COMPOUNDS THAT PARTICIPATE IN COOPERATIVE BINDING AND USES THEREOF

Cross-reference to Related Applications

This application claims benefit of U.S. Provisional Application Nos. 62/783,816, filed December 21, 2018, 62/894,493, filed August 30, 2019, and 62/930,489, filed November 4, 2019, each of which is hereby incorporated by reference.

Background

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

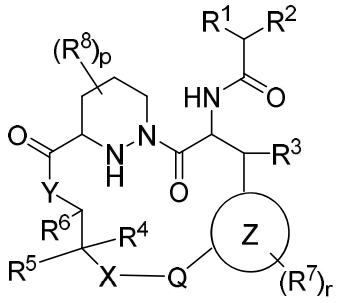
It has been well established in literature that RAS proteins (KRAS, HRAS and NRAS) play an essential role in various human cancers and are therefore appropriate targets for anticancer therapy. Dysregulation of RAS proteins by activating mutations, overexpression or upstream activation is common in human tumors, and activating mutations in RAS are found in approximately 30% of human cancer. Of the RAS proteins, KRAS is the most frequently mutated and is therefore an important target for cancer therapy. Despite extensive small molecule drug discovery efforts against RAS during the last several decades, a drug directly targeting RAS is still not available for clinical use.

Covalent drugs bond covalently to their biological target. Covalent drugs have a long history in medicine and will continue to impact drug discovery and human health into the future. Biological targets with nucleophilic reactive groups such as -SH, -OH, -NH_2, -COOH and others are potentially amenable to a covalent drug discovery approach.

Summary

The present dislcosure features compounds (e.g., macrocyclic compounds) of Formula I capable of modulating biological processes, for example through binding to a presenter protein that is a member of the cyclophilin A ("CYPA") family and a target protein that is a mutated RAS protein in which the mutation replaces an amino acid in the wild-type amino acid sequence with a cysteine, e.g., KRAS G12C, KRAS G13C, NRAS G12C, NRAS G13C, HRAS G12C and HRAS G13C. In some examples, provided compounds may be useful in the treatment of diseases and disorders in which the above-described RAS mutants play a role, such as cancer.

In an aspect, there is provided 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;

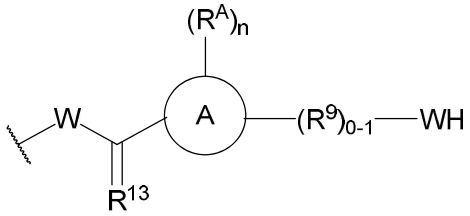
X is a bond; a straight chain C_1-C_3 alkylene optionally substituted with 1 to 3 substituents independently selected from fluoro, -CN, -C_1-C_3 alkyl, and -O-C_1-C_3 alkyl; -O-; -S(O)$_{0-2}$-; *-CH_2-O-; *-CH_2-S(O)$_{0-2}$-; *-O-CH_2-; or *-CH_2-S(O)$_{0-2}$-, wherein "*" represents a portion of X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

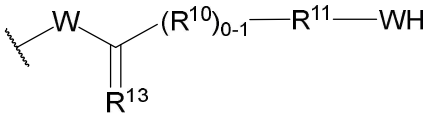
Y is -O-, -NH-, or -N(C_1-C_3 alkyl)-;

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;

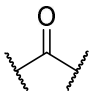
W is -N(R^{12})-, -O-, or -C(R^{12a})(R^{12b})-;

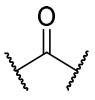
each R^A is each independently fluoro; chloro; -CN; -OH; -NH_2; -C_1-C_3 alkyl optionally substituted with CN, OH, NH_2 or -O-C_1-C_3 alkyl; -O-C_1-C_3 alkyl; or -NH-C_1-C_3 alkyl;

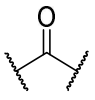
R^9, if present, is -N(C_0-C_5 alkylene-H)-, -N(C(O)-(C_0-C_5 alkylene-H)-, -C(C_0-C_3 alkylene-H)(C_0-C_5 alkylene-H)-, or -C(C_0-C_3 alkylene-H)(C(O)-C_0-C_5 alkylene-H)-, wherein each alkylene portion of R^9 is optionally substituted with one or more substituent, wherein each substituent is, independently, 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^{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 ;

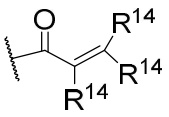
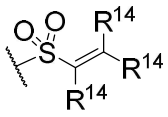
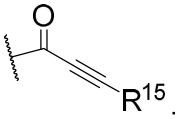
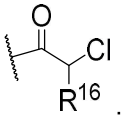
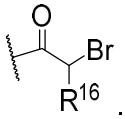
each R^8 is independently halo, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

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.

In some examples Y is -O-. In some examples, Y is -NH-. In some examples, Y is -N(C_1-C_3 alkyl)-.

In some examples, WH is . In some examples, WH is . In some examples, WH is . In some examples, WH is . In some examples, WH is .

In some examples, Z is phenyl or pyridyl. In some examples, Z is phenyl. In some examples, Z is 3-hydroxyphen-1,5-diyl. In some examples, Z is 6-membered hyeteroaryl. In some examples, Z is pyridyl.

In some examples, n is 0. In some examples, n is 1. In some examples, n is 2. In some examples, n is 3. In some examples, n is 4. In some examples, n is 5. In some examples, n is 6.

In some examples, p is 0. In some examples, p is 1. In some examples, p is 2. In some examples, p is 3.

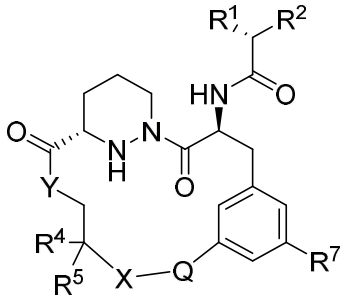
In some examples, r is 0. In some examples, r is 1. In some examples, r is 2. In some examples, r is 3. In some examples, r is 4.

In some examples, R^3 is H. In some examples, R^3 is halogen. In some examples, R^3 is C_1-C_3 alkyl. In some examples, R^3 is C_1-C_3 hydroxyalkyl.

In some examples, X is -CH_2-. In some examples, X is a bond.

