chloro, -OH, -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -CH_2OH, -CH_2OCH_3, -CH_2F, -CHF_2, CH_2CN, -CH_2-cyclopropyl, cyclopropyl, pyridyl, phenyl, or -CH_2-phenyl, where any phenyl portion of R^5 is optionally substituted with up to 4 substituents independently selected from halo, -CN, and -O-C_1-C_3 alkyl;R^4 and R^5 are taken together to form =CH_2 or cyclopropyl, or cyclobutyl, or cyclopentyl, or cyclohexyl; or R^5 is taken together with the carbon atom to which it is bound, a ring atom of Q, and X to form oxazepane.

In some examples, R^7 is -OH, -NH_2, or -CHF_2. In some examples, R^7 is -OH.

In some examples, the compound has the structure of any of compounds 1-418, or 1-461, a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof.

In yet another aspect, there is provided a compound, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, selected from FIG. 1.

In an example, the disclosure features a pharmaceutical composition including any compound of the present disclosure or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

In yet another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, and a pharmaceutically acceptable carrier.

In an example, the disclosure features a complex including a presenter protein, a RAS protein, and any compound of the present disclosure or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, or any of the pharmaceutical compositions comprising such a compound as described herein.

In yet another aspect, there is provided a complex comprising a presenter protein, a RAS protein, and a compound as defined above, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined above.

In some examples, the RAS protein is KRAS. In some examples, the RAS protein is NRAS. In some examples, the RAS protein is HRAS. In some examples the RAS protein is KRAS G12C. In some examples, the RAS protein is KRAS G13C. In some examples, the RAS protein is NRAS G12C. In some examples, the RAS protein is NRAS G13C. In some examples, the RAS protein is HRAS G12C. In some examples, the RAS protein is HRAS G13C.

In some examples, the presenter protein is a cyclophilin. In some examples, the presenter protein is CYPA, CYPB, CYPC, CYP40, CYPE, CYPD, NKTR, SRCyp, CYPH, CWC27, CYPL1, CYP60, CYPJ, PPIL4, PPIL6, RANBP2, or PPWD1. In some examples, the presenter protein is CYPA.

In an example, the disclosure features a method of producing a complex, the method including contacting a presenter protein and a KRAS G12C protein with a compound of the present disclosure under conditions suitable to permit complex formation.

~~In yet another aspect, there is provided a method of producing a complex, the method comprising contacting a presenter protein and a KRAS G12C protein with a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, under conditions suitable to permit complex formation.~~

In another aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof in a method of producing a complex, the method comprising contacting a presenter protein and a KRAS G12C protein

with said compound, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, under conditions suitable to permit complex formation.

In some examples, the disclosure features a method of producing a complex, the method including contacting a presenter protein and a KRAS G13C protein, an NRAS G12C protein, an NRAS G13C protein, an HRAS G12C protein or an HRAS G13C protein, with a compound of the present disclosure under conditions suitable to permit complex formation. In some examples, the presenter protein is a cyclophilin protein. In some examples, the presenter protein is PP1A, CYPA, CYPB, CYPC, CYP40, CYPE, CYPD, NKTR, SRCyp, CYPH, CWC27, CYPL1, CYP60, CYPJ, PPIL4, PPIL6, RANBP2, or PPWD1. In some examples, the presenter protein is CYPA.

In an example, the disclosure features a method of producing a complex, the method including contacting a presenter protein and a KRAS G12C protein with a compound of the present disclosure under conditions suitable to permit complex formation if the compound is capable of forming a complex with the presenter protein and the KRAS G12C protein. In an example, the disclosure features a method of producing a complex, the method including contacting a presenter protein and a KRAS G13C protein, an NRAS G12C protein, an NRAS G13C protein, an HRAS G12C protein or an HRAS G13C protein, with a compound of the present disclosure under conditions suitable to permit complex formation if the compound is capable of forming a complex with the presenter protein and the RAS protein. In some examples,

the presenter protein is a cyclophilin protein. In some examples, the presenter protein is PP1A, CYPA, CYPB, CYPC, CYP40, CYPE, CYPD, NKTR, SRCyp, CYPH, CWC27, CYPL1, CYP60, CYPJ, PPIL4, PPIL6, RANBP2, or PPWD1. In some examples, the presenter protein is CYPA.

In an example, the disclosure features a method of treating cancer in a subject in need thereof, the method including administering to the subject an effective amount of a compound of the present disclosure or any of pharmaceutical compositions comprising such a compound.

~~In yet another aspect, there is provided a method of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, or a pharmaceutical composition as defined above.~~

In some examples, the cancer is pancreactic cancer, colorectal cancer, non-small cell lung cancer, or small cell lung cancer.

In an example, the disclosure features a method of inhibiting a KRAS G12C protein in a cell, the method including contacting the cell with an effective amount of a compound of the present disclosure or any pharmaceutical composition comprising such a compound.

~~In yet another aspect, there is provided a method of inhibiting a KRAS G12C protein in a cell, the method comprising contacting the cell with an effective amount of a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, or a pharmaceutical composition as defined above.~~

In another aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof for inhibiting a KRAS G12C protein in a cell.

In an example, the disclosure features a method of inhibiting a KRAS G13C protein, an NRAS G12C protein, an NRAS G13C protein, an HRAS G12C protein or an HRAS G13C protein in a cell, the method including contacting the cell with an effective amount of a compound of the present disclosure or any pharmaceutical composition comprising such a compound. In some examples, the cell is a cancer cell.

In an example, the disclosure features a method of treating a KRAS G12C protein-related disorder in a subject in need thereof, the method including administering to the subject an effective amount of a compound of the present disclosure or any pharmaceutical composition comprising such a compound.

~~In yet another aspect, there is provided a method of treating a KRAS G12C protein-related disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, a pharmaceutical composition as defined above.~~

In an example, the disclosure features a method of treating a KRAS G13C protein-related disorder, an NRAS G12C protein-related disorder, an NRAS G13C protein-related disorder, an HRAS G12C protein-related disorder, or an HRAS G13C protein-related disorder, in a subject in need thereof, the method including administering to the subject an effective amount of a compound of the present disclosure or any pharmaceutical composition comprising such a compound.

In some examples, the cell is a cancer cell. In some examples, the cancer is pancreatic cancer, colorectal cancer, non-small cell lung cancer, or small cell lung cancer. In some examples, the cancer is pancreatic cancer, colorectal cancer, non-small cell lung cancer, small cell lung cancer, acute myeloid leukemia, multiple myeloma, thyroid gland adenocarcinoma, a myelodysplastic syndrome, or squamous cell lung carcinoma.

In an example, the disclosure features a method of inhibiting RAF-RAS binding in a cell, the method including contacting the cell with an effective amount of a compound of the present disclosure or any pharmaceutical composition comprising such a compound.

~~In an aspect, there is provided a method of inhibiting RAF-RAS binding in a cell, the method comprising contacting the cell with an effective amount of a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, or a pharmaceutical composition as defined above.~~

In another aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof for inhibiting RAF-RAS binding in a cell.

In some examples, the cell is a cancer cell. In some examples, the cancer is pancreatic cancer, colorectal cancer, non-small cell lung cancer, or small cell lung cancer. In some examples, the cancer is pancreatic cancer, colorectal cancer, non-small cell lung cancer, small cell lung cancer, acute myeloid leukemia, multiple myeloma, thyroid gland adenocarcinoma, a myelodysplastic syndrome, or squamous cell lung carcinoma.

In an example, the disclosure features the use of a compound of the present disclosure, any pharmaceutical composition comprising such a compound, or any of the complexes described herein for treating cancer in a subject in need thereof.

In yet another aspect, there is provided a use of a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, for treating cancer in a subject in need thereof.

In an example, the disclosure features the use of any a compound of the present disclosure, any pharmaceutical composition comprising such a compound, or any of the complexes described herein for treating a KRAS G12C protein-related disorder in a subject in need thereof.

In yet another aspect, there is provided a use of a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, for treating a KRAS G12C protein-related disorder in a subject in need thereof.

In an example, the disclosure

WO20181309928; WO2018136264; WO2018136265; WO2018160731; WO2018172984; and WO2010121212, each of which is incorporated herein by reference.

