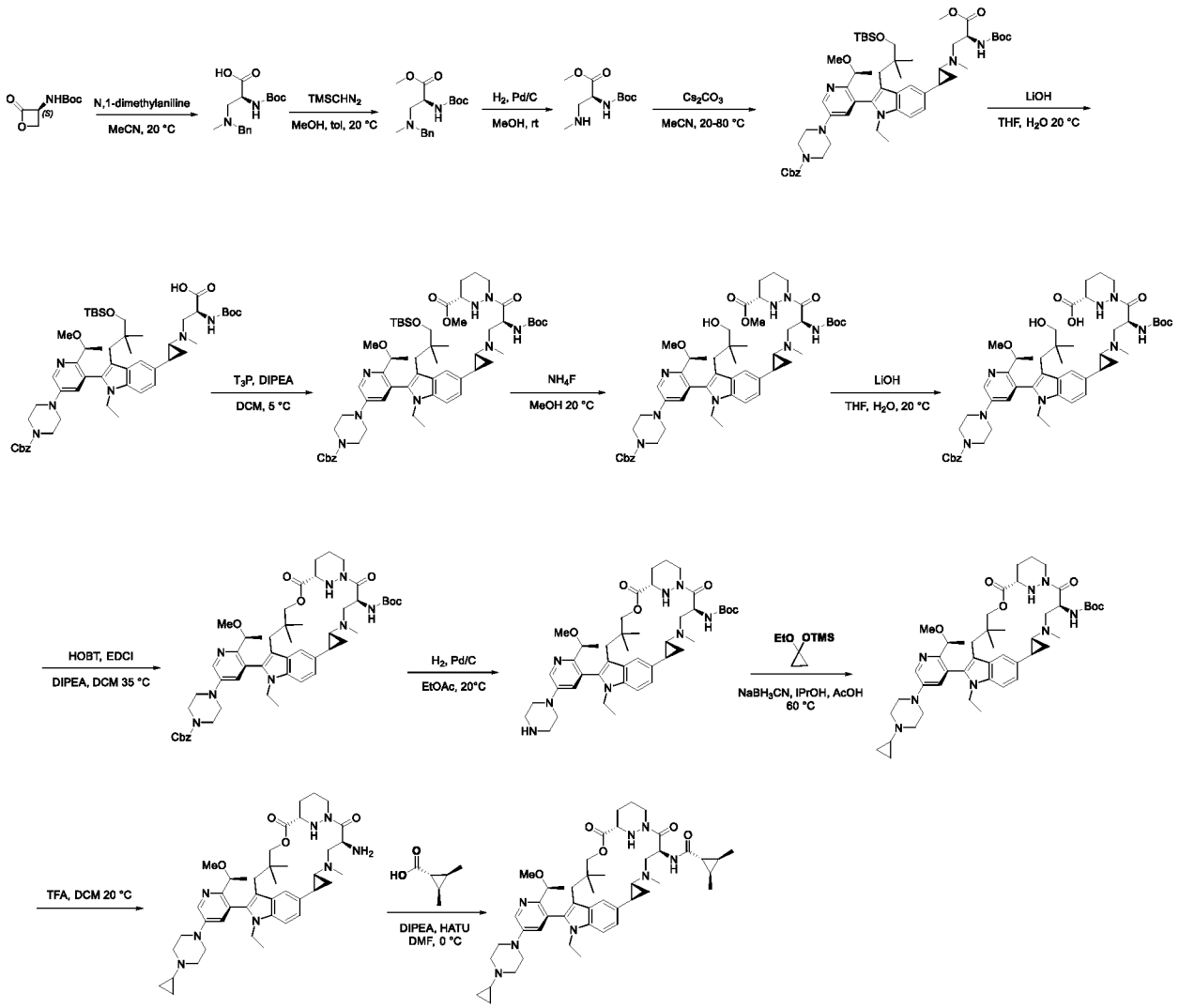
Step 3. Flame dry a 100 mL round bottom flask was equipped with a stir bar, charge the vessel with $ZnEt_2$ (1M solution in hexanes, 39.8 mL, 39.8 mmol) and DCM (160 mL). CH_2I_2 (21.3 g, 79.5 mmol) was added dropwise via syringe to the reaction mixture at -5 °C. The resulting mixture was stirred at -5 °C for 1 h, then 3-{3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-dimethylpropyl}-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}-5-[(*E*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]indole (12 g, 15.9 mmol) was added dropwise to the flask as a solution in DCM (30 mL). The reaction mixture was warmed to 20 °C and stirred vigorously for 16 h. Then reaction mixture was quenched with saturated NH4Cl (aq), extracted with DCM (50 x 2 mL), and washed with brine (50 x 2 mL). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by silica gel chromatography to give 3-{3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-dimethylpropyl}-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}-5-[(1*S*,2*S*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]indole (10 g, 77% yield) as a pale yellow semi-solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{48}H_{63}BN_2O_4Si$ 771.5; found 771.4.

Step 4. To a solution of 3-{3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-dimethylpropyl}-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}-5-[(1*S*,2*S*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]indole (12 g, 15.6 mmol) in THF (120 mL) and NaOH (12 mL) was added 30% H_2O_2 (6 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 0.5 h. The reaction mixture was quenched by saturated $Na_2S_2O_3$ a.q, extracted with EtOAc (20 x 3 mL), and washed with brine (30 mL x 2). The organic phase was collected, dried over Na_2SO_4, then concentrated to give a residue. The residue was purified by silica gel chromatography to afford the (1*S*,2*R*)-2-(3-{3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-dimethylpropyl}-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl)cyclopropan-1-ol (10 g, 92 % yield) as a pale green semi-solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{42}H_{52}N_2O_3Si$ 661.4; found 661.3.

Step 5. To a solution of (1*S*,2*R*)-2-(3-{3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-dimethylpropyl}-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl)cyclopropan-1-ol (7.2 g, 10.9 mmol, 1.0 equiv) in DCM (72 mL) was added Et_3N (2.21 g, 21.8 mmol), DMAP (0.27 g, 2.18 mmol). Then methanesulfonyl chloride (1.86 g, 16.4 mmol) was added dropwise at 0 °C, the reaction mixture was stirred at 20 °C for 1 h. The mixture was quenched by saturated $NaHCO_3$ (aq), extracted by DCM (50 x 2 mL), and washed with brine (50 x 2 mL). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated to give the residue. The

residue was purified by silica gel chromatography to afford (1*S*,2*R*)-2-(3-(3-((*tert*-butyldiphenylsilyl)oxy)-2,2-dimethylpropyl)-1-ethyl-2-(2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-1*H*-indol-5-yl)cyclopropyl methanesulfonate (two diastereomers mixture, ratio 1:1.6, 6.8 g, 80% yield) as a pale green semi-solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{43}H_{54}N_2O_5SSi$ 739.4; found 739.3.

Example A7: Synthesis of (1*SR*,2*RS*,3*SR*)-*N*-((2^1*RS*,2^2*SR*,7^3*RS*,5*RS*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-3,11,11-trimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-9-oxa-3-aza-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-5-yl)-2,3-dimethylcyclopropane-1-carboxamide



Step 1. To a solution of *tert*-butyl N-[(3S)-2-oxooxetan-3-yl]carbamate (20 g, 0.107 mol) in MeCN (100 mL) was added N,1-dimethylaniline (13 g, 0.11 mol) at 20 °C. The resulting solution was stirred at 20 °C for 1 h then concentrated under reduced pressure. The residue was purified by silica gel chromatography to give desired product of (R)-3-(benzyl(methyl)amino)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (25 g, 65% yield) as a light yellow solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{16}H_{25}N_2O_4$ 309.2; found 309.2.

Step 2. To a stirred solution of *rac*-(*R*)-3-(benzyl(methyl)amino)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (29 g, 0.09 mol) in MeOH (70 mL) and toluene (210 mL) was added (trimethylsilyl)diazomethane (21 g, 0.19 mol) at 20 °C. The resulting solution was stirred for 2 hours at 20 °C. After it was quenched with

H_2O (20 mL) and concentrated to dryness to give a residue. The residue was diluted with EtOAc (800 mL) and H_2O (100 mL). The organic layer was washed with H_2O (100 mL × 3), brine (100 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure to give a residue. The residue was purified by silica gel chromatography to give methyl (*R*)-3-(benzyl(methyl)amino)-2-((*tert*-butoxycarbonyl)amino)propanoate (23 g, 72% yield) as a light yellow oil. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{16}H_{25}N_2O_4$ 323.2; found 323.3.

Step 3. To a solution of *rac*-methyl (*R*)-3-(benzyl(methyl)amino)-2-((*tert*-butoxycarbonyl)amino)propanoate (7.1 g, 0.02 mol) in MeOH (50 mL) was added Pd/C (1 g, 14% weight) at 20 °C. The resulting solution was stirred at 20 °C for 16 hours under H_2 atmosphere (1 atm). The mixture was filtered, the filtrate was concentrated under reduced pressure to give crude desired product of methyl (R)-2-((*tert*-butoxycarbonyl)amino)-3-(methylamino)propanoate (4 g, purity>90%) as a light yellow oil. This crude product was used in the next step without further purification.

Step 4. To a stirred solution of (3-{4-[5-(3-{3-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethylpropyl}-1-ethyl-5-[(1*S*,2*R*)-2-(methanesulfonyloxy)cyclopropyl]indol-2-yl)-6-[(1*S*)-1-methoxyethyl]pyridin-3-yl]piperazin-1-yl}phenyl)methyl formate (3.28 g, 0.004 mol) and *rac*-methyl (*R*)-3-(benzyl(methyl)amino)-2-((*tert*-butoxycarbonyl)amino)propanoate (4.55 g, 0.02 mol) in MeCN (5 mL) was added Cs_2CO_3 (3.81 g, 0.012 mol) at 20 °C. The resulting solution was stirred for 3 days at 80 °C under an N_2 atmosphere. The solution was diluted with EtOAc (600 mL) and H_2O (100 mL). The organic layer was washed with H_2O (50 mL × 3), brine (100 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure to give a residue. The residue was purified by silica gel chromatography) to give desired product of benzyl 4-(5-(5-((1*RS*,2*SR*)-2-(((*RS*)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)(methyl)amino)cyclopropyl)-3-(3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropyl)-1-ethyl-1*H*-indol-2-yl)-6-((*RS*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (1.8 g, 50% purity) as a light yellow solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{54}H_{80}N_6O_8Si$ 969.6; found 969.4.