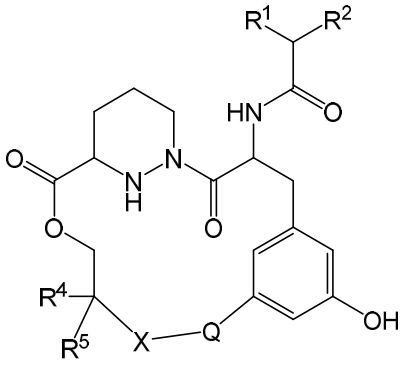
In some examples, the compound has the structure of formula (Ia):

In some examples, the compound has the structure of formula (Ib):



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

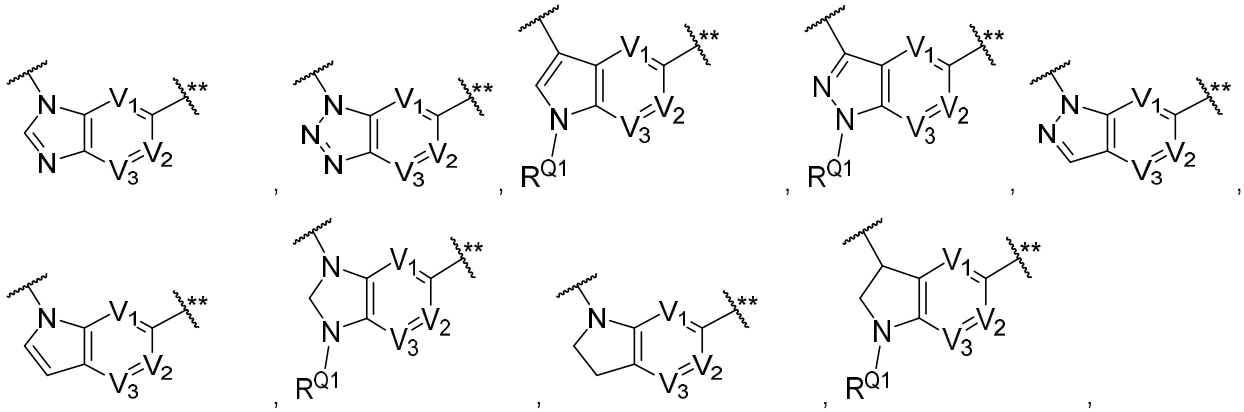
In some examples, the compound has the structure of formula (Ic):

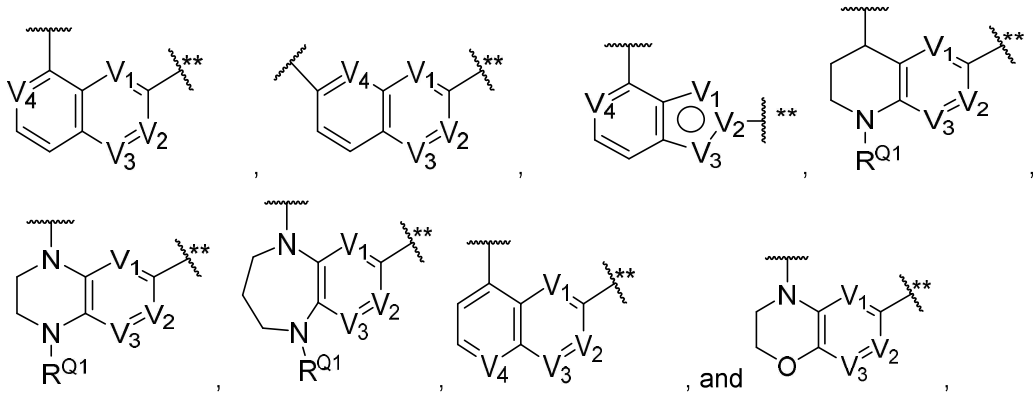


(Ic), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof.

In some examples, Q is a 5,6 bicyclic heteroarylene, a 5,6 bicyclic heterocyclylene, a 6,6 bicyclic heteroarylene, or a 6,6 bicyclic heterocyclylene; and where Q is optionally substituted. In some examples, Q is a 5,6 bicyclic heteroarylene, wherein Q is optionally substituted. In some examples, Q is a 5,6 bicyclic heterocyclylene, wherein Q is optionally substituted. In some examples, Q is a 6,6 bicyclic heteroarylene, wherein Q is optionally substituted. In some examples, Q is a 6,6 bicyclic heterocyclylene, wherein Q is optionally substituted.

In some examples, 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, where 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, where each of R^{Q11} and R^{Q12} is optionally substituted; or

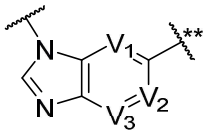
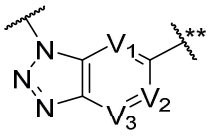
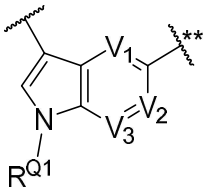
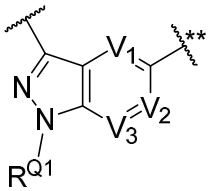
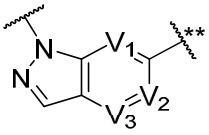
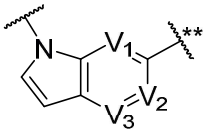
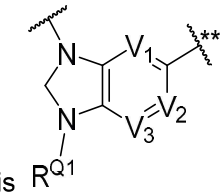
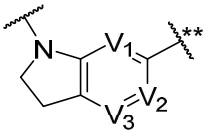
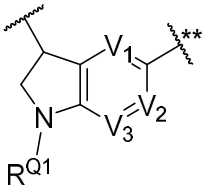
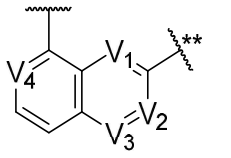
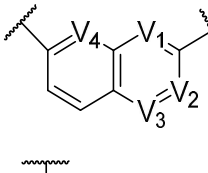
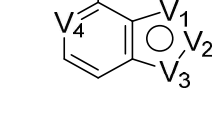
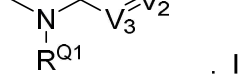
R^{Q11} and R^{Q12} are taken together with the nitrogen atom to which they are both attached to form an optionally substituted 4-8 membered ring, where the ring formed by taking R^{Q11} and R^{Q12} together is optionally fused to another 5-6 membered ring.