In some examples, a SHP2 inhibitor binds in the active site. In some examples, a SHP2 inhibitor is a mixed-type irreversible inhibitor. In some examples, a SHP2 inhibitor binds an allosteric site e.g., a non-covalent allosteric inhibitor. In some examples, 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 examples a SHP2 inhibitor is a reversible inhibitor. In some examples, a SHP2 inhibitor is an irreversible inhibitor. In some examples, the SHP2 inhibitor is SHP099. In some examples, the SHP2 inhibitor is TNO155. In some examples, the SHP2 inhibitor is RMC-4550. In some examples, the SHP2 inhibitor is RCM-4630. In some examples, the SHP2 inhibitor is JAB-3068.

In another aspect, there is provided a compound as defined above, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, for use in therapy.

Chemical Terms

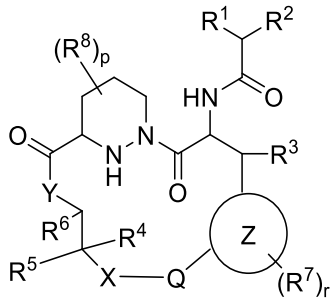
Those skilled in the art will appreciate that certain compounds described herein can exist in one or more different isomeric (e.g., stereoisomers, geometric isomers, tautomers) and/or isotopic (e.g., in which one or more atoms has been substituted with a different isotope of the atom, such as hydrogen 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 states 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, e.g., the interconversion illustrated in the scheme below:

CLAIMS

1. A compound of formula I:



(I), a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein:

Q is a bicyclic arylene, a bicyclic heteroarylene, or a bicyclic heterocyclylene, wherein a first ring in Q is bonded to X, and a second ring in Q is bonded to Z, and wherein Q is optionally substituted;

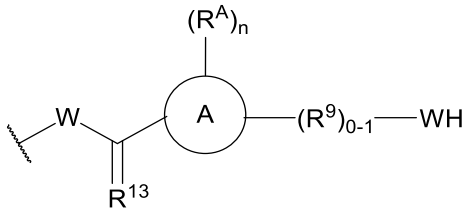
X is a bond; a straight chain C_1-C_3 alkylene optionally substituted with 1 to 3 substituents independently selected from fluoro, -CN, -C_1-C_3 alkyl, and -O-C_1-C_3 alkyl; -O-; -S(O)$_{0-2}$-; *-CH_2-O-; *-CH_2-S(O)$_{0-2}$-; *-O-CH_2-; or *-CH_2-S(O)$_{0-2}$-, wherein "*" represents a portion of X bound to -C(R^4)(R^5)-;

Y is -O-, -NH- or -N(C_1-C_3 alkyl)-;

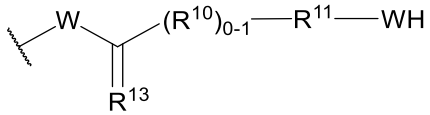
ring Z is phenyl or a 6-membered heteroaryl;

R^1 is optionally substituted C_1-C_6 alkyl, -(CH_2)$_{0-1}$-(C_3-C_6 optionally substituted cycloalkyl), -(CH_2)$_{0-1}$-(optionally substituted aryl), or optionally substituted heterocyclyl;

R^2 is:



or



,

wherein:

ring A is a 4-8 membered cycloalkyl or a 4-8 membered heterocyclyl;

W is -N(R^{12})-, -O-, or -C(R^{12a})(R^{12b})-;

each R^A is each independently fluoro; chloro; -CN; -OH; -NH_2; -C_1-C_3 alkyl optionally substituted with CN, OH, NH_2 or -O-C_1-C_3 alkyl; -O-C_1-C_3 alkyl; or -NH-C_1-C_3 alkyl;

R^9, if present, is -N(C_0-C_5 alkylene-H)-, -N(C(O)-(C_0-C_5 alkylene-H)-, -C(C_0-C_3 alkylene-H)(C_0-C_5 alkylene-H)-, or -C(C_0-C_3 alkylene-H)(C(O)-C_0-C_5 alkylene-H)-, wherein each alkylene portion of R^9 is optionally substituted with one or more substituent, wherein each substituent is, independently, selected from halo, -CN, -OH, -C_1-C_3 alkyl, and -O-C_1-C_3 alkyl;

R^{10}, if present, is C_1-C_4 alkylene optionally substituted with one or more substituent, wherein each substituent is, independently, selected from halo, -CN, -OH, -C_1-C_3 alkyl, and -O-C_1-C_3 alkyl;

R^{11} is -N(C_0-C_5 alkylene-H)-, -N(C(O)-(C_0-C_5 alkylene-H)-, -C(C_0-C_3 alkylene-H)(C_0-C_5 alkylene-H)-, -C(C_0-C_3 alkylene-H)(C(O)-C_0-C_5 alkylene-H)-, or a saturated, nitrogen-containing heterocyclyl, where each alkylene portion of R^{11} is optionally substituted with one or more

substituent, wherein each substituent is, independently, selected from halo, -CN, -OH, -C_1-C_3 alkyl, and -O-C_1-C_3 alkyl;

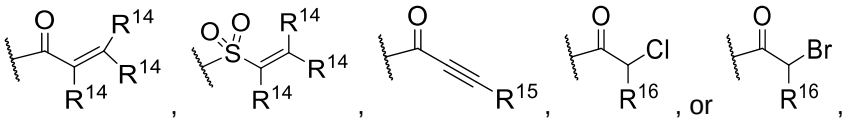
R^{12} is hydrogen, or -C_1-C_3 alkyl, or

R^{12} is taken together with one R^A, the atoms to which they are respectively attached and any intervening atoms to form an optionally substituted, 5-8 membered heterocyclyl that is fused or spiro-fused to ring A, or

R^{12} is taken together with any methylene unit in R^{10}, or any methylene unit in R^{11}, the atoms to which they are respectively attached and any intervening atoms to form an optionally substituted, 5-8 membered heterocyclyl;

each of R^{12a} and R^{12b} are independently hydrogen, or -C_1-C_3 alkyl, or R^{12a} and R^{12b} are taken together with the carbon atom to which they are bound to form a 3-6 membered cycloalkyl ring;

R^{13} is O, S, N-CN, or N-O-C_1-C_3 alkyl; and

WH is  , , , , or ,

each R^{14} is independently hydrogen, -CN, or -C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or an optionally substituted 4-7 membered saturated heterocyclyl;

R^{15} is -C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or an optionally substituted 4-7 membered saturated heterocyclyl;

R^{16} is hydrogen, -C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or an optionally substituted 4-7 membered saturated heterocyclyl; or

R^{14} is taken together with either of R^9 or R^{11}, the atoms to which they are attached and any intervening atoms to form an optionally substituted 5-8 membered ring system; or

R^{16} is taken together with either of R^9 or R^{11}, the atoms to which they are attached and any intervening atoms to form an optionally substituted 5-8 membered ring system;

R^3 is hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 hydroxyalkyl;

R^4 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl;

R^5 is hydrogen, halogen, -OH, -CN, -O-(optionally substituted C_1-C_3 alkyl), optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, -(CH_2)$_{0-1}$-aryl, -(CH_2)$_{0-1}$-heteroaryl, -(CH_2)$_{0-1}$-cycloalkyl, or -(CH_2)$_{0-1}$-heterocyclyl; or

R^4 and R^5 are taken together to form =CH_2, an optionally substituted C_3-C_6 cycloalkyl, or a 3-7 membered saturated heterocyclyl; or

R^5 is taken together with a ring atom in Q, the carbon atom to which R^4 is bound and X to form a 4-9 membered saturated or unsaturated heterocyclyl that is fused to Q;

R^6 is hydrogen or -CH_3;

each R^7 is independently halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 hydroxyalkyl, -OH, -O-C_1-C_3 alkyl, -O-C_1-C_3 haloalkyl, -$NR^{n1}R^{n2}$, -$NR^{n1}OR^{n2}$, -$ONR^{n1}R^{n2}$, or -$NR^{n1}NR^{n2}R^{n3}$;

