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 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 another aspect, there is provided the *in vitro* 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 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 another aspect, there is provided the *in vitro* 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, in the manufacture of a medicament for treating cancer in a subject in need thereof.

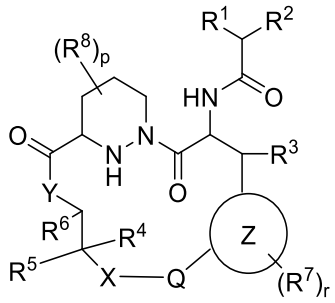
In an example, the disclosure features the use of any a compound of the present disclosure, any pharmaceutical composition comprising such a compound, or any of the complexes described herein for treating a KRAS G12C protein-related disorder in a subject in need thereof.

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, in the manufacture of a medicament for treating a KRAS G12C protein-related disorder in a subject in need thereof.

In an example, the disclosure

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;

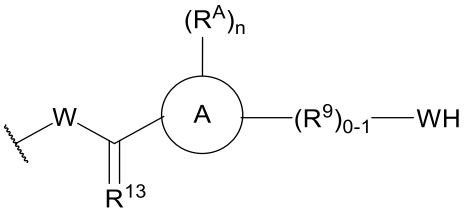
X is a bond; a straight chain C_1-C_3 alkylene optionally substituted with 1 to 3 substituents independently selected from fluoro, -CN, -C_1-C_3 alkyl, and -O-C_1-C_3 alkyl; -O-; -S(O)$_{0-2}$-; *-CH_2-O-; *-CH_2-S(O)$_{0-2}$-; *-O-CH_2-; or *-CH_2-S(O)$_{0-2}$-, wherein "*" represents a portion of X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

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

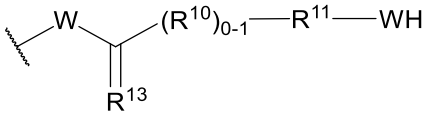
ring Z is phenyl or a 6-membered heteroaryl;

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;

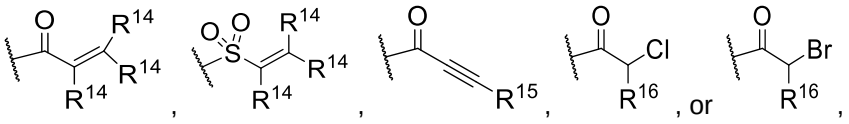
R^{12} is hydrogen, or -C_1-C_3 alkyl, or

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 ;

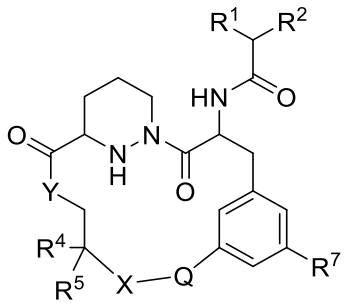
each R^8 is independently halo, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

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,

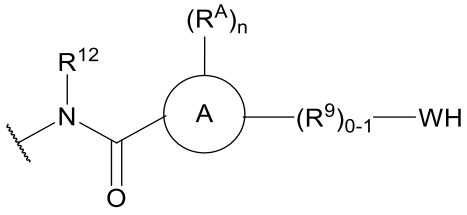
wherein:

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 $C(R^4)(R^5)$;

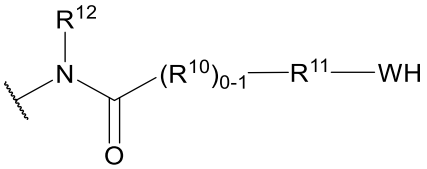
Y is -O- or -NH-;

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;

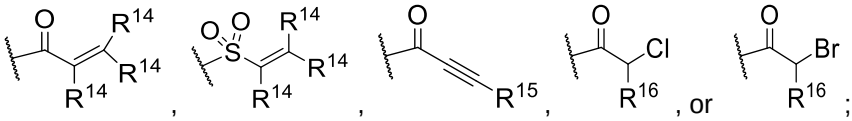
R^{10}, if present, is C_1-C_4 alkylene optionally substituted with one or more substituent independently selected from halo, -CN, -OH, -C_1-C_3 alkyl, and -O-C_1-C_3 alkyl;

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:

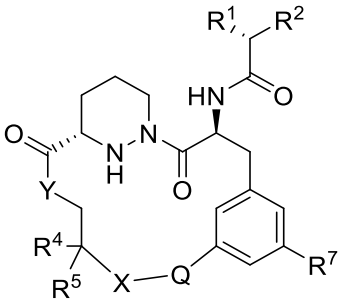
a first ring in Q is bonded to X, and a second ring in Q is bonded Z; and