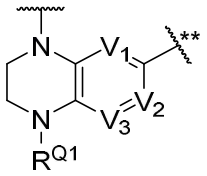
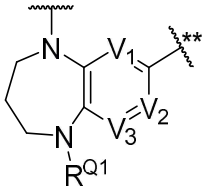
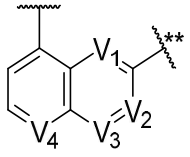
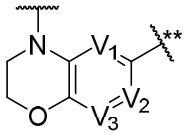
In some examples, Q is optionally additionally substituted with 1 to 4 substituents independently selected from =O; halo; -OH; -CN; -C_1-C_5 alkyl optionally substituted with one or more independently selected halo, CN, OH, -O-(C_1-C_3 alkyl), -C(O)-(C_1-C_3 alkyl), -O-C(O)-N(C_1-C_3 alkyl)$_2$, -O-(C_2-C_3 alkynyl), -(C_3-C_6 cycloalkyl), a 5-6 membered heteroaryl optionally substituted with one or more C_1-C_3 alkyl, 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 optionally substituted with a heteroaryl; $-S(O)_2-C_1-C_3$ 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, -C(O)-O-C_1-C_3 alkyl, C_1-C_3 alkylene-O-C_1-C_3 alkyl, -O-C_1-C_3 alkyl, NO_2, -C(O)-saturated heterocyclyl, $-CH_2$-saturated heterocyclyl, -O-saturated heterocyclyl, O-cycloalkyl, or -O-aryl; $-CH_2$-O-heteroaryl, -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 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; and

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

In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is


. In some examples, Q is 
. In some examples, Q is 
. In some examples, Q is 
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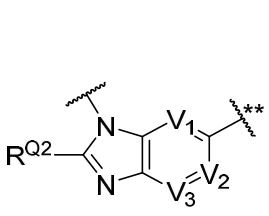
In some examples, Q is optionally additionally substituted with 1 to 4 substituents independently selected from chloro, fluoro, -CN, $-CH_3$, $-CF_3$, $-CHF_2$, $-CH_2CH_3$, $-CH_2$-CN, $-(CH_2)_2$-CN, $-OCH_3$, $-CH_2-O-CH_3$, $-(CH_2)_2-O-CH_3$, $-CH_2-O-CH_2$-CN, -CH(CN)-CH_3, $-C(O)-N(CH_3)_2$, -C(O)-NH-CH_3, $-C(O)-CH_3$, $-S(O)_2CH_3$, $-C(CH_3)=N-O-CH(CH_3)_2$, $-C(CH_3)=N-O-CH_3$, $-C\equiv C-CH_3$, -C≡CH, -CH=CH-CN, $-CH_2-O-CH_2-C\equiv CH$, $-C(CH_3)(CN)CH_2CN$, $-CH_2-O-C(O)-N(CH_3)_2$, 1-(cyclopentyl)-1-cyanoethan-1-yl, 1-(tetrahydrofuran-3-yl)-1-cyanoethan-1-yl, 1-(tetrahydropyran-4-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-methylpiperidin-4-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-5-yl, (1-methylpyrazol-4-yl)cyanomethyl, 1-oxoindolin-5-yl, 1-oxoisoindolin-4-yl, 1-oxoisoindolin-6-yl, 2-(2-methoxyethan-1-yl)phenyl, 3-(1,1-dioxothiomorpholin-1-ylmethyl)phenyl, 2-(tetrahydropyran-4-yloxy)phenyl, 2,2-difluoro-benzo[d][1,3]dioxol-4-yl, 2-chlorophenyl, 2-cyano-2-tetrahydrofuran-3-ylpropanyl, 2-cyano-3-chlorophenyl, 2-cyano-3-fluorophenyl, 2-cyano-3-methoxyphenyl, 2-cyano-4-fluorophenyl, 2-cyano-4-chlorophenyl, 2-cyano-4-methoxybutan-2-yl, 2-cyano-5-chlorophenyl, 2-cyano-5-fluorophenyl, 2-cyano-5-methoxyphenyl, 2-cyano-5-(methoxymethyl)phenyl, 2-cyano-6-chlorophenyl, 2-cyano-6-fluorophenyl, 2-cyano-6-bromophenyl, 2-cyano-6-(methoxymethyl)phenyl, 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-(methoxymethyl)phenyl, 2-nitrophenyl, 2-oxopyrrolidin-1-yl, 2-phenoxyphenyl, 3-(2-methoxyethan-1-yl)phenyl, 3-methoxycarbonylphenyl, 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-methoxyphenyl, 3-methoxymethyl-5-methylisoxazol-4-yl, 3-oxo-2-methylbutan-2-yl, 3-(tetrahydropyran-4-yl)-2-cyanopropan-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, morpholin-4-ylmethyl, N-methoxycyclopropanecarbimidoyl, phenyl, pyrazol-1-ylmethyl, pyridin-2-yl, pyridin-2-ylmethyl, pyridin-2-yloxymethyl, pyridin-3-yl, pyridin-3-yl-ethynyl, pyridin-3-ylmethyl, pyridin-4-ylmethyl, pyridin-4-yl-ethynyl, tetrahydrofuran-3-ylmethyl, tetrahydrofuran-3-ylcyanomethyl, tetrahydropyridin-4-yl,

tetrahydropyran-4-ylmethyl, 2-(tetrahydropyran-4-yl)ethan-1-yl, tetrahydropyran-4-ylcyanomethyl, or tetrahydropyran-4-yl, or

two substituents attached to the same carbon atom are taken together to form =O, 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-6,6-diyl, or tetrahydropyran-4,4-diyl, or

two substituents attached to adjacent carbon atoms 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.