R^{n1} is H, C_1-C_3 alkyl, C_1-C_3 heteroalkyl, C_1-C_3 haloalkyl, -C_1-C_3 hydroxyalkyl, or C_1-C_3 aminoalkyl, wherein one methylene unit of R^{n1} is optionally substituted with  ;

R^{n2} is H, C_1-C_3 alkyl, C_1-C_3 heteroalkyl, C_1-C_3 haloalkyl, C_1-C_3 hydroxyalkyl, or C_1-C_3 aminoalkyl, wherein one methylene unit of R^{n2} is optionally substituted with  ;

R^{n3} is H, C_1-C_3 alkyl, C_1-C_3 heteroalkyl, C_1-C_3 haloalkyl, C_1-C_3 hydroxyalkyl, or C_1-C_3 aminoalkyl, wherein one methylene unit of R^{n3} is optionally substituted with  ;

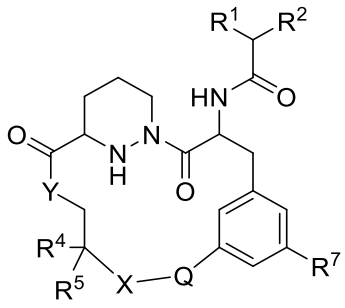
each R^8 is independently halo, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

n is 0, 1, 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3; and

r is 0, 1, 2, 3, or 4.

2. The compound of claim 1, wherein said compound has the structure of formula (Ia):



(Ia), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof,

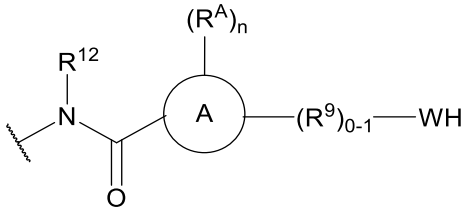
wherein:

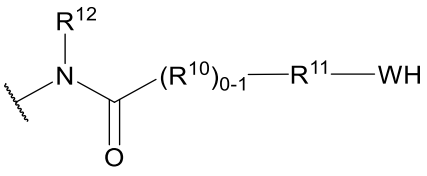
X is a bond, -O-, -CH_2-, -$CH(CH_3)$-, *-CH_2-O-, or -CH_2-CH_2-, wherein "*" represents a portion of X bound to $C(R^4)(R^5)$;

Y is -O- or -NH-;

R^1 is -C_1-C_4 alkyl, -$(CH_2)_{0\text{-}1}$-(C_3-C_6 cycloalkyl), or -C_4-C_6 cycloalkyl;

R^2 is:



or  ,

wherein:

ring A is a 4-8 membered cycloalkyl or a 4-8 membered saturated heterocyclyl;

each R^A is each independently fluoro; chloro; -CN; -OH; -NH_2; -C_1-C_3 alkyl optionally substituted with CN, OH, NH_2 or -O-C_1-C_3 alkyl; -O-C_1-C_3 alkyl; or -NH-C_1-C_3 alkyl;

n is 0, 1, 2, 3, 4, 5, or 6;

R^9, if present, is -N(C_0-C_5 alkylene-H)-, -N(C(O)-(C_0-C_5 alkylene-H)-, -C(C_0-C_3 alkylene-H)(C_0-C_5 alkylene-H)-, or -C(C_0-C_3 alkylene-H)(C(O)-C_0-C_5 alkylene-H)-, wherein each alkylene portion of R^9 is optionally substituted with one or more substituent independently selected from halo, -CN, -OH, -C_1-C_3 alkyl, and -O-C_1-C_3 alkyl;

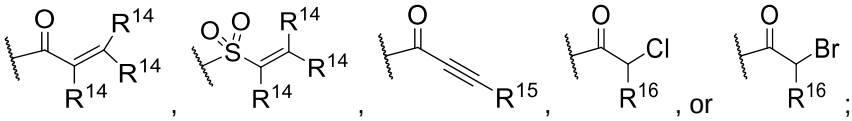
R^{10}, if present, is C_1-C_4 alkylene optionally substituted with one or more substituent independently selected from halo, -CN, -OH, -C_1-C_3 alkyl, and -O-C_1-C_3 alkyl;

R^{11} is -N(C_0-C_5 alkylene-H)-, -N(C(O)-(C_0-C_5 alkylene-H)-, -C(C_0-C_3 alkylene-H)(C_0-C_5 alkylene-H)-, or -C(C_0-C_3 alkylene-H)(C(O)-C_0-C_5 alkylene-H)-, wherein each alkylene portion of R^{11} is optionally substituted with one or more substituent independently selected from halo, -CN, -OH, -C_1-C_3 alkyl, and -O-C_1-C_3 alkyl;

R^{12} is hydrogen, or -C_1-C_3 alkyl, or

R^{12} is taken together with one R^A, the atoms to which they are respectively attached and any intervening atoms to form an optionally substituted, 5-8 membered heterocyclyl that is fused to ring A, or

R^{12} is taken together with any methylene unit in R^{10}, or any methylene unit in R^{11}, the atoms to which they are respectively attached and any intervening atoms to form an optionally substituted, 5-8 membered heterocyclyl;

WH is  ;

each R^{14} is independently hydrogen, -CN, -C_1-C_3 alkyl, -C_1-C_3 hydroxyalkyl, -O-C_1-C_3 alkyl;

R^{15} is -C_1-C_3 alkyl, -C_1-C_3 hydroxyalkyl, or -C_1-C_3 alkylene-O-C_1-C_3 alkyl;

R^{16} is hydrogen, -C_1-C_3 alkyl, -C_1-C_3 hydroxyalkyl, or -C_1-C_3 alkylene-O-C_1-C_3 alkyl; or

R^{14} is taken together with either of R^9 or R^{11}, the atoms to which they are attached and any intervening atoms to form an optionally substituted 5-8 membered ring system, or

R^{16} is taken together with either of R^9 or R^{11}, the atoms to which they are attached and any intervening atoms to form an optionally substituted 5-8 membered ring system;

R^4 is hydrogen, halo, or C_1-C_3 alkyl;

R^5 is hydrogen, halo, -OH, C_1- C_3 alkyl, C_1-C_3 hydroxyalkyl, C_1-C_3 alkylene-O-C_1-C_3 alkyl, C_1-C_3 haloalkyl, -$(CH_2)_{0\text{-}1}$-C_3-C_6 cycloalkyl, C_1-C_3 cyanoalkyl, or -$(CH_2)_{0\text{-}1}$-aryl (benzyl), or

R^4 and R^5 are taken together to form =CH_2, or a C_3-C_6 cycloalkyl, or

R^5 is taken together with a ring atom of Q, the carbon atom to which it is bound and X to form a 5-7 membered saturated heterocyclyl;

R^7 is -OH, -NH_2, or C_1-C_3 haloalkyl;

Q is a bicyclic arylene, a bicyclic heteroarylene, or a bicyclic heterocyclylene, wherein:

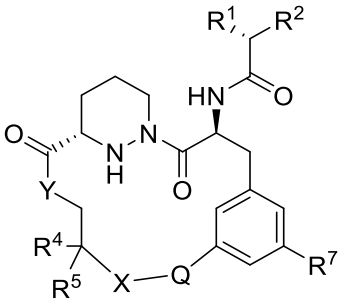
a first ring in Q is bonded to X, and a second ring in Q is bonded Z; and