Step 5. To a stirred solution of benzyl 4-(5-(5-((1*RS*,2*SR*)-2-(((*RS*)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)(methyl)amino)cyclopropyl)-3-(3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropyl)-1-ethyl-1*H*-indol-2-yl)-6-((*RS*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (1.7 g, 0.002 mol) in THF (18 mL) and H_2O (6 mL) was added LiOH (0.09 g, 0.004 mol) at 20 °C, the resulting solution was stirred for 2 hours. After the pH was adjusted to 7 with 1N HCl at 5 °C and concentrated, the residue was dissolved with DCM (200 ml), washed with H_2O (20 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to afford (*RS*)-3-(((1*SR*,2*RS*)-2-(2-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropyl)-1-ethyl-1*H*-indol-5-yl)cyclopropyl)(methyl)amino)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (1.7 g, 50% purity) as gray foam, which was used directly for the next step without further purification.

Step 6. To a stirred solution of (*RS*)-3-(((1*SR*,2*RS*)-2-(2-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropyl)-1-ethyl-1*H*-indol-5-yl)cyclopropyl)(methyl)amino)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (1.9 g , 1.67 mmol) and methyl (3*S*)-1,2-diazinane-3-carboxylate dihydrochloride (363 mg, 1.67 mmol) in DCM (16 mL) were added DIPEA

(1.08 g, 8.37 mmol) followed by T_3P (1.28 g, 2.01 mmol) at 5 °C and stirred for 1 hour. The solution was diluted with DCM (300 mL) and H_2O (50 mL). The organic layer was washed with H_2O (30 mL × 3), brine (30 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography to give desired product of methyl (*S*)-1-((*RS*)-3-(((1*SR*,2*RS*)-2-(2-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropyl)-1-ethyl-1*H*-indol-5-yl)cyclopropyl)(methyl)amino)-2-((*tert*-butoxycarbonyl)amino)propanoyl)hexahydropyridazine-3-carboxylate (two diastereomers separated, V-0173-03-P1; 590 mg, 30% yield; V-0173-03-P2: 470 mg, 23% yield) as a light yellow solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{59}H_{88}N_8O_9Si$ 1081.6; found 541.4 $[M/2+H]^+$

Step 7. To a stirred solution of methyl (*S*)-1-((*RS*)-3-(((1*SR*,2*RS*)-2-(2-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropyl)-1-ethyl-1*H*-indol-5-yl)cyclopropyl)(methyl)amino)-2-((*tert*-butoxycarbonyl)amino)propanoyl)hexahydropyridazine-3-carboxylate (300 mg, 0.28 mmol) in MeOH (3 mL) was added NH_4F (410 mg, 11.2 mol) at 20 °C. The resulting solution was stirred for 48 hours at 60 °C. The solution was concentrated under reduced pressure to afford a residue, which was diluted with EtOAc (40 mL) and H_2O (20 mL). The organic layer was washed with H_2O (20 mL × 3), brine (30 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure to afford methyl (3*S*)-1-[(2*S*)-2-{[*tert*-butyl(formyl)-$l^{3}-oxidanyl]amino}-3-{[(1*R*,2*S*)-2-{1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1S)-1-methoxyethyl]pyridin-3-yl]-3-(3-hydroxy-2,2-dimethylpropyl)indol-5-yl}cyclopropyl](methyl)amino}propanoyl]-1,2-diazinane-3-carboxylate (200 mg, 70% purity) as a pale green semi oil. The crude product was used in the next step without further purification.

Step 8. To a stirred solution of methyl (*S*)-1-((*RS*)-3-(((1*SR*,2*RS*)-2-(2-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)cyclopropyl)(methyl)amino)-2-((*tert*-butoxycarbonyl)amino)propanoyl)hexahydropyridazine-3-carboxylate (300 mg, 0.31 mmol), HOBT (424.3 mg, 3.1 mmol) and DIPEA (1.62 g, 12.4 mmol) in DCM (30 mL) was added EDCI (1.81 g, 9.3 mmol). The reaction mixture was stirred at 35 °C for 5 h. The mixture was quenched with H_2O (60 mL), and the obtained mixture was extracted with DCM (50 mL x 3). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by silica gel chromatography to afford benzyl 4-(5-((2^1*RS*,2^2*SR*,7^3*S*,5*RS*)-5-((*tert*-butoxycarbonyl)amino)-1^1-ethyl-3,11,11-trimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-9-oxa-3-aza-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-12-yl)-6-((*RS*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (50 mg, 16% yield) as a pale yellow semi solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{52}H_{70}N_8O_8$ 935.5; found 936.1.

Step 9. To a solution of benzyl 4-(5-((2^1*RS*,2^2*SR*,7^3*S*,5*RS*)-5-((*tert*-butoxycarbonyl)amino)-1^1-ethyl-3,11,11-trimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-9-oxa-3-aza-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-12-yl)-6-((*RS*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (120 mg, 0.13 mmol) in EtOAc (2 mL) was added Pd/C (50% w/w, 60mg). Then under the H_2 atmosphere (1 atm), the reaction mixture was stirred at 20 °C for 6 hours. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure to afford *tert*-butyl ((2^1*RS*,2^2*SR*,7^3*S*,5*RS*)-1^1-ethyl-1^2-(2-((*RS*)-1-

methoxyethyl)-5-(piperazin-1-yl)pyridin-3-yl)-3,11,11-trimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1H-9-oxa-3-aza-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-5-yl)carbamate (90 mg, 70% purity) as a pale yellow solid. It was used directly to the next step without further purification.

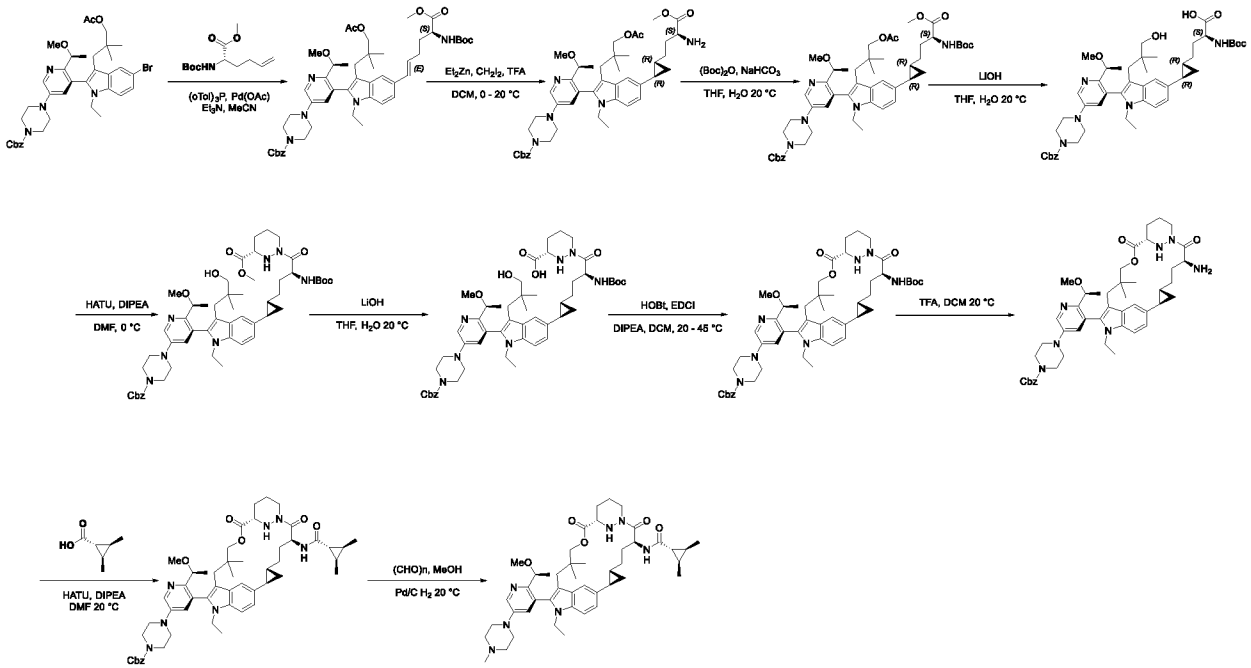
Step 10. To a solution of the *tert*-butyl ((2^1*RS*,2^2*SR*,7^3*S*,5*RS*)-1^1-ethyl-1^2-(2-((*RS*)-1-methoxyethyl)-5-(piperazin-1-yl)pyridin-3-yl)-3,11,11-trimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1H-9-oxa-3-aza-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-5-yl)carbamate (45 mg, 0.06 mmol), (1-ethoxycyclopropoxy)trimethylsilane (586 mg, 3.37 mmol) in ^{i}PrOH (2 mL) stirred at 20 °C was added AcOH (5.1 mg, 0.08 mmol) and Sodium cyanoborohydride (14.1 mg, 0.24 mmol). The reaction mixture was stirred at 60 °C for 3 hours. The mixture was diluted in EtOAc (20 mL), washed with H_2O (10 mL x 2) and brine (20 mL). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by silica gel chromatography to afford *tert*-butyl ((2^1*RS*,2^2*SR*,7^3*S*,5*RS*)-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-3,11,11-trimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1H-9-oxa-3-aza-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-5-yl)carbamate (20 mg, 38% yield) as a pale green semi solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{47}H_{68}N_8O_6$ 841.5; found 841.2.

Step 11. To a solution of *tert*-butyl ((2^1*RS*,2^2*SR*,7^3*S*,5*RS*)-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-3,11,11-trimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1H-9-oxa-3-aza-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-5-yl)carbamate (20 mg, 0.02 mmol) in DCM (0.5 mL) was added TFA (0.2 mL) at 20 °C, then the reaction mixture was stirred for 1 hour. The mixture was concentrated to dryness to give (2^1*RS*,2^2*SR*,7^3*S*,5*RS*)-5-amino-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-3,11,11-trimethyl-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1H-9-oxa-3-aza-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-6,8-dione (20 mg TFA salt, purity 90%) as pale green oil. It was used directly to the next step without further purification.