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

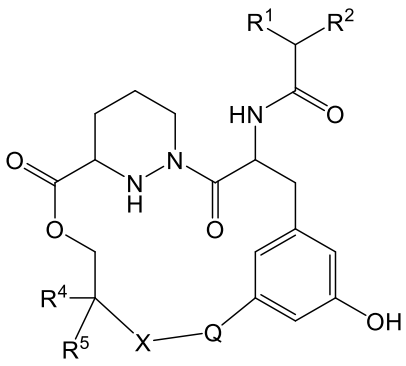
two substituents on the same or adjacent ring atoms of Q are taken together to form a 5-7 membered monocyclic ring or a 6-12 membered bicyclic ring optionally substituted with one or more independently selected halo, =O, -CN, C_1-C_3 alkyl, or -O-C_1-C_3 alkyl; and fused to Q.

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

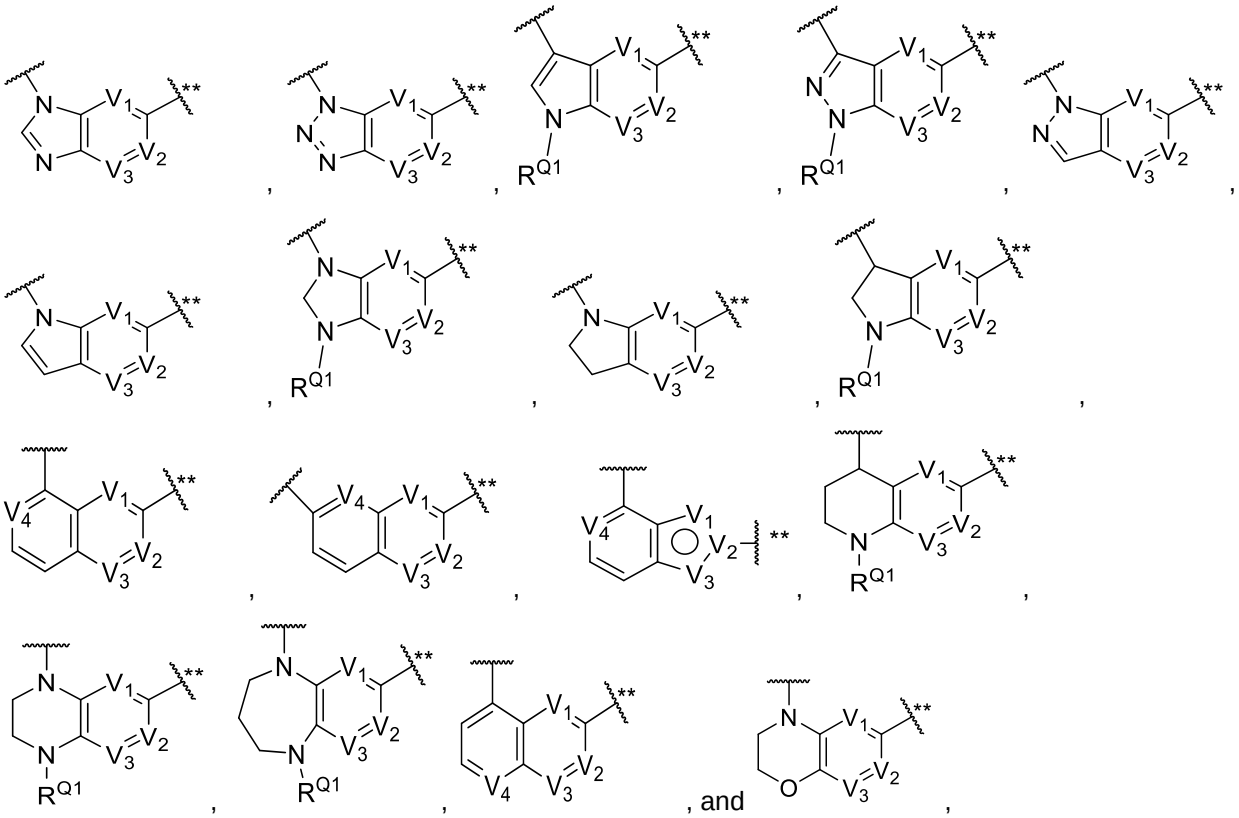
said compound has the structure of formula (Ic):



(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;

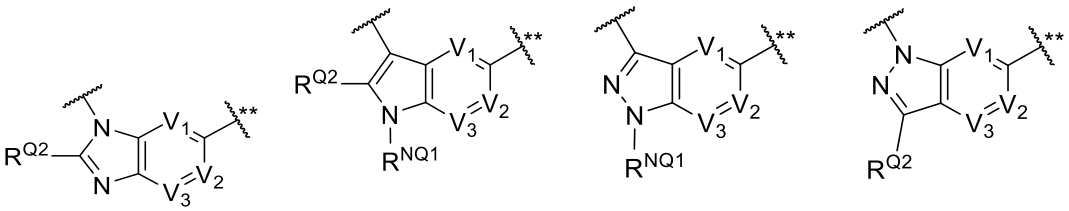
R^{Q1} is $-S(O)_2-R^{Q11}$, $-C(O)-R^{Q11}$, $-S(O)_2-N(R^{Q11})R^{Q12}$, $-C(O)-N(R^{Q11})R^{Q12}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, a 4-14 membered heterocyclyl, aryl, or heteroaryl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted; or

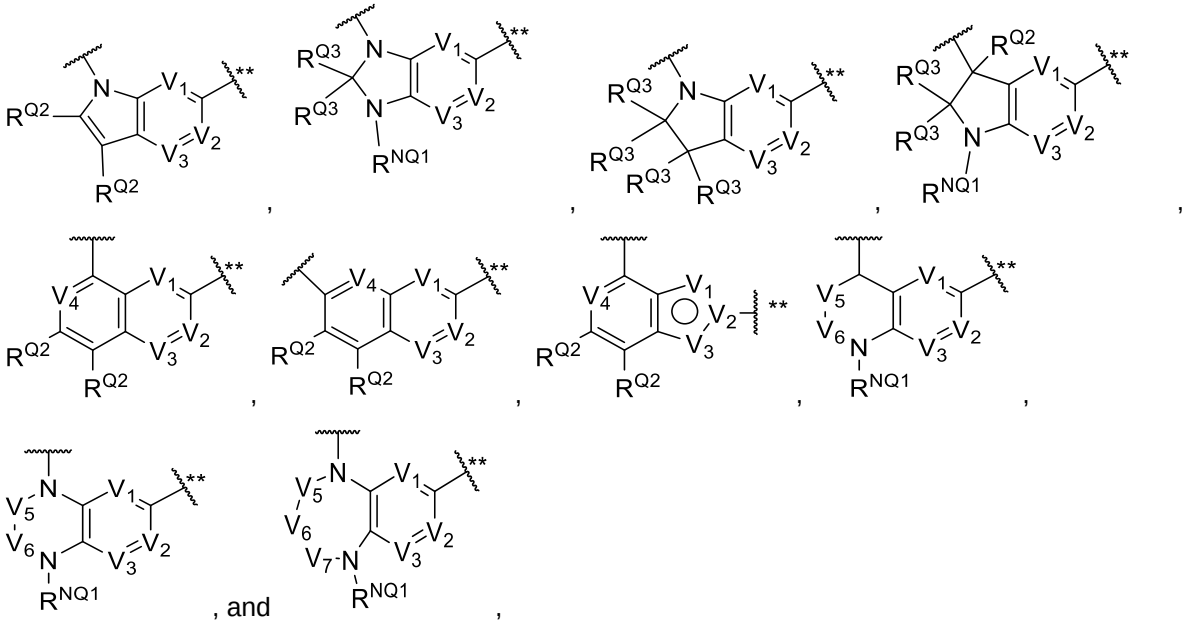
R^{Q1} is taken together with the nitrogen atom to which it is attached and an adjacent ring atom to form an optionally substituted 4-8 membered ring, which is optionally further fused to a 5-6 membered ring;

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

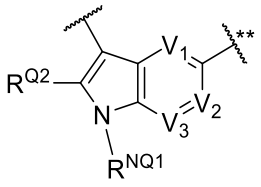
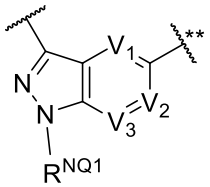
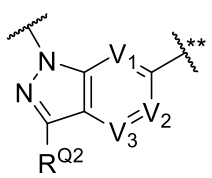
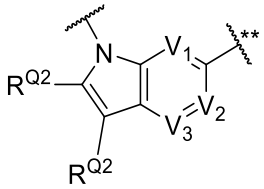
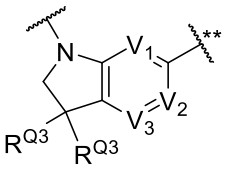
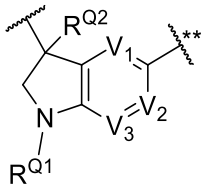
R^{NQ1} and one R^{Q3} are taken together with the atoms to which they are bound to form an optionally substituted 4-8 membered ring, wherein the ring formed by taking R^{NQ1} and R^{Q3} together is optionally further fused to a 5-6 membered ring;