Q is optionally substituted with one or more independently selected substituents selected from =O; -CN; -C_1-C_5 alkyl optionally substituted with one or more independently selected halo, CN, OH, -O-(C_1-C_3 alkyl), -C(O)-(C_1-C_3 alkyl), -O-(C_2-C_3 alkynyl), -(C_3-C_6 cycloalkyl), or a 4-7 membered saturated heterocyclyl; -O-(C_1-C_3 alkyl) optionally substituted with one or more independently selected

halo; C_2-C_5 alkenyl optionally substituted with one or more independently selected -CN, or -OH; C_2-C_3 alkynyl; -S(O)$_2$-C_1-C_3 alkyl; -$(CH_2)_{0-1}$-C_3-C_6 cycloalkyl optionally substituted with one or more independently selected halo, =O, -CN, C_1-C_3 alkyl optionally substituted with -CN or -O-C_1-C_3 alkyl, -C(O)-saturated heterocyclyl, -O-saturated heterocyclyl, O-cycloalkyl, or -O-aryl; -$(CH_2)_{0-1}$-heteroaryl optionally substituted with one or more independently selected halo, -CN, C_1-C_3 alkyl optionally substituted with -CN or -O-C_1-C_3 alkyl, -C(O)-saturated heterocyclyl, -O-saturated heterocyclyl, O-cycloalkyl, or -O-aryl; -$(CH_2)_{0-1}$-heterocyclyl optionally substituted with one or more independently selected halo, =O, -CN, C_1-C_3 alkyl optionally substituted with -CN or -O-C_1-C_3 alkyl, -C(O)-saturated heterocyclyl, -O-saturated heterocyclyl, O-cycloalkyl, or -O-aryl; -$(CH_2)_{0-1}$-aryl optionally substituted with one or more independently selected halo, -CN, -C_1-C_3 alkyl optionally substituted with -CN or -O-C_1-C_3 alkyl, -C(O)-saturated heterocyclyl, -O-saturated heterocyclyl, O-cycloalkyl, or -O-aryl; -C(O)-NH-(C_1-C_3 alkyl); -C(O)-N(C_1-C_3 alkyl)$_2$; C_2-C_3 alkenylene=N-O-(C_1-C_3 alkyl) optionally substituted with C_3-C_6 cycloalkyl; or

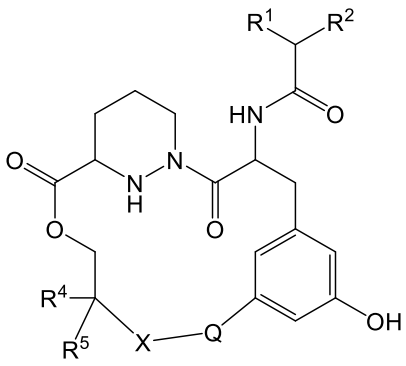
two substituents on the same or adjacent ring atoms of Q are taken together to form a 5-7 membered monocyclic ring or a 6-12 membered bicyclic ring optionally substituted with one or more independently selected halo, =O, -CN, C_1-C_3 alkyl, or -O-C_1-C_3 alkyl; and fused to Q.

3. The compound of claim 2, wherein said compound has the structure of formula (Ib):



(Ib), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof or

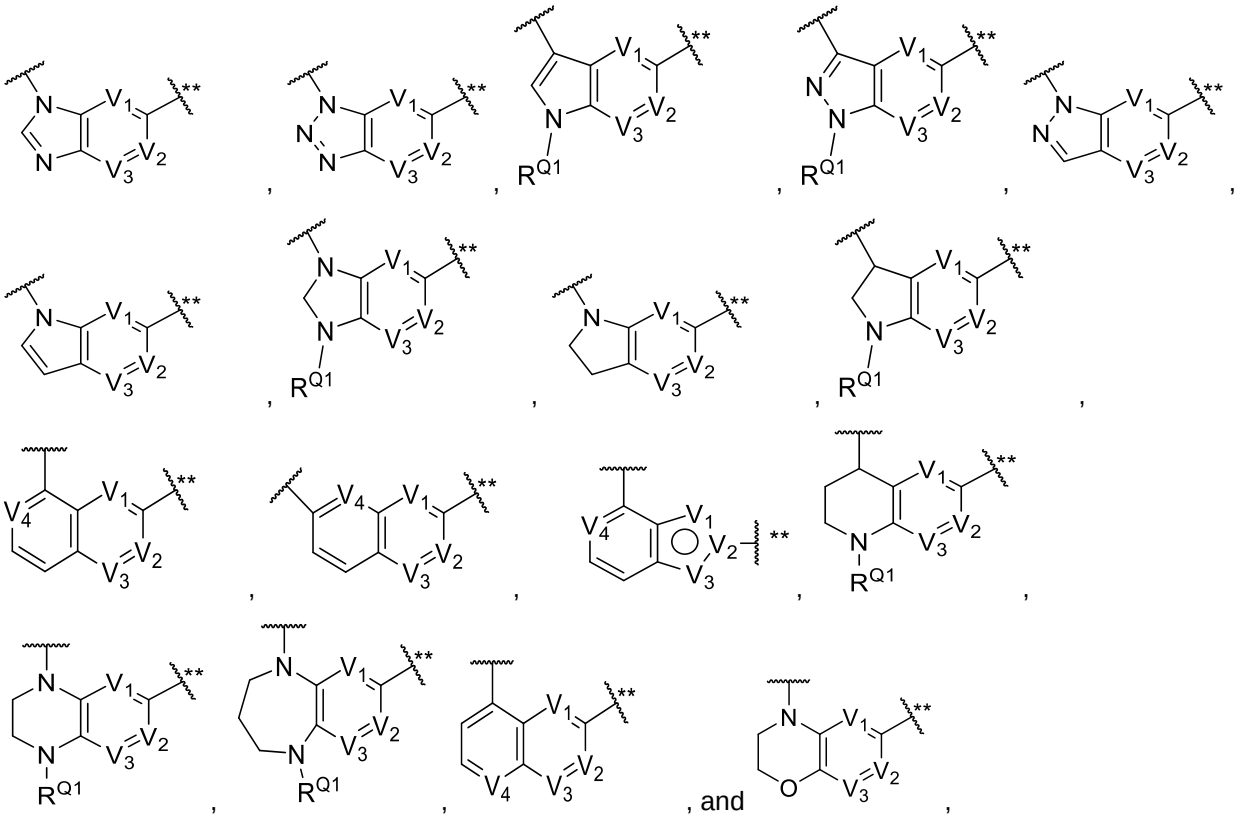
said compound has the structure of formula (Ic):



(Ic), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein Q is a 5,6 bicyclic heteroarylene, a 5,6 bicyclic heterocyclylene, a 6,6 bicyclic heteroarylene, or a 6,6 bicyclic heterocyclylene; and wherein Q is optionally substituted.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein Q is selected from the group consisting of:



wherein:

each of V_1, V_2, V_3 and V_4 is independently C, CH, or N;

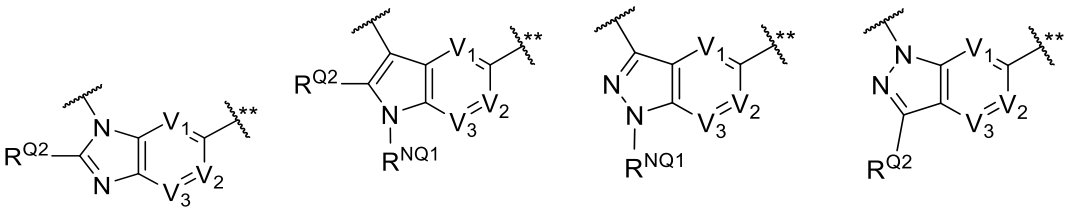
R^{Q1} is $-S(O)_2-R^{Q11}$, $-C(O)-R^{Q11}$, $-S(O)_2-N(R^{Q11})R^{Q12}$, $-C(O)-N(R^{Q11})R^{Q12}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, a 4-14 membered heterocyclyl, aryl, or heteroaryl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted; or

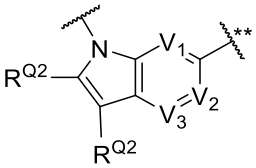
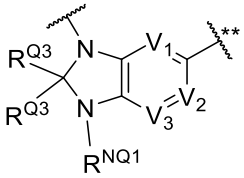
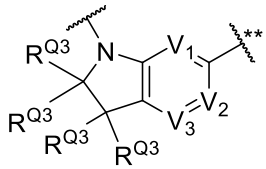
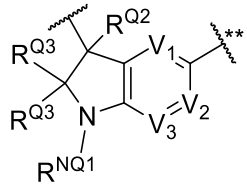
R^{Q1} is taken together with the nitrogen atom to which it is attached and an adjacent ring atom to form an optionally substituted 4-8 membered ring, which is optionally further fused to a 5-6 membered ring;