Step 12. To a solution of (2^1*RS*,2^2*SR*,7^3*S*,5*RS*)-5-amino-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-3,11,11-trimethyl-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1H-9-oxa-3-aza-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-6,8-dione (6.2 mg, 0.06 mmol) in DMF (0.5 mL) stirred at 0 °C was added HATU (15.4 mg, 0.05 mmol) and DIPEA (34.9 mg, 0.30 mmol) dropwise. The reaction mixture was stirred at 0 °C for 0.5 hour. The mixture was diluted in EtOAc (30 mL), washed with H_2O (20 mL x 2) and brine (20 mL). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Preperatory-HPLC to give (1*SR*,2*RS*,3*SR*)-*N*-((2^1*RS*,2^2*SR*,7^3*RS*,5*RS*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-3,11,11-trimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1H-9-oxa-3-aza-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-5-yl)-2,3-dimethylcyclopropane-1-carboxamide (5.0 mg, 21% yield) as a white solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{48}H_{68}N_8O_5$ 837.5; found 837.5. ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (d, *J* = 2.8, 1H), 7.95 (s, 1H), 7.37 – 7.30 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.67 – 6.63 (m, 1H), 6.31 – 6.24 (m, 1H), 5.66 – 5.62 (m, 1H), 4.48 (d, J = 13.2 Hz, 1H), 4.19 – 4.12 (m, 2H), 4.06 – 3.88 (m, 3H), 3.77 – 3.75 (m, 1H), 3.48 – 3.40 (m, 1H), 3.28 – 3.08 (m, 6H), 2.93 – 2.70 (m, 8H), 2.60 – 2.53 (m, 1H), 2.35 (s, 3H), 2.19 – 2.15 (m, 1H), 1.93 – 1.90 (m, 1H), 1.75 –

1.60 (m, 3H), 1.40 (d, *J* = 6.4 Hz, 3H), 1.30 – 1.19 (m, 4H), 1.16 – 0.99 (m, 10H), 0.81 (s, 3H), 0.66 (s, 3H), 0.56 – 0.45 (m, 4H).

Example A6: Synthesis of (1*r*,2*R*,3*S*)-*N*-((2^{1}R,2^{2}R,7^{3}S,5S)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-11,11-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-9-oxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-5-yl)-2,3-dimethylcyclopropane-1-carboxamide



Step 1. To a solution of 3-(5-bromo-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-3-yl)-2,2-dimethylpropyl acetate(10 g, 0.014 mol) and methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}hex-5-enoate(10.2 g, 0.042 mol) in MeCN (100 mL) was added Tri-o-tolylphosphine (3.4 g, 0.011 mol), Et_3N (4.25 g, 0.042 mol) and $Pd(OAc)_2$ (1.9 g, 0.008 mol) at 20 °C. The solution was stirred at 90 °C under N_2 for 16 h. The mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layer was washed bine (20 mL), dried over Na_2SO_4 and concentrated to give a crude product, which was purified by silica gel chromatography to give methyl (2*S*,5*E*)-6-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]pyridin-3-yl]indol-5-yl}-2-{[(*tert*-butoxy)carbonyl]amino}hex-5-enoate (10 g, 75% yield) as a pale yellow solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{49}H_{65}N_5O_9$ 868.5; found 868.5.

Step 2. To a solution of Et_2Zn (92 mL, 92 mmol) in DCM (160 mL) was added TFA (10.5 g, 92 mmol) at 0 °C. The solution was stirred at 0 °C under N_2 for 1 h. To this solution was added CH_2I_2 (24.6 g, 92 mmol) at 0 °C and the solution was stirred for 1 h. To this solution was added methyl (2*S*,5*E*)-6-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]pyridin-3-yl]indol-5-yl}-2-{[(*tert*-butoxy)carbonyl]amino}hex-5-enoate (8 g, 9.2 mmol) at 0 °C. The solution was stirred at 20 °C under N_2 for 14 hours. The mixture was quenched with saturated $NaHCO_3$ and extracted with DCM (30 mL x 3). The combined organic layers were washed with bine (20 mL), dried over Na_2SO_4 and concentrated to give a crude product, which was purified by silica gel

chromatography to give methyl (2*S*)-4-[(1*R*,2*R*)-2-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1S)-1-methoxyethyl]pyridin-3-yl]indol-5-yl}cyclopropyl]-2-aminobutanoate(5.4 g, 59% yield) as a pale yellow solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{45}H_{59}N_5O_7$ 782.4; found 782.3.

Step 3. To a solution of methyl (2*S*)-4-[(1*R*,2*R*)-2-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]pyridin-3-yl]indol-5-yl}cyclopropyl]-2-aminobutanoate (5.5 g, 7 mmol) and $NaHCO_3$ (2.9 g, 35 mmol) in THF/H_2O (1:1, 60 mL) was added $(Boc)_2O$ (4.58 g, 21 mmol) at 20 °C and stirred for 1 h. The mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layer was washed bine (20 mL), dried over Na_2SO_4 and concentrated to give a crude product, which was purified by silica gel chromatography to give methyl (2*S*)-4-[(1*R*,2*R*)-2-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]pyridin-3-yl]indol-5-yl}cyclopropyl]-2-{[(*tert*-butoxy)carbonyl]amino}butanoate(5.4 g, 61% yield) as a yellow solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{50}H_{67}N_5O_9$ 882.5; found 882.4.

Step 4. To a solution of methyl (2*S*)-4-[(1*R*,2*R*)-2-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]pyridin-3-yl]indol-5-yl}cyclopropyl]-2-{[(*tert*-butoxy)carbonyl]amino}butanoate (5.3 g, 0.006 mol) in THF/H_2O (5:1, 60 mL) was added LiOH (2.16 g, 0.09 mol) at 20 °C. The solution was stirred at 20 °C for 16 hours. The mixture was quenched with 1 M HCl and extracted with EtOAc (50 mL x 3). The combined organic layers was washed bine (20 mL), dried over Na_2SO_4 and concentrated to give (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-[(1*R*,2*R*)-2-{1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1S)-1-methoxyethyl]pyridin-3-yl]-3-(3-hydroxy-2,2-dimethylpropyl)indol-5-yl}cyclopropyl]butanoic acid (5.7 g, two isomers mixture from LCMS, 70% purity) as a yellow solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{47}H_{63}N_5O_8$ 826.4; found 826.4.

Step 5. To a solution of (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-[(1*R*,2*R*)-2-{1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]pyridin-3-yl]-3-(3-hydroxy-2,2-dimethylpropyl)indol-5-yl}cyclopropyl]butanoic acid (5.5 g, 6.7 mmol) and methyl (3*S*)-1,2-diazinane-3-carboxylate (1.9 g, 13.4 mmol) in DMF (55 mL) was added DIPEA (25.98 g, 0.2 mol) and HATU (3.8 g, 0.01 mol) at 0 °C. and stirred for 1 hour. The mixture was quenched with H_2O (200 mL) and extracted with EtOAc (100 mL x 3). The combined organic layer was washed bine (20 mL), dried over Na_2SO_4 and concentrated to give a crude product, which was purified by silica gel chromatography to give methyl (3*S*)-1-[(2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-[(1*R*,2*R*)-2-{1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]pyridin-3-yl]-3-(3-hydroxy-2,2-dimethylpropyl)indol-5-yl}cyclopropyl]butanoyl]-1,2-diazinane-3-carboxylate(5 g, 58% yield) as a yellow solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{53}H_{73}N_7O_9$ 952.6; found 952.4.

Step 6. To a solution of methyl (3*S*)-1-[(2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-[(1*R*,2*R*)-2-{1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]pyridin-3-yl]-3-(3-hydroxy-2,2-dimethylpropyl)indol-5-yl}cyclopropyl]butanoyl]-1,2-diazinane-3-carboxylate (2.5 g, 2.6 mmol) in THF/H_2O (3:1, 24 mL) was added LiOH (0.19 g, 7.8 mmol) at 20 °C. The solution was stirred at 20 °C for 1 hour.

The mixture was adjusted pH value to 7 with 1N HCl and extracted with EtOAc (30 mL x 3). The combined organic layer was washed bine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give (3*S*)-1-[(2*S*,3*R*)-2-{[(1*R*,2*R*,3*S*)-2,3-dimethylcyclopropyl]formamido}-3-ethoxy-3-[(3*R*)-1-{1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]pyridin-3-yl]-3-(3-hydroxy-2,2-dimethylpropyl)indol-5-yl}pyrrolidin-3-yl]propanoyl]-1,2-diazinane-3-carboxylic acid (2.5 g, 70% purity) as a yellow solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{52}H_{71}N_7O_9$ 938.5; found 938.4.

Step 7. To a solution of (3*S*)-1-[(2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-[(1*R*,2*R*)-2-{1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]pyridin-3-yl]-3-(3-hydroxy-2,2-dimethylpropyl)indol-5-yl}cyclopropyl]butanoyl]-1,2-diazinane-3-carboxylic acid (2.5 g, 2.7 mmol) in DCM (250 mL) was added DIPEA (10.47 g, 81 mmol), HOBt (3.65 g, 27 mmol) and EDCI (15.5 g, 81 mmol) at 20 °C. The solution was stirred at 45 °C under N_2 for 16 hours. The reaction mixture was purified by Preparatory-HPLC to give benzyl 4-(5-((2^1*R*,2^2*R*,7^3*S*,5*S*)-5-((*tert*-butoxycarbonyl)amino)-1^1-ethyl-11,11-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-9-oxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-12-yl)-6-((*S*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (120 mg, 4.8% yield) as a white solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{52}H_{69}N_7O_8$ 920.5; found 920.5.