In some examples, Q is selected from the group consisting of: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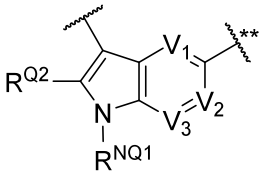
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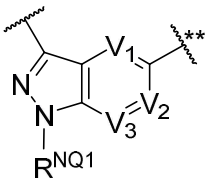
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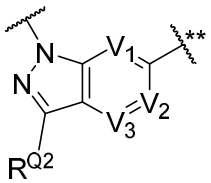
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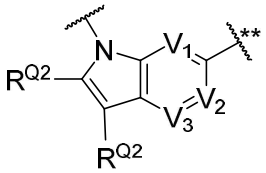
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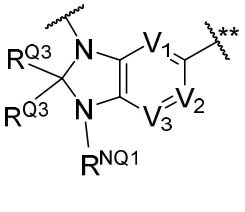
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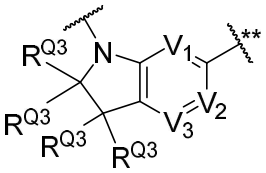
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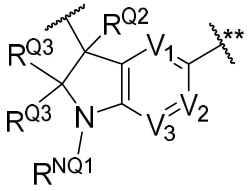
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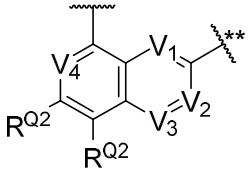
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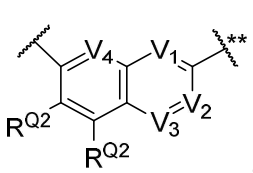
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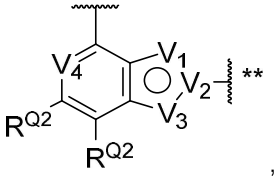
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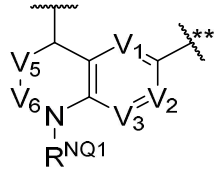
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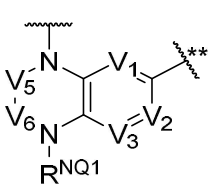
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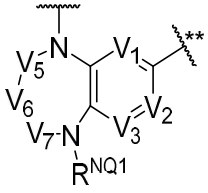
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wherein:

each of V_1, V_2, V_3 and V_4 is independently 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), where 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, where 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, where 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, where 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, where 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, where the ring formed by taking each R^{Q3} together is optionally further fused to a 5-6 membered ring; or

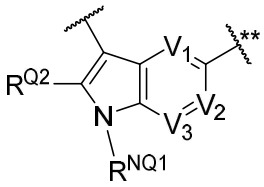
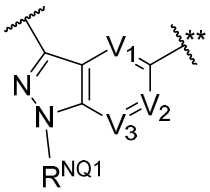
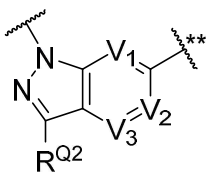
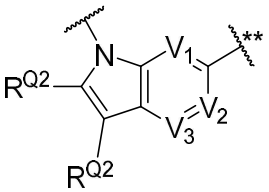
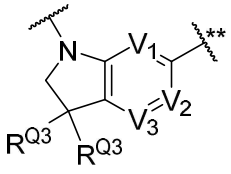
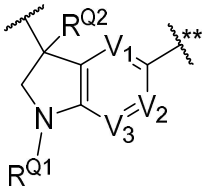
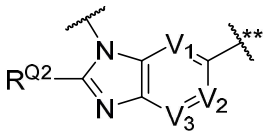
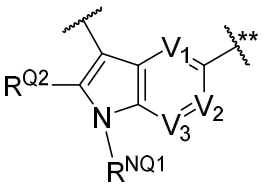
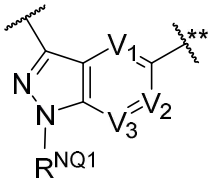
R^{NQ1} and one R^{Q3} are taken together with the atoms to which they are bound to form an optionally substituted 4-8 membered ring, where the ring formed by taking R^{NQ1} and R^{Q3} together is optionally further fused to a 5-6 membered ring;

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, where each of R^{Q11} and R^{Q12} is optionally substituted; or

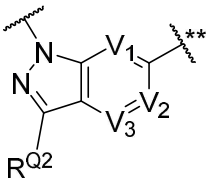
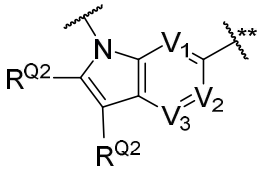
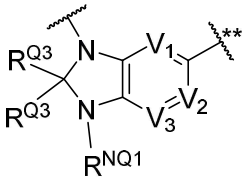
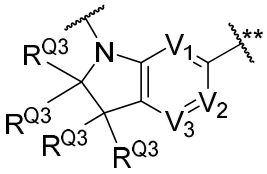
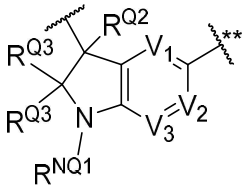
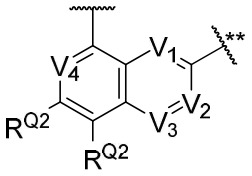
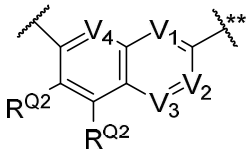
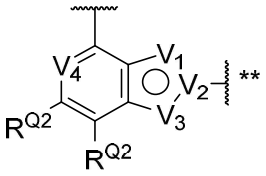
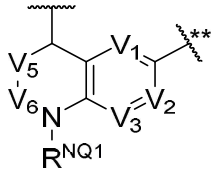
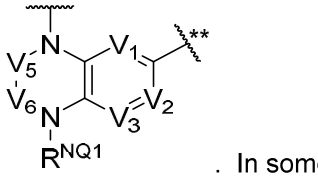
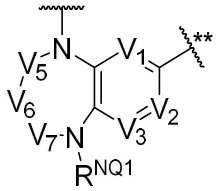
R^{Q11} and R^{Q12} are taken together with the atoms to which they are attached to form an optionally substituted 4-8 membered ring, where the ring formed by taking R^{Q11} and R^{Q12} together is optionally fused to another 5-6 membered ring; and

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

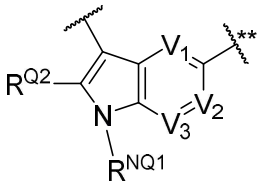
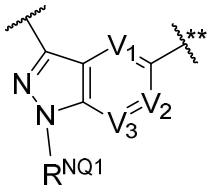
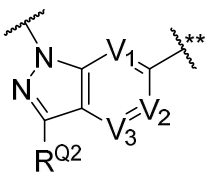
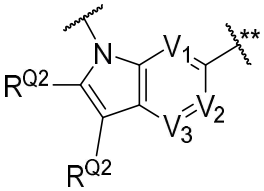
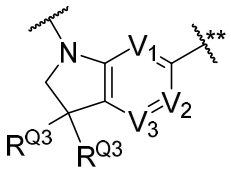
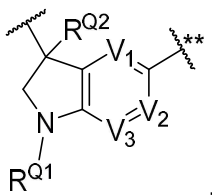
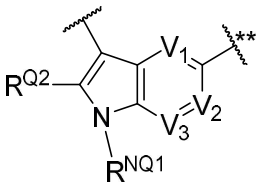
In some examples, Q is