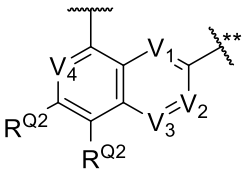
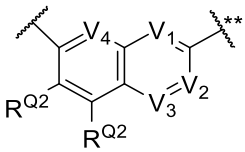
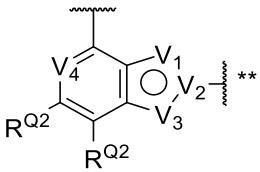
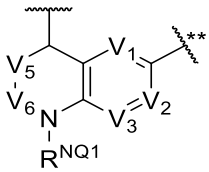
each of R^{Q11} and R^{Q12} is independently C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, a 4-14 membered heterocyclyl, aryl, or heteroaryl, wherein each of R^{Q11} and R^{Q12} is optionally substituted; or

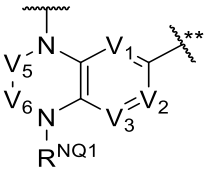
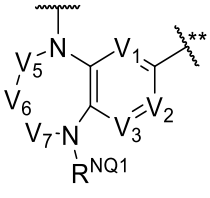
R^{Q11} and R^{Q12} are taken together with the nitrogen atom to which they are both attached to form an optionally substituted 4-8 membered ring, wherein the ring formed by taking R^{Q11} and R^{Q12} together is optionally fused to another 5-6 membered ring.

6. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein Q is selected from the group consisting of:



 ,  ,  ,  ,

 ,  ,  ,  ,

 , and  ,

wherein:

each of V_1, V_2, V_3 and V_4 is independently C, CH, N, C(F), $C(CH_3)$, C(OH), $C(OCH_3)$, or C(CN);

each of V_5, V_6, and V_7 is independently, $C(R^{17a})(R^{17b})$, or C(=O), wherein each of R^{17a} and R^{17b} is independently selected from hydrogen, halo, $-C_1-C_3$ alkyl, $-C_1-C_3$ haloalkyl, $-O-C_1-C_3$ alkyl, $-O-C_1-C_3$ haloalkyl, and no more than two of V_5, V_6, and V_7 is C(=O);

R^{NQ1} is hydrogen, optionally substituted $-S(O)_2-R^{Q11}$, $-C(O)-R^{Q11}$, $-S(O)_2-N(R^{Q11})R^{Q12}$, $-C(O)-N(R^{Q11})R^{Q12}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, a 4-14 membered heterocyclyl, aryl, or heteroaryl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted;

each R^{Q2} is independently hydrogen, CN, optionally substituted $-S(O)_2-R^{Q11}$, $-C(O)-R^{Q11}$, $-S(O)_2-N(R^{Q11})R^{Q12}$, $-C(O)-N(R^{Q11})R^{Q12}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, a 4-14 membered heterocyclyl, aryl, or heteroaryl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted; or

R^{NQ1} and one R^{Q2} are taken together with the atoms to which they are bound to form an optionally substituted 4-8 membered ring, wherein the ring formed by taking R^{NQ1} and one R^{Q2} together is optionally further fused to a 5-6 membered ring;

each R^{Q3} is independently hydrogen, CN, optionally substituted $-S(O)_2-R^{Q11}$, $-C(O)-R^{Q11}$, $-S(O)_2-N(R^{Q11})R^{Q12}$, $-C(O)-N(R^{Q11})R^{Q12}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, a 4-14 membered heterocyclyl, aryl, or heteroaryl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted, or

two R^{Q3} bound to the same atom are taken together to form =CH, =O, =S, or $=NR^{V4}$; or

two R^{Q3} bound to the same atom are taken together with the atom to which they are bound to form an optionally substituted 4-8 membered ring, wherein the ring formed by taking each R^{Q3} together is optionally further fused to a 5-6 membered ring; or

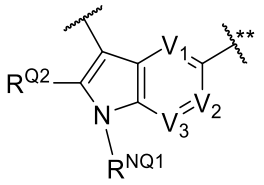
R^{NQ1} and one R^{Q3} are taken together with the atoms to which they are bound to form an optionally substituted 4-8 membered ring, wherein the ring formed by taking R^{NQ1} and R^{Q3} together is optionally further fused to a 5-6 membered ring;

each of R^{Q11} and R^{Q12} is independently C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, a 4-14 membered heterocyclyl, aryl, or heteroaryl, wherein each of R^{Q11} and R^{Q12} is optionally substituted; or

R^{Q11} and R^{Q12} are taken together with the atoms to which they are attached to form an optionally substituted 4-8 membered ring, wherein the ring formed by taking R^{Q11} and R^{Q12} together is optionally fused to another 5-6 membered ring; and

"**" represents a portion of Q that is bound to ring Z.

7. The compound of claim 6~~any one of claims 1-4~~, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein Q is selected from the group consisting of: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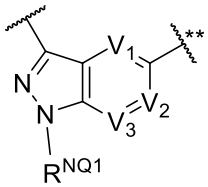
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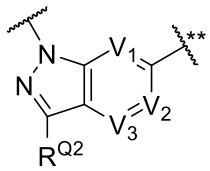
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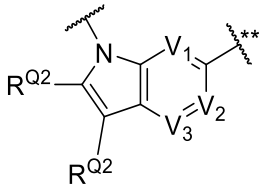
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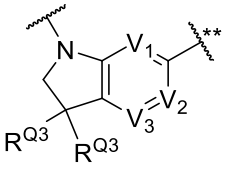
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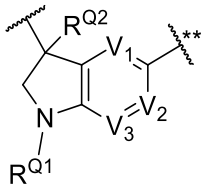
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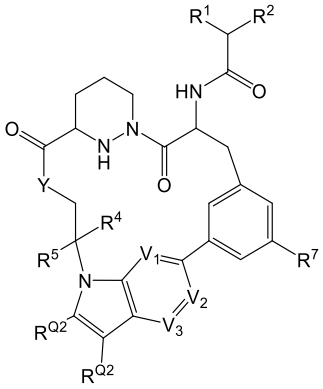
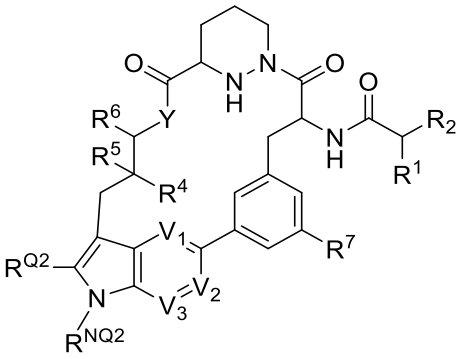
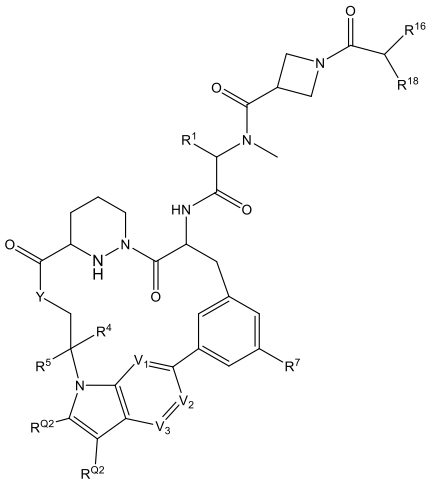
8. The compound of claim 7, wherein said compound has the structure of formula (Id):


(Id), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof or

said compound has the structure of formula (Ij):

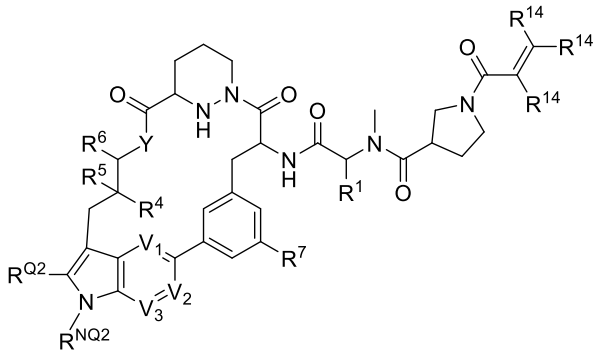

(Ij), a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof.