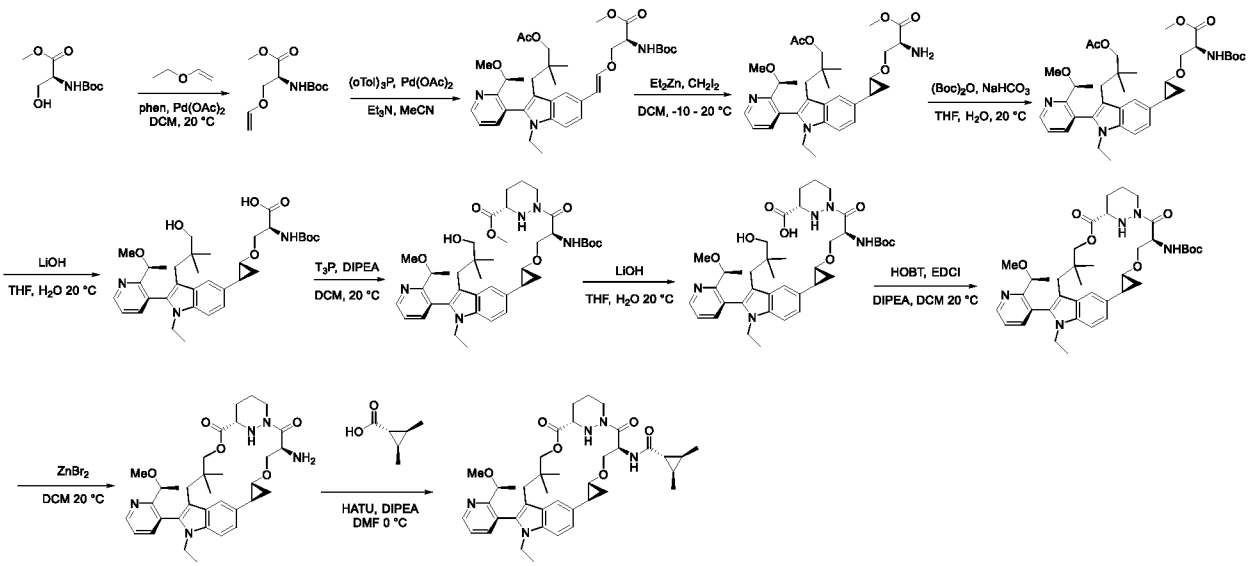
Step 8. To a solution of benzyl 4-(5-((2^1*R*,2^2*R*,7^3*S*,5*S*)-5-((*tert*-butoxycarbonyl)amino)-1^1-ethyl-11,11-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-9-oxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-12-yl)-6-((*S*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (80 mg, 0.087 mmol) in DCM (3 mL) was added TFA (1 mL) at 20 °C and stirred for 1 hour. The mixture was quenched with saturated $NaHCO_3$ and extracted with DCM (30 mL x 3). The combined organic layer was washed bine (20 mL), dried over Na_2SO_4 and concentrated to give benzyl 4-(5-((2^1*R*,2^2*R*,7^3*S*,5*S*)-5-amino-1^1-ethyl-11,11-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-9-oxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-1^2-yl)-6-((*S*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (116 mg, Purity>90%) as a white solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{47}H_{61}N_7O_6$ 820.5; found 820.4.

Step 9. To a solution of benzyl 4-(5-((2^1*R*,2^2*R*,7^3*S*,5*S*)-5-amino-1^1-ethyl-11,11-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-9-oxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-1^2-yl)-6-((*S*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (96 mg, 0.12 mmol) and (1*R*,2*R*,3*S*)-2,3-dimethylcyclopropane-1-carboxylic acid (27 mg, 0.23 mmol) in DMF (2 mL) was added DIPEA (151 mg, 1.17 mmol) and HATU (66 mg, 0.17 mmol) at 0 °C and stirred for 1 hour. The mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layer was washed bine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a crude, which was purified by Preparatory-TLC to give benzyl 4-(5-((2^1*R*,2^2*R*,7^3*S*,5*S*)-5-((1r,2*R*,3*S*)-2,3-dimethylcyclopropane-1-carboxamido)-1^1-ethyl-11,11-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-9-oxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-1^2-yl)-6-((*S*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (80 mg, 67% yield) as a white solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{53}H_{69}N_7O_7$ 916.5; found 916.4.

Step 10. To a solution of benzyl 4-(5-((2^1*R*,2^2*R*,7^3*S*,5*S*)-5-((1r,2*R*,3*S*)-2,3-dimethylcyclopropane-1-carboxamido)-1^1-ethyl-11,11-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-9-oxa-1(5,3)-indola-7(1,3)-

pyridazina-2(1,2)-cyclopropanacyclododecaphane-1^2-yl)-6-((*S*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (70 mg, 0.076 mmol) and Paraformaldehyde (3.2 mg, 0.107 mmol) in MeOH (1 mL) was added Pd/C (23.2 mg, 50% w/w) at 20 °C. The solution was stirred at 20 °C under H_2 (1 atm) for 16 hours. The mixture was filtered and the filtrate was concentrated to give a crude product, which was purified by Preparatory-TLC to give (1*r*,2*R*,3*S*)-*N*-((2^{1}R,2^{2}R,7^{3}S,5S)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-11,11-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-9-oxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-5-yl)-2,3-dimethylcyclopropane-1-carboxamide (40.5 mg, 64% yield) as a white solid. LCMS (ESI): m/z [M+H]$^+$ calc'd for $C_{46}H_{65}N_7O_5$ 796.5; found 796.4. ^{1}H NMR (400 MHz, MeOD) δ 8.44 (d, *J* = 2.7 Hz, 1H), 7.50 (s, 1H), 7.38 (d, *J* = 2.8 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 5.71 (d, *J* = 7.2 Hz, 1H), 4.43 (s, 1H), 4.08 – 3.97 (m, 3H), 3.86 – 3.69 (m, 3H), 3.36 (d, *J* = 4.3 Hz, 4H), 3.24 (d, *J* = 14.2 Hz, 1H), 2.98 (s, 3H), 2.88 (s, 1H), 2.70 (t, *J* = 4.7 Hz, 4H), 2.41 (s, 3H), 2.09 (t, *J* = 15.0 Hz, 2H), 1.98 (d, *J* = 11.8 Hz, 1H), 1.90 (dd, *J* = 11.4, 7.3 Hz, 3H), 1.66 (dd, *J* = 23.0, 8.7 Hz, 2H), 1.52 – 1.45 (m, 1H), 1.42 (d, *J* = 6.3 Hz, 3H), 1.32 (d, *J* = 7.0 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 5H), 1.08 (dd, *J* = 9.0, 4.2 Hz, 8H), 0.92 (s, 3H), 0.68 – 0.62 (m, 4H), 0.51 (dt, *J* = 8.5, 4.4 Hz, 1H).

Example A5: Synthesis of (1*SR*,2*RS*,3*SR*)-*N*-((2^1*RS*,2^2*SR*,7^3*RS*,5*RS*)-1^1-ethyl-1^2-(2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-11,11-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-3,9-dioxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-5-yl)-2,3-dimethylcyclopropane-1-carboxamide



Step 1. To a stirred flask containing ethyl vinyl ether/DCM (375:225 mL) solution was added $Pd(OAc)_2$ (3.07 g, 13.6 mmol) and 1,10-phenanthroline (2.47 g, 13.6 mmol) at 20 °C. After stirring for 30 min under N_2 atmosphere, methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-hydroxypropanoate (60 g, 273.7 mmol) was added into the solution, the resulting reaction mixture was stirred for 4 days at 20 °C. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography to give methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-(ethenyloxy)propanoate (30 g, 43% yield) as a colorless oil. LCMS (ESI): m/z [M+H]$^+$ calc'd for $C_{11}H_{19}NO_5$ 246.1; found 268.1 [M+Na]$^+$;

Step 2. A solution of the 3-(5-bromo-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-3-yl)-2,2-dimethylpropyl acetate (5.0 g, 10.26 mmol), methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-(ethenyloxy)propanoate (6.29 g, 25.65 mmol), $Pd(OAc)_2$ (1.38 g, 6.2 mmol), Tri-o-tolylphosphine (2.5 g, 8.21 mmol) and Et_3N (3.12 g, 30.78 mmol) in MeCN (50 mL) under N_2 was stirred at 90 °C for 12 hours. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography to give methyl (2*S*)-3-{[(*E*)-2-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-{2-[(1S)-1-methoxyethyl]pyridin-3-yl}indol-5-yl}ethenyl]oxy}-2-{[(*tert*-butoxy)carbonyl]amino}propanoate (0.9 g, 14% yield) as a green semi-oil. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{36}H_{49}N_3O_8$ 652.4; found 652.4.

Step 3. A flame dried 100 mL round bottom flask equipped with a stir bar, was charged with $ZnEt_2$ (1M solution in hexanes, 11.1 mL, 11.1 mmol) and DCM (13mL). CH_2I_2 (5.91 g, 22.1 mmol) was added dropwise via syringe to the reaction mixture at -10 °C and the reaction was stirred for 1 hour, then methyl (2*S*)-3-{[(*E*)-2-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl}ethenyl]oxy}-2-{[(*tert*-butoxy)carbonyl]amino}propanoate (900 mg, 1.38 mmol) was added dropwise to the flask as a solution in DCM (5 mL). The reaction mixture was warmed to 20 °C and stirred vigorously for 11 hours. Then the reaction mixture was concentrated to give a residue. The residue was dissolved in EtOAc (50 mL), washed with H_2O (50 mL x 2). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by preperatory-HPLC to give methyl (2*S*)-3-[(1*R*,2*S*)-2-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl}cyclopropoxy]-2-{[(*tert*-butoxy)carbonyl]amino}propanoate (400 mg, 51% yield) as a yellow semi-solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for : $C_{32}H_{43}N_3O_6$ 566.3; found 566.3.

Step 4. To a solution of methyl (2*S*)-3-[(1*R*,2*S*)-2-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl}cyclopropoxy]-2-aminopropanoate (0.73 g, 1.3 mmol) and $(Boc)_2O$ (850 mg, 3.9 mmol) in THF (15 mL) and H_2O (5 mL) was added $NaHCO_3$ (330 mg, 3.9 mmol). The reaction mixture was stirred at 20 °C for 1 hour. The reaction mixture was diluted with H_2O (20 mL) and EtOAc (20 mL), the organic phase was separated and dried over Na2SO4. Solvent was removed under reduced pressure to afford the methyl (2*S*)-3-[(1*R*,2*S*)-2-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl}cyclopropoxy]-2-{[(*tert*-butoxy)carbonyl]amino}propanoate (0.9 g) as a green semi-solid. It was used for the next step directly without further purification.