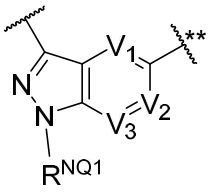
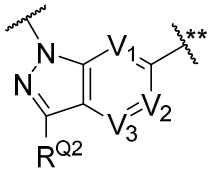
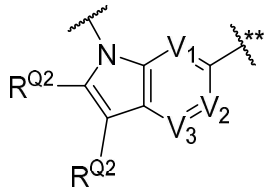
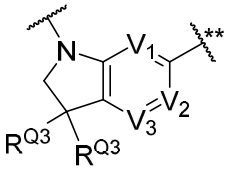
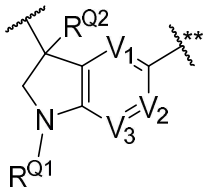










examples, Q is . In some examples, Q is . In some examples, Q is . In

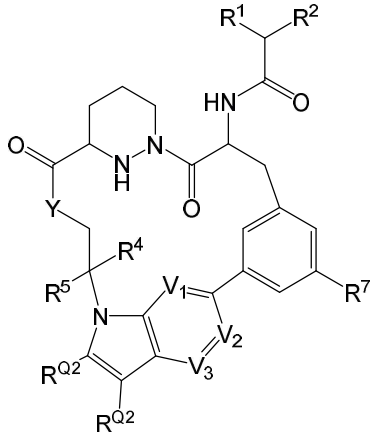
some examples, Q is  . In some examples, Q is  . In some examples, Q is  . In some examples, Q is  . In some examples, Q is  . In some examples, Q is  . In some examples, Q is  . In some examples, Q is  . In some examples, Q is  . In some examples, Q is  . In some examples, Q is . In some examples, Q is . In some examples, Q is  .

In some examples, Q is selected from the group consisting of:

 ,  ,  ,  ,  , and  . In some examples, Q is  . In

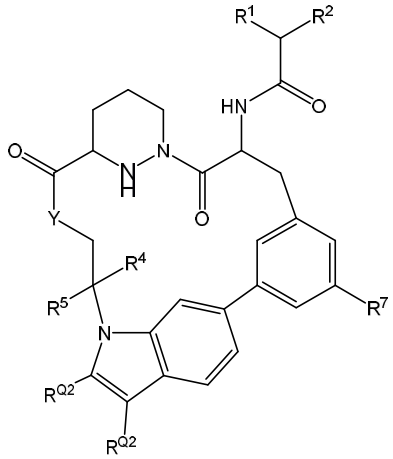
some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is .

In some examples, the compound has the structure of formula (Id):



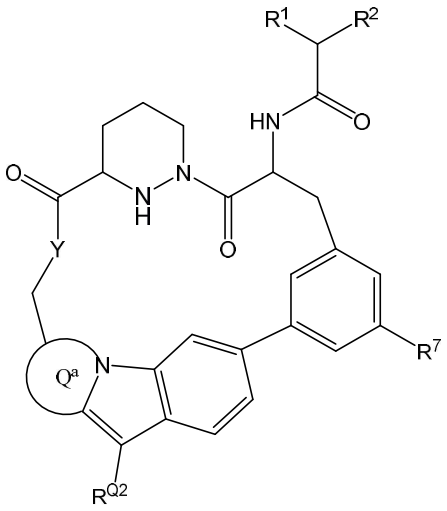
(Id), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof.

In some examples, the compound has the structure of formula (Ie):



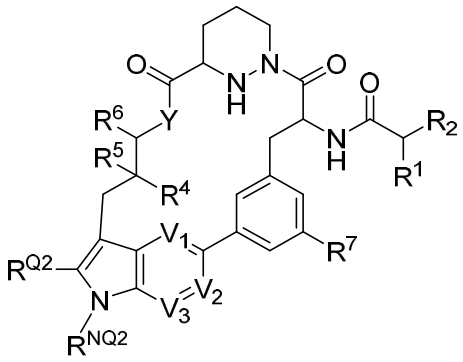
(Ie), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof.

In some examples, the compound has the structure of formula (Ig):



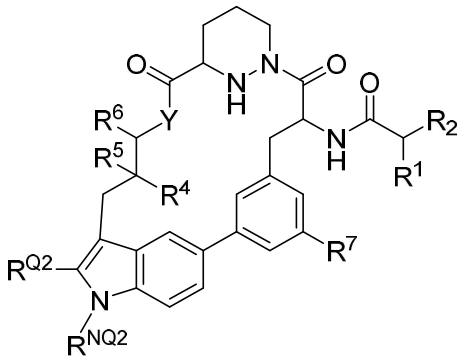
(Ig), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, where Q^a is a 4-9 membered saturated heterocyclyl.

In some examples, the compound has the structure of formula (Ij):



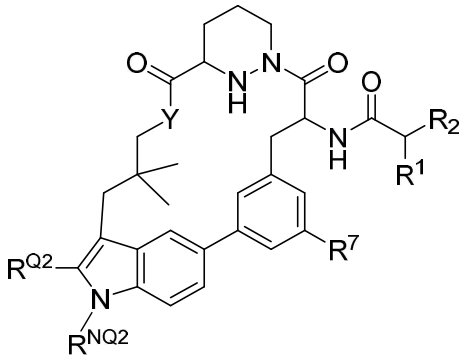
(Ij), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, where Q^a is a 4-9 membered saturated heterocyclyl.

In some examples, the compound has the structure of formula (Ik):



(Ik), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, where Q^a is a 4-9 membered saturated heterocyclyl.