9. The compound of any one of claims 1-8, wherein said compound has the structure of formula (IL):



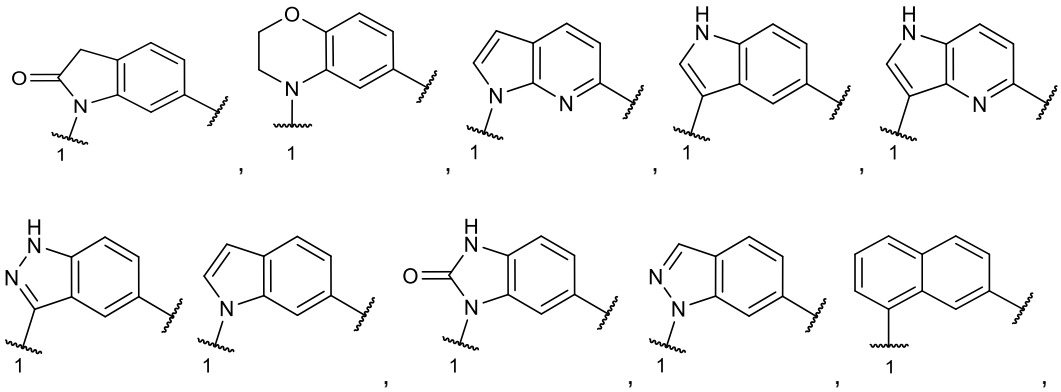
(IL), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein R^{18} is Br or Cl or

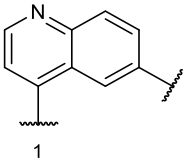
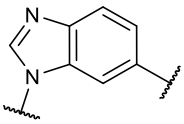
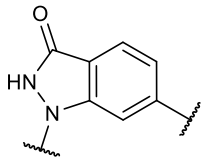
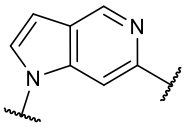
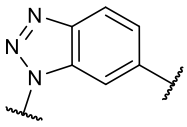
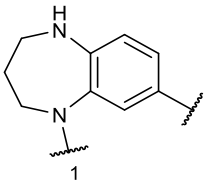
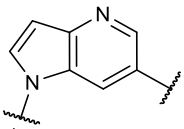
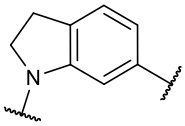
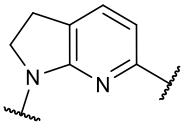
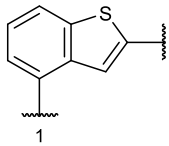
said compound has the structure of formula (Im):



(Im), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein each R^{14} is H.

10. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein Q is selected from the group consisting of:



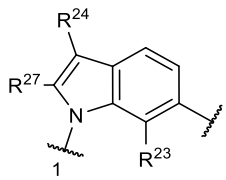
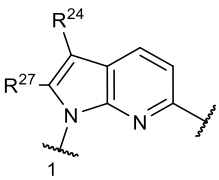
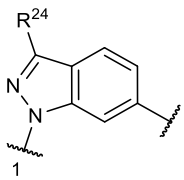
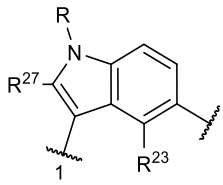
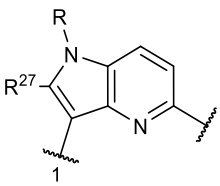
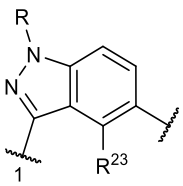
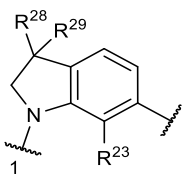
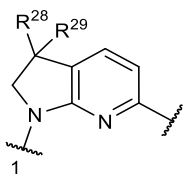











wherein:

“1” indicates a portion of Q bound to X; and

Q is further optionally substituted.

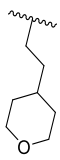
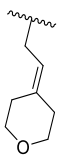
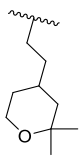
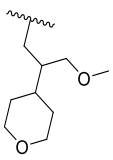
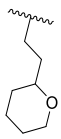
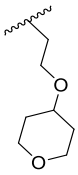
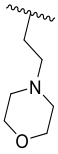
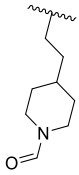
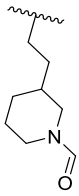
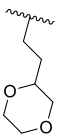
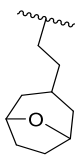
11. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein Q is selected from the group consisting of:

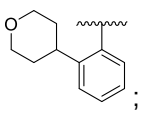









wherein:

R is $-CH_2CH_3$,

$-CH_2CH_2-OCH_3$, $-CH_2CHF_2$, $-CH_2-CN$, $-C(CH_3)_2-CN$, $-C(CH_3)_2-CH_2CN$, $-CH_2CH_2-CN$, cyclohexyl, cyclobutyl, cyclopropyl, pyridin-4-yl, tetrahydropyran-4-yl, tetrahydropyran-4-ylmethyl, oxetan-3-ylmethyl, 2-cyano-5-methoxyphenyl, 2-cyano-5-methoxymethylphenyl, 2-cyano-6-(methoxymethyl)phenyl, 2-cyano-6-bromophenyl, 2-methoxyethan-1-yl, 2-cyanopropan-2-yl, 2-tetrahydropyran-4-ylethan-1-yl, 3-cyanopentan-3-yl, or 2-cyano-4-methoxybutan-2-yl, , or

R is 










, or


;

R^{23} is hydrogen or fluoro;

R^{24} is hydrogen,

chloro, $-CN$, $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, $-CH_2-CN$, $-CH(CN)-CH_3$, $--C(CH_3)_2-CN$, $-C(CH_2CH_3)_2-CN$, $-CH_2$

$-CH_2-CN$, $-C(CH_3)=N-O-CH(CH_3)_2$, $-C(CH_3)=N-O-CH_3$, $-C(O)-N(CH_3)_2$, $-C(O)-NH-CH_3$, $-OCH_3$, $-CH_2-O-CH_3$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-S(O)_2CH_3$, 1-(cyclopentyl)-1-cyanoethan-1-yl, 1-(tetrahydropyran-4-yl)-1-cyanoethan-1-yl, 1-(tetrahydrofuran-3-yl)-1-cyanoethan-1-yl, 1,3-dimethoxy-2-cyanopropan-2-yl, 1,4-dimethylpyrazol-5-yl, 1-cyanocyclobutyl, 1-cyanocyclopropyl, 1-cyanocylopentyl, 1-methyl-1,2,3,6-tetrahydropyridin-4-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-ylcyanomethyl, 1-methylpiperidin-4-yl, 1-methylpyrazol-5-yl, 1-oxoindolin-5-yl, 1-oxoisoindolin-4-yl, 1-oxoisoindolin-6-yl, 2-(2-methoxyethan-1-yl)phenyl, 2-(methoxymethyl)phenyl, 2-(tetrahydropyran-4-yloxy)phenyl, 2,2-difluoro-benzo[d][1,3]dioxol-4-yl, 2,3-dicyanopropan-2-yl, 2-chlorophenyl, 2-cyano-3-(tetrahydropyran-4-yl)propan-2-yl, 2-cyano-3-chlorophenyl, 2-cyano-3-fluorophenyl, 2-cyano-3-methoxyphenyl, 2-cyano-4-fluorophenyl, 2-cyano-4-chlorophenyl, 2-cyano-5-chlorophenyl, 2-cyano-5-fluorophenyl, 2-cyano-5-methoxyphenyl, 2-cyano-6-chlorophenyl, 2-cyano-6-fluorophenyl, 2-cyano-6-(tetrahydropyran-4-yloxy)phenyl, 2-cyanomethylphenyl, 2-cyanophenyl, 2-cyanopropan-2-yl, 2-cyclopentylphenyl, 2-difluoromethoxyphenyl, 2-fluorophenyl, 2-methoxy-6-cyanophenyl, 2-methoxyphenyl, 2-methoxycarbonylphenyl, 2-nitrophenyl, 2-oxopyrrolidin-1-yl, 2-phenoxyphenyl, 3-(1,1-dioxothiomorpholin-4-ylmethyl)phenyl, 3-(2-methoxyethan-1-yl)phenyl, 3,5-difluoro-4-(pyrrolidin-1-ylcarbonyl)phenyl, 3-cyano-2-methylpropan-2-yl, 3-cyanomethylphenyl, 3-cyanopentan-3-yl , 3-cyanophenyl, 3-hydroxy-2-methylbutan-2-yl, 3-hydroxy-3-methyl-but-1-yne-1-yl, 3-methoxy-2-methylbutan-2-yl, 3-methoxymethyl-5-methylisoxazol-4-yl, 3-methoxyphenyl, 3-methoxycarbonylphenyl, 3-oxo-2-methylbutan-2-yl, 4-cyanophenyl, 4-cyanotetrahydropyran-4-yl, 4-methoxyphenyl, benzo[d][1,3]dioxol-4-yl, benzo[d]oxazol-7-yl, benzo[d]thiazol-2-yl, benzo[d]thiazol-4-yl, benzo[d]thiazol-5-yl, benzo[d]thiazol-6-yl, benzo[d]thiazol-7-yl, cyclobutyl, cyclopropyl, cyclopropylcyanomethyl, N-methoxycyclopropanecarbimidoyl, phenyl, pyridin-2-ylmethyl, pyridin-3-yl, pyridin-3-ylmethyl, pyridin-4-ylmethyl, tetrahydrofuran-3-ylmethyl, tetrahydrofuran-3-ylcyanomethyl, tetrahydropyran-4-yl, or tetrahydropyran-4-ylcyanomethyl;