Step 5. To a solution of methyl (2*S*)-3-[(1*R*,2*S*)-2-{3-[3-(acetyloxy)-2,2-dimethylpropyl]-1-ethyl-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl}cyclopropoxy]-2-{[(*tert*-butoxy)carbonyl]amino}propanoate (0.9 g, 1.57 mmol) in THF (10 mL) and H_2O (2 mL) was added LiOH (0.16 g, 6.75 mmol), then the reaction mixture was stirred at 20 °C for 12 hours. The mixture was poured into H_2O (20 mL). To the mixture 1 N HCl was added until pH value 7 and the obtained mixture was extracted with EtOAc (20 mL x 3). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-[(1*R*,2*S*)-2-[1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-2-{2-[(1S)-1-methoxyethyl]pyridin-3-yl}indol-5-yl]cyclopropoxy]propanoic acid (0.85 g, 90% yield). LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{34}H_{47}N_3O_7$ 610.3; found 610.4.

Step 6. To a solution of (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-[(1*R*,2*S*)-2-[1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl]cyclopropoxy]propanoic acid (700 mg, 1.15 mmol), methyl (3S)-1,2-diazinane-3-carboxylate (248.3 mg, 1.72 mmol) and DIPEA (445 mg, 3.44 mmol) in DCM (7 mL) was added T_3P (1.46 g, 2.30 mmol) at 0 °C, then the reaction mixture was stirred at 0 °C for 1 hour. The mixture was quenched with H_2O (50 mL), and the obtained mixture was extracted with DCM (50 ml x 3). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Preparatory-HPLC to give methyl (3*S*)-1-[(2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-[(1*R*,2*S*)-2-[1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl]cyclopropoxy]propanoyl]-1,2-diazinane-3-carboxylate (0.45 g, 48% yield) as pale green solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{40}H_{57}N_5O_8$ 736.4; found 736.4.

Step 7. To a solution of methyl (3*S*)-1-[(2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-[(1*R*,2*S*)-2-[1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl]cyclopropoxy]propanoyl]-1,2-diazinane-3-carboxylate (450 mg, 0.61 mmol) in THF (4.5 mL) and H_2O (0.9 mL) was added LiOH (73 mg, 3.1 mmol), then the reaction mixture was stirred at 0 °C for 2 hours. The mixture was poured into H_2O (50 mL). To the mixture 1 N HCl was added until pH value 7 and the obtained mixture was extracted with EtOAc (50 ml x 3). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (3*S*)-1-[(2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-[(1*R*,2*S*)-2-[1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl]cyclopropoxy]propanoyl]-1,2-diazinane-3-carboxylic acid (440 mg, 90% yield) as a green semi-oil. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{39}H_{55}N_5O_8$ 722.4; found 722.4.

Step 8. To a stirred solution of (3*S*)-1-[(2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-[(1*R*,2*S*)-2-[1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-2-{2-[(1*S*)-1-methoxyethyl]pyridin-3-yl}indol-5-yl]cyclopropoxy]propanoyl]-1,2-diazinane-3-carboxylic acid (450 mg, 0.62 mmol), HOBT (842 mg, 6.2 mmol) and DIPEA (3.22 g, 24.9 mmol) in DCM (45 mL) was added EDCI (3.59 g, 18.6 mmol), then the reaction mixture was stirred at 20 °C for 12 hours. The mixture was quenched with H_2O (60 mL), and the obtained mixture was extracted with DCM (50 mL x 3). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography to afford *tert*-butyl ((2^1*RS*,2^2*SR*,7^3*RS*,5*RS*)-1^1-ethyl-1^2-(2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-11,11-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-3,9-dioxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-5-yl)carbamate (180 mg, 37% yield) as a pale yellow semi solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{39}H_{53}N_5O_7$ 704.3; found 704.4.

Step 9. To a solution of methyl (3*S*)-1-[(2*S*,3*R*)-2-{[(1*R*,2*R*,3*S*)-2,3-dimethylcyclopropyl]formamido}-3-ethoxy-3-[3-({1-ethyl-2-[5-(4-{3-[(formyloxy)methyl]phenyl}piperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]pyridin-3-yl]-3-(3-hydroxy-2,2-dimethylpropyl)indol-5-yl}oxy)cyclobutyl]propanoyl]-1,2-diazinane-3-carboxylate (180 mg, 0.26 mmol) in DCM (10 mL) was added $ZnBr_2$ (1.15 g, 5.11 mmol), then the reaction mixture was stirred at 20 °C for 12 hours. The mixture was diluted with DCM (10 mL) and H_2O (10 mL). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford (2^1*RS*,2^2*SR*,7^3*RS*,5*RS*)-5-amino-1^1-ethyl-1^2-(2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-11,11-dimethyl-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-3,9-dioxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-

cyclopropanacyclododecaphane-6,8-dione (170 mg, purity 90%) as pale green solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{34}H_{45}N_5O_5$ 604.3; found 604.3.

Step 10. To a solution of the (2^1*RS*,2^2*SR*,7^3*RS*,5*RS*)-5-amino-1^1-ethyl-1^2-(2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-11,11-dimethyl-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-3,9-dioxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-6,8-dione (170 mg, 0.28 mmol), (1*r*,2*R*,3*S*)-2,3-dimethylcyclopropane-1-carboxylic acid (63 mg, 0.56 mmol) in DMF (1.7 mL) stirred at 0 °C was added HATU (129.3 mg, 0.34 mmol) and DIPEA (361 mg, 2.8 mmol) dropwise. The reaction mixture was stirred at 0 °C for 0.5 hour. The mixture was diluted in EtOAc (30 mL), washed with water (20 mL x 2) and brine (20 mL). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated under vacuum to give a residue. The residue was purified by silica gel chromatography to give (1*SR*,2*RS*,3*SR*)-*N*-((2^1*RS*,2^2*SR*,7^3*RS*,5*RS*)-1^1-ethyl-1^2-(2-((*RS*)-1-methoxyethyl)pyridin-3-yl)-11,11-dimethyl-6,8-dioxo-7^1,7^2,7^3,7^4,7^5,7^6-hexahydro-1^1*H*-3,9-dioxa-1(5,3)-indola-7(1,3)-pyridazina-2(1,2)-cyclopropanacyclododecaphane-5-yl)-2,3-dimethylcyclopropane-1-carboxamide (5.8 mg, 2.6% yield) as a white solid. LCMS (ESI): m/z $[M+H]^+$ calc'd for $C_{40}H_{53}N_5O_6$ 700.3; found 700.4. ^{1}H NMR (400 MHz, CD_3OD) δ 8.72 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.88 – 7.86 (m, 1H), 7.71 (s, 1H), 7.52 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 5.70 (dd, *J* = 7.6, 5.6 Hz, 1H), 4.47 (d, *J* = 12.4 Hz, 1H), 4.47 (q, *J* = 6.0 Hz, 1H), 4.14 – 4.02 (m, 2H), 3.95 – 3.89 (m, 1H), 3.84 – 3.80 (m, 2H), 3.72 – 3.67 (m, 1H), 3.59 – 3.56 (m, 1H), 3.36 – 3.33 (m, 1H), 3.14 (s, 3H), 2.99 – 2.96 (m, 1H), 2.86 – 2.80 (m, 1H), 2.51 – 2.48 (m, 1H), 2.28 – 2.21 (m, 2H), 1.98 – 1.93 (m, 1H), 1.81 – 1.64 (m, 2H), 1.45 (d, J = 6.0 Hz, 3H), 1.32 – 1.29 (m, 2H), 1.23 – 1.18 (m, 2H), 1.13 – 1.04 (m, 10H), 0.72 – 0.71 (m, 6H).

In vitro and In vivo Experiments:

The following assays may be conducted to assess various properties of compounds of the present invention. Compounds A1-A6 herein exhibit (i) a pERK (Capan-1, K-Ras G12V) IC50 of less than 8 μM; (ii) a MOA (G13C) IC50 of less than 30 μM; or (iii) both (i) and (ii).

Potency assay: pERK

The purpose of this assay was to measure the ability of test compounds to inhibit K-Ras in cells. Activated K-Ras induces increased phosphorylation of ERK at Threonine 202 and Tyrosine 204 (pERK). This procedure measures a decrease in cellular pERK in response to test compounds. The procedure described below in NCI-H358 cells is applicable to K-Ras G12C.

Note: this protocol may be executed substituting other cell lines to characterize inhibitors of other RAS variants, including, for example, AsPC-1 (K-Ras G12D), Capan-1 (K-Ras G12V), NCI-H1355 (K-Ras G13C), Hs 766T (K-Ras Q61H), NCI-H2347 or KU-19-19 (N-Ras Q61R), or SK-MEL-30 (N-Ras Q61K).

NCI-H358 cells were grown and maintained using media and procedures recommended by the ATCC. On the day prior to compound addition, cells were plated in 384-well cell culture plates (40 μl/well) and grown overnight in a 37°C, 5% CO2 incubator. Test compounds were prepared in 10, 3-fold dilutions in DMSO, with a high concentration of 10 mM. On day of assay, 40 nl of test compound was added to each well of cell culture plate using an Echo550 liquid handler (LabCyte®). Concentrations of test compound were tested in duplicate. After compound addition, the plates are shaken for 15 seconds at 300 rpm,

centrifuged, and cells were incubated 4 hours at 37°C, 5% CO2. Following incubation, culture medium was removed and cells were washed once with phosphate buffered saline.