In some examples, the compound has the structure of formula (Ik'):

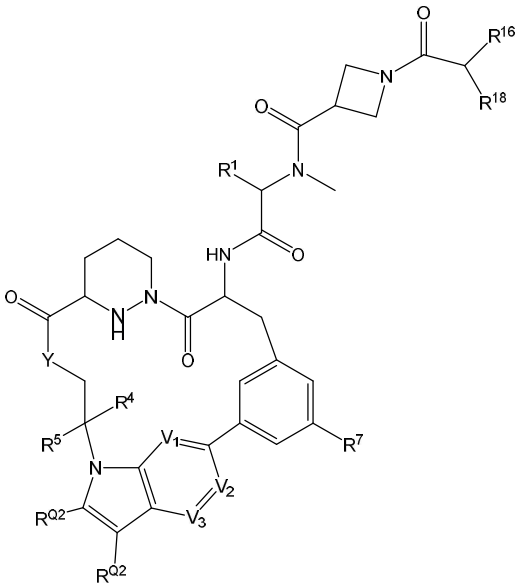


(Ik'), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, where Q^a is a 4-9 membered saturated heterocyclyl.

In some examples, R^9 is absent and ring A is a 4-8 membered heterocyclyl; or R^{11} is -N(C_0-C_5 alkylene-H)-, or -N(C(O)-(C_0-C_5 alkylene-H)-, where 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.

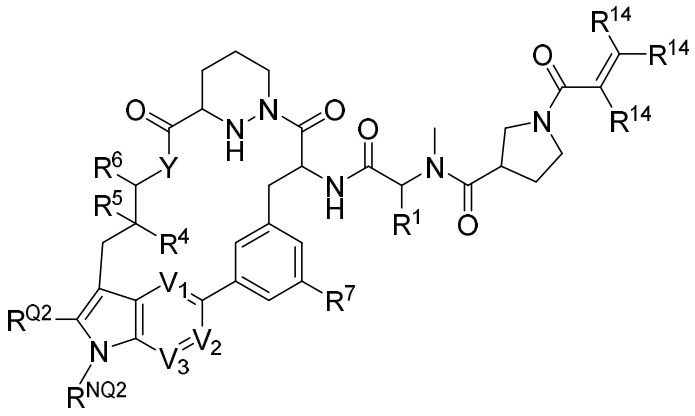
In some examples, W is -N(R^{12})-; and R^{13} is =O.

In some examples, the compound has the structure of formula (IL):



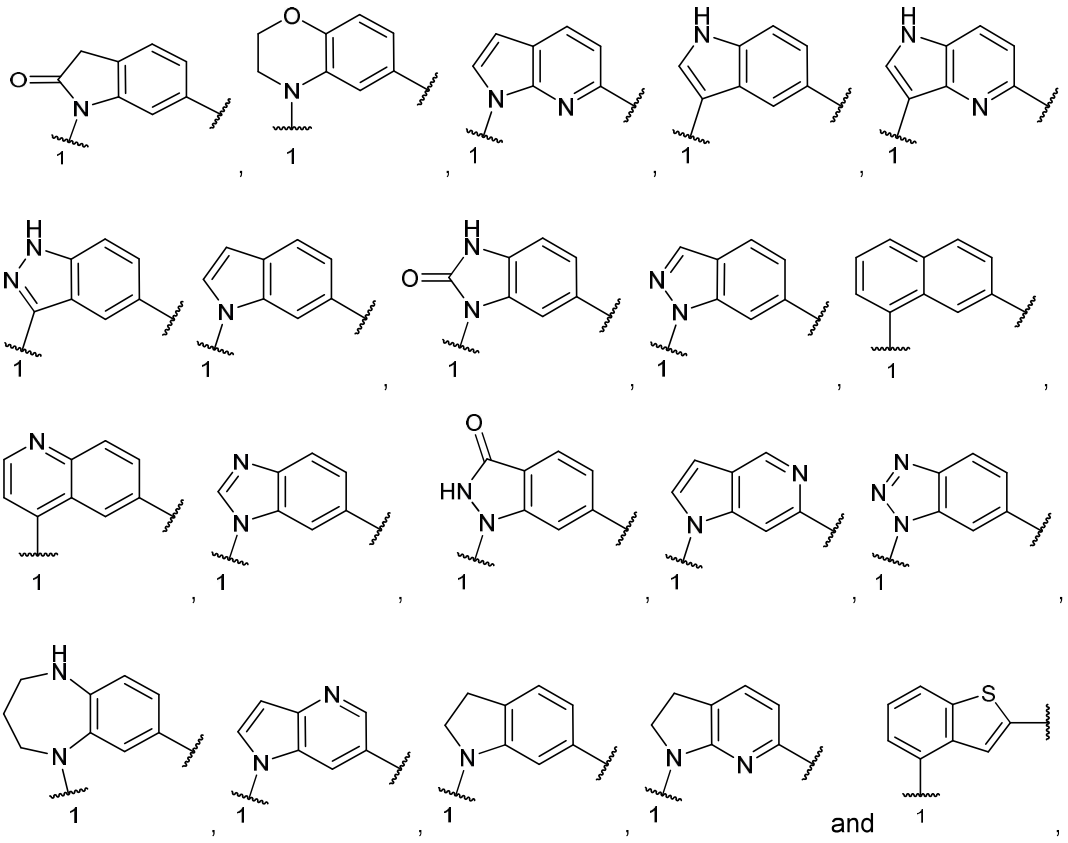
(IL), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, where R^{18} is Br or Cl.

In some examples, the compound has the structure of formula (Im):



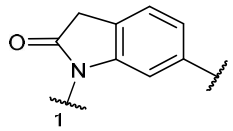
(Im), or a pharmaceutically acceptable salt, an enantiomer, a stereoisomer, or a tautomer thereof, wherein R^{14} is H.