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

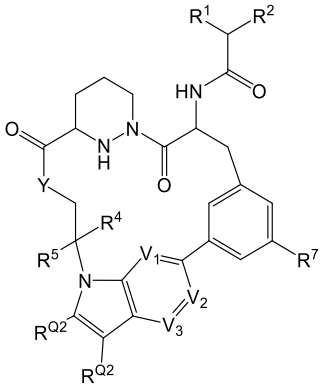
R^{Q11} and R^{Q12} are taken together with the atoms to which they are attached to form an optionally substituted 4-8 membered ring, wherein the ring formed by taking R^{Q11} and R^{Q12} together is optionally fused to another 5-6 membered ring; and

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

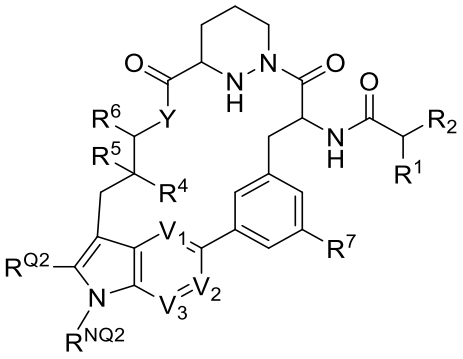
7. The compound of claim 6, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein Q is selected from the group consisting of:


,

,

,

,

, and

.

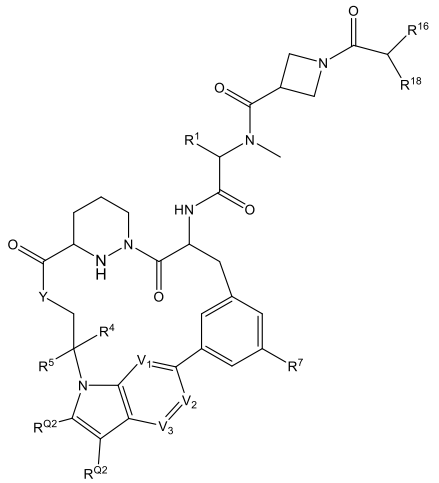
8. The compound of claim 7, wherein said compound has the structure of formula (Id):


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

said compound has the structure of formula (Ij):

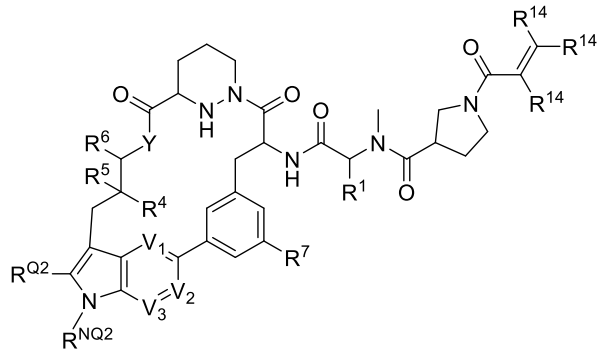

(Ij), a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof.

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



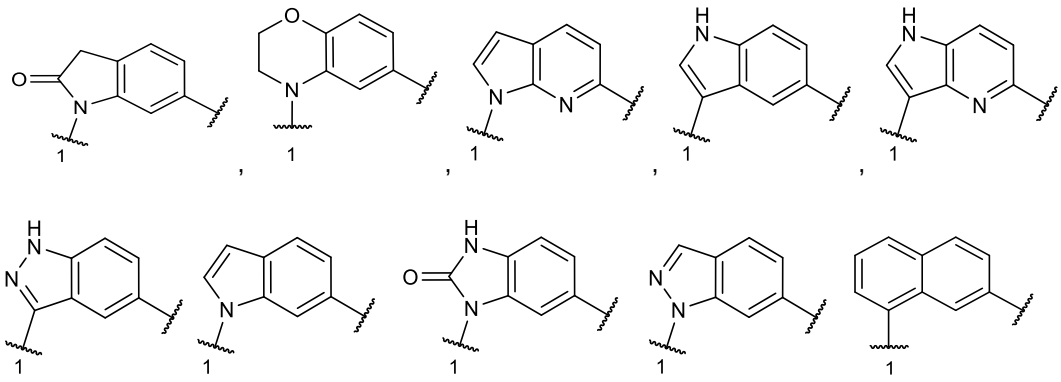
(IL), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein R^{18} is Br or Cl or

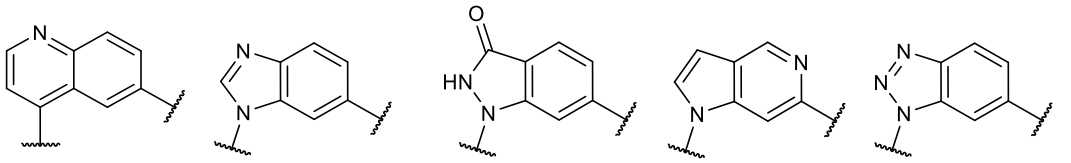
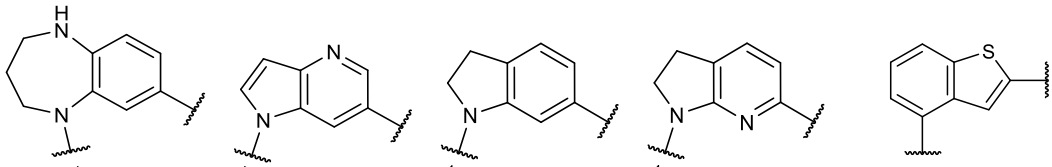
said compound has the structure of formula (Im):



(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:



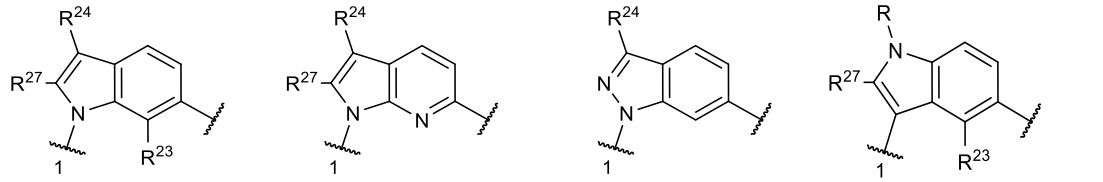
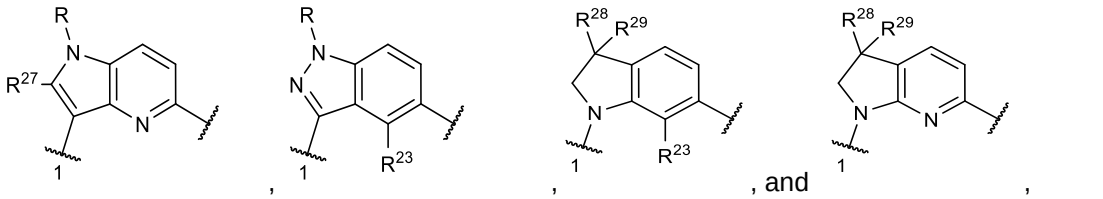


and ,

wherein:

"1" indicates a portion of Q bound to X; and

Q is further optionally substituted.

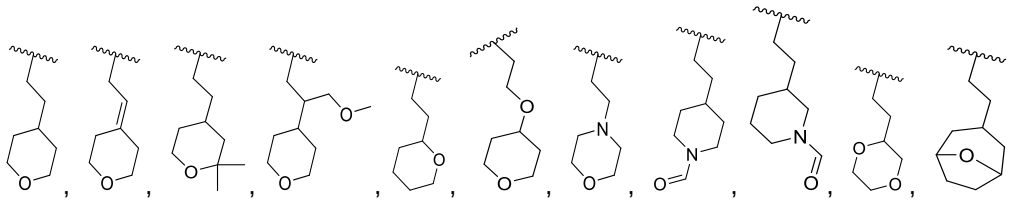
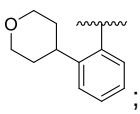
11. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein Q is selected from the group consisting of:



, and ,

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

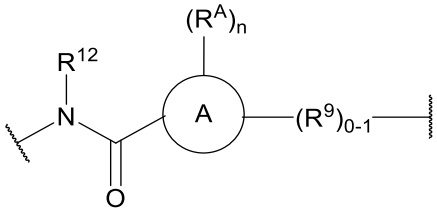
R^{29} is hydrogen, acetyl, CN, $-CH_2-CN$, $-CH_2-CH_2-CN$, $-CH_2-O-CH_3$, $-CH=CH-CN$, $-CH_2-O-C(O)-N(CH_3)_2$, morpholin-4-ylmethyl, pyrazol-1-ylmethyl, pyridin-3-yl, pyridin-3-ylethynyl, pyridin-2-yloxymethyl, or 2-cyanopropan-2-yl, or

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.

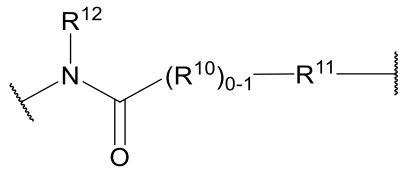
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein R^1 is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl,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

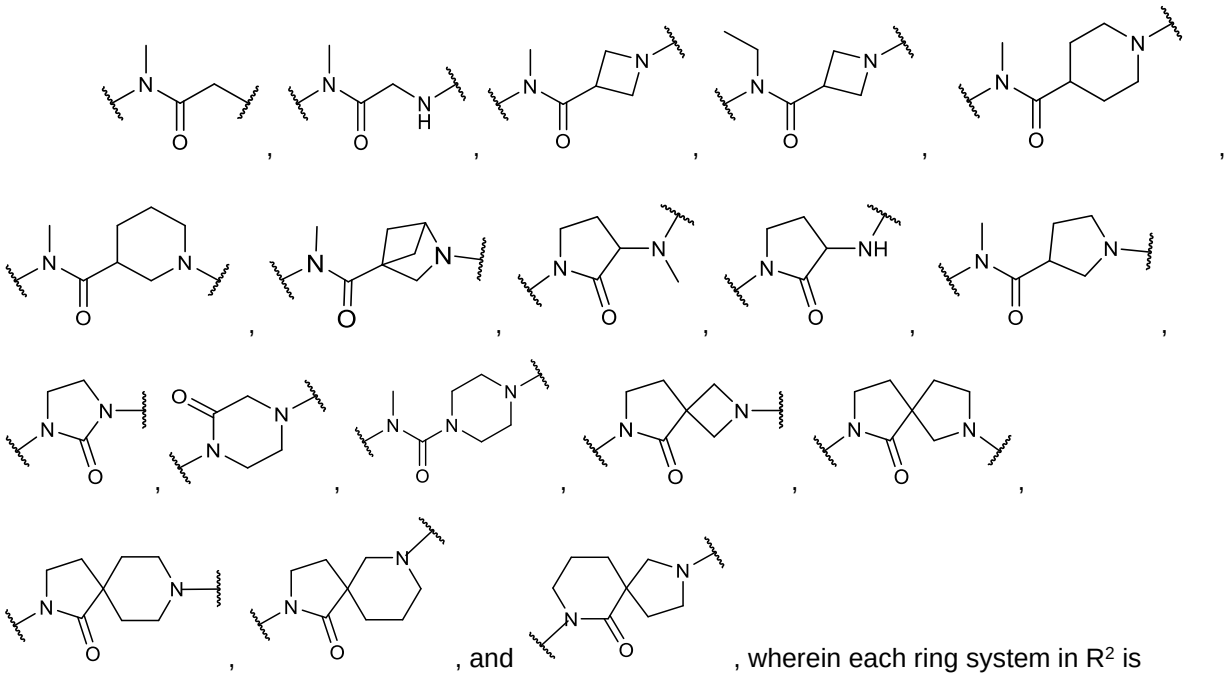
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein the portion of R^2 represented by:



or



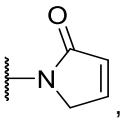
is selected from the group consisting of:

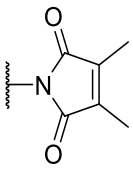


, and , wherein each ring system in R^2 is optionally substituted with up to 4 substituents independently selected from fluoro; chloro; -CN; -OH; $-NH_2$; $-C_1$-C_3 alkyl optionally substituted with CN, OH, NH_2 or $-O-C_1$-C_3 alkyl; $-O-C_1$-C_3 alkyl; and $-NH-C_1$-C_3 alkyl.

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 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.

23. An *in vitro* 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 inhibiting a KRAS G12C protein in a cell.

24. An *in vitro* 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 inhibiting RAF-RAS binding in a cell.

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, in the manufacture of a medicament for treating cancer in a subject in need thereof.

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, in the manufacture of a medicament for treating a KRAS G12C protein-related disorder in a subject in need thereof.

27. The use of any one of claims 22-26, wherein the use further comprises an additional therapeutic agent to be administered.

28. The use of claim 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.