In some experiments, cellular pERK level was determined using the AlphaLISA SureFire Ultra p-ERK1/2 Assay Kit (PerkinElmer). Cells were lysed in 25 µl lysis buffer, with shaking at 600 RPM at room temperature. Lysate (10 µl) was transferred to a 384-well Opti-plate (PerkinElmer) and 5 µl acceptor mix was added. After a 2-hour incubation in the dark, 5 µl donor mix was added, plate was sealed and incubated 2 hours at room temperature. Signal was read on an Envision plate reader (PerkinElmer) using standard AlphaLISA settings. Analysis of raw data was carried out either a) in Excel (Microsoft) and Prism (GraphPad). Signal was plotted vs. the decadal logarithm of compound concentration, and IC_{50} was determined by fitting a 4-parameter sigmoidal concentration response model or b) using Genedata Screener (Genedata). Normalized signal was plotted vs the decadal logarithm of compounds concentration, and IC50 was determined by fitting a 4-parameter sigmoidal concentration response model.

In other experiments, cellular pERK was determined by In-Cell Western. Following compound treatment, cells were washed twice with 200 µl tris buffered saline (TBS) and fixed for 15 minutes with 150 µl 4% paraformaldehyde in TBS. Fixed cells were washed 4 times for 5 minutes with TBS containing 0.1% Triton X-100 (TBST) and then blocked with 100 µl Odyssey blocking buffer (LI-COR) for 60 minutes at room temperature. Primary antibody (pERK, CST-4370, Cell Signaling Technology) was diluted 1:200 in blocking buffer, and 50 µl was added to each well and incubated overnight at 4°C. Cells were washed 4 times for 5 minutes with TBST. Secondary antibody (IR-800CW rabbit, LI-COR, diluted 1:800) and DNA stain DRAQ5 (LI-COR, diluted 1:2000) were added and incubated 1-2 hours at room temperature. Cells were washed 4 times for 5 minutes with TBST. Plates were scanned on a Li-COR Odyssey CLx Imager. Analysis of raw data was carried out in Excel (Microsoft) and Prism (GraphPad). Signal was plotted vs. the decadal logarithm of compound concentration, and IC_{50} was determined by fitting a 4-parameter sigmoidal concentration response model.

Disruption of B-Raf Ras-binding Domain ($BRAF^{RBD}$) Interaction with K-Ras by Compounds of the Invention (also known as a MOA assay)

Note – The following protocol describes a procedure for monitoring disruption of K-Ras G12C (GMP-PNP) binding to $BRAF^{RBD}$ by a compound of the invention. This protocol may also be executed substituting other Ras proteins or nucleotides.

The purpose of this biochemical assay was to measure the ability of test compounds to facilitate ternary *complex* formation between a nucleotide-loaded K-Ras isoform and Cyclophilin A; the resulting ternary complex disrupts binding to a $BRAF^{RBD}$ construct, inhibiting K-Ras signaling through a RAF effector. Data was reported as IC50 values.

In assay buffer containing 25 mM HEPES pH 7.3, 0.002% Tween20, 0.1% BSA, 100 mM NaCl and 5 mM $MgCl_2$, tagless Cyclophilin A, His6-K-Ras-GMPPNP, and GST-$BRAF^{RBD}$ were combined in a 384-well assay plate at final concentrations of 25 µM, 12.5 nM and 50 nM, respectively. Compound was present in plate wells as a 10-point 3-fold dilution series starting at a final concentration of 30 µM. After incubation at 25 °C for 3 hours, a mixture of Anti-His Eu-W1024 and anti-GST allophycocyanin was then added to assay sample wells at final concentrations of 10 nM and 50 nM, respectively, and the reaction incubated for an additional 1.5 hours. TR-FRET signal was read on a microplate reader (Ex 320 nm, Em 665/615 nm).

Compounds that facilitate disruption of a K-Ras:RAF complex were identified as those eliciting a decrease in the TR-FRET ratio relative to DMSO control wells.

Determination of Cell Viability in RAS Mutant Cancer Cell Lines

Protocol: CellTiter-Glo® Cell Viability Assay

Note – The following protocol describes a procedure for monitoring cell viability of KRAS mutant cancer cell lines in response to a compound of the invention. Other RAS isoforms may be employed, though the number of cells to be seeded will vary based on cell line used.

The purpose of this cellular assay is to determine the effects of test compounds on the proliferation of three human cancer cell lines (NCI-H358 (KRAS G12C), AsPC-1 (KRAS G12D), Capan-1 (KRAS G12V)) over a 5-day treatment period by quantifying the amount of ATP present at endpoint using the CellTiter-Glo® 2.0 Reagent (Promega).

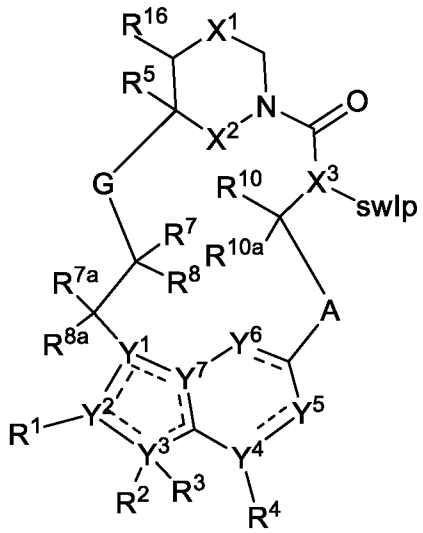
Cells are seeded at 250 cells/well in 40 µl of growth medium in 384-well assay plates and incubated overnight in a humidified atmosphere of 5% CO_2 at 37 °C. On the day of the assay, test compounds are prepared in 9, 3-fold dilutions in DMSO, with a high concentration of 1 or 10 mM as appropriate. The test compounds (40 nl) are directly dispensed to each well of cell culture plate using an Echo550 liquid handler (LabCyte®). The plates are shaken for 15 seconds at 300 rpm, centrifuged, and incubated in a humidified atmosphere of 5% CO_2 at 37°C for 5 days. On day 5, assay plates and their contents are equilibrated to room temperature for approximately 30 minutes. CellTiter-Glo® 2.0 Reagent (25 µl) is added, and plate contents are mixed for 2 minutes on an orbital shaker before incubation at room temperature for 10 minutes. Luminescence is measured using the PerkinElmer Enspire. Data is normalized by the following: (Sample signal/Avg. DMSO)*100. The data is fit using a four-parameter logistic fit.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure come within known or customary practice within the art to which the invention pertains and may be applied to the essential features set forth herein.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

Claims

1. A compound, or a pharmaceutically acceptable salt thereof, having the structure of Formula Ia:



Formula Ia

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is optionally substituted C_2-C_4 alkylene, optionally substituted C_1-C_4 heteroalkylene, or optionally substituted C_2-C_4 alkenylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

swlp (Switch I/P-loop) is an organic moiety that non-covalently binds to both the Switch I binding pocket and residues 12 or 13 of the P-loop of a Ras protein;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', $S(O)_2$R', or $S(O)_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

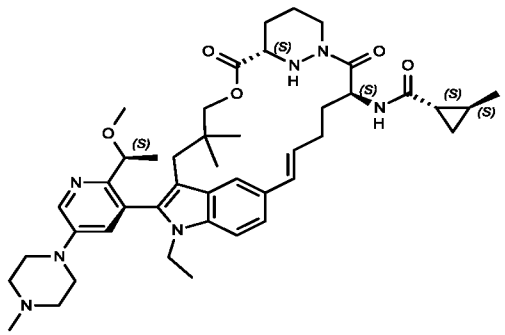
R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo;

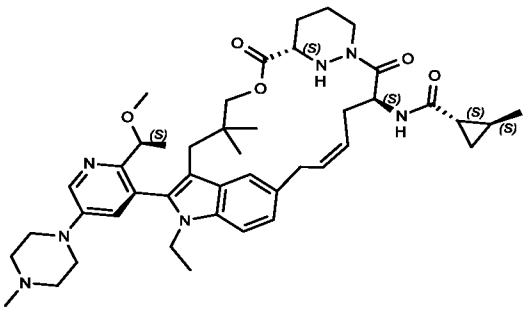
R^{16} is hydrogen or C_1-C_3 alkyl; and

wherein

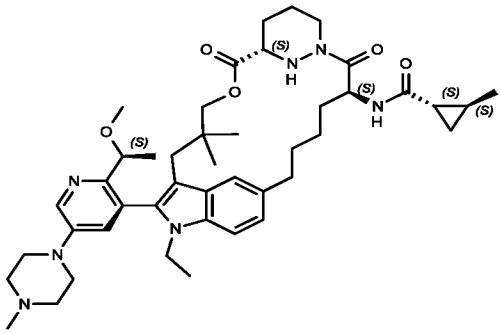
i. the compound is not



Example A,

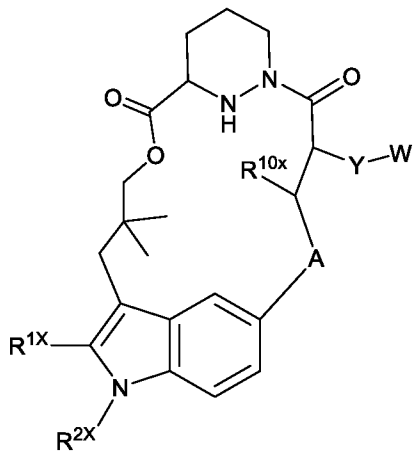


Example B, or



Example C; or

ii. when W is cyclopropyl, then the compound is not of Formula X, wherein Formula X is:



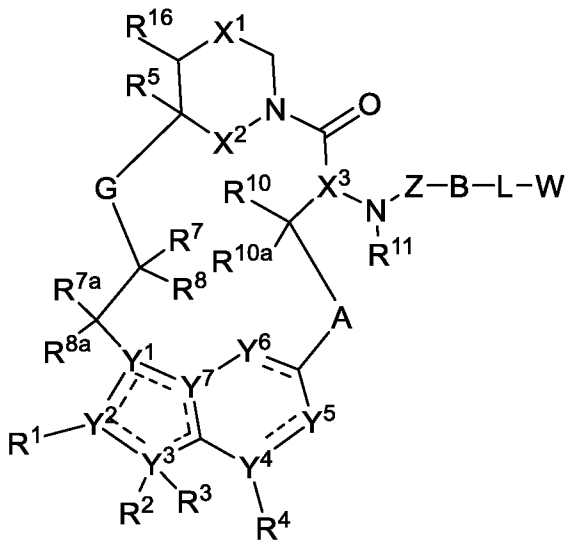
(Formula X)

wherein R^{1X} is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^{2X} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; and

Y is -NHC(O)-, -NHC(O)NH-, -NHC(O)NCH_3-, -NHC(O)O-, -NHS(O)-, -NHS(O)NH-, -NHS$(O)_2$, or -NHS$(O)_2$NH-.

2. A compound, or pharmaceutically acceptable salt thereof, having the structure of Formula Ib:



Formula Ib

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is optionally substituted C_2-C_4 alkylene, optionally substituted C_1-C_4 heteroalkylene, or optionally substituted C_2-C_4 alkenylene;

B is absent, -NH-, -N(CH_3)-, -O-, -CH(R^9)- or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is hydrogen, cyano, optionally substituted amino, optionally substituted amido, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 3 to 10-membered heteroaryl;

Z is -C(O)- or -S$(O)_2$-;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent or R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally

substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

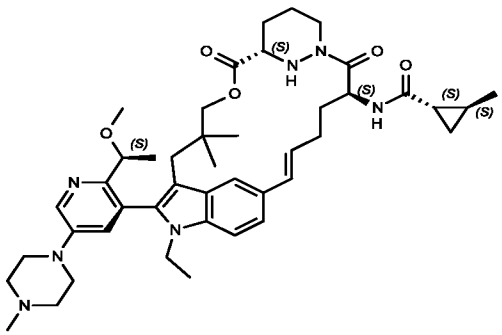
R^{10a} is hydrogen or halo;

R^{11} is hydrogen or C_1-C_3 alkyl;

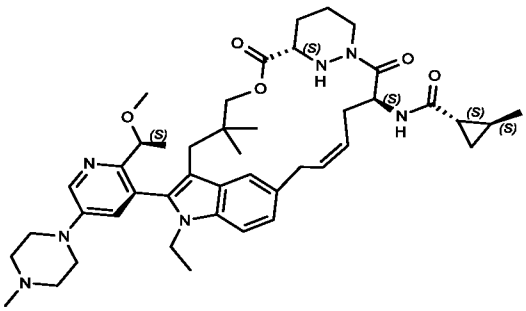
R^{16} is hydrogen or C_1-C_3 alkyl; and

wherein:

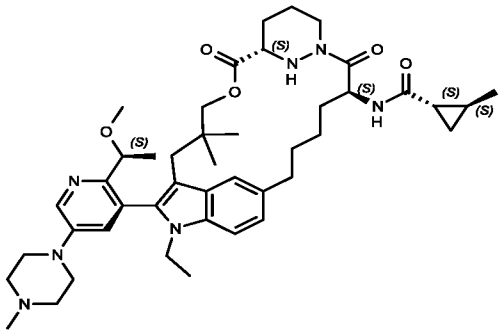
i. the compound is not



Example A,

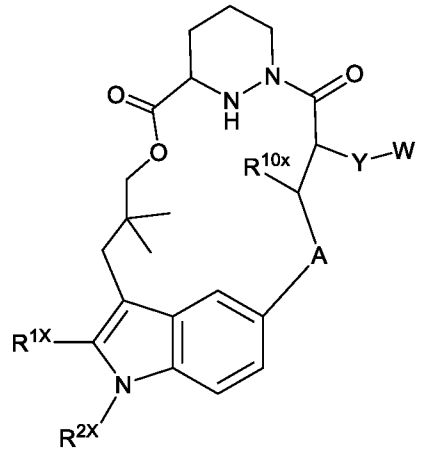


Example B, or



Example C; or

ii. when W is cyclopropyl, then the compound is not of Formula X, wherein Formula X is:



(Formula X)

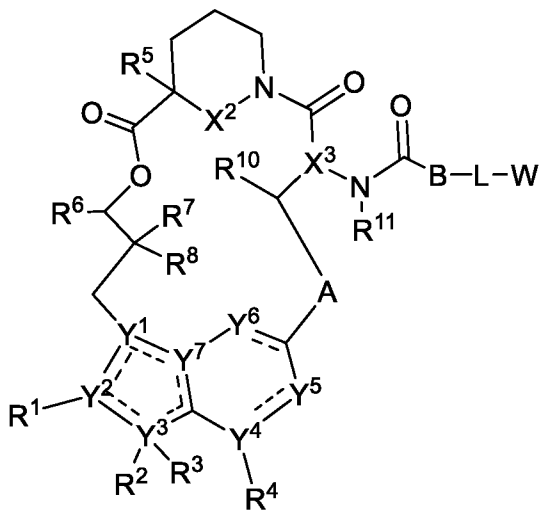
wherein R^{1X} is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^{2X} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; and

Y is -NHC(O)-, -NHC(O)NH-, -NHC(O)NCH_3-, -NHC(O)O-, -NHS(O)-, -NHS(O)NH-, -$NHS(O)_2$, or -$NHS(O)_2$NH-.

3. The compound of claim 2, or pharmaceutically acceptable salt thereof, wherein Z is -C(O)-.

4. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-3, wherein the compound has the structure of Formula Ic:



Formula Ic

wherein Y^5 and Y^6 are, independently, CH or N;

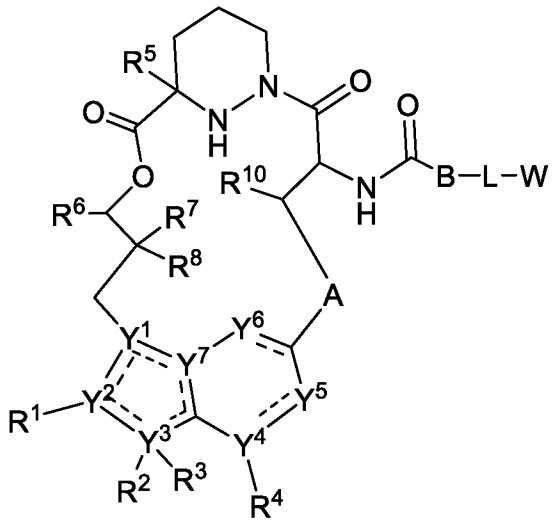
R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent or R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; and

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl.

5. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 4, wherein the compound has the structure of Formula Id:



Formula Id

wherein B is absent, -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally susbtituted 3 to 8-membered heteroaryl;

Y^5 and Y^6 are, independently, CH or N;

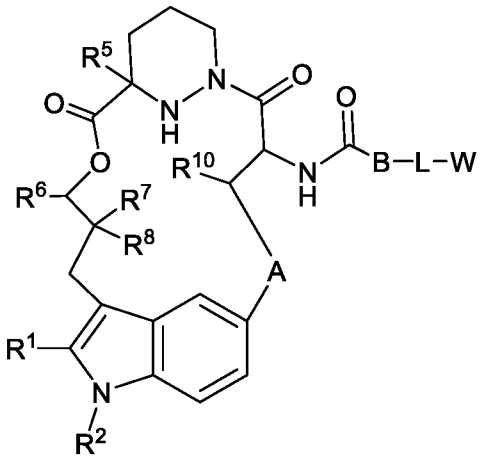
R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent or R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; and

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl.

6. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 5, wherein the compound has the structure of Formula Ie:



Formula Ie

wherein B is absent, -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally susbtituted 3 to 8-membered heteroaryl;

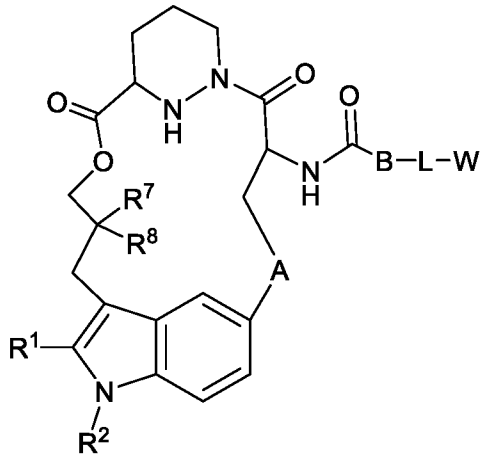
R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent or R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; and

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl.

7. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 6, wherein the compound has the structure of Formula If:



Formula If

B is absent, -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally susbtituted 3 to 8-membered heteroaryl;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

R^7 is C_1-C_3 alkyl;

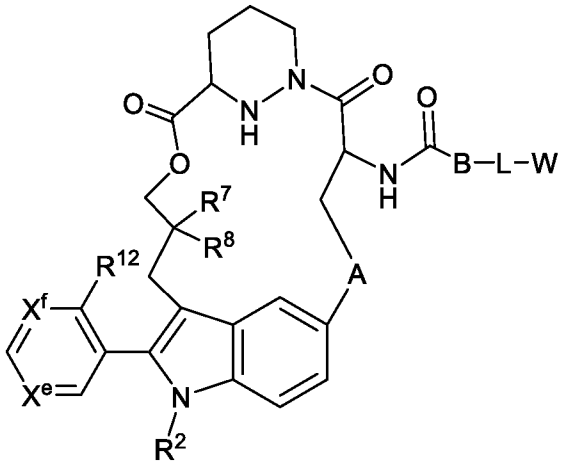
R^8 is C_1-C_3 alkyl; and

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

8. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 7, wherein R^1 is optionally substituted 5 to 10-membered heteroaryl.

9. The compound, or pharmaceutically acceptable salt thereof, of claim 8, wherein R^1 is optionally substituted 6-membered aryl or optionally substituted 6-membered heteroaryl.

10. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 9, wherein the compound has the structure of Formula Ig:



Formula Ig

B is absent, -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally susbtituted 3 to 8-membered heteroaryl;

R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

R^7 is C_1-C_3 alkyl;

R^8 is C_1-C_3 alkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

X^e is N, CH, or CR^{17};

X^f is N or CH;

R^{12} is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl; and

R^{17} is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

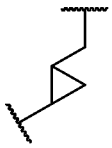
11. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 10, wherein R^7 is methyl.

12. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 11, wherein R^8 is methyl.

13. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 12, wherein A is optionally substituted C_2-C_4 alkylene.

14. The compound, or pharmaceutically acceptable salt thereof, of claim 13 wherein A is optionally substituted C_3 alkylene.

15. The compound, or pharmaceutically acceptable salt thereof, of claim 14 wherein A is



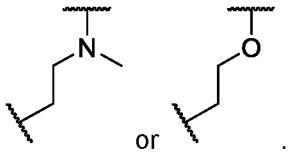
16. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 12, wherein A is optionally substituted C_2-C_4 alkenylene.

17. The compound, or pharmaceutically acceptable salt thereof, of claim 16, wherein A is optionally substituted C_3 alkenylene.

18. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 12, wherein A is optionally substituted C_1-C_4 heteroalkylene.

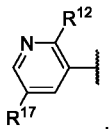
19. The compound, or pharmaceutically acceptable salt thereof, of claim 18, wherein A is optionally substituted C_2 heteroalkylene.

20. The compound, or pharmaceutically acceptable salt thereof, of claim 19, wherein A is



or .

21. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 10 to 20, wherein R^1 is



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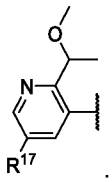
22. The compound, or pharmaceutically acceptable salt thereof, of claim 21, wherein R^1 is



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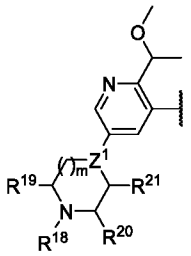
23. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein R^1 is



wherein Z^1 is N or CH;

m is 1 or 2;

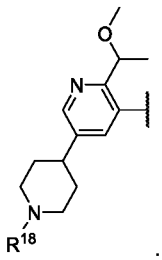
R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^{18} and R^{20} combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^{20} and R^{21} combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^{19} and R^{20} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

24. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein R^1 is



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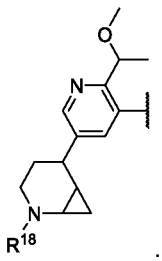
25. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein R^1 is



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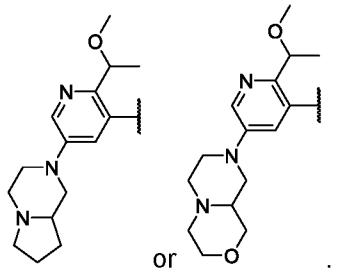
26. The compound, or pharmaceutically acceptable salt thereof, of claim 24 or 25, wherein R^{18} is methyl.

27. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein R^1 is



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28. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 27, wherein B is -CHR^9-.

29. The compound, or pharmaceutically acceptable salt thereof, of claim 28, wherein R^9 is optionally substituted C_1-C_6 alkyl or optionally substituted 3 to 6-membered cycloalkyl.

30. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 27, wherein B is optionally substituted 6-membered arylene.

31. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 27, wherein B is absent.

32. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 31, wherein the linker has the structure of Formula II:

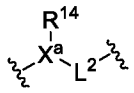
$$A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h\text{-}(D^1)\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$$

Formula II

where A^1 is a bond between the linker and B; A^2 is a bond between W and the linker; B^1, B^2, B^3, and B^4 each, independently, is selected from optionally substituted C_1-C_2 alkylene, optionally substituted C_1-C_3 heteroalkylene, O, S, and NR^N; R^N is hydrogen, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_3 cycloalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted C_1-C_7 heteroalkyl; C^1 and C^2 are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; f, g, h, i, j, and k are each, independently, 0 or 1; and D^1 is optionally substituted C_1-C_{10} alkylene, optionally substituted C_2-C_{10} alkenylene, optionally substituted C_2-C_{10} alkynylene, optionally substituted 3 to 14-membered heterocycloalkylene, optionally substituted 5 to 10-membered heteroarylene, optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 6 to 10-membered arylene, optionally substituted C_2-C_{10} polyethylene glycolene, or optionally substituted C_1-C_{10} heteroalkylene, or a chemical bond linking A^1-$(B^1)_f$-$(C^1)_g$-$(B^2)_h$- to -$(B^3)_i$-$(C^2)_j$-$(B^4)_k$–A^2.

33. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 32, wherein the linker is acyclic.

34. The compound, or pharmaceutically acceptable salt thereof, of claim 33, wherein the linker has the structure of Formula IIa:



Formula IIa

wherein X^a is absent or N;

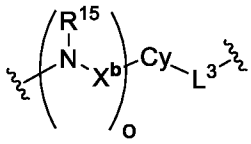
R^{14} is absent, hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_3 cycloalkyl; and

L^2 is absent, -C(O)-, -SO_2-, optionally substituted C_1-C_4 alkylene or optionally substituted C_1-C_4 heteroalkylene,

wherein at least one of X^a, R^{14}, or L^2 is present.

35. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 32, wherein the linker is or comprises a cyclic group.

36. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 32 or 31, wherein the linker has the structure of Formula IIb:



Formula IIb

wherein o is 0 or 1;

X^b is C(O) or SO_2;

R^{15} is hydrogen or optionally substituted C_1-C_6 alkyl;

Cy is optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 3 to 8-membered heterocycloalkylene, optionally substituted 6-10 membered arylene, or optionally substituted 5 to 10-membered heteroarylene; and

L^3 is absent, -C(O)-, -SO_2-, optionally substituted C_1-C_4 alkylene or optionally substituted C_1-C_4 heteroalkylene.

37. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 31, wherein the linker is absent.

38. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is hydrogen.

39. The compound of any one of claims 2 to 37, or pharmaceutically acceptable salt thereof, wherein W is optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclohexyl, optionally substituted piperidine, optionally substituted piperazine, optionally substituted pyridine, or optionally substituted phenyl.

40. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is optionally substituted amino.

41. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is optionally substituted amido.

42. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is optionally substituted C_1-C_4 alkoxy.

43. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is optionally substituted C_1-C_4 alkyl.

44. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is optionally substituted C_1-C_4 hydroxyalkyl.

45. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is optionally substituted C_1-C_4 aminoalkyl.

46. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is optionally substituted C_1-C_4 haloalkyl.

47. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is optionally substituted C_1-C_4 guanidinoalkyl.

48. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl.

49. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is optionally substituted 3 to 10-membered cycloalkyl.

50. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is optionally substituted 3 to 10-membered heteroaryl.

51. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 2 to 37, wherein W is optionally substituted 6- to 10-membered aryl.

52. A compound, or pharmaceutically acceptable salt thereof, of Table 1.

53. A pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 52 and a pharmaceutically acceptable excipient.

54. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 52 or a pharmaceutical composition of claim 53.

55. The method of claim 54, wherein the cancer is pancreatic cancer, colorectal cancer, non-small cell lung cancer, gastric cancer, esophageal cancer, ovarian cancer or uterine cancer.

56. The method of claim 55, wherein the cancer comprises a Ras mutation.

57. The method of claim 56, wherein the Ras mutation is at position 12, 13 or 61.

58. The method of claim 56 or 57, wherein the Ras mutation is at position 12.

59. The method of claim 57, wherein the Ras mutation is at a position selected from the group consisting of G12C, G12D, G12V, G12R, G13C, G13D, and Q61K, or a combination thereof.

60. The method of claim 59, wherein the Ras mutation is at a position selected from the group consisting of G12D, G12V and G12R, or a combination thereof.

61. The method of claim 60, wherein the Ras mutation is at a position selected from the group consisting of G12D and G12V, or a combination thereof.

62. The method of any one of claims 54 to 61, wherein the cancer is pancreatic cancer.

63. The method of any one of claims 54 to 61, wherein the cancer is lung cancer.

64. The method of any one of claims 54 to 61, wherein the cancer is colorectal cancer.

65. A method of treating a Ras protein-related disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 52 or a pharmaceutical composition of claim 53.

66. A method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 52 or a pharmaceutical composition of claim 53.

67. The method of claim 66, wherein more than one Ras protein is inhibited in the cell.

68. The method of claim 66 or 67, wherein the cell is a cancer cell.

69. The method of claim 68, wherein the cancer cell is a pancreatic cancer cell.

70. The method of claim 68, wherein the cancer cell is a lung cancer cell.

71. The method of claim 68, wherein the cancer cell is a colorectal cancer cell.

72. The method of any one of claims 56 to 71, wherein the Ras protein is KRAS.

73. The method or use of any one of claims 54 to 72, wherein the method further comprises administering an additional anticancer therapy.

74. The method of claim 73, wherein the additional anticancer therapy is an EGFR inhibitor, a second Ras inhibitor, a SHP2 inhibitor, a SOS1 inhibitor, a Raf inhibitor, a MEK inhibitor, an ERK inhibitor, a PI3K inhibitor, a PTEN inhibitor, an AKT inhibitor, an mTORC1 inhibitor, a BRAF inhibitor, a PD-L1 inhibitor, a PD-1 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, or a combination thereof.

75. The method of claim 73 or 74, wherein the additional anticancer therapy is a SHP2 inhibitor.

76. The method of claim 73 or 74, wherein the additional anticancer therapy comprises a SHP2 inhibitor and a PD-L1 inhibitor.

77. The method of claim 73 or 74, wherein the additional anticancer therapy comprises a second Ras inhibitor and a PD-L1 inhibitor.

78. The method of claim 74 or 75, wherein the second Ras inhibitor is a $KRAS^{G12C}$ inhibitor.

79. The method of claim 78, wherein the second Ras inhibitor is a $KRAS^{G12C}$(ON) inhibitor.

80. The method of claim 78, wherein the second Ras inhibitor is a $KRAS^{G12C}$(OFF) inhibitor.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/068235

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 C07D498/12 A61K31/504
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X Y	US 2021/130326 A1 (AGGEN JAMES [US] ET AL) 6 May 2021 (2021-05-06) claim 1	1-51, 53-80 1-51, 53-80

X Y	US 2021/130303 A1 (KOLTUN ELENA S [US] ET AL) 6 May 2021 (2021-05-06) claim 1	1-51, 53-80 1-51, 53-80

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
10 August 2023	21/08/2023

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US 2020/197391 A1 (JIN MEIZHONG [US] ET AL) 25 June 2020 (2020-06-25) claim 1	1-51, 53-80
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