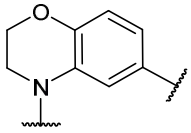
In some examples, Q is selected from the group consisting of:

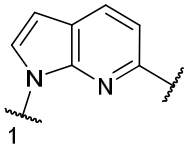


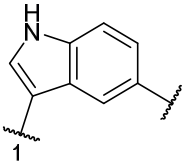
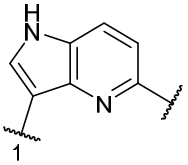
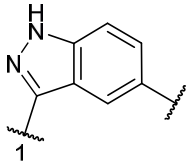
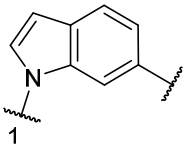
wherein:

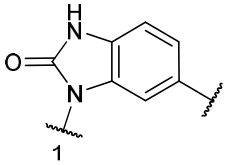
"1" indicates a portion of Q bound to X; and Q is further optionally substituted. In some examples,



Q is . In some examples, Q is  . In some examples, Q is



. In some examples, Q is  . In some examples, Q is  . In some examples, Q is  . In some examples, Q is  . In some examples, Q is



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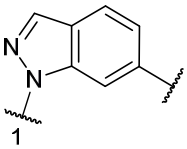
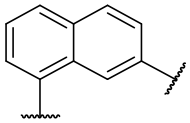
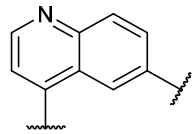
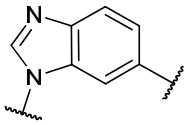
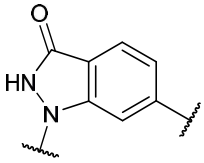
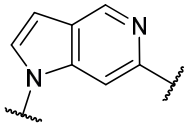
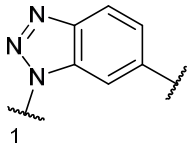
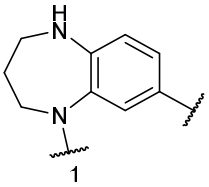
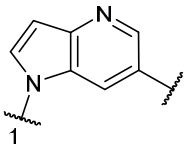
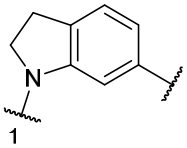
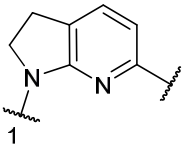
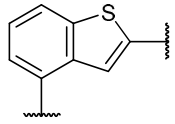
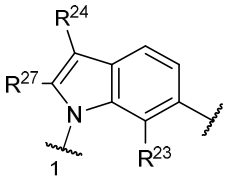
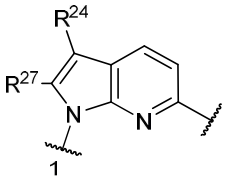
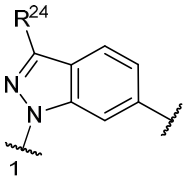
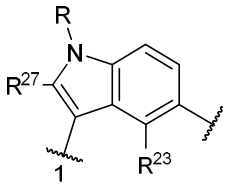
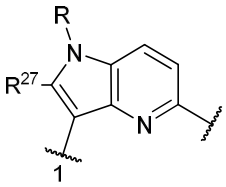
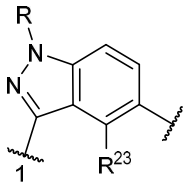
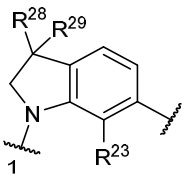
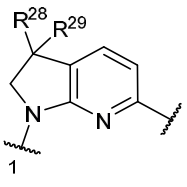
examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is .

In some examples, Q is selected from the group consisting of:

, , , , , , , and ,

wherein:

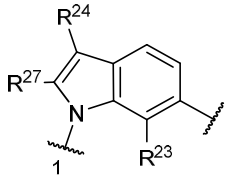
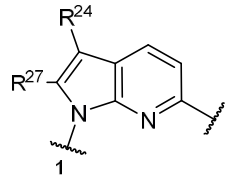
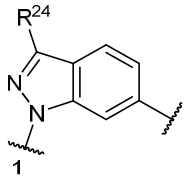
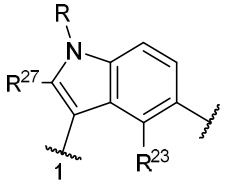
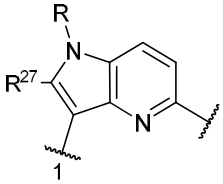
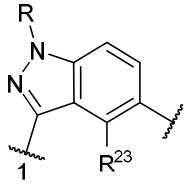
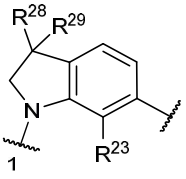
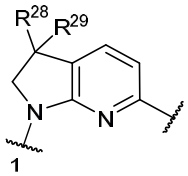
methyl ether, 2-(2-methoxyethyl) benzene, 2-(2-difluoromethoxyethyl)benzene, 2-(2-dimethylmethoxyethyl)benzene, pyridin-3-yl, pyridin-2-yl, pyridin-3-ylmethyl, or tetrahydropyridin-4-yl, or

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

R29 is hydrogen, acetyl,

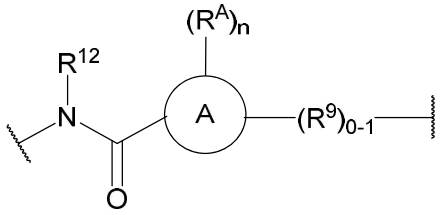
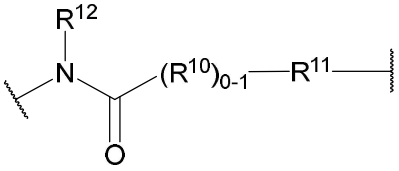
CN, -CH2-CN, -CH2-CH2-CN, -CH2-O-CH3, -CH=CH-CN, -CH2-O-C(O)-N(CH3)2, morpholin-4-ylmethyl, pyrazol-1-ylmethyl, pyridin-3-yl, pyridin-3-ylethynyl, pyridin-2-yloxymethyl, or 2-cyanopropan-2-yl, or

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. In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is . In some examples, Q is .

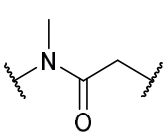
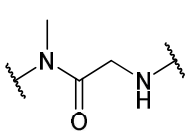
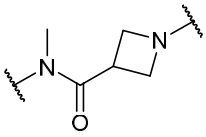
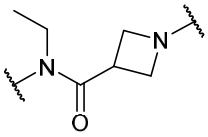
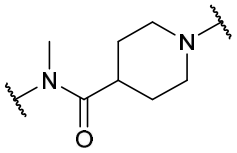
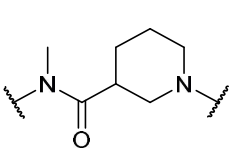
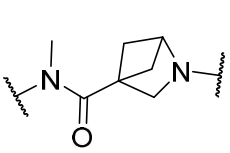
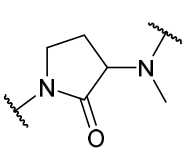
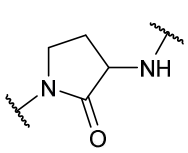
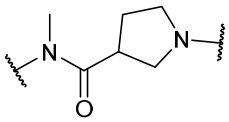
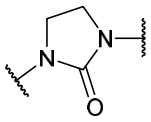
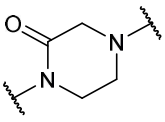
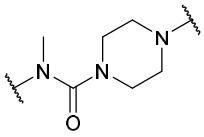
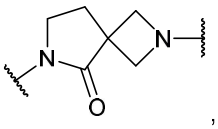
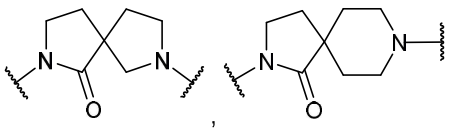
In some examples, R^1 is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, 4-methoxybenzyl, or tetrahydropyran-4-yl.