R^{27} is hydrogen, $-CH_3$, $-CHF_2$, $-CH_2CH_3$, $-CH_2-O-CH_3$, CH_2CN, $-CN$, $-CH_2-O-CH_2-CN$, $-C(O)-N(CH_3)_2$, $-C(O)-NH-CH_3$, $-CH_2-O-CH_2-C\equiv CH$, 2-methoxyphenyl, 3-methoxyphenyl, 2,2-difluorobenzo[d][1,3]dioxol-4-yl, 2-cyanophenyl, 3-cyanophenyl, phenyl, 2-benzyl methyl ether, 2-(2-methoxyethyl) benzene, 2-(2-difluoromethoxyethyl)benzene, 2-(2-dimethylmethoxyethyl)benzene, pyridin-3-yl, pyridin-2-yl, pyridin-3-ylmethyl, or tetrahydropyridin-4-yl, or

R^{24} and R^{27} are taken together to form 4-cyanobenzene-1,2-diyl, 3-cyanobenzene-1,2-diyl, 5-methyl-5-cyanotetrahydropyran-3,4-diyl, 3-cyanocyclohexan-1,2-diyl, 3-methoxybenzene-1,2-diyl, benzene-1,2-diyl, 3-oxocyclohexyl-1,2-diyl, 3-cyanocyclopentan-1,2-diyl, or pyridin-3,4-diyl;

R^{28} is hydrogen, $-CH_3$, or $-CH_2-O-CH_3$; and

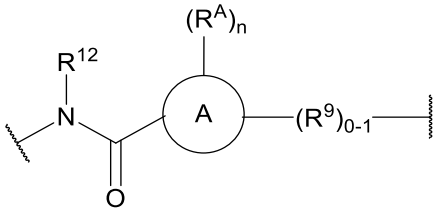
R^{29} is hydrogen, acetyl, CN, $-CH_2-CN$, $-CH_2-CH_2-CN$, $-CH_2-O-CH_3$, $-CH=CH-CN$, $-CH_2-O-C(O)-N(CH_3)_2$, morpholin-4-ylmethyl, pyrazol-1-ylmethyl, pyridin-3-yl, pyridin-3-ylethynyl, pyridin-2-yloxymethyl, or 2-cyanopropan-2-yl, or

R^{28} and R^{29} are taken together to form 2,3-dihydrobenzofuran-3,3-diyl, 2,3-dihydrofuro[2,3-b]pyridin-3,3-diyl, tetrahydropyran-3,3-diyl, 6,7-dihydro-5H-cyclopenta[c]pyridin-6-yl, tetrahydropyran-4,4-diyl, or 4-methoxycyclohexane.

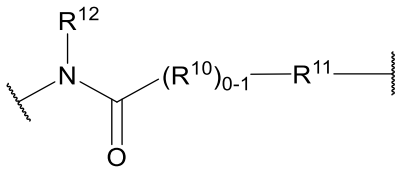
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein R^1 is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, 4-methoxybenzyl, or tetrahydropyran-4-yl.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein R^9 is absent and ring A is a saturated, nitrogen-containing heterocyclyl.

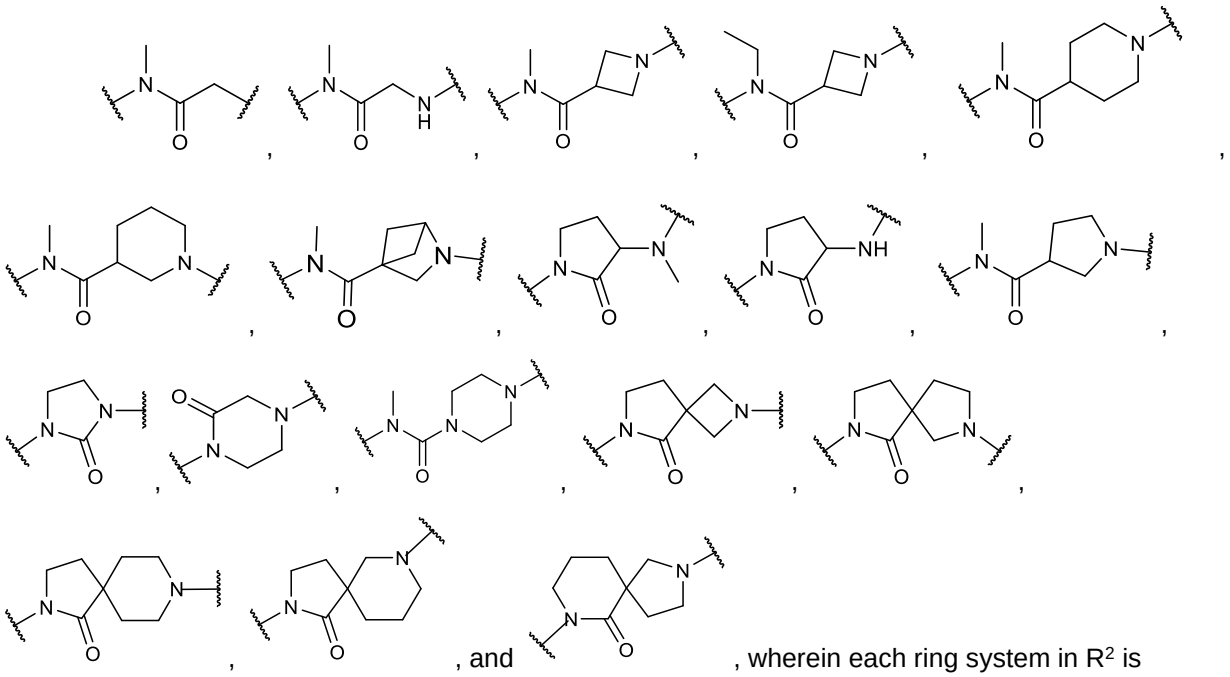
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein the portion of R^2 represented by:



or



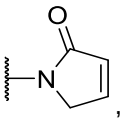
is selected from the group consisting of:

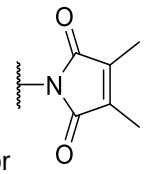


, and , wherein each ring system in R^2 is optionally substituted with up to 4 substituents independently selected from fluoro; chloro; -CN; -OH; $-NH_2$; $-C_1$-C_3 alkyl optionally substituted with CN, OH, NH_2 or $-O-C_1$-C_3 alkyl; $-O-C_1$-C_3 alkyl; and $-NH-C_1$-C_3 alkyl.

15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein:

the portion of R^2 represented by WH is $-C(O)-C\equiv C-CH_3$, $-C(O)-CH=CH_2$, $-S(O)_2-CH=CH_2$, $-C(O)-CH_2Cl$, $-C(O)-CH(CH_3)Cl$, or $-C(O)-CH(Cl)-CH_2-O-CH_3$, or

the portion of R^2 represented by -R^{11}-WH, when R^{11} is taken together with one R^{14} is  ,

or  .

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein R^2 is selected from the group consisting of:
1-(2-chloro-3-methoxypropanoyl)azetidin-3-yl-N-methylcarboxamido,
1-(2-chloroacetyl)azetidin-3-ylcarboxamido, 1-(2-chloroacetyl)azetidin-3-yl-N-ethylcarboxamido,
1-(2-chloroacetyl)azetidin-3-yl-N-methylcarboxamido,
1-(2-chloroacetyl)piperidin-3-yl-N-methylcarboxamido,
1-(2-chloroacetyl)piperidin-4-yl-N-methylcarboxamido,
1-(2-chloroacetyl)pyrrolidin-3-yl-N-methylcarboxamido,
1-(2-chloropropanoyl)-piperidin-4-yl-N-methylcarboxamido,
1-(2-chloropropanoyl)-3-fluoroazetidin-3-yl-N-methylcarboxamido,
1-(2-chloropropanoyl)azetidin-3-yl-N-methylcarboxamido,
1-(2-chloropropanoyl)pyrrolidin-3-yl-N-methylcarboxamido,
1-(but-2-ynoyl)-4-fluoropiperidin-4-ylcarbonylmethylamino,
1-(but-2-ynoyl)azetidin-2-yl-N-methylcarboxamido, 1-(but-2-ynoyl)azetidin-3-yl-N-methylcarboxamido,
1-(but-2-ynoyl)-piperidin-3-ylcarbonylmethylamino, 1-(but-2-ynoyl)-piperidin-4-ylcarbonylmethylamino,
1-(but-2-ynoyl)pyrrolidin-2-ylcarbonyl-N-methylamino,
1-(but-2-ynoyl)pyrrolidin-3-ylcarbonyl-N-methylamino, 1-acryloyl-2-oxo-imidazolidin-3-yl,
1-acryloyl-3-fluoroazetidin-3-yl-N-methylcarboxamido,
1-acryloyl-3-fluoropyrrolidin-3-yl-N-methylcarboxamido,
1-acryloyl-4-fluoropiperidin-4-ylcarbonylmethylamino, 1-acryloylazetidin-2-yl-N-methylcarboxamido,
1-acryloylazetidin-3-yl-N-methylcarboxamido, 1-acryloyl-piperidin-3-ylcarbonylmethylamino,
1-acryloyl-piperidin-4-ylcarbonylmethylamino, 1-acryloylpyrrolidin-2-yl-N-methylcarboxamido,
1-acryloylpyrrolidin-3-yl-N-methylcarboxamido, 1-oxo-7-(2-chloroacetyl)-2,7-diazaspiro[4.3]octan-2-yl,
1-oxo-7-(2-chloroacetyl)-2,7-diazaspiro[4.4]nonan-2-yl,
1-oxo-2-(2-chloroacetyl)-2,7-diazaspiro[4.5]decan-7-yl,
1-oxo-7-(2-chloroacetyl)-2,7-diazaspiro[4.5]decan-2-yl,
1-oxo-7-(2-chloropropanoyl)-2,7-diazaspiro[4.3]octan-2-yl,
1-oxo-7-(but-2-ynoyl)-2,7-diazaspiro[4.4]nonan-2-yl, 1-oxo-7-acryloyl-2,7-diazaspiro[4.3]octan-2-yl,
1-oxo-7-acryloyl-2,7-diazaspiro[4.4]nonan-2-yl, 1-oxo-7-acryloyl-2,7-diazaspiro[4.5]decan-2-yl,
1-oxo-8-(2-chloroacetyl)-2,8-diazaspiro[4.5]decan-2-yl,
1-oxo-8-(but-2-ynoyl)-2,8-diazaspiro[4.5]decan-2-yl, 1-oxo-8-acryloyl-2,8-diazaspiro[4.5]decan-2-yl,
1-vinylsulfonyl-2-oxoimidazolidin-3-yl, 1-vinylsulfonylazetidin-3-yl-N-methylcarboxamido,
2-(1-acryloylpiperidin-4-yl)-N-methylacetamido, 2-(but-2-ynoyl)-5-oxo-2,6-diazaspiro[3.4]octan-6-yl,
2,5-dioxo-3,4-dimethyl-2,5-dihydropyrrol-1-yl-N-methylacetamido,

2-acryloyl-2-azabicyclo[2.1.1]hexan-4-yl-N-methylcarboxamido,
2-chloroacetamidomethyl-N-methylcarboxamido, 2-oxo-2,5-dihydro-1H-pyrrol-1-yl-N-methylacetamido,
2-oxo-3-(2-chloroacetamido)pyrrolidin-1-yl, 2-oxo-3-(N-methyl-2-chloroacetamido)pyrrolidin-1-yl,
2-oxo-3-(N-methylacrylamido)pyrrolidin-1-yl, 2-oxo-3-acrylamidopyrrolidin-1-yl,
2-oxo-4-(2-chloroacetyl)piperazin-1-yl, 2-oxo-4-acryloylpiperazin-1-yl, 2-oxo-4-vinylsulfonylpiperazin-1-yl,
2-oxocyclopent-3-en-1-yl-N-methylacetamido,
3-(4-(dimethylamino)but-2-enamido)phenyl-N-methylcarboxamido,
4-(but-2-ynoyl)-piperazin-1-yl-N-methylcarboxamido, 4-acryloylpiperazin-1-yl-N-methylcarboxamido,
6-oxo-2-(2-chloroacetyl)-2,7-diazaspiro[4.5]decan-7-yl, and
6-oxo-2-acryloyl-2,7-diazaspiro[4.5]decan-7-yl.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein:

R^4 is hydrogen, fluoro, or $-CH_3$; and

R^5 is hydrogen, fluoro,
chloro, -OH, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2F$, $-CHF_2$, CH_2CN, $-CH_2$-cyclopropyl, cyclopropyl, pyridyl, phenyl, or $-CH_2$-phenyl, wherein any phenyl portion of R^5 is optionally substituted with up to 4 substituents independently selected from halo, -CN, and $-O-C_1-C_3$ alkyl; or

R^4 and R^5 are taken together to form $=CH_2$ or cyclopropyl, or cyclobutyl, or cyclopentyl, or cyclohexyl; or

R^5 is taken together with the carbon atom to which it is bound, a ring atom of Q, and X to form oxazepane.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein R^7 is -OH, $-NH_2$, or $-CHF_2$.

19. A compound, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, selected from FIG. 1.

20. A pharmaceutical composition comprising a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, and a pharmaceutically acceptable carrier.

21. A complex comprising a presenter protein, a RAS protein, and a compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 20.

22. Use of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof in ~~A~~a method of producing a complex, the method comprising contacting a presenter protein and a KRAS G12C protein with ~~a~~said compound ~~of any one of claims 1-19~~, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, under conditions suitable to permit complex formation.

~~23. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, or a pharmaceutical composition of claim 20.~~

~~24~~23. Use of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof for ~~A method of~~ inhibiting a KRAS G12C protein in a cell~~, the method comprising contacting the cell with an effective amount of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, or a pharmaceutical composition of claim 20~~.

~~25. A method of treating a KRAS G12C protein-related disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, a pharmaceutical composition of claim 20.~~

~~26~~24. Use of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof for ~~A method of~~ inhibiting RAF-RAS binding in a cell~~, the method comprising contacting the cell with an effective amount of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, or a pharmaceutical composition of claim 20~~.

~~27~~25. Use of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, for treating cancer in a subject in need thereof.

~~28~~26. Use of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, for treating a KRAS G12C protein-related disorder in a subject in need thereof.

~~29~~27. The ~~method or~~ use of any one of claims 22-~~28~~26, wherein the method or use further comprises administering an additional therapeutic agent.

~~30~~28. The ~~method~~use of claim ~~29~~27, wherein the additional therapeutic agent 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 CDK 4/6 inhibitor, or a combination thereof.

29. A compound of any one of claims 1-19, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, for use in therapy.