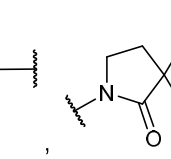
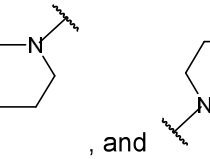
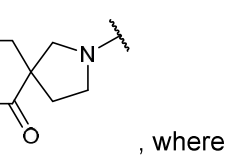
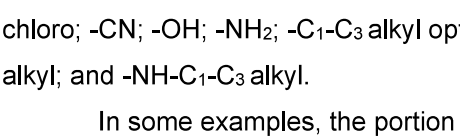
In some examples, R^9 is absent and ring A is a saturated, nitrogen-containing heterocyclyl.

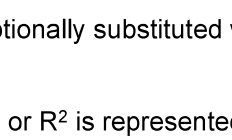
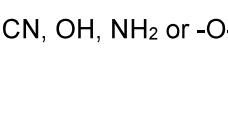
In some examples, the portion of R^2 represented by:

or is selected from the group consisting of:

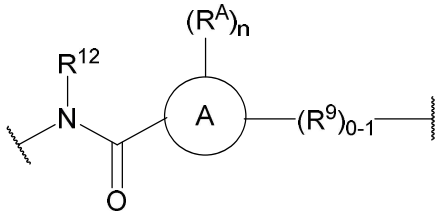
















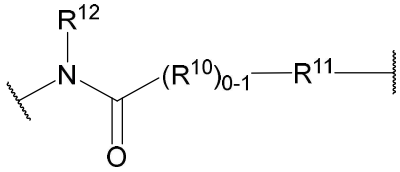



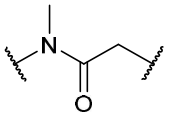
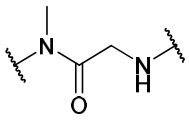
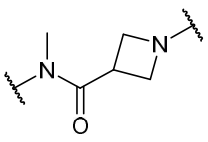
, where each ring system in R^2 is optionally substituted with up to 4 substituents independently selected from fluoro; chloro; -CN; -OH; -NH_2; -C_1-C_3 alkyl optionally substituted with CN, OH, NH_2 or -O-C_1-C_3 alkyl; -O-C_1-C_3 alkyl; and -NH-C_1-C_3 alkyl.

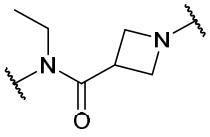
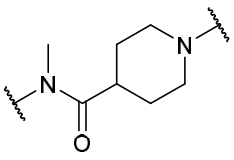
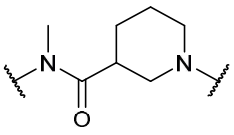
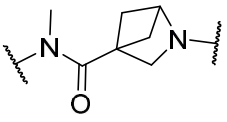
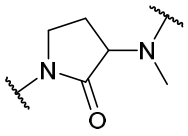
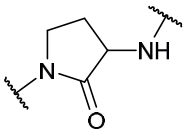
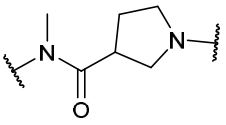
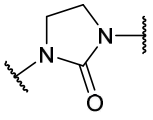
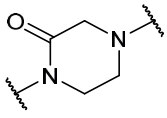
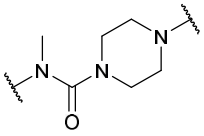
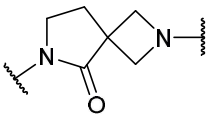
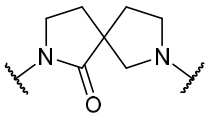
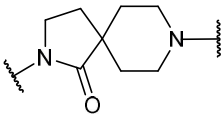
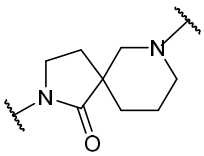
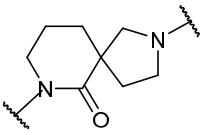
In some examples, the portion or R^2 is represented by

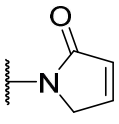
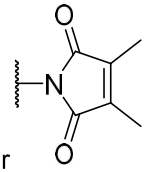


. In some examples, the portion of R^2 is represented by



. In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some

examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is . In some examples, R^2 is .

In some examples, the portion of R^2 represented by WH is -C(O)-C≡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 .

In some examples, 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.

In some examples, 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, 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 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 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 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

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 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.

In some examples, a method may further include administering an additional therapeutic agent (e.g., an anti-cancer agent). In some examples, 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, or a combination thereof.

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

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

Non-limiting examples of such SHP2 inhibitors that are known in the art, include: Chen *et al. Mol Pharmacol*. 2006, *70*, 562; Sarver *et al.*, *J. Med. Chem.* 2017, 62, 1793; Xie *et al.*, *J. Med. Chem.* 2017, 60, 113734; and Igbe *et al.*, *Oncotarget*, 2017, 8, 113734; and PCT applications: WO2015107493; WO2015107494; WO201507495; WO2016203404; WO2016203405; WO2016203406; WO2011022440; WO2017156397; WO2017079723; WO2017211303; WO2012041524; WO2017211303; WO2019051084; WO2017211303; US20160030594; US20110281942; WO2010011666; WO2014113584; WO2014176488; WO2017100279; WO2019051469; US8637684; WO2007117699; WO2015003094; WO2005094314; WO2008124815; WO2009049098; WO2009135000; WO2016191328; WO2016196591; WO2017078499; WO2017210134; WO2018013597; WO2018129402; WO2018130928;

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.

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: