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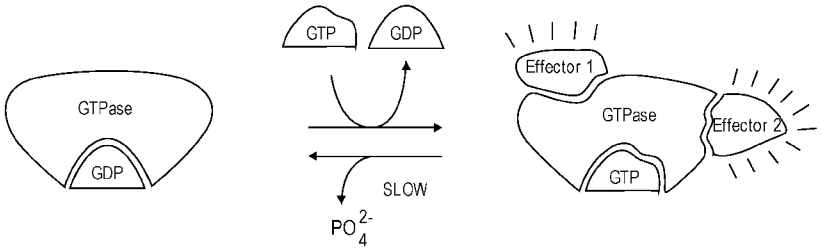

FIG. 1

(57) Abstract: The present disclosure provides inhibitors of Ras protein. Also disclosed are methods to modulate the activity of Ras protein and methods of treatment of disorders mediated by Ras protein.

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SUBSTITUTED QUINAZOLINE COMPOUNDS AND METHODS OF USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/315,532, filed on March 30, 2016, and U.S. Provisional Application No. 62/404,539, filed on October 5, 2016, each incorporated herein by reference in its entirety.

BACKGROUND

[0002] Ras represents a group of closely related monomeric globular proteins of 189 amino acids (21 kDa molecular mass) which are associated with the plasma membrane and which bind either GDP or GTP. Ras acts as a molecular switch. When Ras contains bound GDP it is in the resting or off position and is "inactive". In response to exposure of the cell to certain growth promoting stimuli, Ras is induced to exchange its bound GDP for a GTP. With GTP bound, Ras is "switched on" and is able to interact with and activate other proteins (its "downstream targets"). The Ras protein itself has a very low intrinsic ability to hydrolyze GTP back to GDP, thus turning itself into the off state. Switching Ras off requires extrinsic proteins termed GTPase-activating proteins (GAPs) that interact with Ras and greatly accelerate the conversion of GTP to GDP. Any mutation in Ras which affects its ability to interact with GAP or to convert GTP back to GDP will result in a prolonged activation of the protein and consequently a prolonged signal to the cell telling it to continue to grow and divide. Because these signals result in cell growth and division, overactive Ras signaling may ultimately lead to cancer.

[0003] Structurally, Ras proteins contain a G domain which is responsible for the enzymatic activity of Ras (e.g., guanine nucleotide binding and hydrolysis (GTPase reaction)). It also contains a C-terminal extension, known as the CAAX box, which may be post-translationally modified and is responsible for targeting the protein to the membrane. The G domain is approximately 21-25 kDa in size and contains a phosphate binding loop (P-loop). The P-loop represents the pocket where the nucleotides are bound in the protein; this is the rigid part of the domain with conserved amino acid residues which are essential for nucleotide binding and hydrolysis (Glycine 12, Threonine 26 and Lysine 16). The G domain also contains the so called Switch I (residues 30-40) and Switch II (residues 60-76) regions, both of which are the dynamic parts of the protein which are often represented as the “spring-loaded” mechanism because of their ability to switch between the resting and loaded state. Threonine-35 and glycine-60 form key hydrogen bonds with the γ-phosphate of GTP, which maintain Switch I and Switch II regions, respectively, in their active conformation. After hydrolysis of GTP and release of

phosphate, the regions relax into the inactive GDP conformation.

[0004] The most notable members of the Ras subfamily are HRAS, KRAS and NRAS, mainly for being implicated in many types of cancer. However, there are many other members including DIRAS1; DIRAS2; DIRAS3; ERAS; GEM; MRAS; NKIRAS1; NKIRAS2; NRAS; RALA; RALB; RAP1A; RAP1B; RAP2A; RAP2B; RAP2C; RASD1; RASD2; RASL10A; RASL10B; RASL11A; RASL11B; RASL12; REM1; REM2; RERG; RERGL; RRAD; RRAS; and RRAS2.

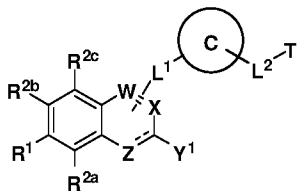
[0005] Mutations in any one of the three main isoforms of RAS (H-Ras, N-Ras, or K-Ras) genes are among the most common events in human tumorigenesis. About 30% of all human tumors are found to carry some mutation in Ras genes. Remarkably, K-Ras mutations are detected in 25-30% of tumors. By comparison, the rates of oncogenic mutation occurring in the N-Ras and H-Ras family members are much lower (8% and 3%, respectively). The most common K-Ras mutations are found at residue G12 and G13 in the P-loop and at residue Q61.

[0006] G12C is a frequent mutation of K-Ras gene (glycine-12 to cysteine). This mutation has been found in about 13% of cancer occurrences, including about 43% of lung cancer occurrences and almost 100% of MYH-associates polyposis (familial colon cancer syndrome). However targeting this gene with small molecules is a challenge.

SUMMARY OF THE INVENTION

[0007] In view of the foregoing, there is a need in the art for small molecules that target Ras (e.g., K-Ras, H-Ras and/or N-Ras) and for use of such compounds in the treatment of various diseases, such as cancer. The present disclosure provides these and other related advantages.

[0008] In certain aspects, the present disclosure provides a compound of Formula (I):



(I), or a salt or prodrug thereof, wherein:

R^1, R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen and R^{50};

W and X are each independently selected from N, NR^5 and CR^6;

Z is selected from bond, N, and CR^6;

Y^1 is selected from $-OR^{55}$; and alkyl, alkenyl, alkynyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with $-OR^{55}$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, -

$C(NR^{51})N(R^{51})$-, -$N(R^{51})C(NR^{51})N(R^{51})$-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})S(O)$-, -$S(O)N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, -$N(R^{51})S(O)N(R^{51})$-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

----indicates a single or double bond such that all valences are satisfied;

R^5 is independently selected at each occurrence from R^{51};

R^6 is independently selected at each occurrence from hydrogen, R^{50}, and a bond to L^1;

R^{50} is independently selected at each occurrence from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -

$NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{55} is selected from:

alkyl, alkenyl, and alkynyl, each of which is independently optionally

substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{55} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

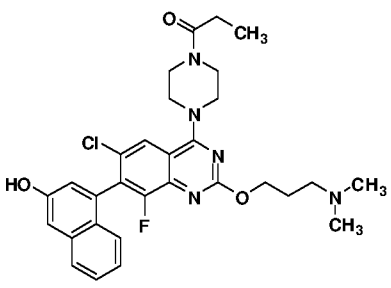
R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl$)$, $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl$)$, $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH);

wherein one of W, X and Z is CR^6 where R^6 is a bond to L^1; and

wherein the compound of Formula (I) is not:



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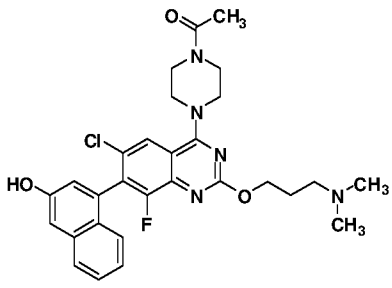

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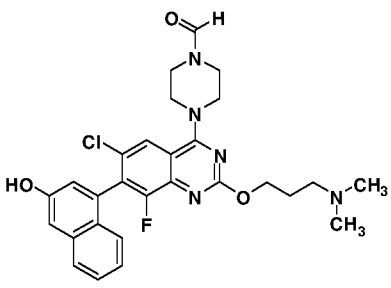

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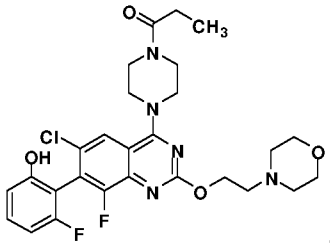
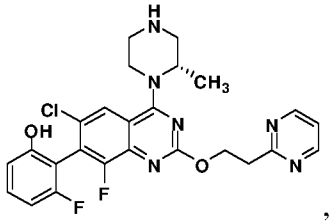
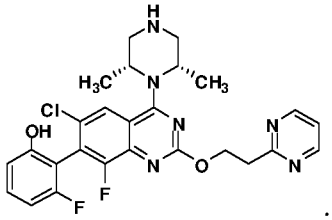

, 
, or 
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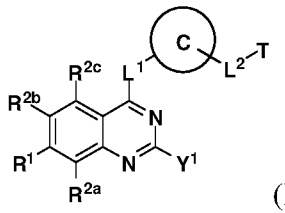
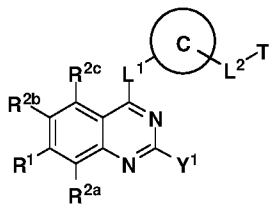
[0009] In certain aspects, a compound of Formula (I) is represented by Formula (I-A):


(I-A), or a salt or prodrug thereof.

[0010] In certain aspects, the present disclosure provides a stereoisomer of a compound of Formula (I-A):


(I-A), or a salt or prodrug thereof, wherein:

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with one or more substituents independently selected from halogen, -OH, -OR^{52}, -NH_2, -NHMe, -NMe_2, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from hydrogen, halogen, -OH, -OR^{52}, C_{1-4} alkyl, and C_{1-4} haloalkyl, wherein at least one of R^{2a} and R^{2b} is not hydrogen;

R^{2c} is selected from hydrogen, halogen, -OH, -OR^{52}, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

Y^1 is selected from -OR^{55}; and C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, each of which is substituted with -OR^{55} and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2$O-, -N(R^{51})$S(O)_2$-, -$S(O)_2$N(R^{51})-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})$S(O)_2$N(R^{51})-, -N(R^{51})S(O)N(R^{51})-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or

more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected

from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{55} is selected from:

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

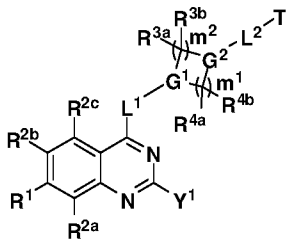
wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{55} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl$)$, $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl$)$, $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

[0011] In certain aspects, a compound of Formula (I) is represented by Formula (I-B):



(I-B), or a salt thereof, wherein:

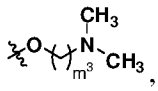
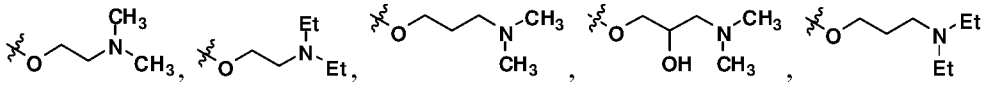
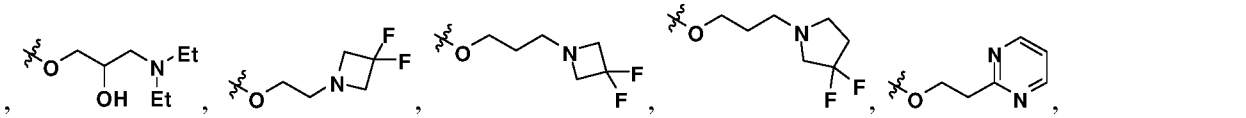
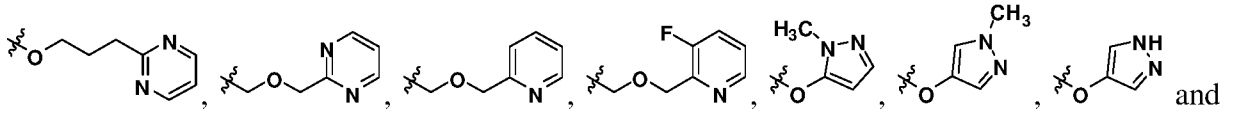
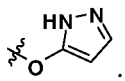
G^1 and G^2 are each independently N or CH;

R^{3a} and R^{3b} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl; or R^{3a} and R^{3b} join to form oxo or a carbocyclic or heterocyclic ring; or R^{3a} is independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl, and R^{3b} joins with R^{4b} to form a carbocyclic or heterocyclic ring;

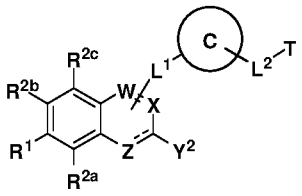
R^{4a} and R^{4b} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl,

carboxyalkyl, aminocarbonylalkyl and aminocarbonyl; or R^{4a} and R^{4b} join to form oxo or a carbocyclic or heterocyclic ring; or R^{4a} is independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl, and R^{4b} joins with R^{3b} to form a carbocyclic or heterocyclic ring; and

m^1 and m^2 are each independently 1, 2 or 3.

[0012] For a compound of Formula (I), (I-A) or (I-B), Y^1 may be $-OR^{55}$. In some embodiments, R^{55} is selected from: alkyl, alkenyl, and alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, and 3- to 12-membered heterocycle; and C_{3-12} carbocycle and 3- to 12-membered heterocycle, wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle is independently optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments, R^{55} is selected from C_{1-4} alkyl substituted with $-N(R^{52})_2$, $-NR^{53}R^{54}$, or 3- to 12-membered heterocycle; and 3- to 12-membered heterocycle, wherein each 3- to 12-membered heterocycle is optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments, Y^1 is  , wherein m^3 is an integer from 1 to 6, such as m^3 is 2 or 3. In some embodiments, Y^1 is selected from:  ,  ,  , and  .

[0013] In certain aspects, the present disclosure provides a compound of Formula (II):



(II), or a salt or prodrug thereof, wherein:

R^1, R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen and R^{50};

W and X are each independently selected from N, NR^5 and CR^6;

Z is selected from bond, N, and CR^6;

Y^2 is selected from $-N(R^{56})_2$; and alkyl, alkenyl, alkynyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with $-N(R^{56})_2$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, -OS(O)-, -S(O)O-, -S(O)-, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, $-N(R^{51})S(O)N(R^{51})-$; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

----- indicates a single or double bond such that all valences are satisfied;

R^5 is independently selected at each occurrence from R^{51};

R^6 is independently selected at each occurrence from hydrogen, R^{50}, and a bond to L^1;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-

membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered

heterocycle, each of which is optionally substituted by halogen, -CN, -NO_2, -NH_2, -$NHCH_3$, -$NHCH_2CH_3$, =O, -OH, -OCH_3, -OCH_2CH_3, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{56} is independently selected at each occurrence from:

hydrogen;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl,

or two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50}; and

R^{57} is independently selected at each occurrence from:

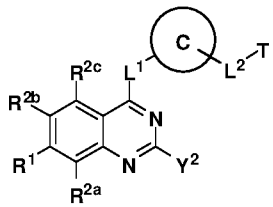
halogen, -CN, -OH, -OMe, -NH_2, -NHC_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$, -$C(O)OH$, -$C(O)H$, -$C(O)C_{1-6}$ alkyl, -$NHC(O)C_{1-6}$ alkyl, -$N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, -$C(O)NH_2$, -$C(O)NH(C_{1-6}$ alkyl), -$C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, -NH_2, -OMe, -NH_2, -NHC_{1-6} alkyl, -$N(C_{1-6}$

alkyl)$_2$, -C(O)OH, -C(O)H, -C(O)C$_{1-6}$ alkyl, -NHC(O)C$_{1-6}$ alkyl, -N(C$_{1-6}$ alkyl)C(O)C$_{1-6}$ alkyl, -C(O)NH$_2$, -C(O)NH(C$_{1-6}$ alkyl), -C(O)N(C$_{1-6}$ alkyl)$_2$, =O, and =N(OH);

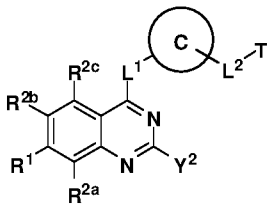
wherein one of W, X and Z is CR^6 where R^6 is a bond to L^1.

[0014] In certain aspects, a compound of Formula (II) is represented by Formula (II-A):



(II-A), or a salt or prodrug thereof.

[0015] In certain aspects, the present disclosure provides a stereoisomer of a compound of Formula (II-A):



(II-A), or a salt or prodrug thereof, wherein:

R^1 is selected from C$_{3-12}$ carbocycle and 3- to 12-membered heterocycle, each of which is substituted with one or more substituents independently selected from halogen, -OH, -OR^{52}, -NH$_2$, -NHMe, -NMe$_2$, C$_{1-3}$ alkyl, C$_{1-3}$ haloalkyl, C$_{3-12}$ carbocycle and 3- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from hydrogen, halogen, -OH, -OR^{52}, C$_{1-4}$ alkyl, and C$_{1-4}$ haloalkyl, wherein at least one of R^{2a} and R^{2b} is not hydrogen;

R^{2c} is selected from hydrogen, halogen, -OH, -OR^{52}, C$_{1-4}$ alkyl, and C$_{1-4}$ haloalkyl; and

Y^2 is selected from -N(R^{56})$_2$; and C$_{1-10}$ alkyl, C$_{2-10}$ alkenyl and C$_{2-10}$ alkynyl, each of which is substituted with -N(R^{56})$_2$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH$_2$-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -S(O)$_2$-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)$_2$-, -S(O)$_2$O-, -N(R^{51})S(O)$_2$-, -S(O)$_2$N(R^{51})-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})S(O)$_2$N(R^{51})-, -N(R^{51})S(O)N(R^{51})-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, -

$S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{56} is independently selected at each occurrence from:

hydrogen;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

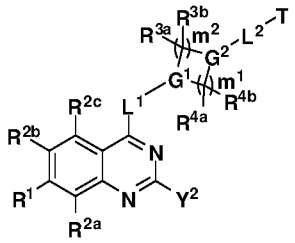
wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl$)$, $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl$)$, $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

[0016] In certain aspects, a compound of Formula (II) is represented by Formula (II-B):



(II-B), or a salt thereof, wherein:

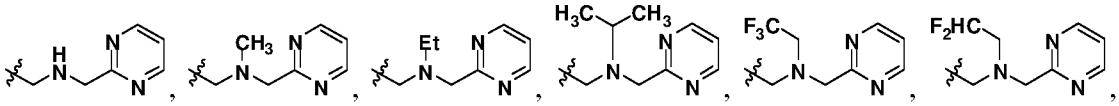
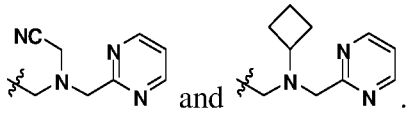
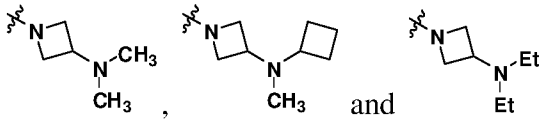
G^1 and G^2 are each independently N or CH;

R^{3a} and R^{3b} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl; or R^{3a} and R^{3b} join to form oxo or a carbocyclic or heterocyclic ring; or R^{3a} is independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl, and R^{3b} joins with R^{4b} to form a carbocyclic or heterocyclic ring;

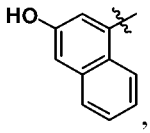
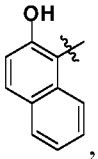
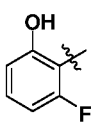
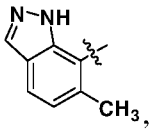
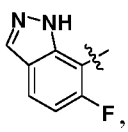
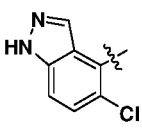
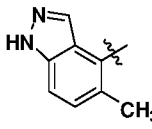
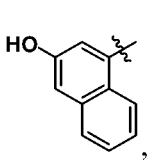
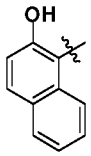
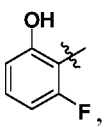
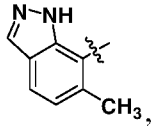
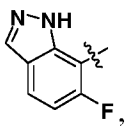
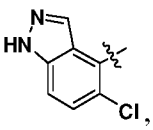
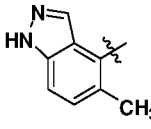
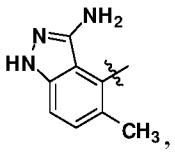
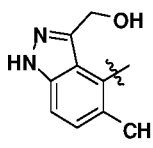
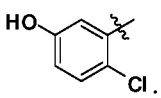
R^{4a} and R^{4b} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl,

carboxyalkyl, aminocarbonylalkyl and aminocarbonyl; or R^{4a} and R^{4b} join to form oxo or a carbocyclic or heterocyclic ring; or R^{4a} is independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl, and R^{4b} joins with R^{3b} to form a carbocyclic or heterocyclic ring; and

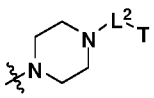
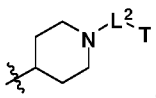
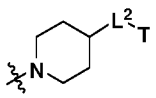
m^1 and m^2 are each independently 1, 2 or 3.

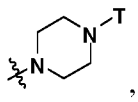
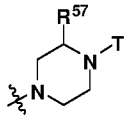
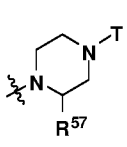
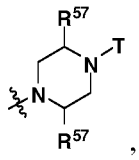
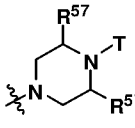
[0017] For a compound of Formula (II), (II-A) or (II-B), Y^2 may be C_{1-4} alkyl substituted with $-N(R^{56})_2$, wherein at least one R^{56} is not hydrogen. In some embodiments, R^{56} is independently selected at each occurrence from: hydrogen; C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and C_{3-12} carbocycle and 3- to 12-membered heterocycle, wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle is independently optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments, R^{56} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl substituted with one or more substituents selected from halogen, -CN, $-N(R^{52})_2$, $-NR^{53}R^{54}$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle is optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments, Y^2 is selected from: 

and . In some embodiments, Y^2 is $-N(R^{56})_2$ and the two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a heterocycle, wherein the heterocycle is optionally substituted with one or more R^{50}. In some embodiments, Y^2 is $-N(R^{56})_2$ and the two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a 3- to 6- membered heterocycle, wherein the heterocycle is substituted with $-N(R^{52})_2$ or $-NR^{53}R^{54}$. In some embodiments, Y^2 is azetidinyl, optionally substituted with one or more R^{50}. In some embodiments, Y^2 is selected from  .

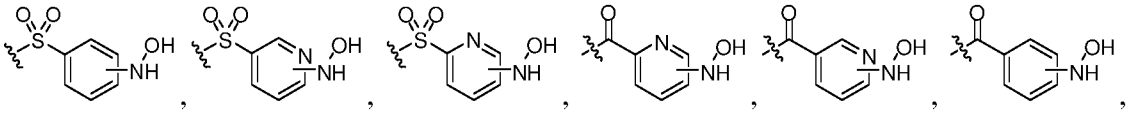
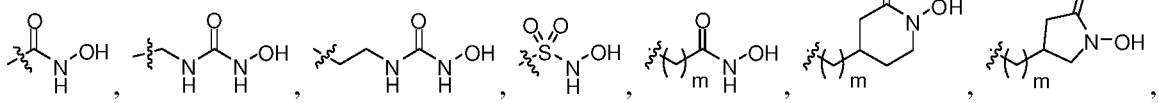
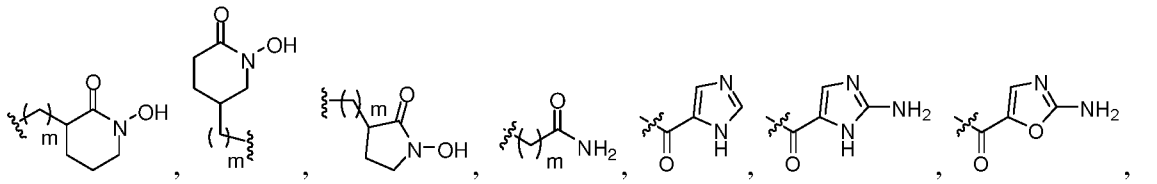
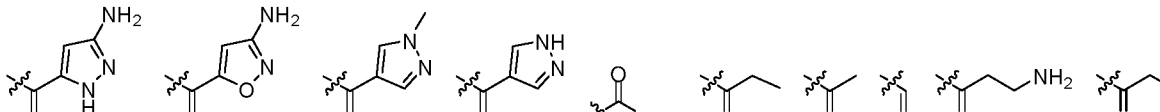
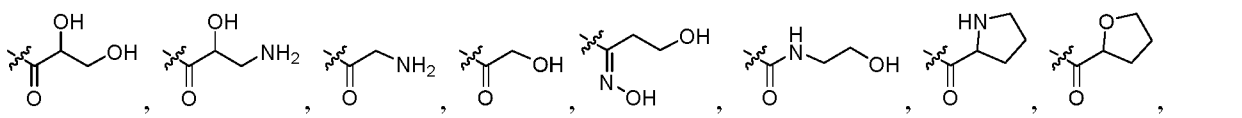
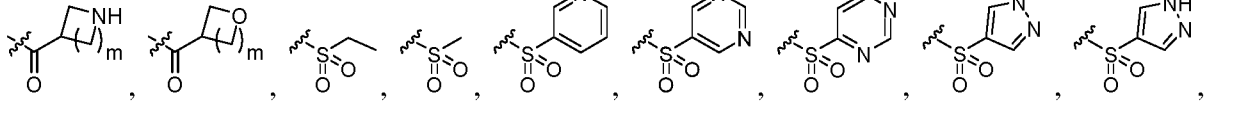
[0018] For a compound of Formula (I), (I-A), (I-B), (II), (II-A) or (II-B), R^1 may be selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, -

$N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl. In some embodiments, R^1 is selected from monocyclic aryl, bicyclic aryl, monocyclic heteroaryl, and bicyclic heteroaryl. In some embodiments, R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl. In some embodiments, R^1 is substituted with one or more substituents selected from halogen, -OH, -OCH_3, C_{1-4} alkyl, and C_{1-4} haloalkyl. In some embodiments, R^1 is selected from:  ,  ,  ,  ,  ,  and  . In some embodiments, R^1 is selected from:  ,  ,  ,  ,  ,  ,  ,  ,  and  .

[0019] For a compound of Formula (I), (I-A), (I-B), (II), (II-A) or (II-B), R^{2a}, R^{2b} and R^{2c} may each be independently selected from hydrogen, halogen, -OH, -OCH_3, C_{1-4} alkyl, and C_{1-4} haloalkyl. In some embodiments, R^{2a} and R^{2b} are each independently selected from halogen. In some embodiments, R^{2a} is fluorine. In some embodiments, R^{2b} is chlorine. In some embodiments, R^{2c} is hydrogen.

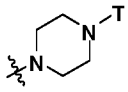
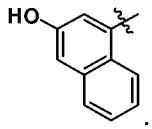
[0020] For a compound of Formula (I), (I-A), (I-B), (II), (II-A) or (II-B), C may be 5- to 8-membered heterocycle, optionally substituted with one or more R^{57}. In some embodiments, C is 6-membered monocyclic heterocycle, optionally substituted with one or more R^{57}. In some embodiments, the heterocycle comprises at least one nitrogen atom. In some embodiments, C is selected from piperidinylene and piperazinylene, optionally substituted with one or more R^{57}. In some embodiments, C is selected from morpholinyl, piperidinylene and piperazinylene, optionally substituted with one or more R^{57}. In some embodiments, C is selected from  ,  , and  , optionally substituted with one or more R^{57}. In some

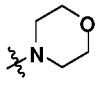
embodiments, C is selected from  ,  ,  ,  , and  . In some embodiments, R^{57} is independently selected at each occurrence from C_{1-6} alkyl, such as CH_3.

[0021] For a compound of Formula (I), (I-A), (I-B), (II), (II-A) or (II-B), T may be capable of forming a complex with a metal ion that is complexed with the Ras protein. In some embodiments, T is capable of forming an interaction with a mutation residue, such as G12D, in the Ras protein. In some embodiments, the mutation residue is selected from G12A, G12C, G12D, G12S and G12V. In some embodiments, T is selected from: -H, $-NH_2$, -OH, $-NH(C_{1-6}$ alkyl),  ,  ,  ,  ,  ,  ,  , and ; and m, when present, is 0, 1, 2, or 3. In some embodiments, T is selected from R^{57}. In some embodiments, T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O. In some embodiments, T is selected from hydrogen, $-CH_3$, -C(O)H, $-C(O)CH_3$, and $-C(O)CH_2CH_3$. In some embodiments, T is selected from hydrogen, C_{1-10} alkyl, C_{1-10} alkyl substituted with one or more R^{52}, $-C(O)R^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-C(S)N(R^{52})_2$, $-C(S)NR^{53}R^{54}$, $-NR^{52}C(S)R^{52}$, -

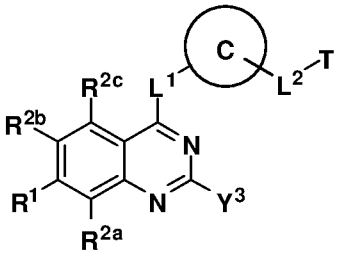
$S(O)_2N(R^{52})_2$, $-S(O)_2NR^{53}R^{54}$, $-NR^{52}S(O)_2R^{52}$, $-C(NR^{52})N(R^{52})_2$, $-C(NR^{52})NR^{53}R^{54}$, and $-NR^{52}C(NR^{52})R^{52}$; and R^{52} is independently selected at each occurrence from: hydrogen; and C_{1-20} alkyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle.

[0022] For a compound of Formula (I), (I-A), (I-B), (II), (II-A) or (II-B), L^1 may be selected from bond and $-N(R^{51})-$, such as L^1 is a bond. In some embodiments, L^2 is a bond.

[0023] For a compound of Formula (I), (I-A), (I-B), (II), (II-A) or (II-B), R^1 may be selected from phenyl, naphthyl, indazolyl, and quinolinyl, optionally substituted with one or more substituents selected from halogen, -OH, and $-CH_3$; R^{2a} and R^{2b} may each be independently selected from halogen; R^{2c} may be hydrogen; C may be  , optionally substituted with one or more R^{57}; T may be selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O; and L^1 and L^2 may each be a bond. In some embodiments, R^1 is  . In some embodiments, R^{57} is $-CH_3$. In some embodiments, T is hydrogen.

[0024] For a compound of Formula (I), (I-A), (I-B), (II), (II-A) or (II-B), R^1 may be selected from phenyl, naphthyl, indazolyl, and quinolinyl, optionally substituted with one or more substituents selected from halogen, -OH, and $-CH_3$; R^{2a} and R^{2b} may each be independently selected from halogen; R^{2c} may be hydrogen; C may be  , optionally substituted with one or more R^{57}; and L^1 may be a bond.

[0025] In certain aspects, the present disclosure provides a stereoisomer of a compound of Formula (III-A):



(III-A), or a salt or prodrug thereof, wherein:

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with one or more substituents independently selected from halogen, -OH, $-OR^{52}$, $-NH_2$, -NHMe, $-NMe_2$, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from hydrogen, halogen, -OH, -OR^{52}, C_{1-4} alkyl, and C_{1-4} haloalkyl, wherein at least one of R^{2a} and R^{2b} is not hydrogen;

R^{2c} is selected from hydrogen, halogen, -OH, -OR^{52}, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

Y^3 is selected from -OR^{55}, -$N(R^{56})_2$; and C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, each of which is substituted with -OR^{55} or -$N(R^{56})_2$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, -$N(R^{51})$-, -$N(R^{51})CH_2$-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)$N(R^{51})$-, -C(O)$N(R^{51})$C(O)-, -C(O)$N(R^{51})$C(O)$N(R^{51})$-, -$N(R^{51})$C(O)-, -$N(R^{51})$C(O)$N(R^{51})$-, -$N(R^{51})$C(O)O-, -OC(O)$N(R^{51})$-, -$C(NR^{51})$-, -$N(R^{51})$$C(NR^{51})$-, -$C(NR^{51})N(R^{51})$-, -$N(R^{51})C(NR^{51})N(R^{51})$-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})$S(O)-, -S(O)$N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, -$N(R^{51})$S(O)$N(R^{51})$-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{50} is independently selected at each occurrence from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -C(O)$R^{52}$, -C(O)$OR^{52}$, -OC(O)$R^{52}$, -OC(O)$OR^{52}$, -OC(O)$N(R^{52})_2$, -OC(O)$NR^{53}R^{54}$, -$NR^{52}$C(O)$R^{52}$, -$NR^{52}$C(O)$OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -C(O)$N(R^{52})_2$, -C(O)$NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -C(O)$R^{52}$, -C(O)$OR^{52}$, -OC(O)$R^{52}$, -OC(O)$OR^{52}$, -OC(O)$N(R^{52})_2$, -OC(O)$NR^{53}R^{54}$, -$NR^{52}$C(O)$R^{52}$, -$NR^{52}$C(O)$OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -C(O)$N(R^{52})_2$, -C(O)$NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-

membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered

heterocycle, each of which is optionally substituted by halogen, -CN, -NO_2, -NH_2, -$NHCH_3$, -$NHCH_2CH_3$, =O, -OH, -OCH_3, -OCH_2CH_3, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{55} is selected from:

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{55} is independently optionally substituted with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{56} is independently selected at each occurrence from:

hydrogen;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-

membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl,

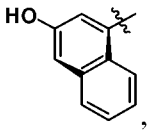
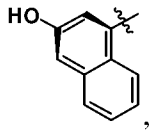
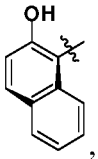
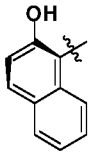
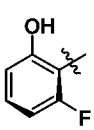
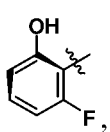
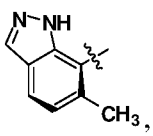
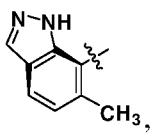
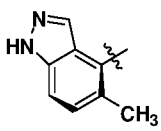
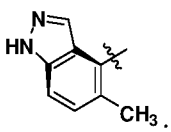
or two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50}; and

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

[0026] For a compound of Formula (I), (I-A), (I-B), (II), (II-A), (II-B) or (III-A), the compound may be provided as a substantially pure atropisomer. In some embodiments, the present disclosure provides a stereoisomer, such as an atropisomer, of a compound of Formula (I), (I-A), (I-B), (II), (II-A), (II-B) or (III-A). In some embodiments, the stereoisomer is provided in at least 90% enantiomeric excess. In some embodiments, the stereoisomer is provided in at least 90% diastereomeric excess. In some embodiments, R^1 is selected from:

-25-

[0027] In certain aspects, the present disclosure provides a compound selected from Table 1, Table 2 or Table 3.

[0028] In certain aspects, the present disclosure provides a pharmaceutical composition comprising a compound or salt of Formula (I), (I-A), (I-B), (II), (II-A), (II-B) or (III-A), and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated for oral administration. In some embodiments, the pharmaceutical composition is formulated for injection.

[0029] In certain aspects, the present disclosure provides a method for treatment of cancer, the method comprising administering an effective amount of the pharmaceutical composition comprising a compound or salt of Formula (I), (I-A), (I-B), (II), (II-A), (II-B) or (III-A) to a subject in need thereof. In some embodiments, the cancer is mediated by a K-Ras, H-Ras, or N-Ras mutant protein. In some embodiments, the cancer is a hematological cancer, pancreatic cancer, MYH associated polyposis, colorectal cancer or lung cancer. In certain aspects, the present disclosure provides a method for regulating activity of a K-Ras, H-Ras or N-Ras mutant protein, the method comprising contacting the Ras mutant protein with a compound or salt of Formula (I), (I-A), (I-B), (II), (II-A), (II-B) or (III-A). In certain aspects, the present disclosure provides a method for inhibiting proliferation of a cell population, the method comprising contacting the cell population with a compound or salt of Formula (I), (I-A), (I-B), (II), (II-A), (II-B) or (III-A). In some embodiments, inhibition of proliferation is measured as a decrease in cell viability of the cell population. In certain aspects, the present disclosure provides a method for treating a disorder mediated by a K-Ras, H-Ras or N-Ras mutant protein in a subject in need thereof, the method comprising: determining if the subject has a K-Ras, H-Ras or N-Ras mutation; and if the subject is determined to have the K-Ras, H-Ras or N-Ras mutation, then administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a compound or salt of Formula (I), (I-A), (I-B), (II), (II-A), (II-B) or (III-A). In some embodiments, the disorder is a cancer, such as a hematological cancer, pancreatic cancer, MYH associated polyposis, colorectal cancer or lung cancer. In certain aspects, the present disclosure provides a method for inhibiting tumor metastasis, the method comprising administering an effective amount of a pharmaceutical composition comprising a compound or salt of Formula (I), (I-A), (I-B), (II), (II-A), (II-B) or (III-A) to a subject in need thereof. In some embodiments, the method further comprises administering a second anti-cancer agent.

INCORPORATION BY REFERENCE

[0030] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent

application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

[0031] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0032] **Fig. 1** illustrates the enzymatic activity of Ras.

[0033] **Fig. 2** depicts a signal transduction pathway for Ras.

[0034] **Fig. 3** shows some common oncogenes, their respective tumor type and cumulative mutation frequencies (all tumors).

DETAILED DESCRIPTION

[0035] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0036] As used in the specification and claims, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

[0037] The term "C_{x-y}" or "C_x-C_y" when used in conjunction with a chemical moiety, such as alkyl, alkenyl, or alkynyl is meant to include groups that contain from x to y carbons in the chain. For example, the term "C_{x-y} alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain.

[0038] "Alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups. An alkyl group may contain from one to twelve carbon atoms (e.g., C_{1-12} alkyl), such as one to eight carbon atoms (C_{1-8} alkyl) or one to six carbon atoms (C_{1-6} alkyl). Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, septyl, octyl, nonyl, and decyl. An alkyl group is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more substituents such as those substituents described herein.

[0039] "Haloalkyl" refers to an alkyl group that is substituted by one or more halogens. Exemplary haloalkyl groups include trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, and 1,2-dibromoethyl.

[0040] "Alkenyl" refers to substituted or unsubstituted hydrocarbon groups, including straight-chain or branched-chain alkenyl groups containing at least one double bond. An alkenyl group

may contain from two to twelve carbon atoms (e.g., C_{2-12} alkenyl). Exemplary alkenyl groups include ethenyl (i.e., vinyl), prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more substituents such as those substituents described herein.

[0041] "Alkynyl" refers to substituted or unsubstituted hydrocarbon groups, including straight-chain or branched-chain alkynyl groups containing at least one triple bond. An alkynyl group may contain from two to twelve carbon atoms (e.g., C_{2-12} alkynyl). Exemplary alkynyl groups include ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents such as those substituents described herein.

[0042] "Alkylene" or "alkylene chain" refers to substituted or unsubstituted divalent saturated hydrocarbon groups, including straight-chain alkylene and branched-chain alkylene groups that contain from one to twelve carbon atoms. Exemplary alkylene groups include methylene, ethylene, propylene, and *n*-butylene. Similarly, "alkenylene" and "alkynylene" refer to alkylene groups, as defined above, which comprise one or more carbon-carbon double or triple bonds, respectively. The points of attachment of the alkylene, alkenylene or alkynylene chain to the rest of the molecule can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene, alkenylene, or alkynylene group is optionally substituted by one or more substituents such as those substituents described herein.

[0043] "Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" refer to substituted or unsubstituted alkyl, alkenyl and alkynyl groups which respectively have one or more skeletal chain atoms selected from an atom other than carbon, e.g., O, N, P, Si, S or combinations thereof, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. If given, a numerical range refers to the chain length in total. For example, a 3- to 8-membered heteroalkyl has a chain length of 3 to 8 atoms. Connection to the rest of the molecule may be through either a heteroatom or a carbon in the heteroalkyl, heteroalkenyl or heteroalkynyl chain. Unless stated otherwise specifically in the specification, a heteroalkyl, heteroalkenyl, or heteroalkynyl group is optionally substituted by one or more substituents such as those substituents described herein.

[0044] "Heteroalkylene", "heteroalkenylene" and "heteroalkynylene" refer to substituted or unsubstituted alkylene, alkenylene and alkynylene groups which respectively have one or more skeletal chain atoms selected from an atom other than carbon, e.g., O, N, P, Si, S or combinations thereof, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The points of attachment of

the heteroalkylene, heteroalkenylene or heteroalkynylene chain to the rest of the molecule can be through either one heteroatom or one carbon, or any two heteroatoms, any two carbons, or any one heteroatom and any one carbon in the heteroalkyl, heteroalkenyl or heteroalkynyl chain. Unless stated otherwise specifically in the specification, a heteroalkylene, heteroalkenylene, or heteroalkynylene group is optionally substituted by one or more substituents such as those substituents described herein.

[0045] "Carbocycle" refers to a saturated, unsaturated or aromatic ring in which each atom of the ring is a carbon atom. Carbocycle may include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. In some embodiments, the carbocycle is an aryl. In some embodiments, the carbocycle is a cycloalkyl. In some embodiments, the carbocycle is a cycloalkenyl. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, are included in the definition of carbocyclic. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, phenyl, indanyl, and naphthyl. Unless stated otherwise specifically in the specification, a carbocycle is optionally substituted by one or more substituents such as those substituents described herein.

[0046] "Heterocycle" refers to a saturated, unsaturated or aromatic ring comprising one or more heteroatoms. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycles include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic heterocycle may be selected from saturated, unsaturated, and aromatic rings. The heterocycle may be attached to the rest of the molecule through any atom of the heterocycle, valence permitting, such as a carbon or nitrogen atom of the heterocycle. In some embodiments, the heterocycle is a heteroaryl. In some embodiments, the heterocycle is a heterocycloalkyl. In an exemplary embodiment, a heterocycle, e.g., pyridyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Exemplary heterocycles include pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiophenyl, oxazolyl, thiazolyl, morpholinyl, indazolyl, indolyl, and quinolinyl. Unless stated otherwise specifically in the specification, a heterocycle is optionally substituted by one or more substituents such as those substituents described herein.

[0047] "Heteroaryl" refers to a 3- to 12-membered aromatic ring that comprises at least one heteroatom wherein each heteroatom may be independently selected from N, O, and S. As used

herein, the heteroaryl ring may be selected from monocyclic or bicyclic and fused or bridged ring systems wherein at least one of the rings in the ring system is aromatic, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The heteroatom(s) in the heteroaryl may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule through any atom of the heteroaryl, valence permitting, such as a carbon or nitrogen atom of the heteroaryl. Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pridinyl, and thiophenyl (*i.e.* thienyl). Unless stated otherwise specifically in the specification, a heteroaryl is optionally substituted by one or more substituents such as those substituents described herein.

[0048] The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons or heteroatoms of the structure. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a

stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, a carbocycle, a heterocycle, a cycloalkyl, a heterocycloalkyl, an aromatic and heteroaromatic moiety. In some embodiments, substituents may include any substituents described herein, for example: halogen, hydroxy, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazino ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); and alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl any of which may be optionally substituted by alkyl, alkenyl, alkynyl, halogen, hydroxy, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); wherein each R^a is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, wherein each R^a, valence permitting, may be optionally substituted with alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-$

R^a, $-R^b$-OC(O)-OR^a, $-R^b$-OC(O)-$N(R^a)_2$, $-R^b$-$N(R^a)_2$, $-R^b$-C(O)R^a, $-R^b$-C(O)OR^a, $-R^b$-C(O)$N(R^a)_2$, $-R^b$-O-R^c-C(O)$N(R^a)_2$, $-R^b$-$N(R^a)$C(O)OR^a, $-R^b$-$N(R^a)$C(O)R^a, $-R^b$-$N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b$-$S(O)_tR^a$ (where t is 1 or 2), $-R^b$-$S(O)_tOR^a$ (where t is 1 or 2) and $-R^b$-$S(O)_tN(R^a)_2$ (where t is 1 or 2); and wherein each R^b is independently selected from a direct bond or a straight or branched alkylene, alkenylene, or alkynylene chain, and each R^c is a straight or branched alkylene, alkenylene or alkynylene chain.

[0049] It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as "unsubstituted," references to chemical moieties herein are understood to include substituted variants. For example, reference to a "heteroaryl" group or moiety implicitly includes both substituted and unsubstituted variants.

[0050] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0051] "Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl group may or may not be substituted and that the description includes both substituted aryl groups and aryl groups having no substitution.

[0052] "Electrophile" or "electrophilic moiety" is any moiety capable of reacting with a nucleophile (e.g., a moiety having a lone pair of electrons, a negative charge, a partial negative charge and/or an excess of electrons, for example an –SH group). Electrophiles typically are electron poor or comprise atoms which are electron poor. In certain embodiments, an electrophile contains a positive charge or partial positive charge, has a resonance structure which contains a positive charge or partial positive charge, or is a moiety in which delocalization or polarization of electrons results in one or more atoms which contains a positive charge or partial positive charge. In some embodiments, an electrophile comprises a conjugated double bond, for example an α,β-unsaturated carbonyl or α,β-unsaturated thiocarbonyl compound.

[0053] A "polar group" refers to a moiety with one or more dipoles as a result of opposing charges from one or more polar bonds arranged asymmetrically. A polar bond is any covalent bond between atoms of non-identical electronegativity. A polar group can be a group that is more hydrophilic than an alkyl group. In some embodiments, a polar group is a metal chelator or a metal chelator moiety. In some embodiments, a polar gorup comprises at least one heteroatom selected from S, O, and N. For example, a polar group can be an alkyl group that is substituted with one or more functional groups comprising a heteroatom. For example, a polar group can be

an alkyl group substituted with one or more alcohol, ether, amine, hydroxyamine, aldehyde, ketone, ester, carboxylic acid, thiol, thioether, thiocarbonyl, sulfonate, sulfunite, phosphonate ester, amide, heterocycle and/or oxime.

[0054] The term "metal chelator" or "metal chelator moiety" is any moiety capable of forming two or more separate coordinate bonds between the metal chelator group and a single central metal atom or metal ion. Metal chelators typically have at least one pair of unbonded electrons which can bind to a metal atom or metal ion. In certain embodiments, a metal chelator moiety comprises at least two heteroatoms selected from S, O, and N. In some embodiments, the metal chelator moiety is a bidentate or tridenate functional group. In some embodiments, a metal chelator moiety comprises a bidentate functional group selected from the group consisting of hydroxyamine, hydroxyamide, sulfonamide, urea, amide and oxime. In some embodiments, a metal chelator moiety comprises two or more monodentate functional groups selected from the group consisting of hydroxy, amino, ether, aldehyde, ketone, amide, thiol, thioether, heterocycle (e.g. imidazole) or oxime.

[0055] Compounds of the present disclosure also include crystalline and amorphous forms of those compounds, pharmaceutically acceptable salts, and active metabolites of these compounds having the same type of activity, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[0056] The compounds described herein may exhibit their natural isotopic abundance, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. For example, hydrogen has three naturally occurring isotopes, denoted ^{1}H (protium), ^{2}H (deuterium), and ^{3}H (tritium). Protium is the most abundant isotope of hydrogen in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increased *in vivo* half-life and/or exposure, or may provide a compound useful for investigating *in vivo* routes of drug elimination and metabolism. Isotopically-enriched compounds may be prepared by conventional techniques well known to those skilled in the art.

[0057] "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. "Enantiomers" are a pair of stereoisomers that are non superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to

designate a racemic mixture where appropriate. "Diastereoisomers" or “diastereomers” are stereoisomers that have at least two asymmetric atoms but are not mirror images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer, the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) in which they rotate plane polarized light at the wavelength of the sodium D line. Certain compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms, the asymmetric centers of which can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible stereoisomers, including racemic mixtures, optically pure forms, mixtures of diastereomers and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. The optical activity of a compound can be analyzed via any suitable method, including but not limited to chiral chromatography and polarimetry, and the degree of predominance of one stereoisomer over the other isomer can be determined.

[0058] Chemical entities having carbon-carbon double bonds or carbon-nitrogen double bonds may exist in *Z*- or *E*- form (or *cis*- or *trans*- form). Furthermore, some chemical entities may exist in various tautomeric forms. Unless otherwise specified, chemical entities described herein are intended to include all *Z*-, *E*- and tautomeric forms as well.

[0059] The term “salt” or “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring

substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0060] "Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye, colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0061] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound described herein that is sufficient to affect the intended application, including but not limited to disease treatment, as defined below. The therapeutically effective amount may vary depending upon the intended treatment application (in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of platelet adhesion and/or cell migration. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0062] As used herein, "treatment" or "treating" refers to an approach for obtaining beneficial or desired results with respect to a disease, disorder, or medical condition including but not limited to a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. In certain embodiments, for prophylactic benefit, the compositions are administered to a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[0063] A "therapeutic effect," as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or

condition, or any combination thereof.

[0064] The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompass administration of two or more agents to an animal, including humans, so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

[0065] The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound having the ability to inhibit a biological function (e.g., activity, expression, binding, protein-protein interaction) of a target protein (e.g., K-Ras, H-Ras or N-Ras G12C). Accordingly, the terms "antagonist" and "inhibitor" are defined in the context of the biological role of the target protein. While preferred antagonists herein specifically interact with (e.g., bind to) the target, compounds that inhibit a biological activity of the target protein by interacting with other members of the signal transduction pathway of which the target protein is a member are also specifically included within this definition. A preferred biological activity inhibited by an antagonist is associated with the development, growth, or spread of a tumor.

[0066] The term "agonist" as used herein refers to a compound having the ability to initiate or enhance a biological function of a target protein, whether by inhibiting the activity or expression of the target protein. Accordingly, the term "agonist" is defined in the context of the biological role of the target polypeptide. While preferred agonists herein specifically interact with (e.g., bind to) the target, compounds that initiate or enhance a biological activity of the target polypeptide by interacting with other members of the signal transduction pathway of which the target polypeptide is a member are also specifically included within this definition.

[0067] "Signal transduction" is a process during which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response. A modulator of a signal transduction pathway refers to a compound which modulates the activity of one or more cellular proteins mapped to the same specific signal transduction pathway. A modulator may augment (agonist) or suppress (antagonist) the activity of a signaling molecule.

[0068] An "anti-cancer agent", "anti-tumor agent" or "chemotherapeutic agent" refers to any agent useful in the treatment of a neoplastic condition. One class of anti-cancer agents comprises chemotherapeutic agents. "Chemotherapy" means the administration of one or more chemotherapeutic drugs and/or other agents to a cancer patient by various methods, including intravenous, oral, intramuscular, intraperitoneal, intravesical, subcutaneous, transdermal, buccal, or inhalation or in the form of a suppository.

[0069] The term “cell proliferation” refers to a phenomenon by which the cell number has changed as a result of division. This term also encompasses cell growth by which the cell morphology has changed (e.g., increased in size) consistent with a proliferative signal.

[0070] The term “selective inhibition” or “selectively inhibit” refers to a biologically active agent refers to the agent’s ability to preferentially reduce the target signaling activity as compared to off-target signaling activity, via direct or indirect interaction with the target.

[0071] “Subject” refers to an animal, such as a mammal, for example a human. The methods described herein can be useful in both human therapeutics and veterinary applications. In some embodiments, the subject is a mammal, and in some embodiments, the subject is human. “Mammal” includes humans and both domestic animals such as laboratory animals and household pets (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

[0072] “Prodrug” is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein (e.g., compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B), or (II-C)). Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some aspects, a prodrug is inactive when administered to a subject but is converted in vivo to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam); Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," (1987) A.C.S. Symposium Series, Vol. 14; and Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press) each of which is incorporated in full by reference herein. The term “prodrug” is also meant to include any covalently bonded carriers, which release the active compound in vivo when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, are typically prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of a hydroxy functional group, or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like.

[0073] The term “in vivo” refers to an event that takes place in a subject’s body.

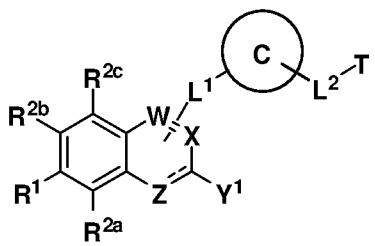
[0074] The term "in vitro" refers to an event that takes places outside of a subject's body. For example, an *in vitro* assay encompasses any assay run outside of a subject. *In vitro* assays encompass cell-based assays in which cells alive or dead are employed. In vitro assays also encompass a cell-free assay in which no intact cells are employed.

[0075] The disclosure is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the disclosure includes compounds produced by a process comprising administering a compound of this disclosure to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabelled compound of the disclosure in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

[0076] The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ACD/Name Version 9.07 software program and/or ChemDraw Ultra Version 11.0.1 software naming program (CambridgeSoft). For complex chemical names employed herein, a substituent group is typically named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with a cyclopropyl substituent. Except as described below, all bonds are identified in the chemical structure diagrams herein, except for all bonds on some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

[0077] The present disclosure provides compounds that are capable of selectively binding to and/or modulating a Ras protein. In some embodiments, the Ras protien includes but is not limited to a mutant K-Ras, H-Ras or N-Ras protein. In some embodiments, the compounds modulate the Ras protein by binding to or interacting with one or more amino acids and/or one or more metal ions. Some subject compounds may also perturb the switch I conformation. The binding of these compounds may disrupt Ras (non-limiting examples include, K-Ras, H-Ras or N-Ras) downstream signaling.

[0078] In certain aspects, the present disclosure provides a compound of Formula (I):



(I), or a salt thereof, wherein:

R^1, R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen and R^{50};

W and X are each independently selected from N, NR^5 and CR^6;

Z is selected from bond, N, and CR^6;

Y^1 is selected from $-OR^{55}$; and alkyl, alkenyl, alkynyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with $-OR^{55}$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, -OS(O)-, -S(O)O-, -S(O)-, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, $-N(R^{51})S(O)N(R^{51})-$; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

----- indicates a single or double bond such that all valences are satisfied;

R^5 is independently selected at each occurrence from R^{51};

R^6 is independently selected at each occurrence from hydrogen, R^{50}, and a bond to L^1;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, -

$OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6}

alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{55} is selected from:

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{55} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

R^{57} is independently selected at each occurrence from:

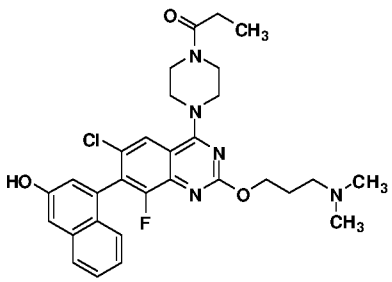
halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl$)$, $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$

alkyl)C(O)C_{1-6} alkyl, -C(O)NH_2, -C(O)NH(C_{1-6} alkyl), -C(O)N(C_{1-6} alkyl)$_2$, =O, and =N(OH);

wherein one of W, X and Z is CR^6 where R^6 is a bond to L^1; and

wherein the compound of Formula (I) is not: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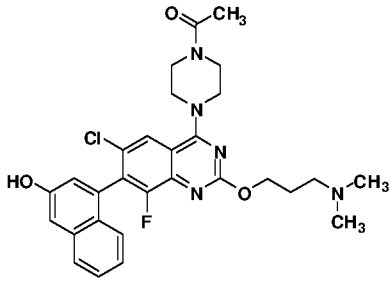
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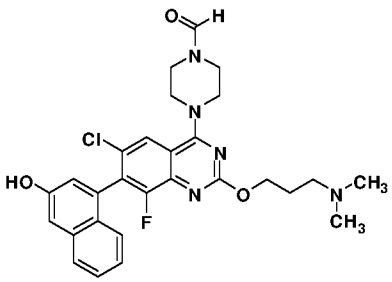
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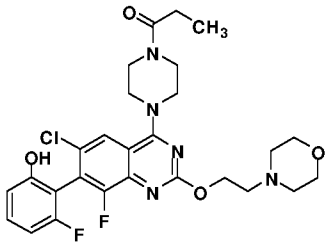
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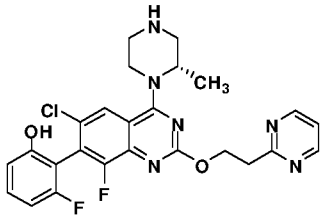
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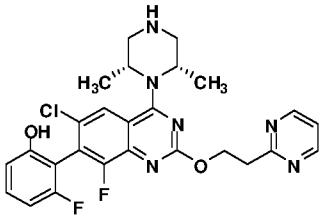
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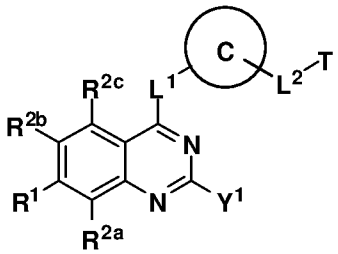
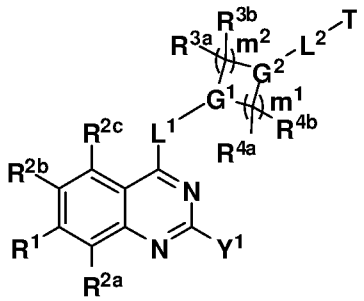
[0079] In some embodiments, for a compound of Formula (I), when R^1, R^{2a}, R^{2b} and R^{2c} are all independently selected from hydrogen and halo, then X and Z are both N and Ring C is substituted by at least one R^{57}. In some embodiments, for a compound of Formula (I), at least one of R^{2a}, R^{2b} or R^{2c} is not H when R^1 is pyridyl.

[0080] In some embodiments, a compound of Formula (I) is represented by Formula (I-A):



(I-A), or a salt thereof.

[0081] In some embodiments, a compound of Formula (I) is represented by Formula (I-B):



(I-B), or a salt thereof, wherein:

G^1 and G^2 are each independently N or CH;

R^{3a} and R^{3b} are independently selected at each occurrence from H, -OH, -NH_2, -CO_2H, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl,

carboxyalkyl, aminocarbonylalkyl and aminocarbonyl; or R^{3a} and R^{3b} join to form oxo or a carbocyclic or heterocyclic ring; or R^{3a} is independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl, and R^{3b} joins with R^{4b} to form a carbocyclic or heterocyclic ring;

R^{4a} and R^{4b} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl; or R^{4a} and R^{4b} join to form oxo or a carbocyclic or heterocyclic ring; or R^{4a} is independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl, and R^{4b} joins with R^{3b} to form a carbocyclic or heterocyclic ring; and

m^1 and m^2 are each independently 1, 2 or 3.

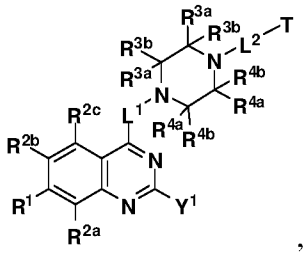
[0082] In some embodiments, for a compound of Formula (I-B), m^1 is 1. In some embodiments, m^1 is 2. In some embodiments, m^2 is 1. In some embodiments, m^2 is 2. In some embodiments, m^1 and m^2 are each 1. In some embodiments, m^1 and m^2 are each 2. In some embodiments, for a compound of Formula (I-B), at least one of G^1 or G^2 is N. In some embodiments, each of G^1 and G^2 is N. In some embodiments, each of G^1 and G^2 is N and m^1 and m^2 are each 2. In some embodiments, at least one of G^1 or G^2 is CH. In other embodiments, each of G^1 and G^2 is CH.

[0083] In some embodiments, for a compound of Formula (I-B), R^{3a}, R^{3b}, R^{4a} and R^{4b} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, hydroxylalkyl, aminoalkyl, cyanoalkyl, carboxyalkyl and aminocarbonyl. In some embodiments, R^{3a}, R^{3b}, R^{4a} and R^{4b} are independently selected at each occurrence from hydrogen and C_{1-6} alkyl, such as hydrogen and $-CH_3$. In some embodiments, R^{3b} and R^{4b} are each H and R^{3a} and R^{4a} are independently selected at each occurrence from H, -OH, C_{1-6} alkyl, hydroxylalkyl, cyano, and aminocarbonyl. In some embodiments, R^{3a} and R^{4a} are each H and R^{3b} and R^{4b} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, hydroxylalkyl, aminoalkyl, cyanoalkyl, carboxyalkyl and aminocarbonyl. In some embodiments, at least one of R^{3a}, R^{3b}, R^{4a} or R^{4b} is H. In some embodiments, each of R^{3a}, R^{3b}, R^{4a} and R^{4b} is H. In some embodiments, at least one R^{3a}, R^{3b}, R^{4a} or R^{4b} is $-CH_3$. In some embodiments, one or two R^{3a}, R^{3b}, R^{4a} or R^{4b} is $-CH_3$.

[0084] In some embodiments, for a compound of Formula (I-B), R^{3a} and R^{4a} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, C_{1-6} alkyl, cyano, hydroxylalkyl, aminoalkyl, cyanoalkyl, carboxyalkyl and aminocarbonyl, and one R^{3b} joins with one R^{4b} to form

a carbocyclic or heterocyclic ring. In some embodiments, one R^{3a} and one R^{3b} join to form a carbocyclic or heterocyclic ring. In some embodiments, one R^{4a} and one R^{4b} join to form a carbocyclic or heterocyclic ring. In some embodiments, R^{3a} and R^{3b} join to form oxo. In some embodiments, R^{4a} and R^{4b} join to form oxo.

[0085] In some embodiments, a compound of Formula (I-B) is represented by a structure selected from: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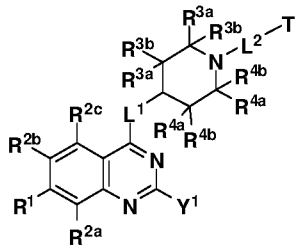
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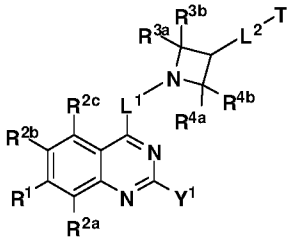
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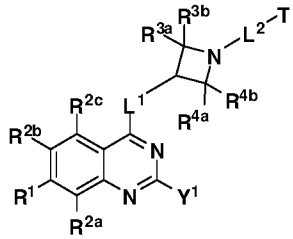
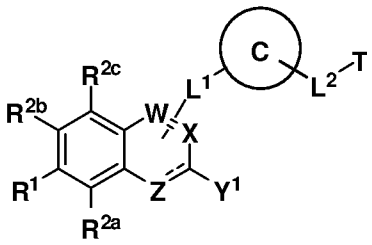

.

[0086] In certain aspects, the present disclosure provides a compound of Formula (I-C):


(I-C), or a salt thereof, wherein:

R^1 is H, cyano, halo, C_{1-6} alkyl, C_{1-6} alkylamino, C_{3-8} cycloalkyl, C_{2-6} alkenyl, C_{3-8} cycloalkenyl, heterocyclyl, heteroaryl, aryloxy or aryl;

R^{2a}, R^{2b} and R^{2c} are each independently H, halo, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl or aryl;

W and X are each independently N, NR^5 or CR^6;

Z is a bond, N or CR^6;

Y^1 is alkoxy, alkoxyalkyl, aminylalkoxy, arylalkoxy, heteroarylalkoxy, aryloxy or heteroaryloxy;

L^1 is a bond or NR^7;

L^2 is a bond or alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{3a} or R^{3b};

R^{3a} and R^{3b} are, at each occurrence, independently -H, -OH, $-NH_2$, $-CO_2H$, halo, cyano,

C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl or aminocarbonyl; or R^{3a} and R^{3b} attached to the same carbon atom join to form oxo; or R^{3a} and R^{3b} attached to the same carbon atom or different carbon atoms form a carbocyclic or heterocyclic ring;

R^5 and R^7 are each independently H or C_{1-6} alkyl;

R^6 is, at each occurrence, independently H, oxo, cyano, cyanoalkyl, amino, aminylalkyl, aminylalkylaminyl, aminocarbonyl, alkylaminyl, haloalkylamino, hydroxylalkyamino, amindinylalkyl, amidinylalkoxy, amindinylalkylaminyl, guanidinylalkyl, guanidinylalkoxy, guanidinylalkylaminyl, C_{1-6} alkoxy, aminylalkoxy, alkylcarbonylaminylalkoxy, C_{1-6} alkyl, heterocyclyl, heterocyclyloxy, heterocyclylalkyloxy, heterocyclylamino, heterocyclylalkylamino, heteroaryl, heteroaryloxy, heteroarylalkyloxy, heteroarylamino, heteroarylalkylamino, aryl, aryloxy, arylamino, arylalkylamino, arylalkyloxy, or a bond to L^1;

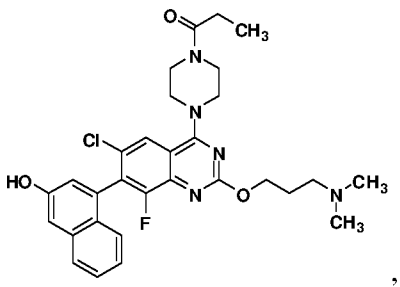
----- indicates a single or double bond such that all valences are satisfied; and

T is H or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

wherein at least one of W, X or Z is CR^6 where R^6 is a bond to L^1, and

provided that when R^1, R^{2a}, R^{2b} and R^{2c} are all independently selected from H and halo, then X and Z are both N and at least one of R^{3a} and R^{3b} is not H, and provided that at least one of R^{2a}, R^{2b} or R^{2c} is not H when R^1 is pyridyl.

[0087] In some embodiments, a compound of Formula (I), (I-A), (I-B) or (I-C) is not: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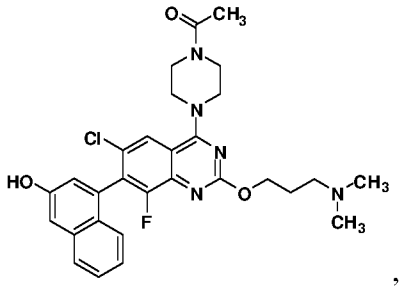
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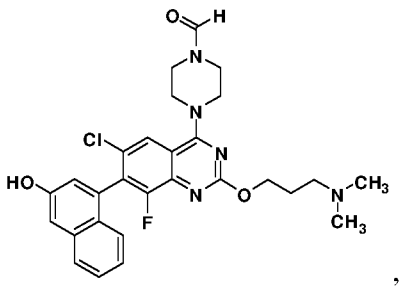
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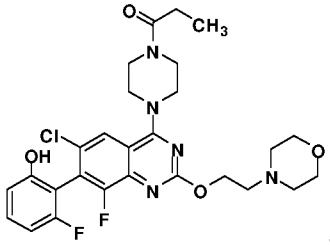
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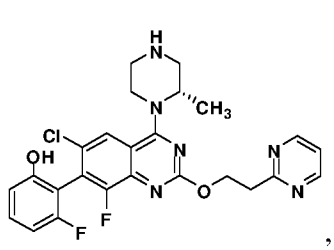
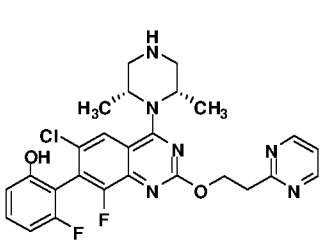

, or

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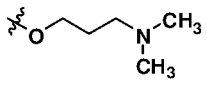
[0088] In some embodiments, for a compound of Formula (I), (I-A), (I-B) or (I-C), Y^1 is not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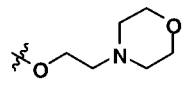
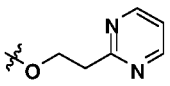
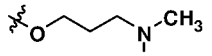
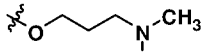
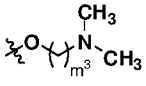
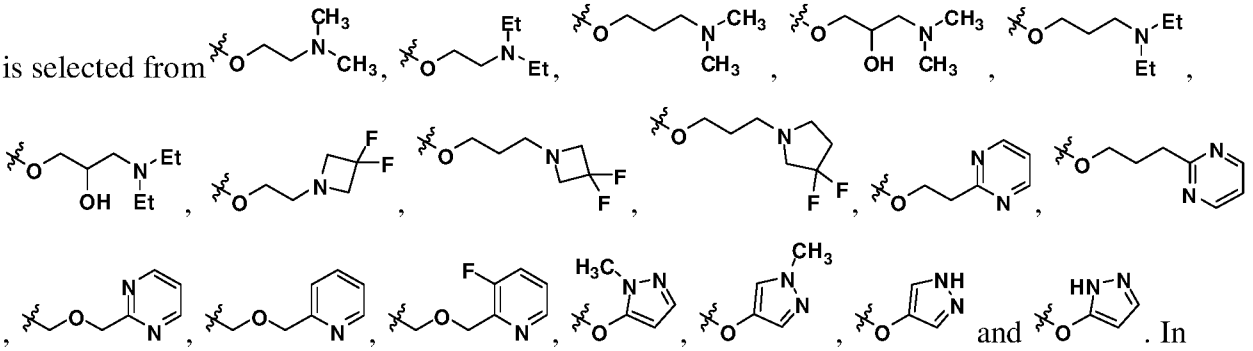

or

. In some embodiments, when R^1 is 3-

hydroxynaphthalenyl, T is -C(O)H, -C(O)CH_3, or -C(O)CH_2CH_3, and C is unsubstituted by R^{57}, then Y^1 is not  . In some embodiments, R^1 is 3-hydroxynaphthalenyl, T is hydrogen, and Y^1 is  .

[0089] In some embodiments, for a compound of Formula (I), (I-A), (I-B) or (I-C), Y^1 is selected from -OR^{55} and -CH_2OR^{55}. In some embodiments, Y^1 is OR^{55}. In some embodiments, Y^1 is  , wherein m^3 is an integer from 1 to 6, such as m^3 is 2 or 3. In some embodiments, Y^1 is selected from  .

[0090] In some embodiments, for a compound of Formula (I), (I-A), (I-B) or (I-C), R^{55} is selected from:

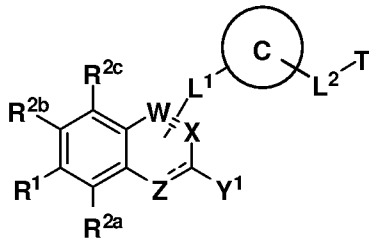
C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle is independently optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl.

[0091] In some embodiments, for a compound of Formula (I), (I-A), (I-B) or (I-C), R^{55} is selected from C_{1-4} alkyl substituted with -$N(R^{52})_2$, -$NR^{53}R^{54}$, or 3- to 12-membered heterocycle; and 3- to 12-membered heterocycle, wherein each 3- to 12-membered heterocycle is optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl.

[0092] In certain aspects, the present disclosure provides a compound of Formula (I):



(I), or a salt thereof, wherein:

R^1, R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen and R^{50};

W and X are each independently selected from N, NR^5 and CR^6;

Z is selected from bond, N, and CR^6;

Y^1 is selected from $-OR^{55}$, $-SR^{55}$ and SO_2R^{55}; and alkyl, alkenyl, alkynyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with $-OR^{55}$, $-SR^{55}$ or SO_2R^{55} and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, -OS(O)-, -S(O)O-, -S(O)-, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, $-N(R^{51})S(O)N(R^{51})-$; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

==== indicates a single or double bond such that all valences are satisfied;

R^5 is independently selected at each occurrence from R^{51};

R^6 is independently selected at each occurrence from hydrogen, R^{50}, and a bond to L^1;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, -

$S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{55} is selected from:

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{55} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

R^{57} is independently selected at each occurrence from:

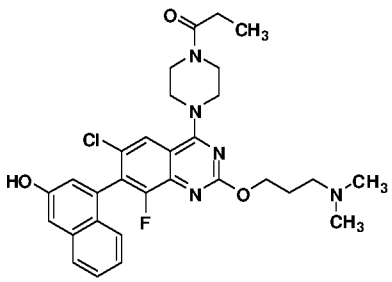
halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -

$C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl$)$, $-C(O)N(C_{1-6}$ alkyl$)_2$, $=O$, $=N(OH)$; and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from $-CN$, $-OH$, $-NH_2$, $-OMe$, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl$)$, $-C(O)N(C_{1-6}$ alkyl$)_2$, $=O$, and $=N(OH)$;

wherein one of W, X and Z is CR^6 where R^6 is a bond to L^1; and

wherein the compound of Formula (I) is not: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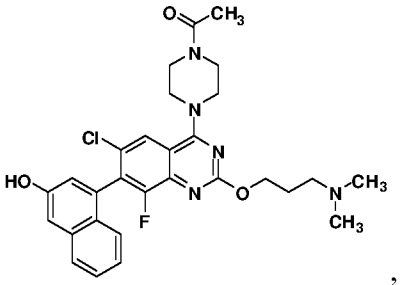
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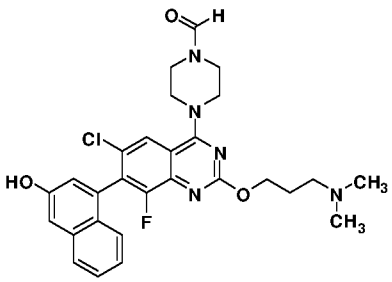
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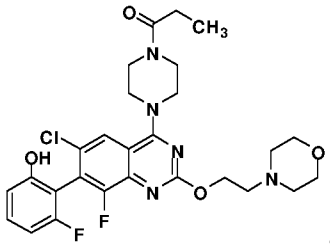
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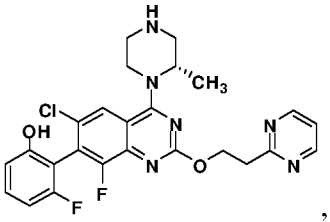
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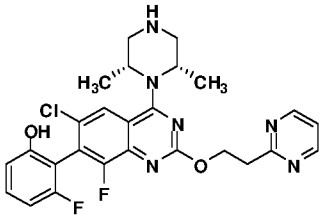
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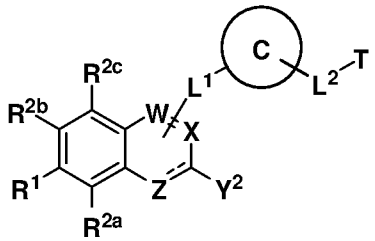
[0093] In certain aspects, the present disclosure provides a compound of Formula (II):



(II), or a salt thereof, wherein:

R^1, R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen and R^{50};

W and X are each independently selected from N, NR^5 and CR^6;

Z is selected from bond, N, and CR^6;

Y^2 is selected from $-N(R^{56})_2$; and alkyl, alkenyl, alkynyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with $-N(R^{56})_2$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, $-O-$, $-S-$, $-N(R^{51})-$, $-N(R^{51})CH_2-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-$

$C(NR^{51})N(R^{51})$-, -$N(R^{51})C(NR^{51})N(R^{51})$-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})S(O)$-, -$S(O)N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, -$N(R^{51})S(O)N(R^{51})$-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

----- indicates a single or double bond such that all valences are satisfied;

R^5 is independently selected at each occurrence from R^{51};

R^6 is independently selected at each occurrence from hydrogen, R^{50}, and a bond to L^1;

R^{50} is independently selected at each occurrence from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -

$NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{56} is independently selected at each occurrence from:

hydrogen;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl,

or two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50}; and

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

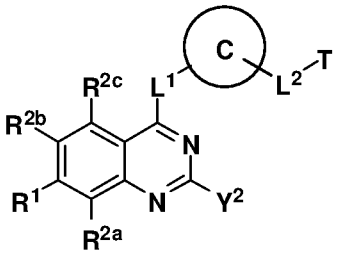
C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH);

wherein one of W, X and Z is CR^6 where R^6 is a bond to L^1.

[0094] In some embodiments, for a compound of Formula (II), when R^1, R^{2a}, R^{2b} and R^{2c} are all independently selected from hydrogen and halo, then X and Z are both N and Ring C is

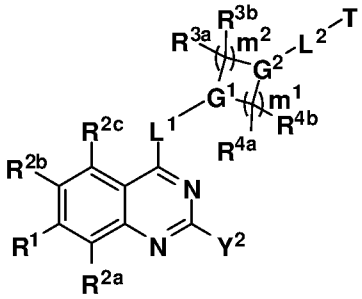
substituted by at least one R^{57}. In some embodiments, for a compound of Formula (II), at least one of R^{2a}, R^{2b} or R^{2c} is not H when R^1 is pyridyl.

[0095] In some embodiments, a compound of Formula (II) is represented by Formula (II-A):



(II-A), or a salt thereof.

[0096] In some embodiments, a compound of Formula (II) is represented by Formula (II-B):



(II-B), or a salt thereof, wherein:

G^1 and G^2 are each independently N or CH;

R^{3a} and R^{3b} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl; or R^{3a} and R^{3b} join to form oxo or a carbocyclic or heterocyclic ring; or R^{3a} is independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl, and R^{3b} joins with R^{4b} to form a carbocyclic or heterocyclic ring;

R^{4a} and R^{4b} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl; or R^{4a} and R^{4b} join to form oxo or a carbocyclic or heterocyclic ring; or R^{4a} is independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl and aminocarbonyl, and R^{4b} joins with R^{3b} to form a carbocyclic or heterocyclic ring; and

m^1 and m^2 are each independently 1, 2 or 3.

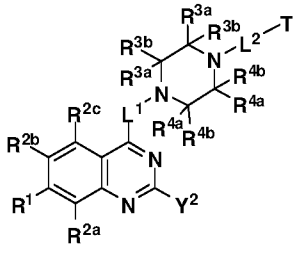
[0097] In some embodiments, for a compound of Formula (II-B), m^1 is 1. In some embodiments, m^1 is 2. In some embodiments, m^2 is 1. In some embodiments, m^2 is 2. In some embodiments, m^1 and m^2 are each 1. In some embodiments, m^1 and m^2 are each 2. In some embodiments, for a

compound of Formula (II-B), at least one of G^1 or G^2 is N. In some embodiments, each of G^1 and G^2 is N. In some embodiments, each of G^1 and G^2 is N and m^1 and m^2 are each 2. In some embodiments, at least one of G^1 or G^2 is CH. In other embodiments, each of G^1 and G^2 is CH.

[0098] In some embodiments, for a compound of Formula (II-B), R^{3a}, R^{3b}, R^{4a} and R^{4b} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, hydroxylalkyl, aminoalkyl, cyanoalkyl, carboxyalkyl and aminocarbonyl. In some embodiments, R^{3a}, R^{3b}, R^{4a} and R^{4b} are independently selected at each occurrence from hydrogen and C_{1-6} alkyl, such as hydrogen and $-CH_3$. In some embodiments, R^{3b} and R^{4b} are each H and R^{3a} and R^{4a} are independently selected at each occurrence from H, -OH, C_{1-6} alkyl, hydroxylalkyl, cyano, and aminocarbonyl. In some embodiments, R^{3a} and R^{4a} are each H and R^{3b} and R^{4b} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, hydroxylalkyl, aminoalkyl, cyanoalkyl, carboxyalkyl and aminocarbonyl. In some embodiments, at least one of R^{3a}, R^{3b}, R^{4a} or R^{4b} is H. In some embodiments, each of R^{3a}, R^{3b}, R^{4a} and R^{4b} is H. In some embodiments, at least one R^{3a}, R^{3b}, R^{4a} or R^{4b} is $-CH_3$. In some embodiments, one or two R^{3a}, R^{3b}, R^{4a} or R^{4b} is $-CH_3$.

[0099] In some embodiments, for a compound of Formula (II-B), R^{3a} and R^{4a} are independently selected at each occurrence from H, -OH, $-NH_2$, $-CO_2H$, halo, C_{1-6} alkyl, cyano, hydroxylalkyl, aminoalkyl, cyanoalkyl, carboxyalkyl and aminocarbonyl, and one R^{3b} joins with one R^{4b} to form a carbocyclic or heterocyclic ring. In some embodiments, one R^{3a} and one R^{3b} join to form a carbocyclic or heterocyclic ring. In some embodiments, one R^{4a} and one R^{4b} join to form a carbocyclic or heterocyclic ring. In some embodiments, R^{3a} and R^{3b} join to form oxo. In some embodiments, R^{4a} and R^{4b} join to form oxo.

[0100] In some embodiments, a compound of Formula (II-B) is represented by a structure selected from: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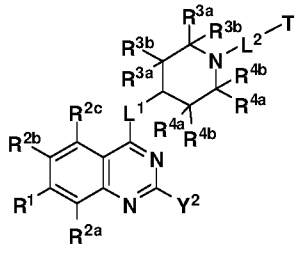
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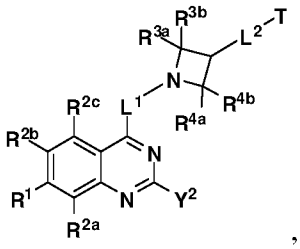
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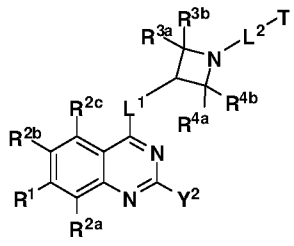
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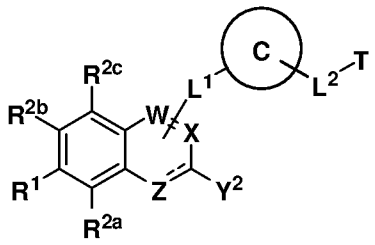
[0101] In certain aspects, the present disclosure provides a compound of Formula (II-C):



(II-C), or a salt thereof, wherein:

R^1 is H, cyano, halo, C_{1-6} alkyl, C_{1-6} alkylamino, C_{3-8} cycloalkyl, C_{2-6} alkenyl, C_{3-8} cycloalkenyl, heterocyclyl, heteroaryl, aryloxy or aryl;

R^{2a}, R^{2b} and R^{2c} are each independently H, halo, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl or aryl;

W and X are each independently N, NR^5 or CR^6;

Z is a bond, N or CR^6;

Y^2 is alkylamino, alkylaminoalkyl, arylalkylamino, arylalkylaminoalkyl, heteroarylalkylamino or heteroarylalkylaminoalkyl;

L^1 is a bond or NR^7;

L^2 is a bond or alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{3a} or R^{3b};

R^{3a} and R^{3b} are, at each occurrence, independently -H, -OH, $-NH_2$, $-CO_2H$, halo, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxylalkyl, aminoalkyl, alkylaminoalkyl, cyanoalkyl, carboxyalkyl, aminocarbonylalkyl or aminocarbonyl; or R^{3a} and R^{3b} attached to the same carbon atom join to form oxo; or R^{3a} and R^{3b} attached to the same carbon atom or different carbon atoms form a carbocyclic or heterocyclic ring;

R^5 and R^7 are each independently H or C_{1-6} alkyl;

R^6 is, at each occurrence, independently H, oxo, cyano, cyanoalkyl, amino, aminylalkyl, aminylalkylaminyl, aminocarbonyl, alkylaminyl, haloalkylamino, hydroxylalkyamino, amindinylalkyl, amidinylalkoxy, amindinylalkylaminyl, guanidinylalkyl, guanidinylalkoxy, guanidinylalkylaminyl, C_{1-6} alkoxy, aminylalkoxy, alkylcarbonylaminylalkoxy, C_{1-6} alkyl, heterocyclyl, heterocyclyloxy, heterocyclylalkyloxy, heterocyclylamino, heterocyclylalkylamino, heteroaryl, heteroaryloxy, heteroarylalkyloxy, heteroarylamino, heteroarylalkylamino, aryl, aryloxy, arylamino, arylalkylamino, arylalkyloxy, or a bond to L^1;

----- indicates a single or double bond such that all valences are satisfied; and

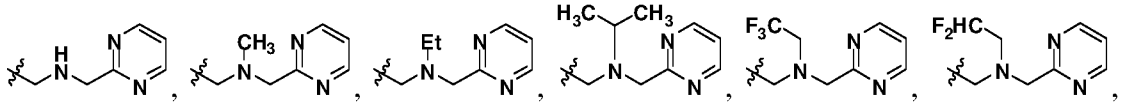
T is H or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of

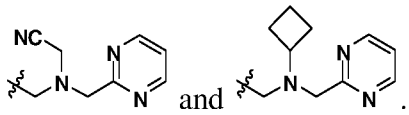
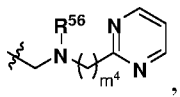
a K-Ras, H-Ras or N-Ras G12C mutant protein;

wherein at least one of W, X or Z is CR^6 where R^6 is a bond to L^1, and

provided that when R^1, R^{2a}, R^{2b} and R^{2c} are all independently selected from H and halo, then X and Z are both N and at least one of R^{3a} and R^{3b} is not H, and provided that at least one of R^{2a}, R^{2b} or R^{2c} is not H when R^1 is pyridyl.

[0102] In some embodiments, for a compound of Formula (II), (II-A), (II-B) or (II-C), Y^2 is selected from $-N(R^{56})_2$ and C_{1-4} alkyl substituted with $-N(R^{56})_2$, wherein at least one R^{56} is not hydrogen. In some embodiments, Y^2 is C_{1-4} alkyl substituted with $-N(R^{56})_2$, wherein at least one R^{56} is not hydrogen, such as $-CH_2N(R^{56})_2$. In some embodiments, Y^2 is selected from



and  . In some embodiments, Y^2 is $-CH_2N(R^{52})CH_2R^{52}$. In some embodiments, Y^2 is $-CH_2N(R^{58})CH_2R^{59}$, wherein R^{58} is selected from hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl substituted with halogen or -CN, C_{3-6} carbocycle, and 3- to 6-membered heterocycle; and R^{59} is selected from 3- to 8-membered heterocycle, optionally substituted with one or more halogens. In some embodiments, Y^2 is $-CH_2N(R^{58})CH_2R^{59}$, wherein R^{58} is selected from hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl; and R^{59} is pyrimidinyl. In some embodiments, Y^2 is  , wherein m^4 is an integer from 1 to 6. In some embodiments, m^4 is 1 or 2. In some embodiments, Y^2 is selected from $-N(R^{56})_2$; and C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, each of which is substituted with $-N(R^{56})_2$ and optionally futher substituted with one or more R^{50}.

[0103] In some embodiments, for a compound of Formula (II), (II-A), (II-B) or (II-C), R^{56} is independently selected at each occurrence from:

hydrogen;

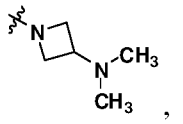
C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle is independently optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl.

[0104] In some embodiments, for a compound of Formula (II), (II-A), (II-B) or (II-C), R^{56} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl substituted with one or more substituents selected from halogen, -CN, $-N(R^{52})_2$, $-NR^{53}R^{54}$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle is optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl.

[0105] In some embodiments, for a compound of Formula (II), (II-A) or (II-B), Y^2 is $-N(R^{56})_2$ and the two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a heterocycle, wherein the heterocycle is optionally substituted with one or more R^{50}. In some embodiments, Y^2 is $-N(R^{56})_2$ and the two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a 3- to 6- membered heterocycle, wherein the heterocycle is substituted with $-N(R^{52})_2$ or $-NR^{53}R^{54}$. In some embodiments, Y^2 is azetidinyl, optionally substituted with one or more R^{50}. In some embodiments, Y^2 is selected from



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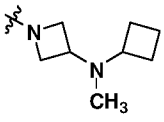
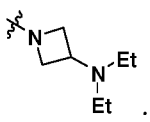


and


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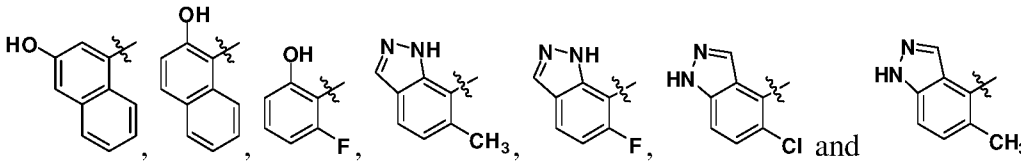
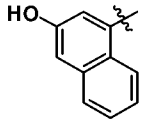
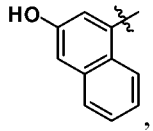
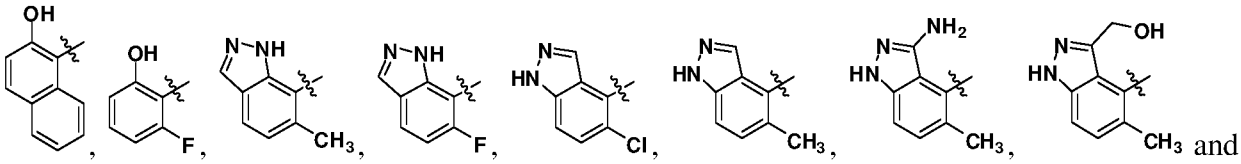
[0106] Without wishing to be bound by a theory, the correct selection of R^1 may contribute to the inhibitory activity of a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) (*e.g.*, against K-Ras, H-Ras or N-Ras G12C). In some embodiments, R^1 is capable of forming a reversible interaction with a K-Ras, H-Ras or N-Ras G12C mutant protein. In some embodiments, R^1 has a high affinity towards K-Ras, H-Ras or N-Ras and is highly specific towards G12C K-Ras, H-Ras or N-Ras. In some embodiments, R^1 is capable of forming a hydrophobic interaction with K-Ras, H-Ras or N-Ras G12C. In some embodiments, R^1 is capable of forming one or more hydrogen bonds to one or more residues of a G12C K-Ras, H-Ras or N-Ras protein.

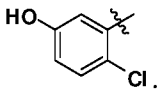
[0107] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl. In some embodiments, R^1 is selected from monocyclic aryl, bicyclic aryl, monocyclic heteroaryl, and bicyclic heteroaryl. In some embodiments, R^1 is selected from phenyl, naphthyl, indazolyl, and

quinolinyl. In some embodiments, R^1 is substituted with one or more substituents selected from halogen, -OH, -OCH_3, C_{1-4} alkyl, and C_{1-4} haloalkyl. In some embodiments, R^1 is selected from:



. In some embodiments, R^1 is  . In some embodiments, R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl, substituted with one or more substituents selected from halogen, -OH, -OCH_3, C_{1-4} alkyl, and C_{1-4} haloalkyl. In some embodiments, R^1 is selected from:  ,

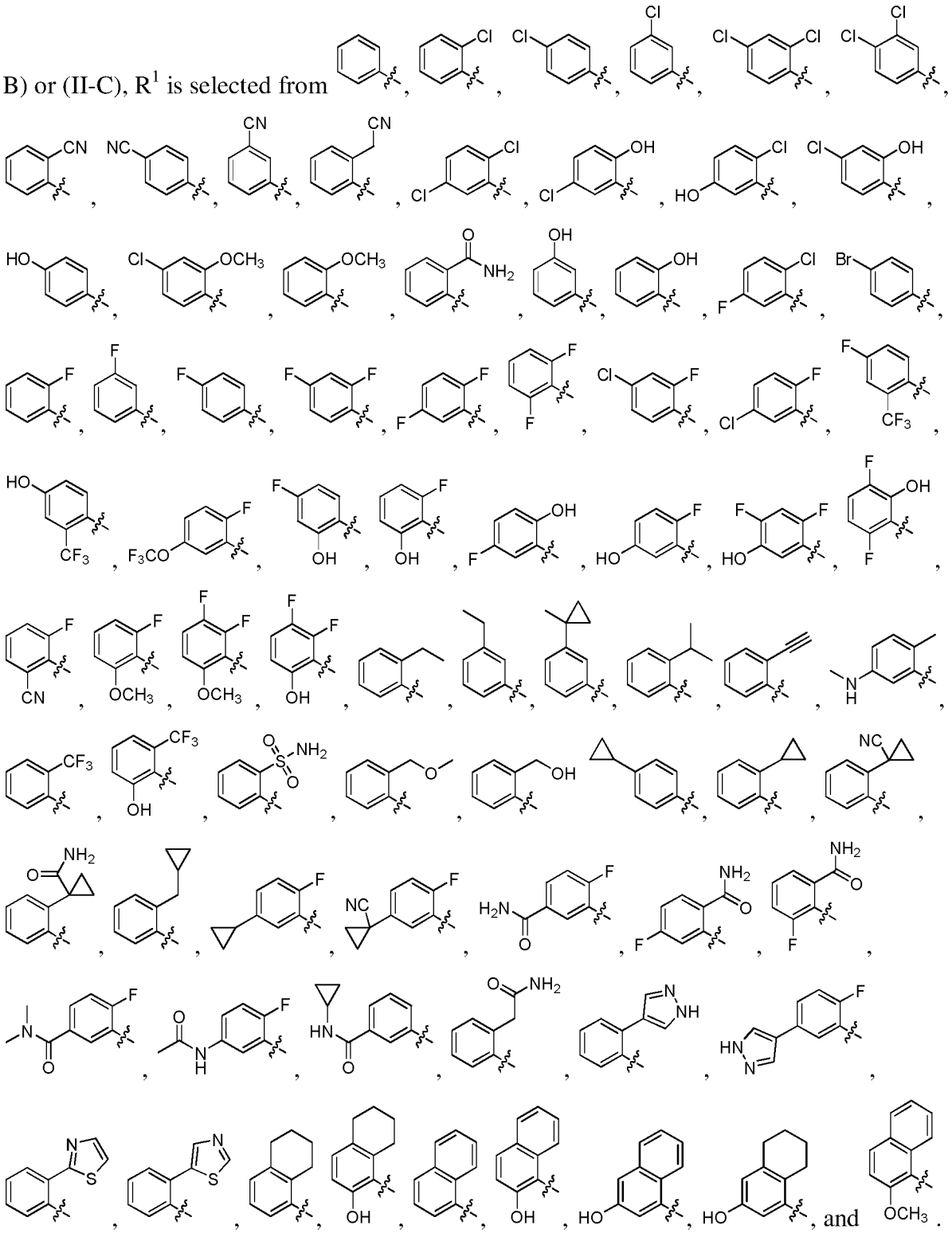


and  . In some embodiments, R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl, substituted with one or more substituents selected from -F, -Cl, -OH, -OCH_3, -NH_2, -CH_2OH, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0108] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), R^1 is heterocyclyl, heteroaryl or aryl. In some embodiments, R^1 is aryl, such as phenyl or napthyl. In some embodiments, R^1 is unsubstituted aryl, such as unsubstituted phenyl or unsubstituted napthyl. In some embodiments, R^1 is substituted with one or more substituents. In some embodiments, the substituents are selected from halo, cyano, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-8} cycloalkyl. In some embodiments, the substituents are selected from fluoro, chloro, bromo, hydroxyl, methoxy and cyclopropyl. In some embodiments, the substituents are selected from -F, -Cl, -OH, -OCH_3, -NH_2, -CH_2OH, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0109] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), R^1 is substituted with one or more substituents selected from halo, cyano, cyanoC_{1-6}alkyl, cyanoC_{3-8}cycloalkyl, hydroxyl, C_{1-6}alkyl, C_{1-6}alkylcycloalky, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{1-6}alkylaminyl, C_{1-6}alkylcarbonylaminyl, C_{1-6}hydroxylalkyl, C_{1-6}haloalkyl, C_{1-6}alkoxyalkyl, aminosulfone, aminocarbonyl, aminocarbonylC_{1-6}alkyl, aminocarbonylC_{3-8}cycloalkyl, C_{1-6}alkylaminocarbonyl, C_{3-8}cycloalkylaminocarbonyl, C_{3-8}cycloalkylalkyl, C_{3-8}cycloalkyl, C_{3-8}fusedcycloalkyl and heteroaryl. In some embodiments, R^1 is substituted with one

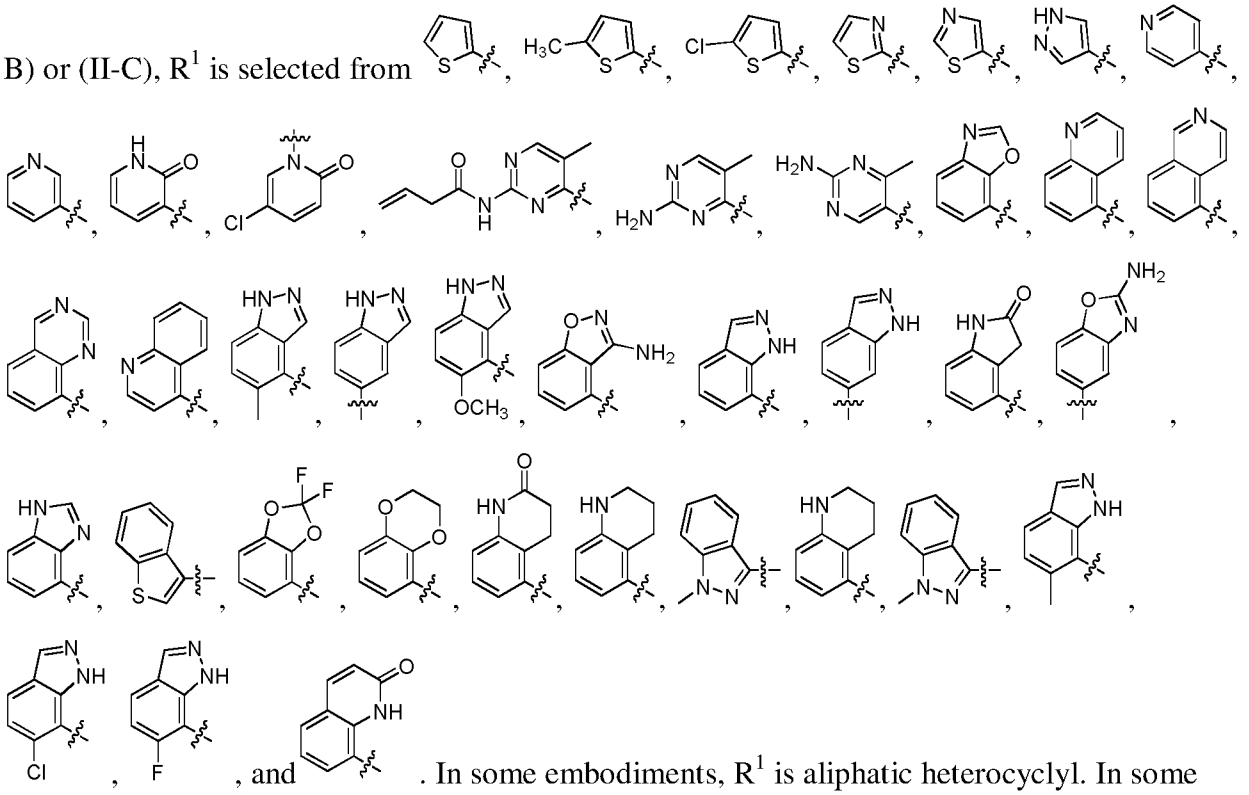
or more substituents selected from fluoro, chloro, bromo, cyano, hydroxyl, hydroxylmethyl, methoxy, methoxymethyl, ethyl, isopropyl, trifluoromethyl, aminocarbonyl and cyclopropyl.

[0110] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), R^1 is selected from  , and .

[0111] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), R^1 is heteroaryl. In some embodiments, R^1 comprises at least one ring heteroatom selected from oxygen, sulfur, nitrogen and combinations thereof. In some embodiments, R^1

comprises at least one ring heteroatom selected from sulfur and nitrogen. In some embodiments, R^1 is thiophenyl, pyridinyl, pyridinonyl, pyrimidinyl, benzooxazolyl, benzoisoxazolyl, benzodioxazolyl, benzoimidazolyl, quinolinyl, quinolinonyl, dihydroquinolinonyl, tetrahydroquinolinyl, quinazolinyl, indazolyl, indolinonyl, benzothiophenyl or dihydrobenzodioxinyl.

[0112] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), R^1 is substituted with one or more substituents. In some embodiments, R^1 is substituted with one or more substituents selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{2-6} alkenylcarbonylaminyl. In some embodiments, R^1 is substituted with one or more substituents selected from halogen, hydroxy, and C_{1-6} alkyl. In some embodiments, R^1 is substituted with one or more substituents selected from -F, -Cl, -OH, and $-CH_3$.

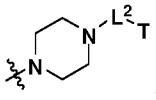
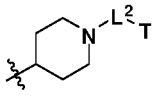
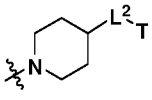
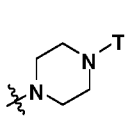
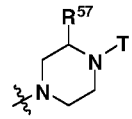
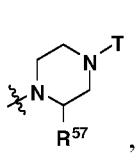
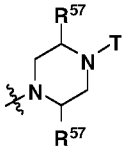
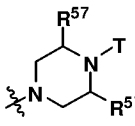
[0113] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), R^1 is selected from  , and . In some embodiments, R^1 is aliphatic heterocyclyl. In some embodiments, the aliphatic heterocyclyl comprises oxygen and/or nitrogen. In some embodiments, R^1 is morpholinyl, such as  .

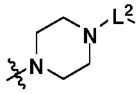
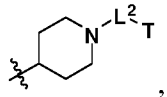
[0114] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, -OH, C_{1-4} alkyl, and C_{1-4} haloalkyl. In some embodiments, R^{2a} and R^{2b} are each independently selected from halogen. In some embodiments, R^{2a} is fluorine. In some embodiments, R^{2b} is chlorine. In some embodiments, R^{2c} is hydrogen. In some embodiments, R^{2a} is fluorine, R^{2b} is chlorine, and

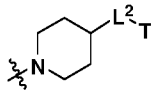
R^{2c} is hydrogen. In some embodiments, R^{2a} and R^{2b} are each independently selected from halogen, and R^{2c} is hydrogen. In some embodiments, R^{2a} and R^{2b} are each independently selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl, and R^{2c} is hydrogen. In some embodiments, R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, and C_{1-4} alkyl.

[0115] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), R^{2a} is hydrogen. In some embodiments, R^{2a} is halogen, such as chloro or fluoro. In some embodiments, R^{2a} is C_{1-6} alkyl. In some embodiments, R^{2a} is C_{3-8} cycloalkyl, such as cyclopropyl.

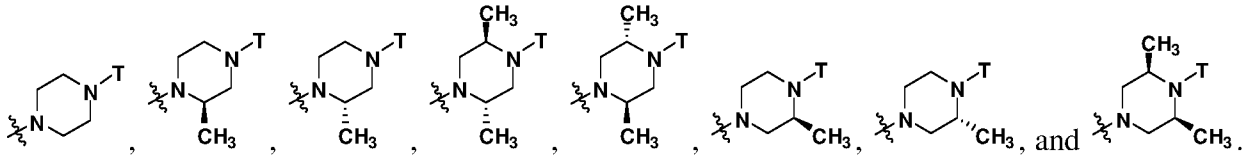
[0116] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), R^{2b} and R^{2c} are each hydrogen. In some embodiments, R^{2b} and R^{2c} are each independently selected from hydrogen and halogen. In some embodiments, R^{2b} is halogen. In some embodiments, R^{2c} is halogen. In some embodiments, said halogen is selected from fluorine and chlorine.

[0117] In some embodiments, for a compound of Formula (I), (I-A), (I-C), (II), (II-A) or (II-C), C is 5- to 8-membered heterocycle, optionally substituted with one or more R^{57}. In some embodiments, C is 6-membered monocyclic heterocycle, optionally substituted with one or more R^{57}. In some embodiments, said heterocycle comprises at least one ring nitrogen atom. In some embodiments, C is selected from piperidinylene and piperazinylene, optionally substituted with one or more R^{57}. In some embodiments, C is piperazinylene, optionally substituted with one or more R^{57}, such as piperazinylene substituted with 0, 1 or 2 R^{57} substituents. In some embodiments, C is selected from  ,  , and  , optionally substituted with one or more R^{57}. In some embodiments, C is selected from  ,  ,  ,  , and  . In some embodiments, R^{57} is independently selected at each occurrence from C_{1-6} alkyl, such as $-CH_3$.

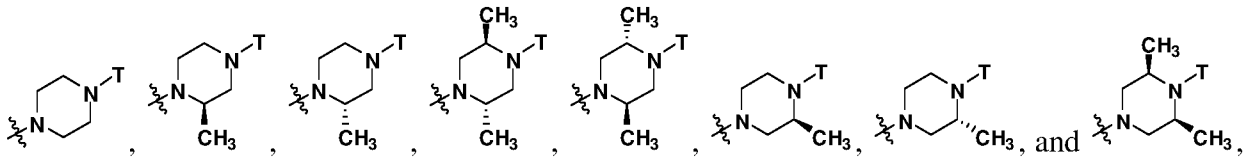
[0118] In some embodiments, for a compound of Formula (I), (I-A), (I-C), (II), (II-A) or (II-C), C is selected from morpholinyl, piperidinylene and piperazinylene, optionally substituted with one or more R^{57}. In some embodiments, C is selected from  ,  ,  ,

and  , optionally substituted with one or more R^{57}.

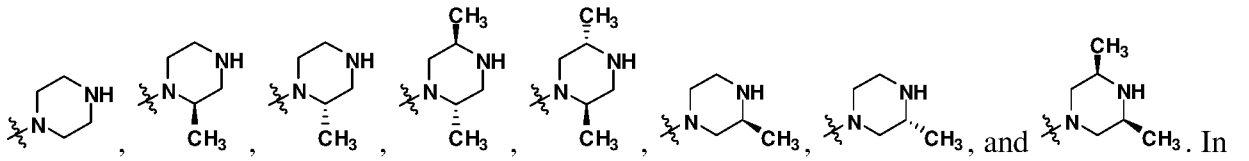
[0119] In some embodiments, for a compound of Formula (I), (I-A), (I-C), (II), (II-A) or (II-C), C is selected from:



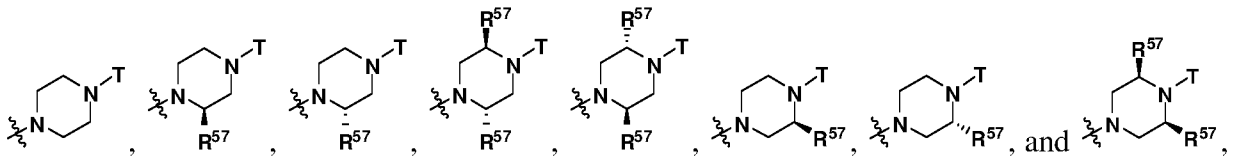
In some embodiments, T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O. In some embodiments, T is selected from hydrogen, $-CH_3$, -C(O)H, $-C(O)CH_3$, and $-C(O)CH_2CH_3$. In some embodiments, C is selected from:



wherein T is selected from hydrogen, $-CH_3$, -C(O)H, $-C(O)CH_3$, and $-C(O)CH_2CH_3$. In some embodiments, C is selected from:



some embodiments, C is selected from:



wherein T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O; and R^{57} is independently selected at each occurrence from C_{1-6} alkyl, such as $-CH_3$.

[0120] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C):

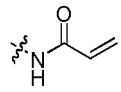
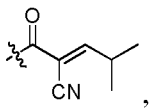
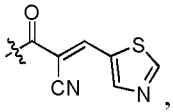
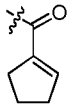
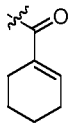
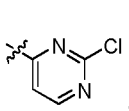
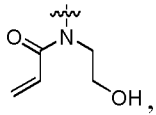
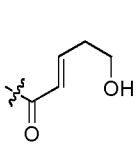
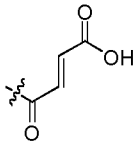
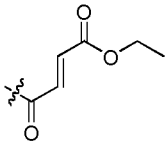
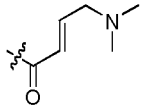
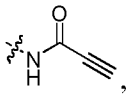
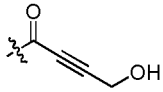
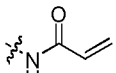
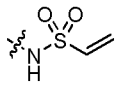
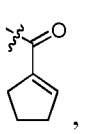
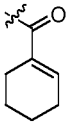
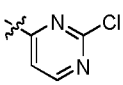
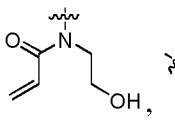
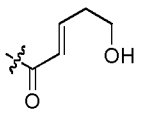
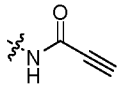
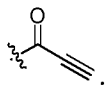
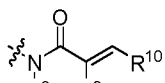
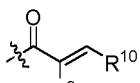
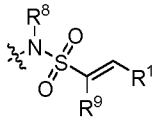
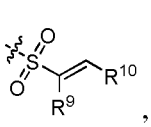
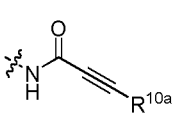
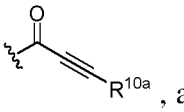
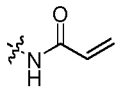
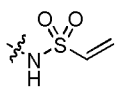
T is selected from hydrogen, C_{1-10} alkyl, C_{1-10} alkyl substituted with one or more R^{52}, $-C(O)R^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-C(S)N(R^{52})_2$, $-C(S)NR^{53}R^{54}$, $-NR^{52}C(S)R^{52}$, $-S(O)_2N(R^{52})_2$, $-S(O)_2NR^{53}R^{54}$, $-NR^{52}S(O)_2R^{52}$, $-C(NR^{52})N(R^{52})_2$, $-C(NR^{52})NR^{53}R^{54}$, and $-NR^{52}C(NR^{52})R^{52}$; wherein

each R^{52} in T is independently selected at each occurrence from:

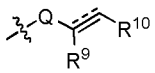
hydrogen; and

C_{1-20} alkyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-

membered heterocycle, each of which is optionally substituted by -CN, -NO_2, -NH_2, -$NHCH_3$, -$NHCH_2CH_3$, =O, -OH, -OCH_3, -OCH_2CH_3, C_{3-12} carbocycle, or 3- to 6-membered heterocycle.

[0121] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), T is not E, wherein E is an electrophile capable of bonding with a K-Ras, H-Ras or N-Ras protein comprising a G12C mutation. In some embodiments, T is not E, wherein the electrophile E is capable of forming an irreversible covalent bond with a G12C mutant K-Ras, H-Ras or N-Ras protein. In some embodiments, the electrophile E binds the cysteine residue at position 12 of a G12C mutant K-Ras, H-Ras or N-Ras protein. In some embodiments, T is not E, wherein E is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  . In some embodiments, T is not E, wherein E is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  . In some embodiments, T is not E, wherein E is selected from  ,  ,  ,  ,  and  , and wherein R^8 is H or C_{1-6} alkyl; R^9 is H, cyano or C_{1-6} alkyl, or R^9 joins with R^{10} to form a carbocycle; R^{10} is H or C_{1-6} alkyl, or R^{10} joins with R^9 to form a carbocycle; and R^{10a} is H or C_{1-6} alkyl. In some embodiments, E is  . In some embodiments, E is  . In some embodiments, E is  .

[0122] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), T is not E, and E has the following structure:

 , wherein:

≡ represents a double or triple bond;

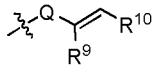
Q is -C(O)-, -$NR^8C(O)$-, -$S(=O)_2$- or -$NR^8S(=O)_2$-; and

R^8 is H, C_{1-6} alkyl or hydroxylalkyl;

wherein when ≡ is a double bond, then R^9 and R^{10} are each independently H, cyano, carboxyl, C_{1-6} alkyl, alkoxycarbonyl, aminoalkyl, alkylaminoalkyl, or hydroxylalkyl, or R^9 and R^{10} join to form a carbocyclic or heterocyclic ring; and

wherein when ≡ is a triple bond; then R^9 is absent and R^{10} is H, C_{1-6} alkyl, aminoalkyl, alkylaminoalkyl or hydroxylalkyl. In some embodiments, when ≡ is a double bond, then R^9 and R^{10} are each independently H, cyano, C_{1-6} alkyl, aminoalkyl, alkylaminoalkyl, or hydroxylalkyl, or R^9 and R^{10} join to form a carbocyclic or heterocyclic ring.

[0123] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), T is not E, and E has the following structure:



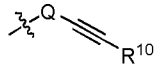
, wherein:

Q is -C(O)-, $-NR^8C(O)-$, $-S(=O)_2-$ or $-NR^8S(=O)_2-$;

R^8 is H, C_{1-6} alkyl or hydroxylalkyl; and

R^9 and R^{10} are each independently H, cyano, C_{1-6} alkyl, aminoalkyl, alkylaminoalkyl, or hydroxylalkyl, or R^9 and R^{10} join to form a carbocyclic or heterocyclic ring.

[0124] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), T is not E, and E has the following structure:



, wherein:

Q is -C(O)-, $-NR^8C(O)-$, $-S(=O)_2-$ or $-NR^8S(=O)_2-$;

R^8 is H, C_{1-6} alkyl or hydroxylalkyl; and

R^{10} is H, C_{1-6} alkyl, aminoalkyl, alkylaminoalkyl or hydroxylalkyl.

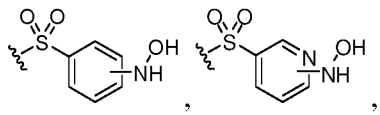
[0125] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein. In some embodiments, T is hydrogen or a group capable of forming a complex with a Ras protein via an interaction other than one resulting in an irreversible covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein. T can form a direct or indirect (e.g., through one or more water molecules) complex with a Ras protein. In some embodiments, T is a polar group capable of forming a bond with a metal ion, wherein the metal ion is complexed to a Ras protein. In some embodiments, T is a metal chelating moiety. In some embodiments, T is a polar group capable of directly or indirectly (e.g., through a water molecule) forming one or more interactions with a beta-phosphate of a nucleotide (GDP) or G12D residue of a Ras protein. In some embodiments,

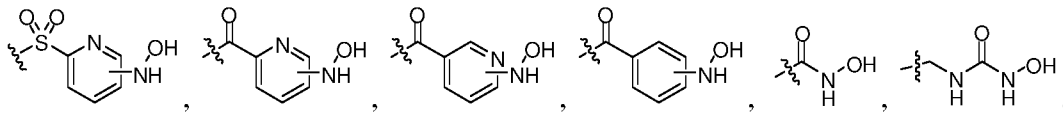
the Ras protein is a K-Ras, H-Ras or N-Ras wild-type protein. In other embodiments, the Ras protein is a K-Ras, H-Ras or N-Ras mutant protein. In some embodiments, the Ras protein is a K-Ras, H-Ras or N-Ras G12C mutant protein. In some embodiments, T is capable of forming an interaction with a mutation residue in the Ras protein. The mutation residue may be G12D. In some embodiments, the mutation residue is G12A, G12C, G12D, G12S or G12V.

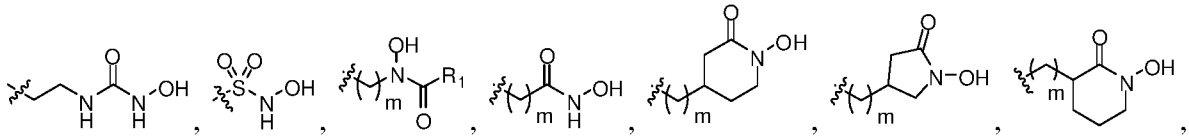
[0126] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), T has a molecular weight less than 400, 350, 300, 250, 200, 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, or 50 Daltons. T may have a molecular weight less than 200 daltons. In some embodiments, T has a molecular weight of greater than 40, 50, 60, 70, 80, 90, 100, or 110 Daltons. T may have a molecular weight of greater than 50 Daltons. In some embodiments, T has a molecular weight between about 50 and 300, 50 and 250, 50 and 200, 50 and 150, or 50 and 100 Daltons.

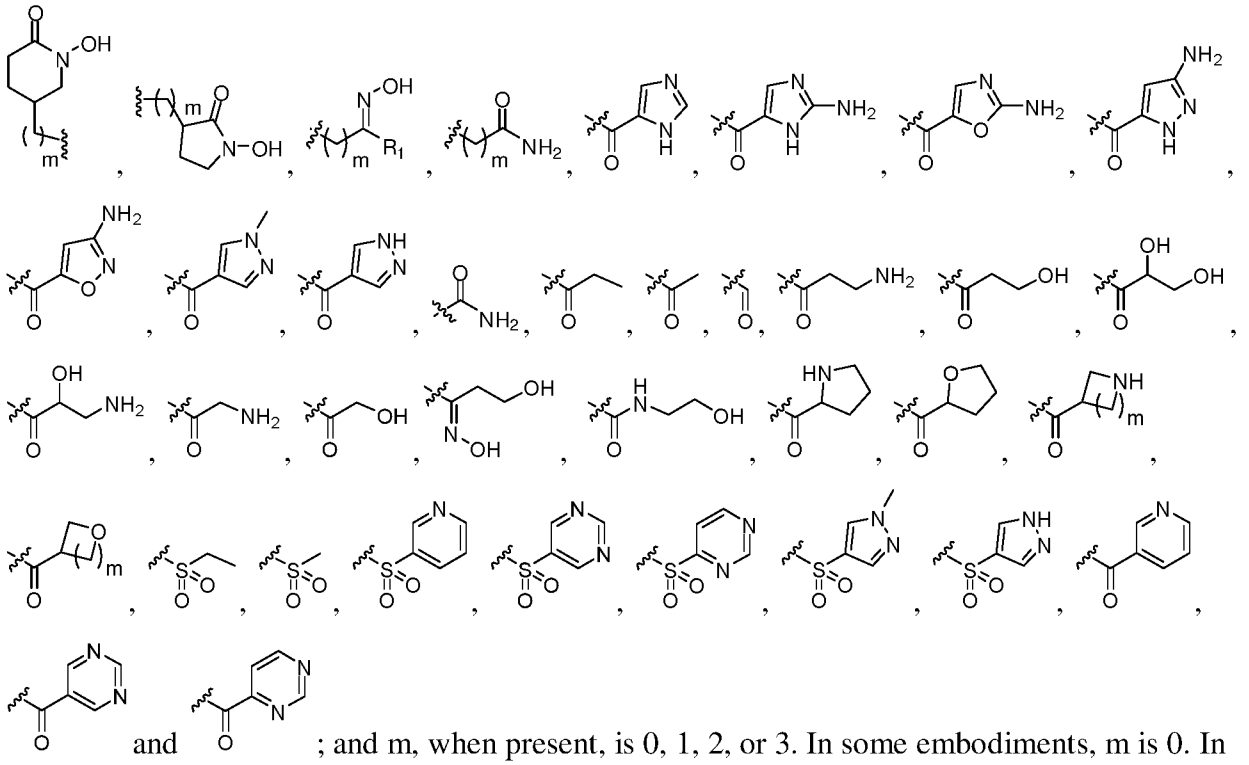
[0127] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), T is an optionally substituted alkyl group comprising at least 1, 2, 3, 4, 5, 6, 7, 8, or 9 heteroatoms selected from N, O, and S. In some embodiments, T is an optionally substituted alkyl group comprising at least 1, 2, 3, 4, or 5 nitrogen atoms. In some embodiments, T is an optionally substituted alkyl group comprising at least 1, 2, 3, 4, or 5 oxygen atoms. In some embodiments, T is an optionally substituted alkyl group comprising at least 1, 2, 3, 4, or 5 sulfur atoms. In some embodiments, T is an optionally substituted alkyl group comprising at least 1, 2, 3, 4, 5, 6, 7, 8, or 9 heteroatoms selected from N, O, and S, wherein T has a molecular weight between 50 and 300 Daltons, and wherein T does not comprise an electrophilic group capable of forming a covalent bond with a cysteine. In some embodiments, T does not comprise a Michael acceptor. In some embodiments, T does not comprise an alpha-beta unsaturated carbonyl group.

[0128] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), T is selected from -H, -NH_2, -OH, -NH(C_{1-6} alkyl),









and ; and m, when present, is 0, 1, 2, or 3. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 1, 2, or 3. In some embodiments, m is 1 or 2.

[0129] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), T is selected from R^{57}. In some embodiments, T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O. In some embodiments, T is selected from hydrogen, $-CH_3$, -C(O)H, $-C(O)CH_3$, and $-C(O)CH_2CH_3$. In some embodiments, T is hydrogen.

[0130] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), L^1 is selected from bond and $-N(R^{51})-$. In some embodiments, L^1 is a bond.

[0131] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), L^2 is selected to provide proper spacing and/or orientation for the T group to form a complex with a K-Ras, H-Ras or N-Ras protein. In some embodiments, L^2 is a bond. In some embodiments, L^2 is alkylene. In some embodiments, the alkylene is substituted. In some embodiments, the alkylene is unsubstituted. In some embodiments, L^2 is CH_2 or CH_2CH_2.

[0132] In some embodiments, for a compound of Formula (I), (I-C), (II), or (II-C), X is N. In some embodiments, Z is N. In some embodiments, X is N and Z is N. In some embodiments, X is N, Z is N, and W is CR^6, wherein R^6 is a bond to L^1. In some embodiments, Z is N, W is CR^6, wherein R^6 is a bond to L^1, and X is CR^6, wherein R^6 is hydrogen, cyano, methoxy or amino. In some embodiments, Z is N, X is CR^6 and R^6 is hydrogen or cyano, and W is CR^6, wherein R^6 is a bond to L^1. In some embodiments, Z is N, W is CR^6, wherein R^6 is a bond to L^1, and X is CR^6, wherein R^6 is hydrogen. In some embodiments, Z is a bond.

[0133] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C):

R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl, optionally substituted with one or more substituents selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl.

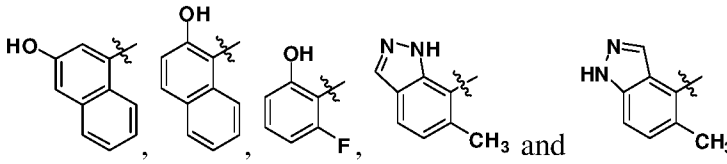
[0134] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C):

R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl, optionally substituted with one or more substituents selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

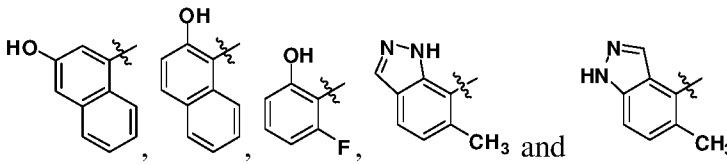
T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O.

[0135] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C):

R^1 is selected from  ; and

R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0136] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C):

R^1 is selected from  ;

R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O.

[0137] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C):

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, -

$NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0138] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C):

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{2a} and R^{2b} are each independently selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

R^{2c} is hydrogen.

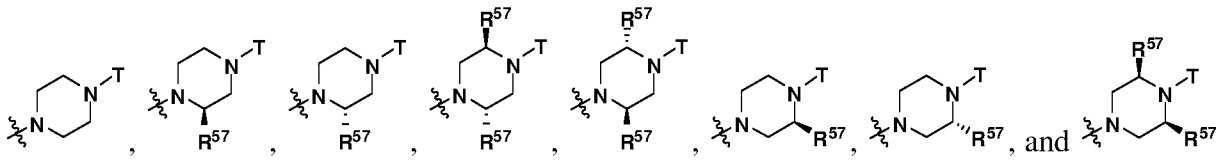
[0139] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C):

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2a} and R^{2b} are each independently selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2c} is hydrogen; and

C is selected from:



[0140] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C):

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents selected from halogen, -OH, $-OCH_3$, C_{1-4}

alkyl, and C_{1-4} haloalkyl;

R^{2a} and R^{2b} are each independently selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

R^{2c} is hydrogen.

[0141] In some embodiments, for a compound of Formula (I), (I-A), (II) or (II-A):

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

C is piperazinylene, optionally substituted with one or more R^{57}.

[0142] In some embodiments, for a compound of Formula (I), (I-A), (II) or (II-A):

R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl, optionally substituted with one or more substituents selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

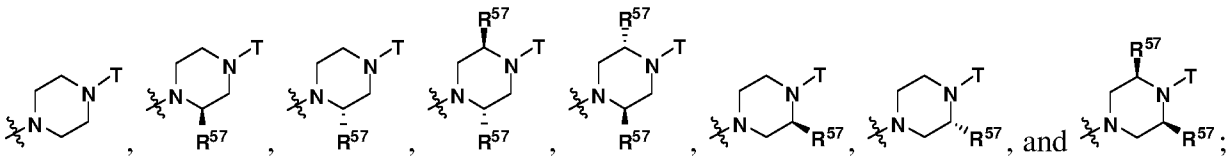
C is piperazinylene, optionally substituted with one or more R^{57}.

[0143] In some embodiments, for a compound of Formula (I), (I-A), (II) or (II-A):

R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl, optionally substituted with one or more substituents selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

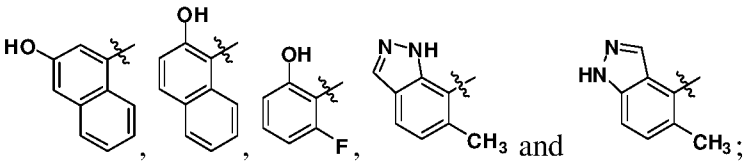
C is selected from:



T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O; and

R^{57} is independently selected at each occurrence from C_{1-6} alkyl, such as $-CH_3$.

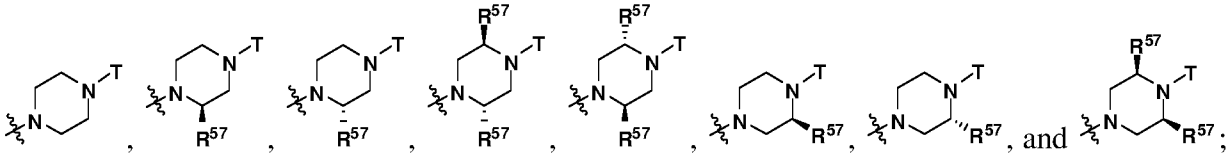
[0144] In some embodiments, for a compound of Formula (I), (I-A), (II) or (II-A):

R^1 is selected from  ;

R^{2a} and R^{2b} are each independently selected from halogen;

R^{2c} is hydrogen;

C is selected from:

 ;

T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O; and

R^{57} is independently selected at each occurrence from C_{1-6} alkyl, such as $-CH_3$.

[0145] In some embodiments, for a compound of Formula (I) or (I-A):

R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen and halogen;

Y^1 is selected from $-OR^{55}$ and $-CH_2OR^{55}$;

C is selected from piperazinylene, optionally substituted with one or more R^{57}; and

T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O.

[0146] In some embodiments, for a compound of Formula (I) or (I-A):

R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl, optionally substituted with one or more substituents selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;

Y^1 is selected from $-OR^{55}$ and $-CH_2OR^{55}$;

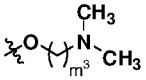
C is selected from piperidinylene and piperazinylene, optionally substituted with one or more R^{57}; and

T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O.

[0147] In some embodiments, for a compound of Formula (I) or (I-A):

R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl, optionally substituted with one or more substituents selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

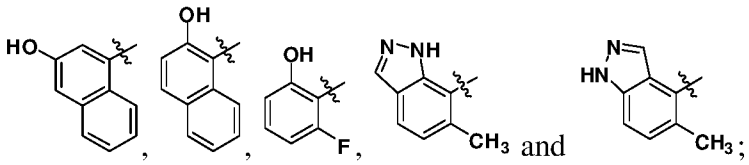
R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;

Y^1 is  , wherein m^3 is an integer from 1 to 6;

C is selected from piperidinylene and piperazinylene, optionally substituted with one or more R^{57}; and

T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O.

[0148] In some embodiments, for a compound of Formula (I) or (I-A):

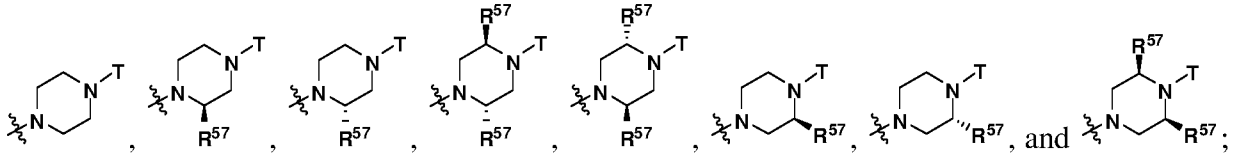
R^1 is selected from  ;

R^{2a} and R^{2b} are each independently selected from halogen;

R^{2c} is hydrogen;

Y^1 is selected from $-OR^{55}$ and $-CH_2OR^{55}$;

C is selected from:

 ;

and

T is selected from hydrogen, $-CH_3$, -C(O)H, $-C(O)CH_3$, and $-C(O)CH_2CH_3$; and

R^{57} is independently selected at each occurrence from C_{1-6} alkyl, such as $-CH_3$.

[0149] In some embodiments, for a compound of Formula (II) or (II-A):

R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen and halogen;

Y^2 is selected from $-N(R^{56})_2$ and $-CH_2N(R^{56})_2$, wherein at least one R^{56} is not hydrogen;

C is selected from piperazinylene, optionally substituted with one or more R^{57}; and

T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O.

[0150] In some embodiments, for a compound of Formula (II) or (II-A):

R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl, optionally substituted with one or more substituents selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

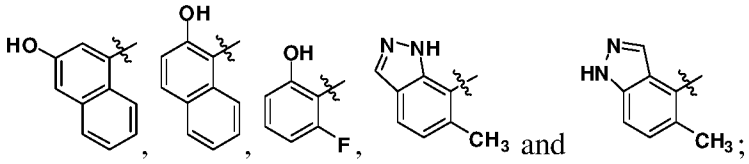
R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;

Y^2 is selected from $-N(R^{56})_2$ and $-CH_2N(R^{56})_2$, wherein at least one R^{56} is not hydrogen;

C is selected from piperidinylene and piperazinylene, optionally substituted with one or more R^{57}; and

T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O.

[0151] In some embodiments, for a compound of Formula (II) or (II-A):

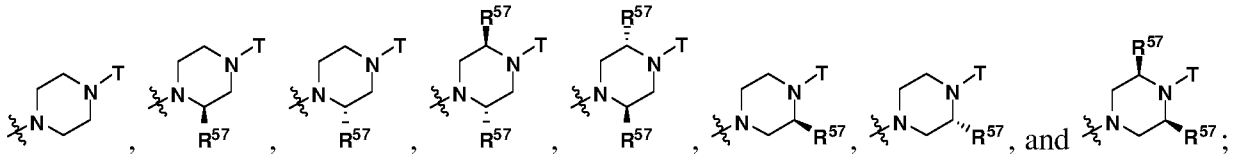
R^1 is selected from  ;

R^{2a} and R^{2b} are each independently selected from halogen;

R^{2c} is hydrogen;

Y^2 is selected from $-N(R^{56})_2$ and $-CH_2N(R^{56})_2$, wherein at least one R^{56} is not hydrogen;

C is selected from:

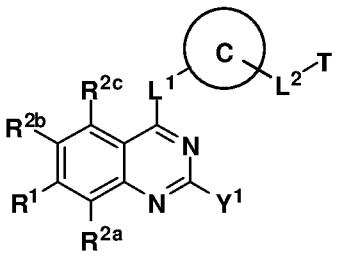


and

T is selected from hydrogen, $-CH_3$, -C(O)H, $-C(O)CH_3$, and $-C(O)CH_2CH_3$; and

R^{57} is independently selected at each occurrence from C_{1-6} alkyl, such as $-CH_3$.

[0152] In certain aspects, the present disclosure provides a compound of Formula (I-A):

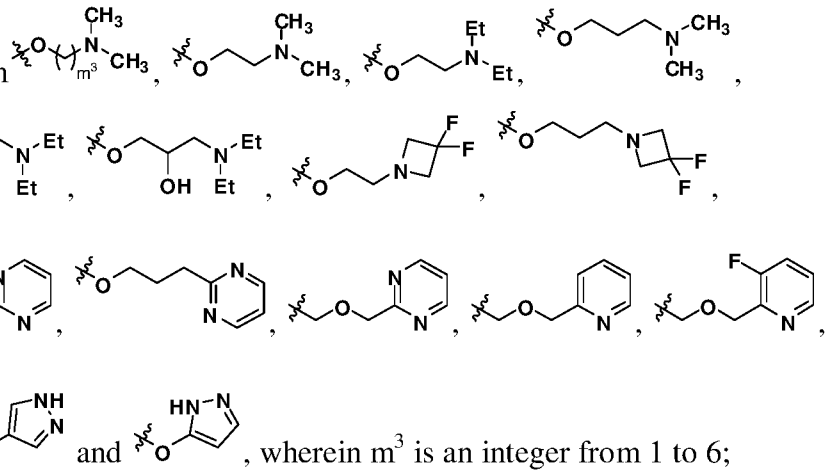


(I-A), or a salt thereof, wherein:

R^1 is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2c} is selected from hydrogen, halogen, -OH, C_{1-4} alkyl, and C_{1-4} haloalkyl;

Y^1 is selected from 

and , wherein m^3 is an integer from 1 to 6;

L^1 and L^2 are each independently selected from bond and C_{1-3} alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of

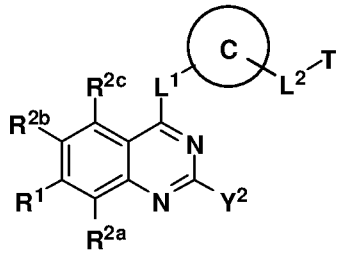
a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

[0153] In certain aspects, the present disclosure provides a compound of Formula (II-A):

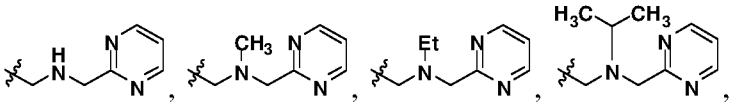
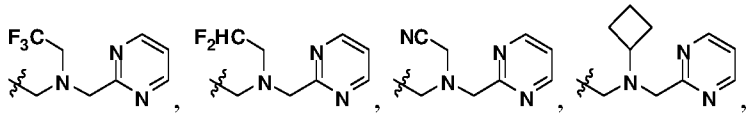


(II-A), or a salt thereof, wherein:

R^1 is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2c} is selected from hydrogen, halogen, -OH, C_{1-4} alkyl, and C_{1-4} haloalkyl;

Y^2 is selected from  ,  , and $-CH_2N(R^{58})CH_2R^{59}$, wherein R^{58} is selected from hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl substituted with halogen or -CN, C_{3-6} carbocycle, and 3- to 6-membered heterocycle; and R^{59} is selected from 3- to 8-membered heterocycle, optionally substituted with one or more halogens;

L^1 and L^2 are each independently selected from bond and C_{1-3} alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

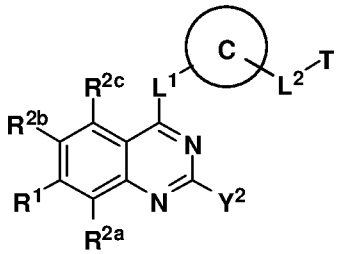
T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

[0154] In certain aspects, the present disclosure provides a compound of Formula (II-A):

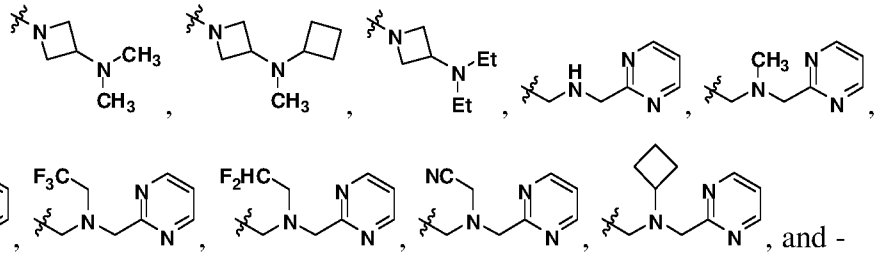


(II-A), or a salt thereof, wherein:

R^1 is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2c} is selected from hydrogen, halogen, -OH, C_{1-4} alkyl, and C_{1-4} haloalkyl;

Y^2 is selected from  , and -$CH_2N(R^{58})CH_2R^{59}$, wherein R^{58} is selected from hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl substituted with halogen or -CN, C_{3-6} carbocycle, and 3- to 6-membered heterocycle; and R^{59} is selected from 3- to 8-membered heterocycle, optionally substituted with one or more halogens;

L^1 and L^2 are each independently selected from bond and C_{1-3} alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

[0155] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof can be chosen to provide stable moieties and compounds.

[0156] In certain embodiments, the present disclosure provides a stereoisomer of a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C). In some embodiments, the stereoisomer is in enantiomeric excess. In some embodiments, the stereoisomer is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some embodiments, the stereoisomer is provided in greater than 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some embodiments, the stereoisomer is in greater than 95% enantiomeric excess, such as greater than 99% enantiomeric excess.

[0157] In certain embodiments, the present disclosure provides a stereoisomer of a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C). In some embodiments, the stereoisomer is in diastereomeric excess. In some embodiments, the stereoisomer is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, diastereomeric excess. In some embodiments, the stereoisomer is provided in greater than 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, diastereomeric excess. In some embodiments, the stereoisomer is in greater than 95% diastereomeric excess, such as greater than 99% diastereomeric excess.

[0158] In certain embodiments, the present disclosure provides an atropisomer of a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C). In some embodiments, the atropisomer is in enantiomeric excess. In some embodiments, the atropisomer is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some

embodiments, the atropisomer is provided in greater than 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some embodiments, the atropisomer is in greater than 95% enantiomeric excess, such as greater than 99% enantiomeric excess.

[0159] In certain embodiments, the compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) is preferably used as a non-racemic mixture, wherein one atropisomer is present in excess of its corresponding enantiomer or epimer. Typically, such mixture will contain a mixture of the two isomers in a ratio of at least about 9:1, preferably at least 19:1. In some embodiments, the atropisomer is provided in at least 96% enantiomeric excess, meaning the compound has less than 2% of the corresponding enantiomer. In some embodiments, the atropisomer is provided in at least 96% diastereomeric excess, meaning the compound has less than 2% of the corresponding diastereomer.

[0160] In certain embodiments, the compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) is preferably used as a non-racemic mixture wherein the (+)-isomer is the major component of the mixture. Typically, such mixture will contain no more than about 10% of the (–)-isomer, meaning the ratio of (+)- to (–)-isomers is at least about 9:1, and preferably less than 5% of the (–)-isomer, meaning the ratio of (+)- to (–)-isomers is at least about 19:1. In some embodiments, the compound used has less than 2% of the (–)-isomer, meaning it has an enantiomeric excess of at least about 96%. In some embodiments, the compound has an enantiomeric excess of at least 98%. In some embodiments, the compound has an enantiomeric excess of at least 99%.

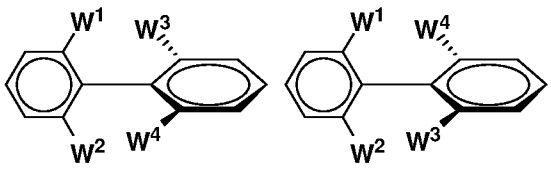
[0161] In certain embodiments, the compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) is preferably used as a non-racemic mixture wherein the (–)-isomer is the major component of the mixture. Typically, such mixture will contain no more than about 10% of the (+)-isomer, meaning the ratio of (–)- to (+)-isomers is at least about 9:1, and preferably less than 5% of the (+)-isomer, meaning the ratio of (–)- to (+)-isomers is at least about 19:1. In some embodiments, the compound used has less than 2% of the (+)-isomer, meaning it has an enantiomeric excess of at least about 96%. In some embodiments, the compound has an enantiomeric excess of at least 98%. In some embodiments, the compound has an enantiomeric excess of at least 99%.

[0162] The term "atropisomers" refers to conformational stereoisomers which occur when rotation about a single bond in the molecule is prevented, or greatly slowed, as a result of steric interactions with other parts of the molecule and the substituents at both ends of the single bond are asymmetrical (*i.e.*, optical activity arises without requiring an asymmetric carbon center or

stereocenter). Where the rotational barrier about the single bond is high enough, and interconversion between conformations is slow enough, separation and isolation of the isomeric species may be permitted. Atropisomers are enantiomers (or epimers) without a single asymmetric atom. By one definition, atropisomerism is defined to exist where the isomers have a half-life ($t_{1/2}$) of at least 1000 seconds, which is a free energy barrier of 22.3 kcal mol^{-1} (93.3 kJ mol^{-1}) at 300 K (Oki, M., "Recent Advances in Atropisomerism," *Topics in Stereochemistry* (1983) 14:1). The atropisomers are considered stable if the barrier to interconversion is high enough to permit the atropisomers to undergo little or no interconversion at room temperature for at least a week, preferably at least a year. In some embodiments, an atropisomeric compound of the disclosure does not undergo more than about 5% interconversion to its opposite atropisomer at room temperature during one week when the atropisomeric compound is in substantially pure form, which is generally a solid state. In some embodiments, an atropisomeric compound of the disclosure does not undergo more than about 5% interconversion to its opposite atropisomer at room temperature (approximately 25 °C) during one year. Preferably, the atropisomeric compounds of the disclosure are stable enough to undergo no more than about 5% interconversion in an aqueous pharmaceutical formulation held at 0 °C for at least one week. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible atropisomers, including racemic mixtures, diastereomeric mixtures, epimeric mixtures, optically pure forms of single atropisomers, and intermediate mixtures.

[0163] The energy barrier to thermal racemization of atropisomers may be determined by the steric hindrance to free rotation of one or more bonds forming a chiral axis. Certain biaryl compounds exhibit atropisomerism where rotation around an interannular bond lacking C2 symmetry is restricted. The free energy barrier for isomerization (enantiomerization) is a measure of the stability of the interannular bond with respect to rotation. Optical and thermal excitation can promote racemization of such isomers, dependent on electronic and steric factors.

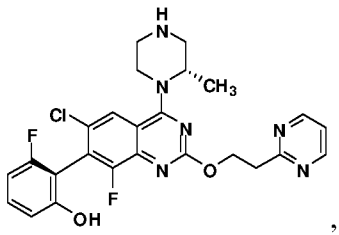
[0164] Ortho-substituted biaryl compounds may exhibit this type of conformational, rotational isomerism. Such biaryls are enantiomeric, chiral atropisomers where the sp^2-sp^2 carbon-carbon, interannular bond between the aryl rings has a sufficiently high energy barrier to prevent free rotation, and where substituents $W^1 \neq W^2$ and $W^3 \neq W^4$ render the molecule asymmetric.



[0165] The steric interaction between W^1:W^3, W^1:W^4, and/or W^2:W^4, W^2:W^3 is large enough to make the planar conformation an energy maximum. Two non-planar, axially chiral enantiomers

then exist as atropisomers when their interconversion is slow enough such that they can be isolated free of each other. Bold lines and dashed lines in the figures shown above indicate those moieties, or portions of the molecule, which are sterically restricted due to a rotational energy barrier. Bolded moieties exist orthogonally above the plane of the page, and dashed moieties exist orthogonally below the plane of the page. The 'flat' part of the molecule (the left ring in each of the two depicted biaryls) is in the plane of the page.

[0166] In certain aspects, the present disclosure provides at least 90% epimeric excess of an atropisomer selected from: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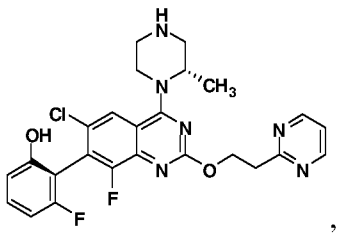
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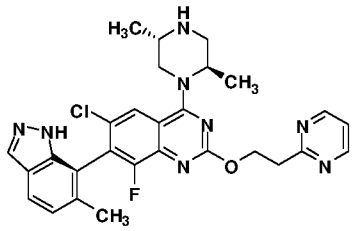
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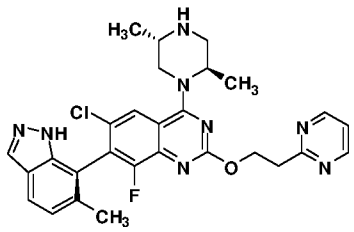
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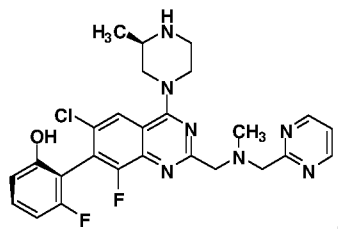
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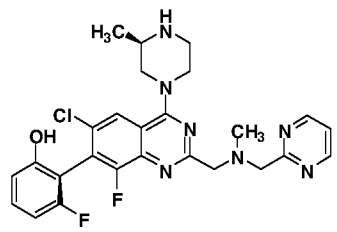
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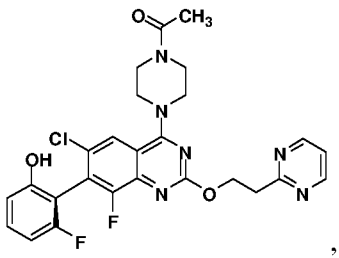
[0167] In certain aspects, the present disclosure provides at least 90% enantiomeric excess of an atropisomer selected from: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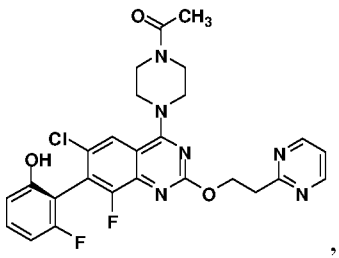
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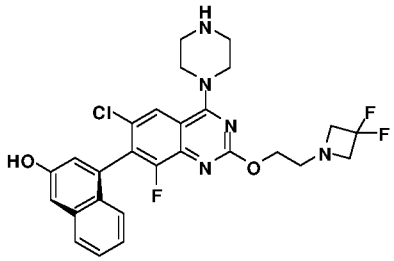
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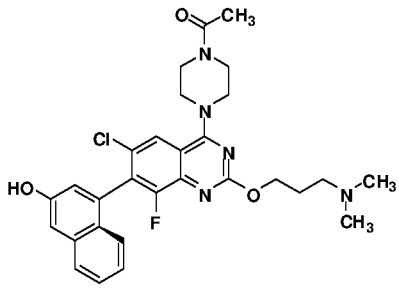
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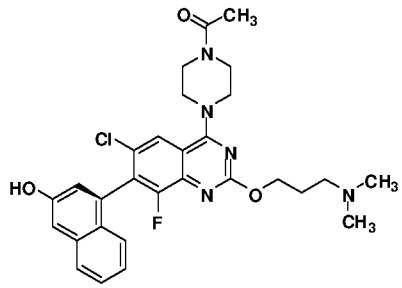
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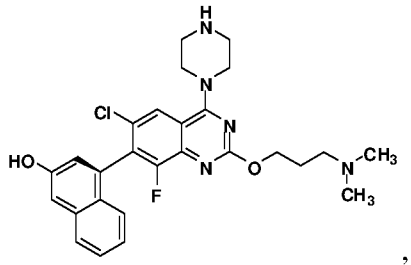
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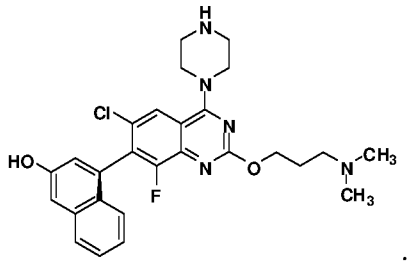
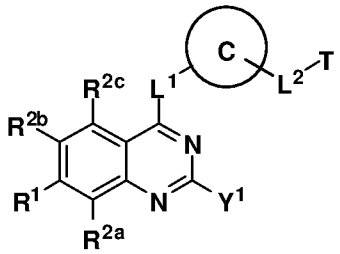


and .

[0168] In certain aspects, the present disclosure provides a stereoisomer of a compound of Formula (I-A):



(I-A), or a salt thereof, wherein:

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with one or more substituents independently selected from halogen, -OH, $-OR^{52}$, $-NH_2$, -NHMe, $-NMe_2$, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from hydrogen, halogen, -OH, $-OR^{52}$, C_{1-4} alkyl, and C_{1-4} haloalkyl, wherein at least one of R^{2a} and R^{2b} is not hydrogen;

R^{2c} is selected from hydrogen, halogen, -OH, $-OR^{52}$, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

Y^1 is selected from $-OR^{55}$; and C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, each of which is substituted with $-OR^{55}$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, -OS(O)-, -S(O)O-, -S(O)-, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, $-N(R^{51})S(O)N(R^{51})-$; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, -

$NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{55} is selected from:

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{55} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, -

$NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

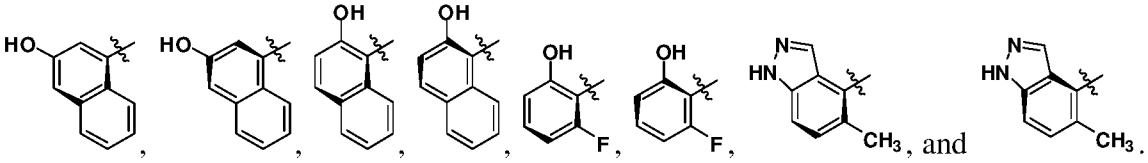
R^{57} is independently selected at each occurrence from:

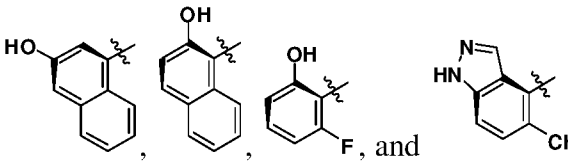
halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

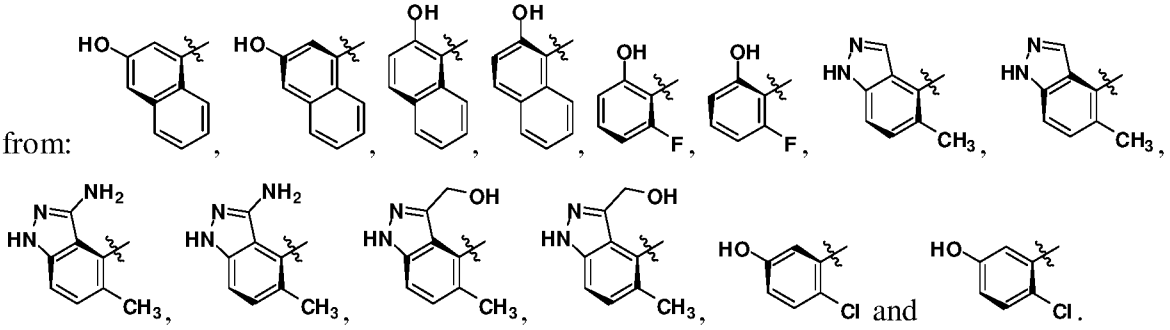
C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

[0169] In some embodiments, the stereoisomer of a compound of Formula (I-A) is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some embodiments, the stereoisomer is provided in greater than 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some embodiments, the stereoisomer is in greater than 95% enantiomeric excess, such as greater than 99% enantiomeric excess. In some embodiments, the stereoisomer of a compound of Formula (I-A) is an atropisomer.

[0170] In some embodiments, the stereoisomer of a compound of Formula (I-A) is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, diastereomeric excess. In some embodiments, the stereoisomer is provided in greater than 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, diastereomeric excess. In some embodiments, the stereoisomer is in greater than 95% diastereomeric excess, such as greater than 99% diastereomeric excess. In some embodiments, the stereoisomer of a compound of Formula (I-A) comprises an atropisomer.

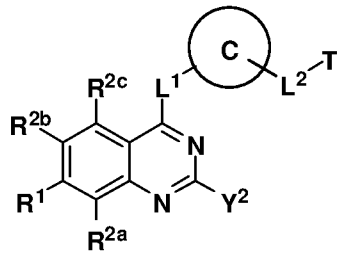
[0171] In some embodiments, for a stereoisomer of a compound of Formula (I-A), R^1 is selected from:  .

In some embodiments, R^1 is selected from:  . In some embodiments, R^{2a} and R^{2b} are each independently selected from halogen. In some embodiments, R^1, R^{2a} and R^{2b} are selected to produce an atropisomer.

[0172] In some embodiments, for a stereoisomer of a compound of Formula (I-A), R^1 is selected from:  .

[0173] Any combination of the groups described above for the various variables of a compound of Formula (I-A) is contemplated herein for the stereoisomer of a compound of Formula (I-A).

[0174] In certain aspects, the present disclosure provides a stereoisomer of a compound of Formula (II-A):



(II-A), or a salt thereof, wherein:

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with one or more substituents independently selected from halogen, -OH, -OR^{52}, -NH_2, -NHMe, -NMe_2, C_{1-3} haloalkyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from hydrogen, halogen, -OH, -OR^{52}, C_{1-4} alkyl, and C_{1-4} haloalkyl, wherein at least one of R^{2a} and R^{2b} is not hydrogen;

R^{2c} is selected from hydrogen, halogen, -OH, -OR^{52}, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

Y^2 is selected from -$N(R^{56})_2$; and C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, each of which is substituted with -$N(R^{56})_2$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, -$N(R^{51})$-, -$N(R^{51})CH_2$-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -$C(O)N(R^{51})$-, -$C(O)N(R^{51})C(O)$-, -$C(O)N(R^{51})C(O)N(R^{51})$-, -$N(R^{51})C(O)$-, -$N(R^{51})C(O)N(R^{51})$-, -$N(R^{51})C(O)O$-, -$OC(O)N(R^{51})$-, -$C(NR^{51})$-, -$N(R^{51})C(NR^{51})$-, -$C(NR^{51})N(R^{51})$-, -$N(R^{51})C(NR^{51})N(R^{51})$-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})S(O)$-, -$S(O)N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, -

$N(R^{51})S(O)N(R^{51})$-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{56} is independently selected at each occurrence from:

hydrogen;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, -

$OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

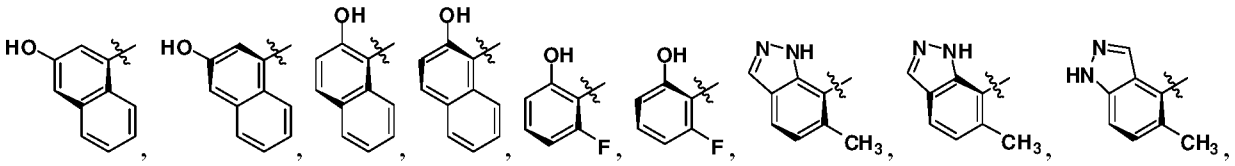
C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

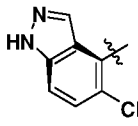
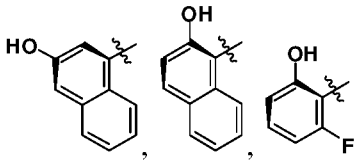
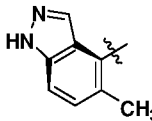
[0175] In some embodiments, the stereoisomer of a compound of Formula (II-A) is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some embodiments, the stereoisomer is provided in greater than 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some embodiments, the stereoisomer is in greater than 95% enantiomeric excess, such as greater than 99% enantiomeric excess. In some embodiments, the stereoisomer of a compound of Formula (II-A) is an atropisomer.

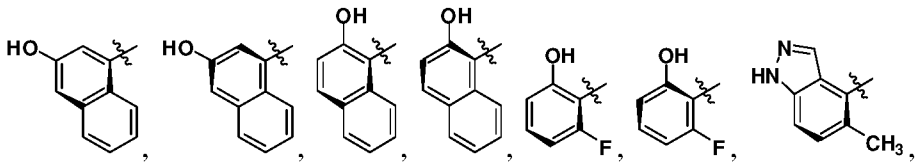
[0176] In some embodiments, the stereoisomer of a compound of Formula (II-A) is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, diastereomeric excess. In some

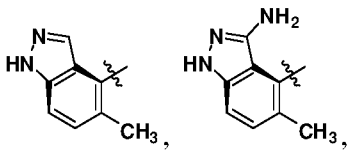
embodiments, the stereoisomer is provided in greater than 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, diastereomeric excess. In some embodiments, the stereoisomer is in greater than 95% diastereomeric excess, such as greater than 99% diastereomeric excess. In some embodiments, the stereoisomer of a compound of Formula (II-A) comprises an atropisomer.

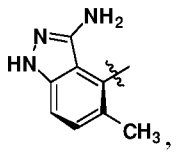
[0177] In some embodiments, for a stereoisomer of a compound of Formula (II-A), R^1 is selected from:

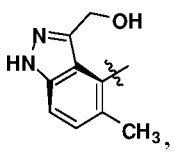


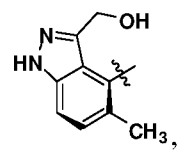
and  . In some embodiments, R^1 is selected from:  , and  . In some embodiments, R^{2a} and R^{2b} are each independently selected from halogen. In some embodiments, R^1, R^{2a} and R^{2b} are selected to produce an atropisomer.

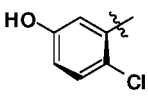
[0178] In some embodiments, for a stereoisomer of a compound of Formula (II-A), R^1 is selected from: 





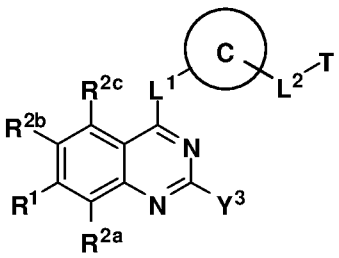




and  .

[0179] Any combination of the groups described above for the various variables of a compound of Formula (II-A) is contemplated herein for the stereoisomer of a compound of Formula (II-A).

[0180] In certain aspects, the present disclosure provides a stereoisomer of a compound of Formula (III-A):



(III-A), or a salt or prodrug thereof, wherein:

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with one or more substituents independently selected from halogen, -OH, -OR^{52}, -NH_2, -NHMe, -NMe_2, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from hydrogen, halogen, -OH, -OR^{52}, C_{1-4} alkyl, and C_{1-4} haloalkyl, wherein at least one of R^{2a} and R^{2b} is not hydrogen;

R^{2c} is selected from hydrogen, halogen, -OH, -OR^{52}, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

Y^3 is selected from -OR^{55}, -$N(R^{56})_2$; and C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, each of which is substituted with -OR^{55} or -$N(R^{56})_2$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, -$N(R^{51})$-, -$N(R^{51})CH_2$-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -$C(O)N(R^{51})$-, -$C(O)N(R^{51})C(O)$-, -$C(O)N(R^{51})C(O)N(R^{51})$-, -$N(R^{51})C(O)$-, -$N(R^{51})C(O)N(R^{51})$-, -$N(R^{51})C(O)O$-, -$OC(O)N(R^{51})$-, -$C(NR^{51})$-, -$N(R^{51})C(NR^{51})$-, -$C(NR^{51})N(R^{51})$-, -$N(R^{51})C(NR^{51})N(R^{51})$-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})S(O)$-, -$S(O)N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, -$N(R^{51})S(O)N(R^{51})$-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{50} is independently selected at each occurrence from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -

$P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected

from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{55} is selected from:

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{55} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{56} is independently selected at each occurrence from:

hydrogen;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl,

or two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50}; and

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

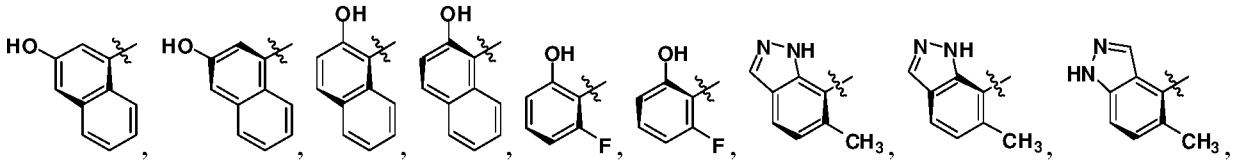
C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

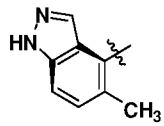
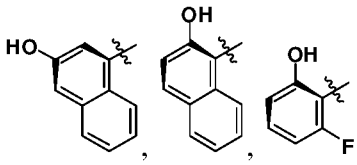
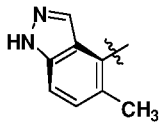
[0181] In some embodiments, the stereoisomer of a compound of Formula (III-A) is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%,

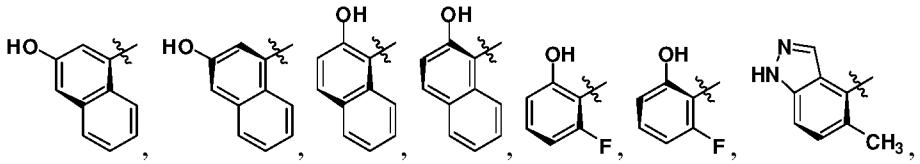
93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some embodiments, the stereoisomer is provided in greater than 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some embodiments, the stereoisomer is in greater than 95% enantiomeric excess, such as greater than 99% enantiomeric excess. In some embodiments, the stereoisomer of a compound of Formula (III-A) is an atropisomer.

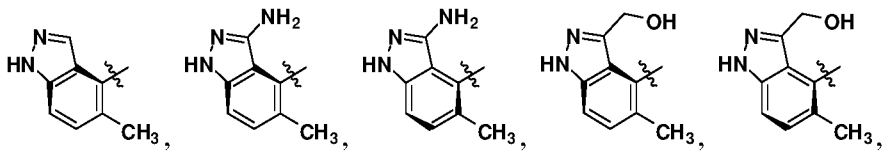
[0182] In some embodiments, the stereoisomer of a compound of Formula (III-A) is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, diastereomeric excess. In some embodiments, the stereoisomer is provided in greater than 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, diastereomeric excess. In some embodiments, the stereoisomer is in greater than 95% diastereomeric excess, such as greater than 99% diastereomeric excess. In some embodiments, the stereoisomer of a compound of Formula (III-A) comprises an atropisomer.

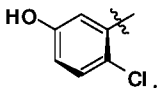
[0183] In some embodiments, for a stereoisomer of a compound of Formula (III-A), R^1 is selected from:



and  . In some embodiments, R^1 is selected from:  , and  . In some embodiments, R^{2a} and R^{2b} are each independently selected from halogen. In some embodiments, R^1, R^{2a} and R^{2b} are selected to produce an atropisomer.

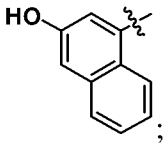
[0184] In some embodiments, for a stereoisomer of a compound of Formula (III-A), R^1 is selected from: 

 and

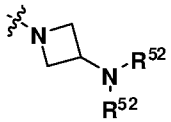


[0185] Any combination of the groups described above for the various variables of a compound of Formulas (I-A) or (II-A) is contemplated herein for the stereoisomer of a compound of Formula (III-A).

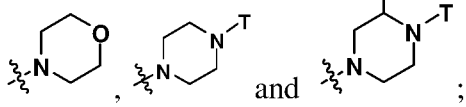
[0186] In certain aspects, the present disclosure provides a stereoisomer of a compound or salt of Formula (III-A), wherein:

R^1 is  ;

R^{2a} and R^{2b} are each independently selected from halogen; R^{2c} is hydrogen;

Y^3 is selected from $-OR^{55}$ and  ;

L^1 is a bond; L^2 is a bond;

C is selected from  ;

T is selected from hydrogen; and $C_{1\text{-}6}$ alkyl, optionally substituted with =O;

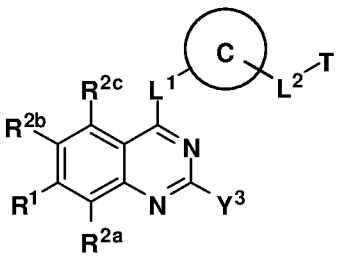
R^{52} is independently selected at each occurrence from hydrogen and halogen; and $C_{1\text{-}20}$ alkyl, $C_{2\text{-}20}$ alkenyl, $C_{2\text{-}20}$ alkynyl, 2- to 6-membered heteroalkyl, $C_{3\text{-}12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, $C_{3\text{-}12}$ carbocycle, or 3- to 6-membered heterocycle; and

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1\text{-}6}$ alkyl, $-N(C_{1\text{-}6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1\text{-}6}$ alkyl, $-NHC(O)C_{1\text{-}6}$ alkyl, $-N(C_{1\text{-}6}$ alkyl$)C(O)C_{1\text{-}6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1\text{-}6}$ alkyl$)$, $-C(O)N(C_{1\text{-}6}$ alkyl$)_2$, =O, =N(OH); and

$C_{1\text{-}10}$ alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1\text{-}6}$ alkyl, $-N(C_{1\text{-}6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1\text{-}6}$ alkyl, $-NHC(O)C_{1\text{-}6}$ alkyl, $-N(C_{1\text{-}6}$ alkyl$)C(O)C_{1\text{-}6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1\text{-}6}$ alkyl$)$, $-C(O)N(C_{1\text{-}6}$ alkyl$)_2$, =O, and =N(OH).

[0187] In certain aspects, the present disclosure provides a stereoisomer of a compound of Formula (III-A):



(III-A), or a salt or prodrug thereof, wherein:

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with one or more substituents independently selected from halogen, -OH, -OR^{52}, -NH_2, -NHMe, -NMe_2, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from hydrogen, halogen, -OH, -OR^{52}, C_{1-4} alkyl, and C_{1-4} haloalkyl, wherein at least one of R^{2a} and R^{2b} is not hydrogen;

R^{2c} is selected from hydrogen, halogen, -OH, -OR^{52}, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

Y^3 is selected from -OR^{55}, -$N(R^{56})_2$, -SR^{55} and SO_2R^{55}; and C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, each of which is substituted with -OR^{55}, -$N(R^{56})_2$, -SR^{55} or SO_2R^{55} and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, -$N(R^{51})$-, -$N(R^{51})CH_2$-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -$C(O)N(R^{51})$-, -$C(O)N(R^{51})C(O)$-, -$C(O)N(R^{51})C(O)N(R^{51})$-, -$N(R^{51})C(O)$-, -$N(R^{51})C(O)N(R^{51})$-, -$N(R^{51})C(O)O$-, -$OC(O)N(R^{51})$-, -$C(NR^{51})$-, -$N(R^{51})C(NR^{51})$-, -$C(NR^{51})N(R^{51})$-, -$N(R^{51})C(NR^{51})N(R^{51})$-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})S(O)$-, -$S(O)N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, -$N(R^{51})S(O)N(R^{51})$-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{50} is independently selected at each occurrence from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -

$P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected

from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{55} is selected from:

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{55} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{56} is independently selected at each occurrence from:

hydrogen;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl,

or two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50}; and

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

[0188] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B), (II-C) or (III-A), R^{52} is further selected at each occurrence from halogen. For example, Y^1

may be $-OR^{55}$, wherein R^{55} is C_{1-10} alkyl substituted with $-S(=O)_2R^{52}$, wherein R^{52} is halogen, such as fluorine.

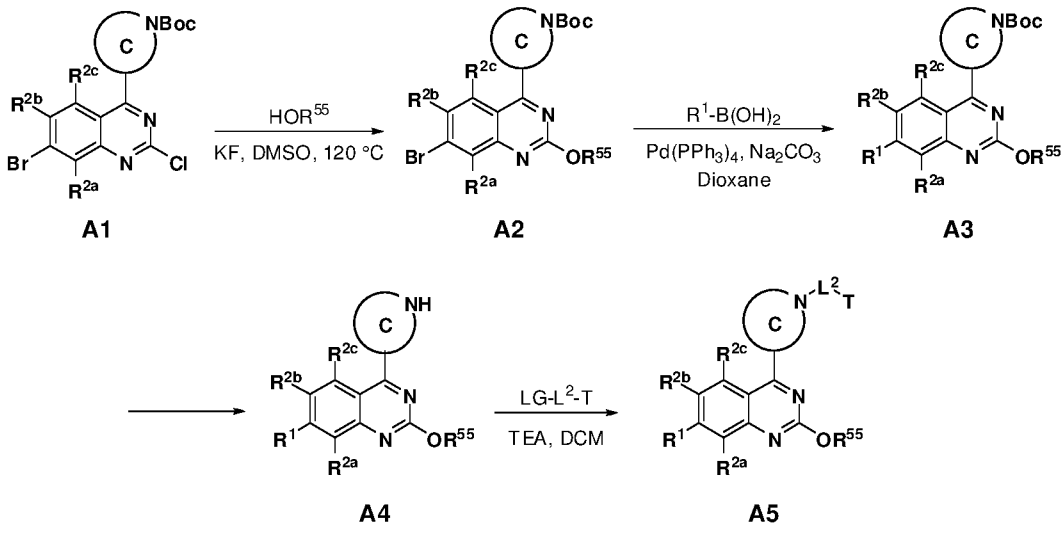
[0189] In some embodiments, for a compound of Formula (I), (I-A), (I-B) or (I-C), Y^1 is selected from $-OR^{55}$, $-SR^{55}$ and SO_2R^{55}; and alkyl, alkenyl, alkynyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with $-OR^{55}$, $-SR^{55}$ or SO_2R^{55} and optionally futher substituted with one or more R^{50}. In some embodiments, for a compound of Formula (III-A), Y^3 is selected from $-OR^{55}$, $-N(R^{56})_2$, $-SR^{55}$ and SO_2R^{55}; and C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, each of which is substituted with $-OR^{55}$, $-N(R^{56})_2$, $-SR^{55}$ or SO_2R^{55} and optionally futher substituted with one or more R^{50}.

[0190] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/or techniques known in the art. Materials used herein are either commercially available or prepared by synthetic methods generally known in the art. These schemes are not limited to the compounds listed in the examples or by any particular substituents, which are employed for illustrative purposes. Although various steps are described and depicted in **Schemes 1-3** and **Examples 1-4**, the steps in some cases may be performed in a different order than the order shown in **Schemes 1-3** and **Examples 1-4**. Various modifications to these synthetic reaction schemes may be made and will be suggested to one skilled in the art having referred to the disclosure contained in this Application. Numberings or R groups in each scheme do not necessarily correspond to that of the claims or other schemes or tables herein.

[0191] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from -10 °C to 200 °C. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, e.g., taking place at about atmospheric pressure within a temperature range of about -10 °C to about 110 °C over a period of about 1 to about 24 hours; reactions left to run overnight average a period of about 16 hours.

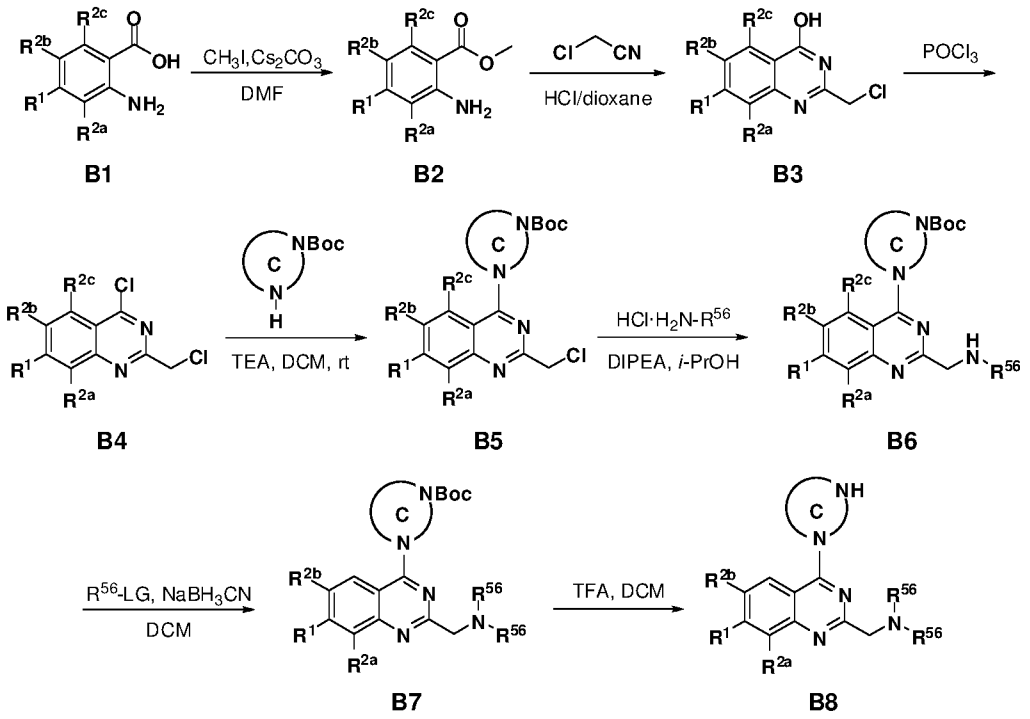
[0192] In general, compounds of the disclosure may be prepared by the following reaction schemes:

Scheme 1



[0193] In some embodiments, a compound of Formula **A5** may be prepared according to **Scheme 1**. For example, 2-chloroquinazoline **A1** can be reacted with an appropriately substituted alcohol to provide ether **A2**. Installation of a desired R^1 substituent may proceed via a Suzuki reaction to give compound **A3**. Boc deprotection provides free amine **A4**, which can optionally be coupled to LG-L^2-T, where LG is a leaving group, to provide a compound of Formula **A5**. In some examples, T is an acyl group, and LG-L^2-T is an acyl chloride group.

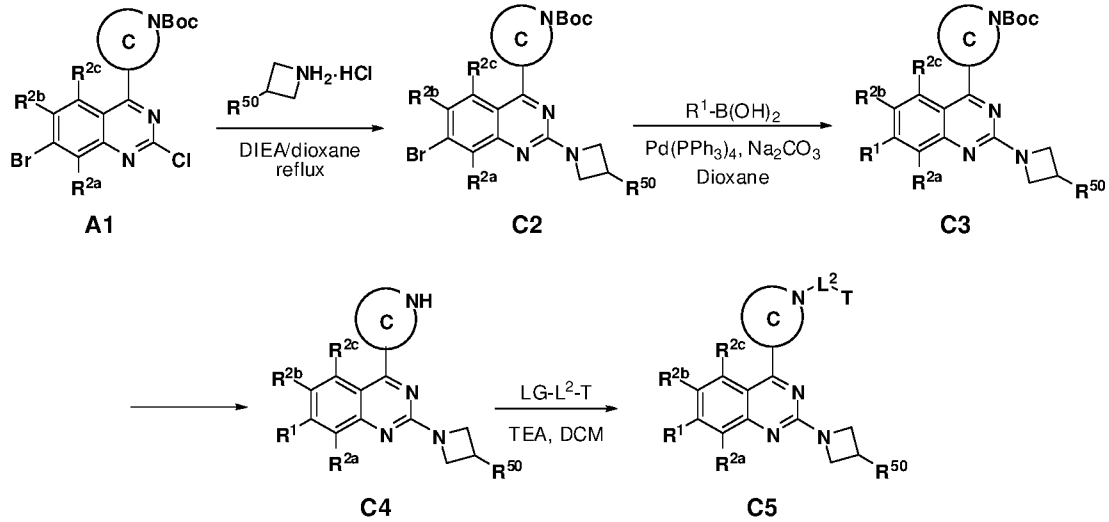
Scheme 2



[0194] In some embodiments, a compound of Formula **B8** may be prepared according to **Scheme 2**. For example, carboxylic acid **B1** can be converted to methyl ester **B2** then cyclized to quinazoline **B3**. Chlorination of **B3** provides **B4**, which can be coupled to Ring C, wherein Ring C comprises a free secondary amine. Addition of an appropriately substituted amine may form

B6. The secondary amine can optionally be further functionalized with an additional R^{56} group to form **B7**, for example, by a reductive amination reaction using formaldehyde or acetaldehyde. Deprotection of the Boc group affords a compound of Formula **B8**, which can optionally be further substituted with a T group as shown in **Scheme 1**.

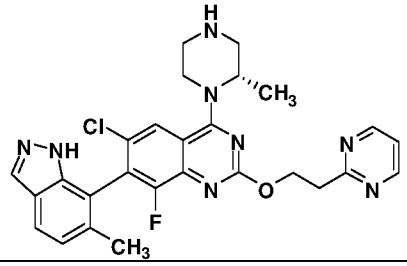
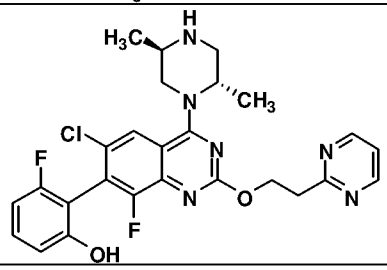
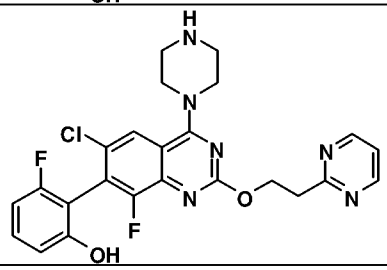
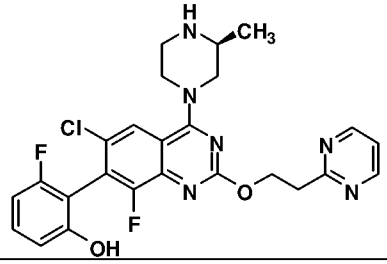
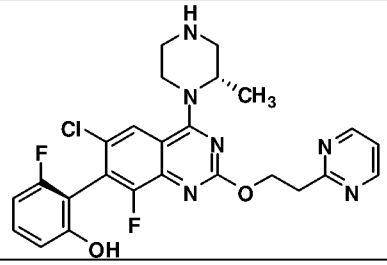
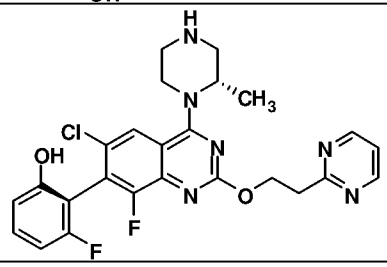
Scheme 3

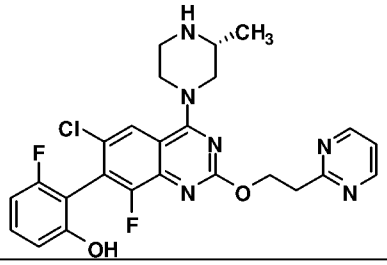
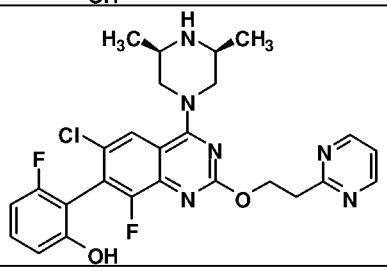
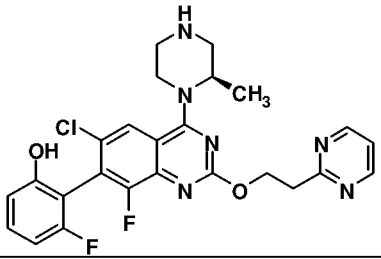
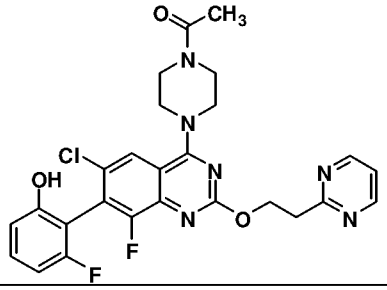
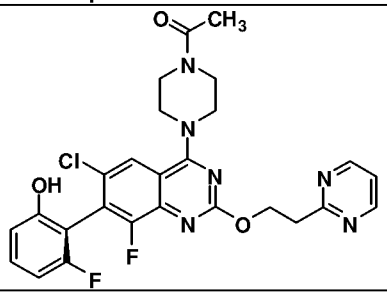
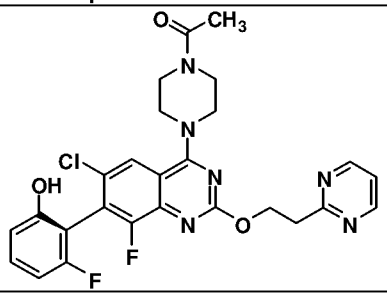


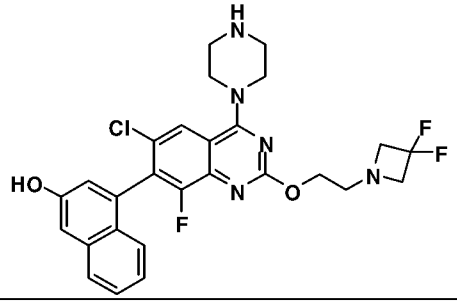
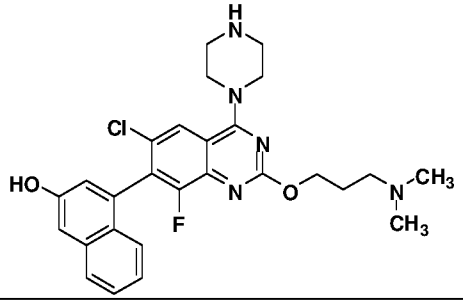
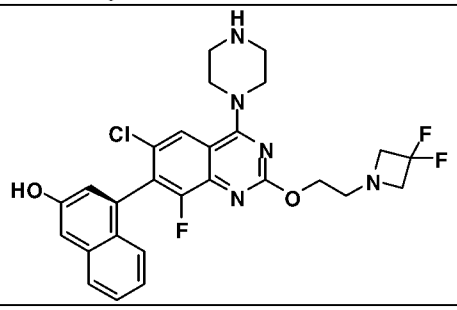
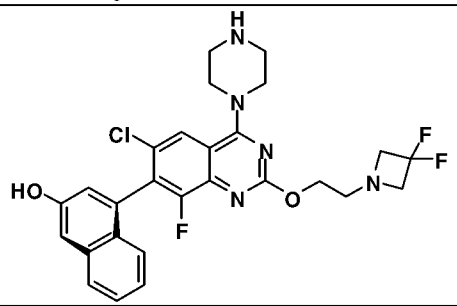
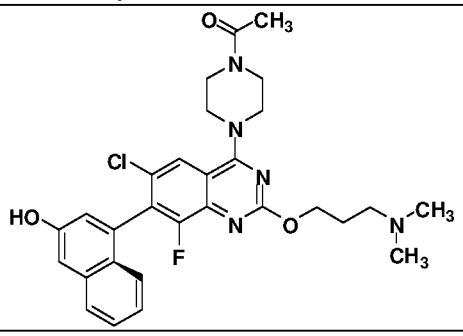
[0195] In some embodiments, a compound of Formula **C5** may be prepared according to **Scheme 3**. For example, 2-chloroquinazoline **A1** can be reacted with an appropriately substituted azetidine to provide **C2**. Installation of a desired R^1 substituent may proceed via a Suzuki reaction to give compound **C3**. Boc deprotection provides free amine **C4**, which can optionally be coupled to LG-L^2-T, where LG is a leaving group, to provide a compound of Formula **C5**. In some examples, T is an acyl group, and LG-L^2-T is an acyl chloride group.

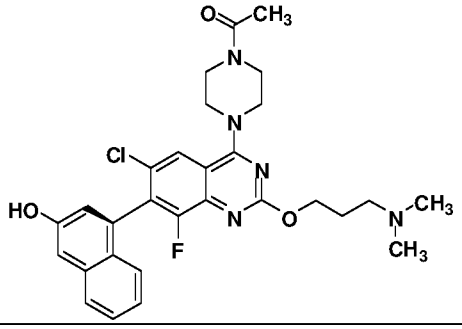
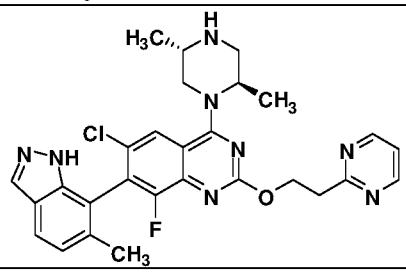
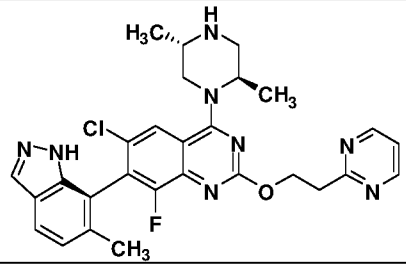
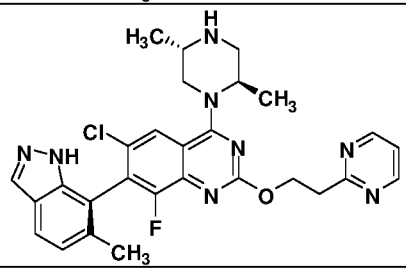
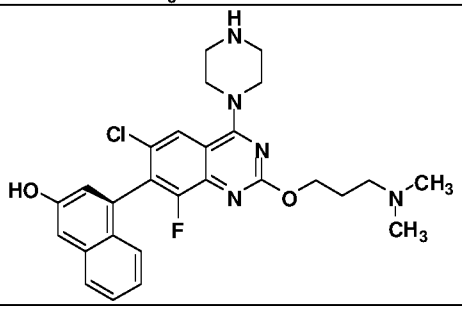
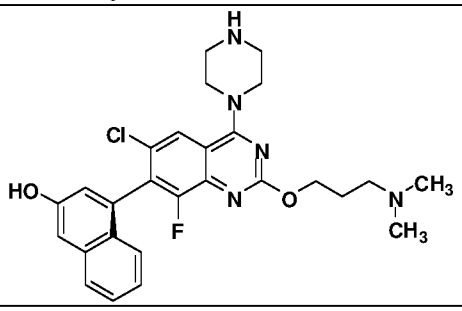
[0196] In some embodiments, a compound of the present disclosure, for example, a compound of a formula given in **Table 1**, **Table 2** or **Table 3** is synthesized according to one of the general routes outlined in **Schemes 1-3**, **Examples 1-4**, or by methods generally known in the art. In some embodiments, exemplary compounds may include, but are not limited to, a compound or salt therof selected from **Table 1**, **Table 2**, or **Table 3**.

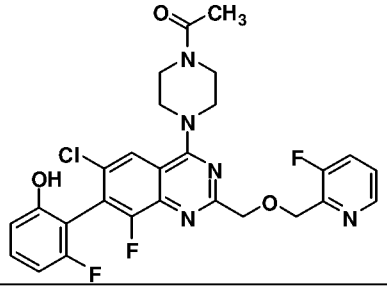
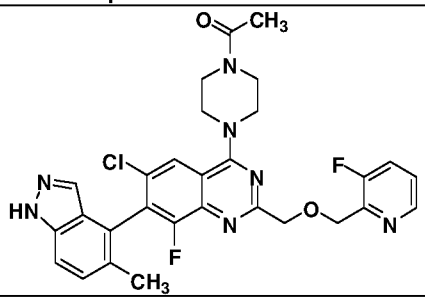
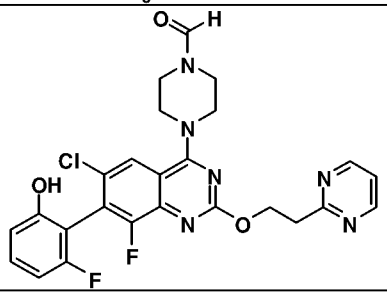
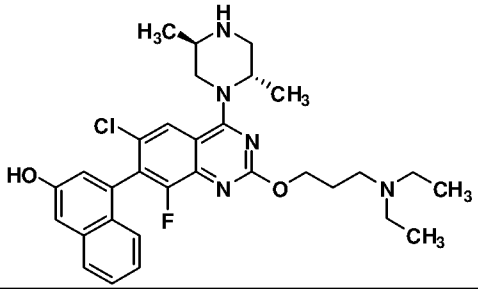
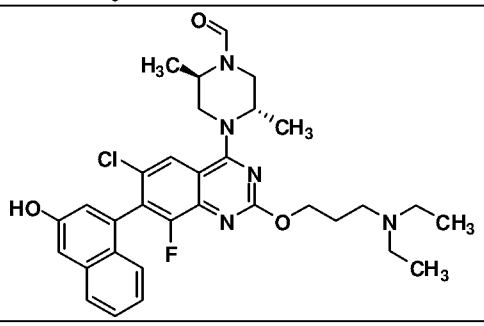
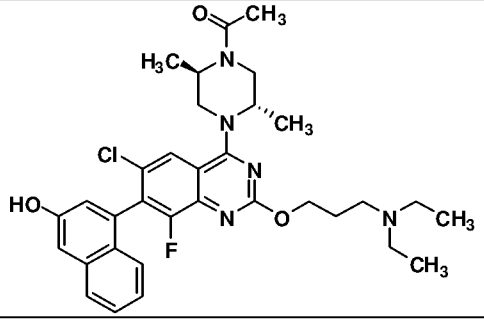
Table 1

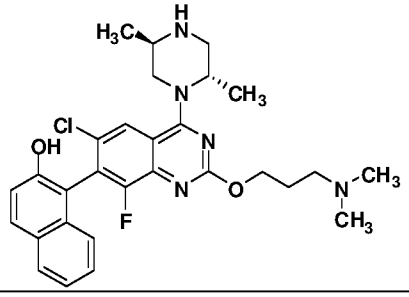
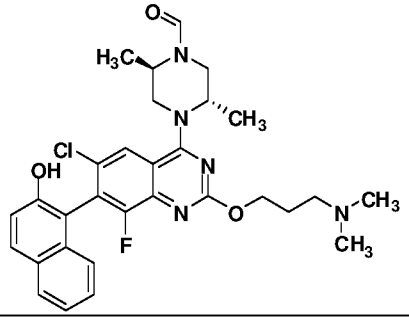
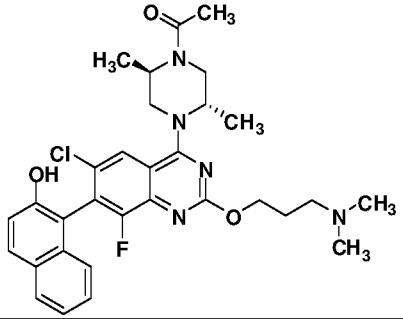
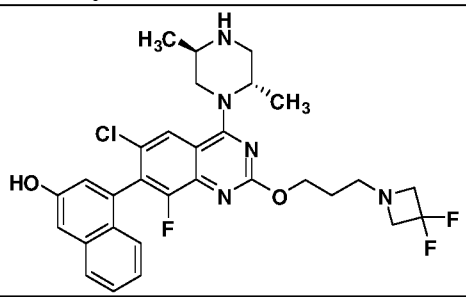
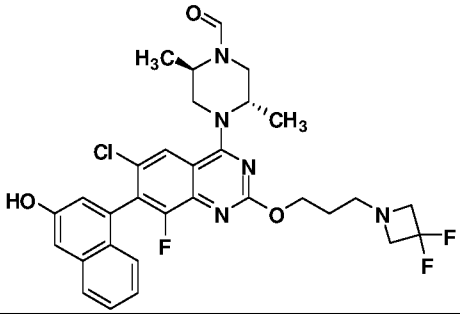
No.	Structure	$[M+H]^+$
1		533.2
2		527.2
3		499.1
4		513.2
5		513.2
6		513.2

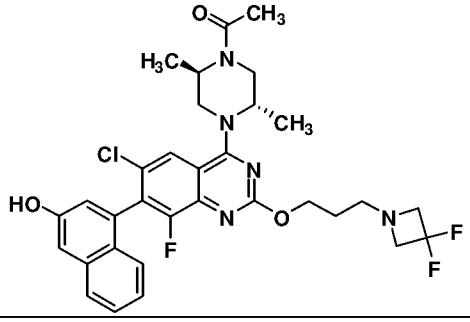
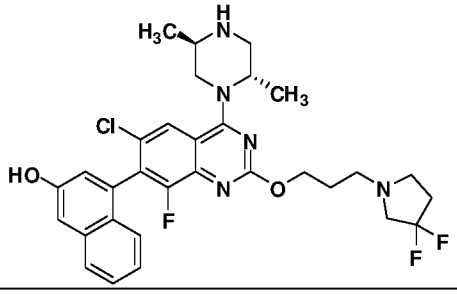
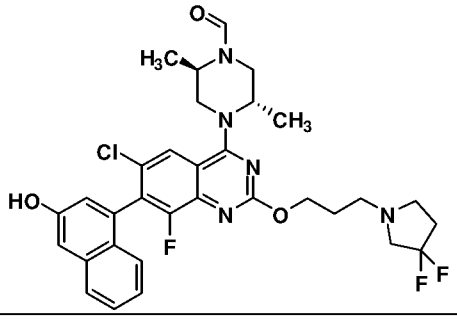
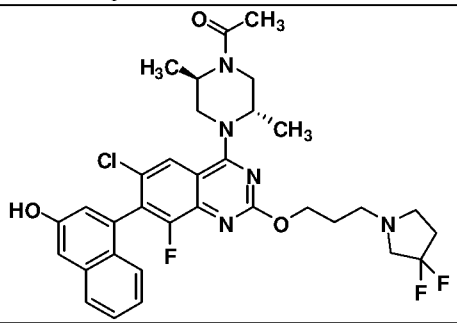
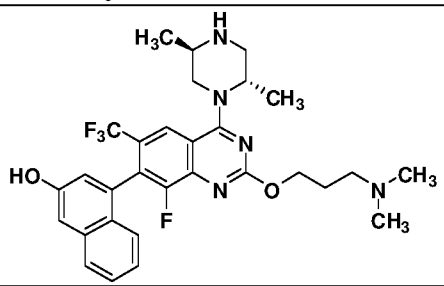
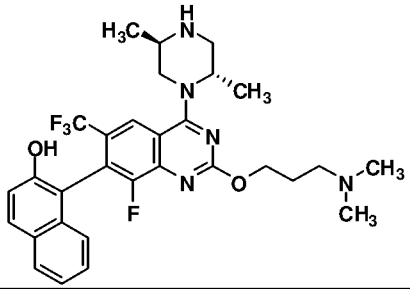
No.	Structure	$[M+H]^+$
7		513.2
8		527.2
9		513.1
10		541.2
11		541.1
12		541.1

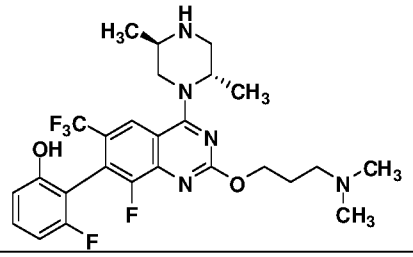
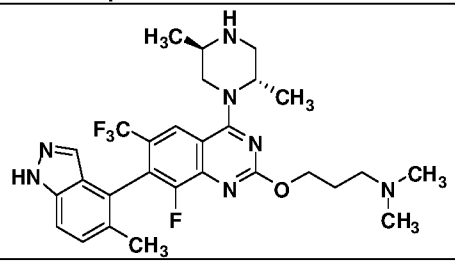
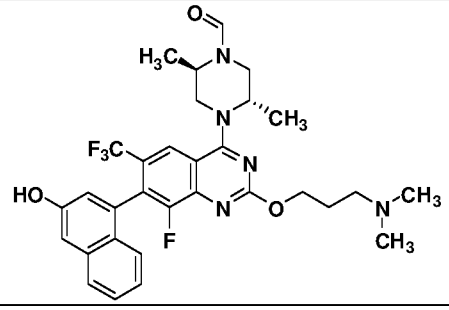
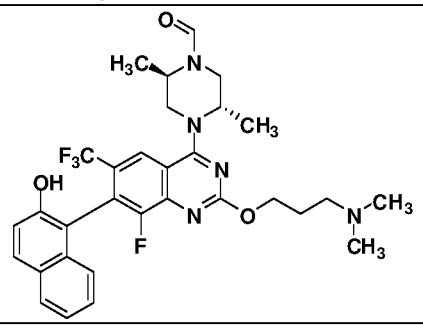
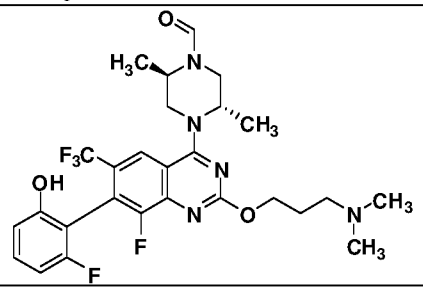
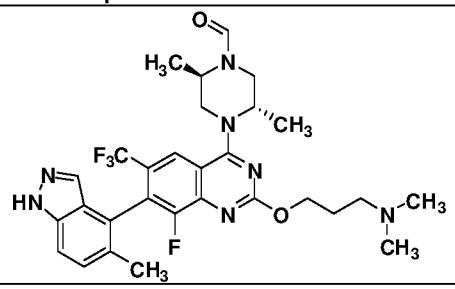
No.	Structure	$[M+H]^+$
13		544.2
14		510.2
15		544.1
16		544.2
17		552.2

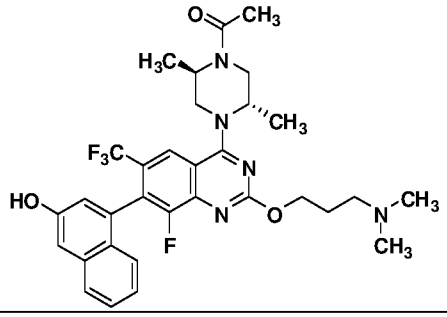
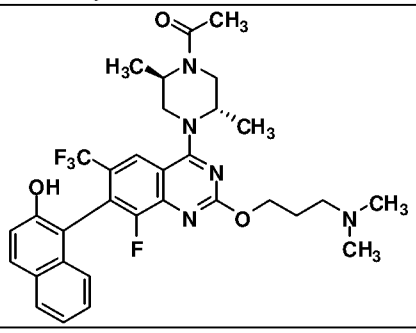
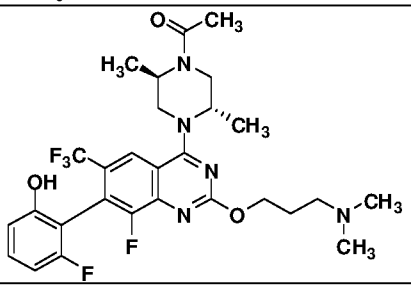
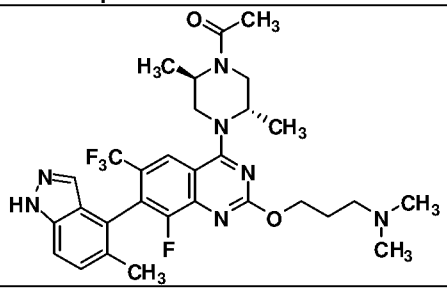
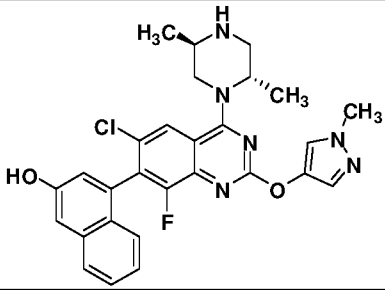
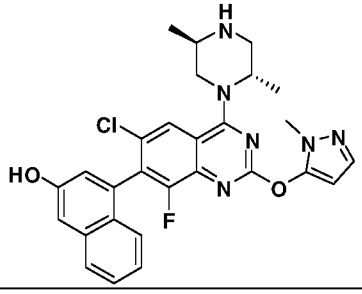
No.	Structure	$[M+H]^+$
18		552.2
19		547.2
20		547.2
21		547.2
22		510.2
23		510.2

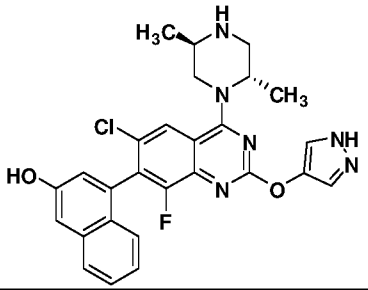
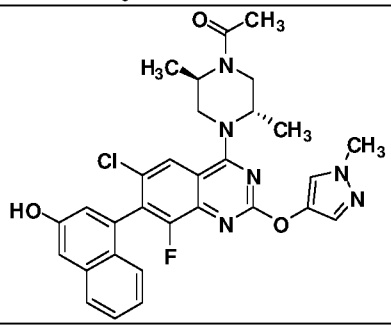
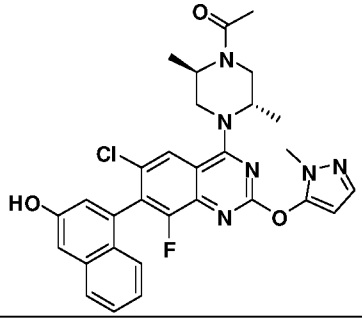
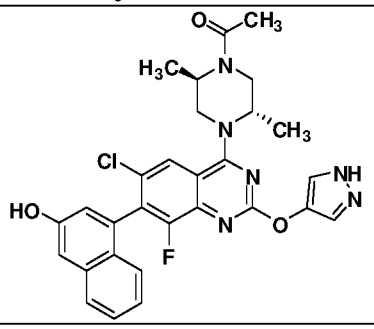
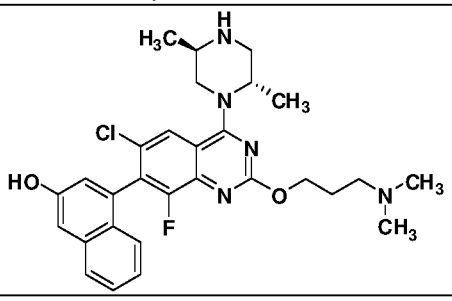
No.	Structure	$[M+H]^+$
24		558.2
25		578.1
26		527.1
27		
28		
29		

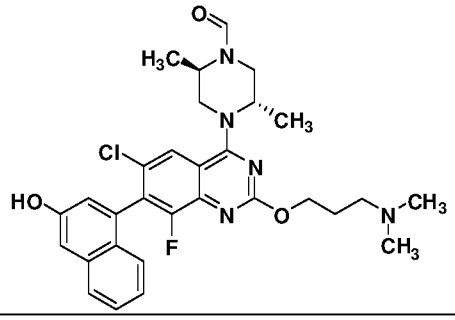
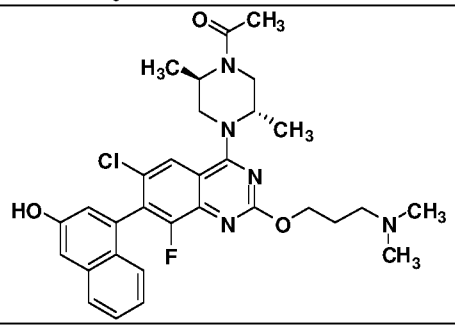
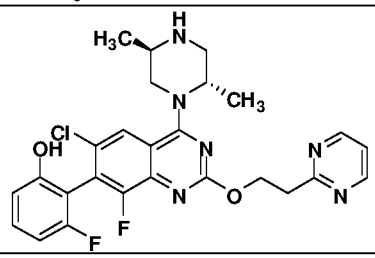
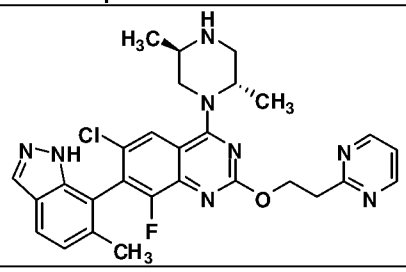
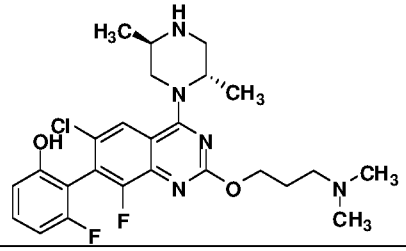
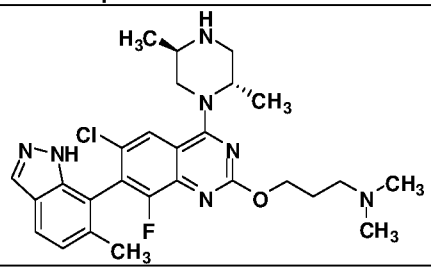
No.	Structure	$[M+H]^+$
30		538.3
31		566.3
32		580.4
33		
34		

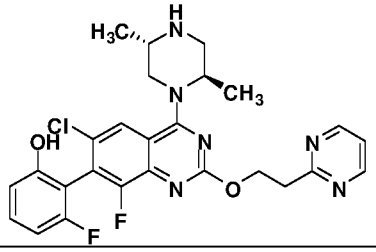
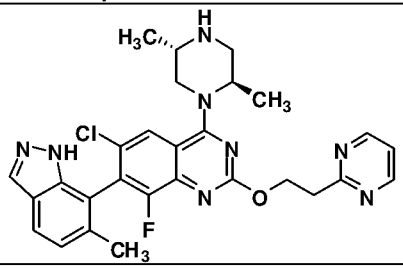
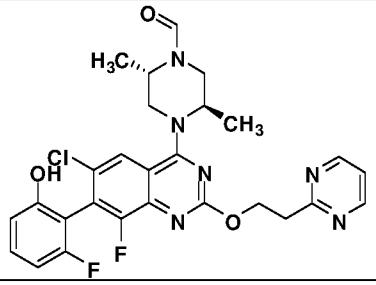
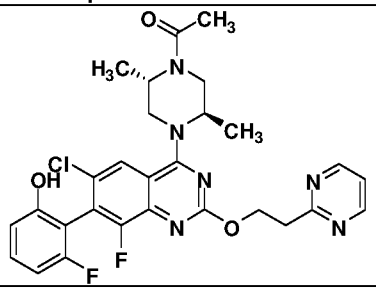
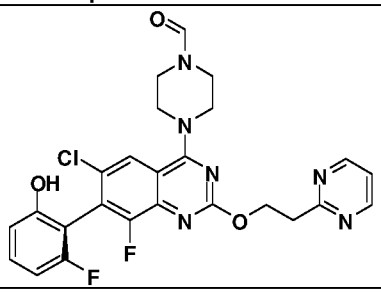
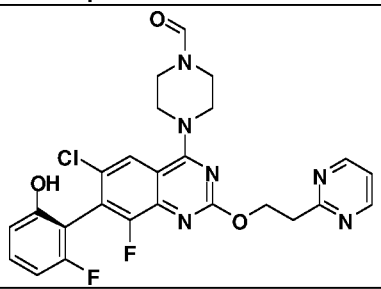
No.	Structure	$[M+H]^+$
35		
36		600.4
37		
38		642.4
39		
40		

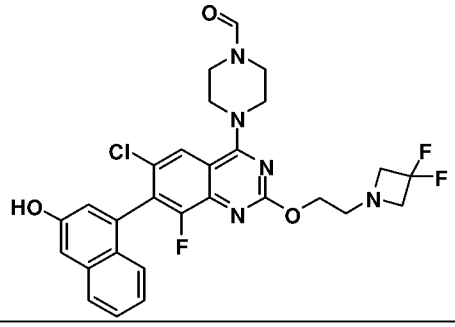
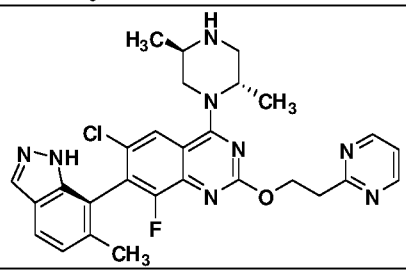
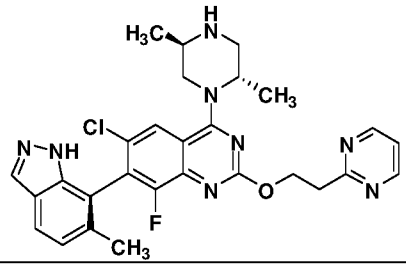
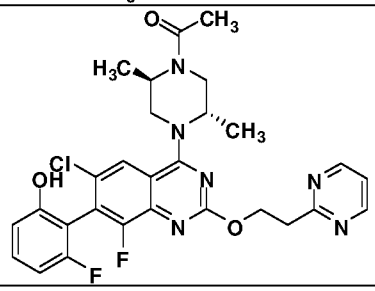
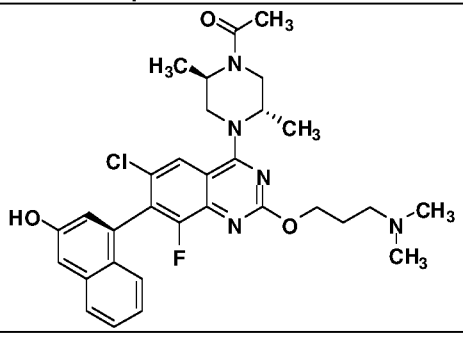
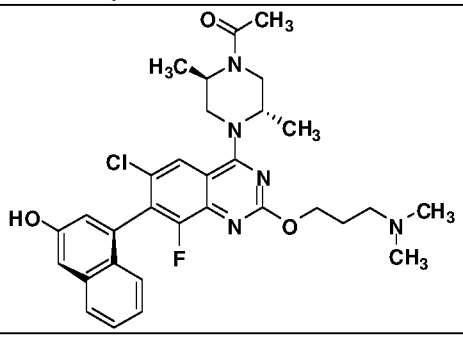
No.	Structure	$[M+H]^+$
41		
42		
43		
44		
45		
46		

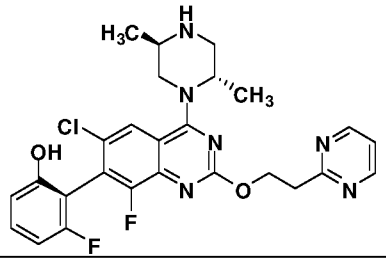
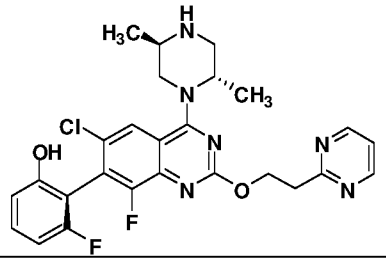
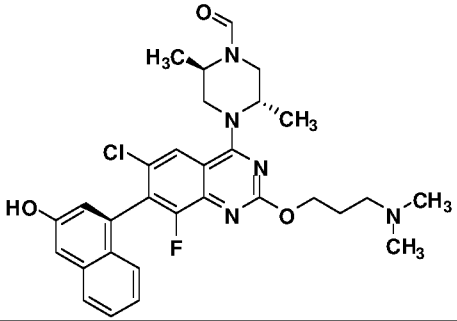
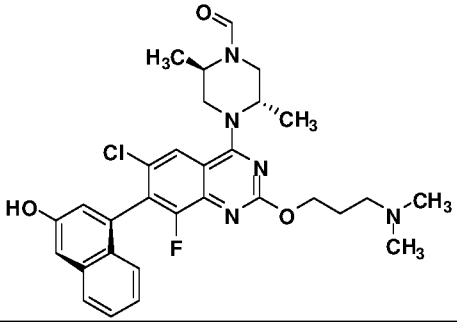
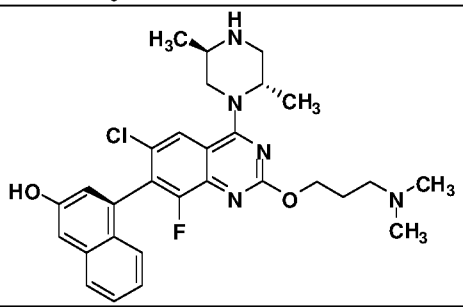
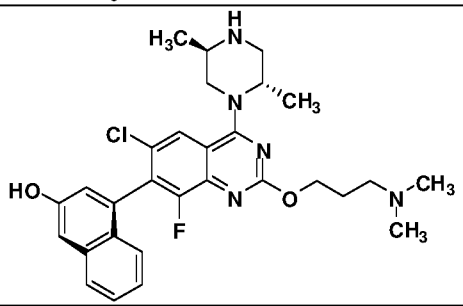
No.	Structure	$[M+H]^+$
47		614.4
48		
49		
50		
51		533.3
52		533.3

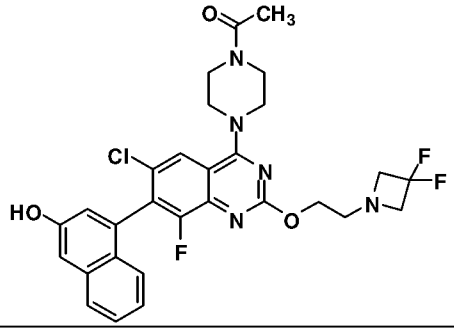
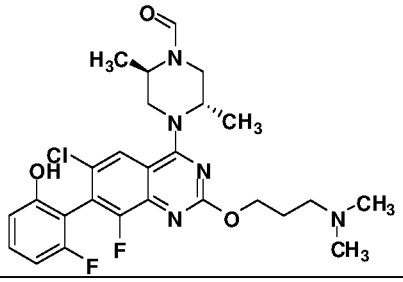
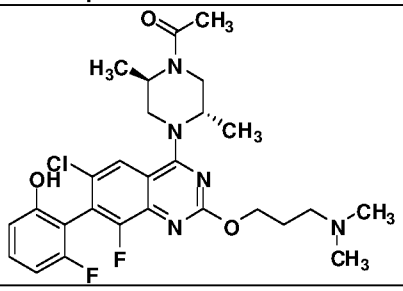
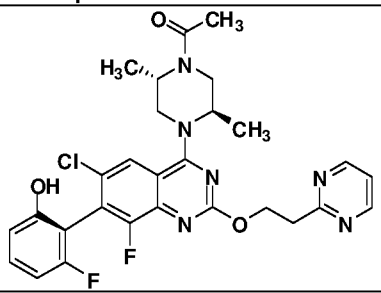
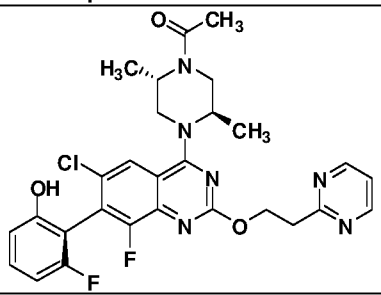
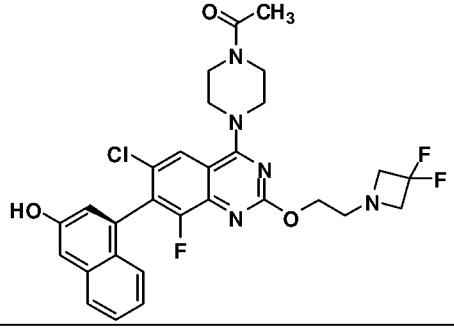
No.	Structure	$[M+H]^+$
53		519.2
54		575.4
55		575.2
56		561.3
57		538.4

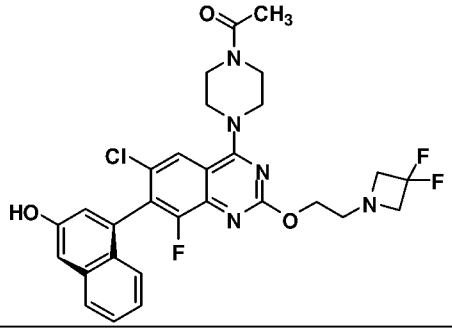
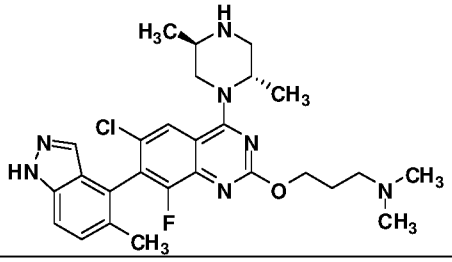
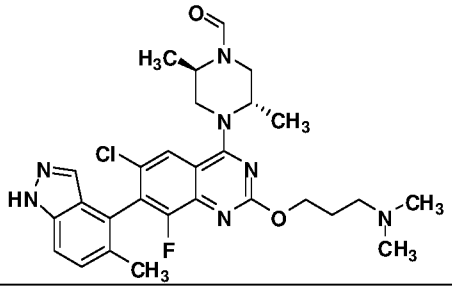
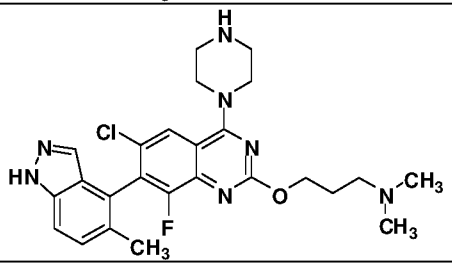
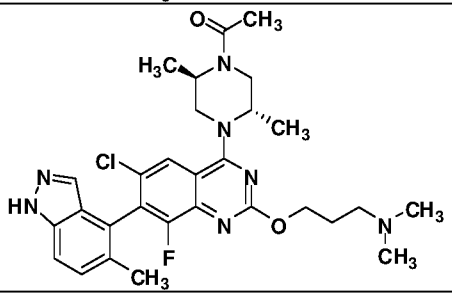
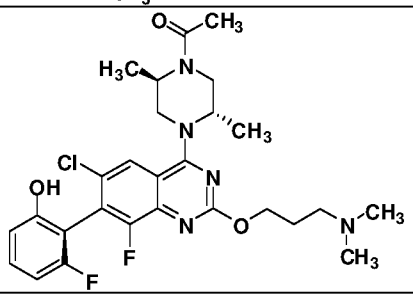
No.	Structure	$[M+H]^+$
58		566.4
59		580.4
60		
61		547.3
62		506.3
63		526.4

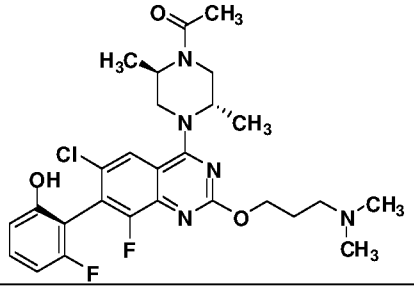
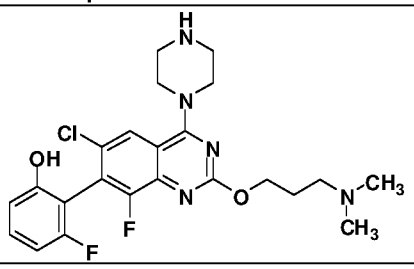
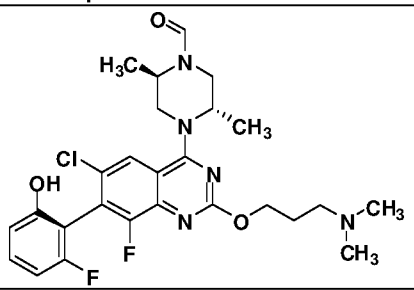
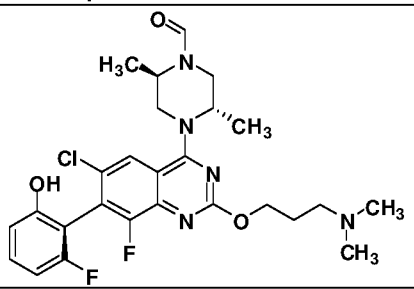
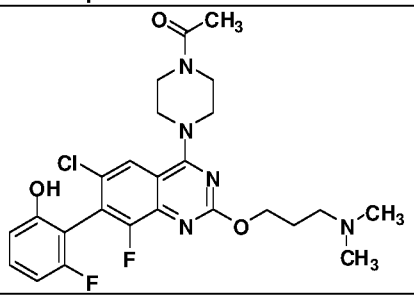
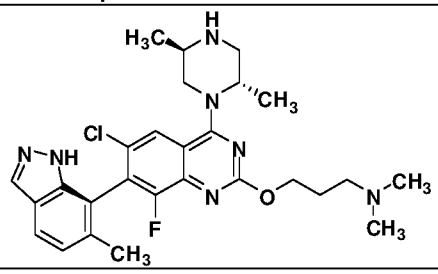
No.	Structure	$[M+H]^+$
64		
65		
66		
67		
85		527.2
86		527.2

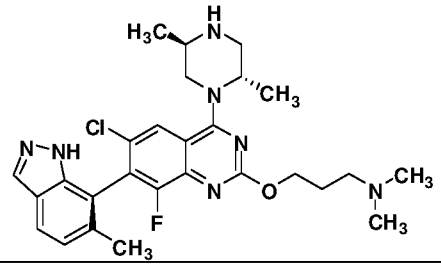
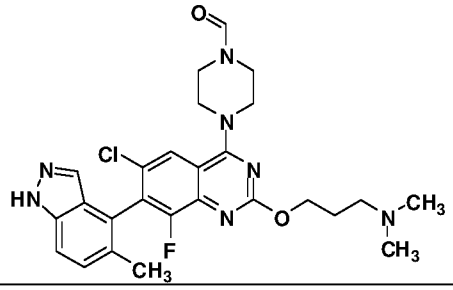
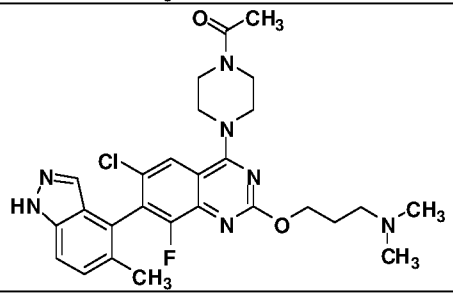
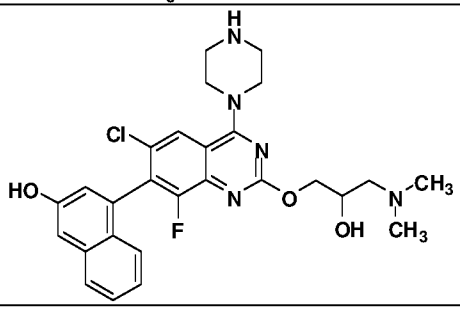
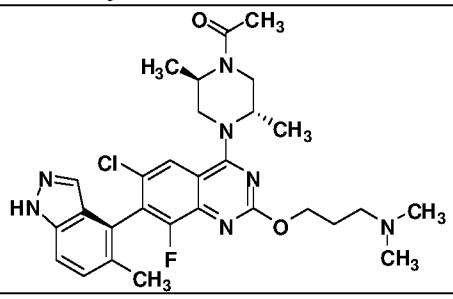
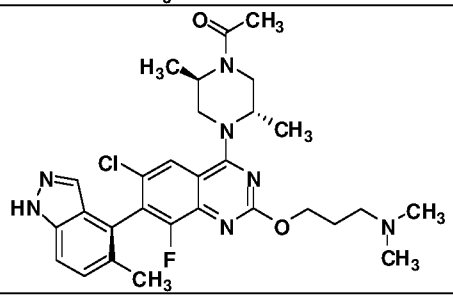
No.	Structure	$[M+H]^+$
87		572.2
88		547.4
89		547.4
90		569.3
91		580.4
92		580.3

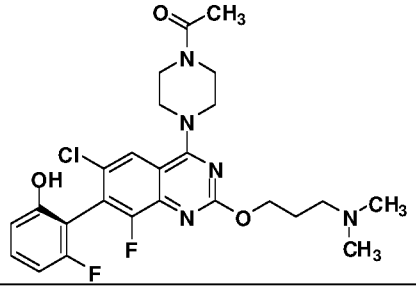
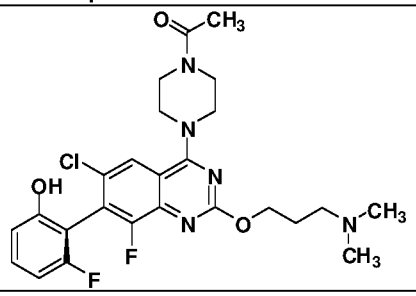
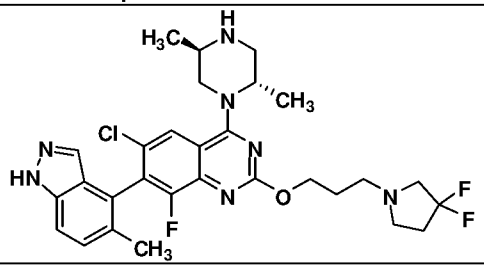
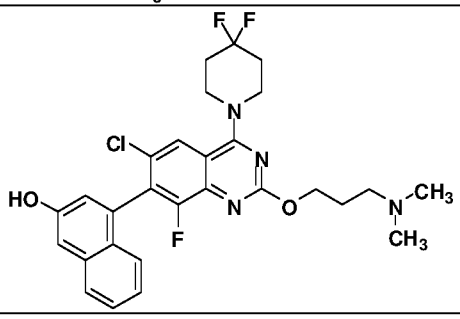
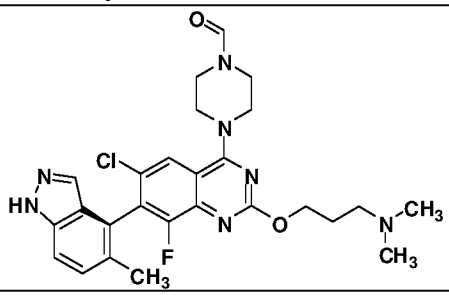
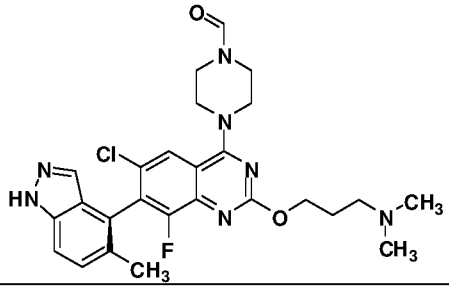
No.	Structure	$[M+H]^+$
93		527.3
94		527.3
95		566.3
96		566.3
97		538.4
98		538.4

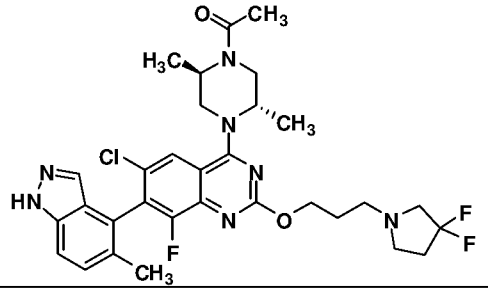
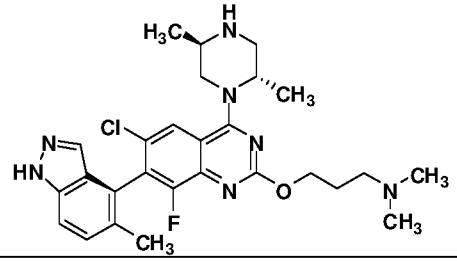
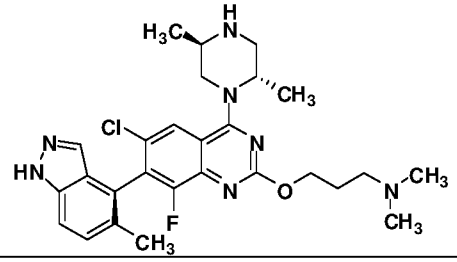
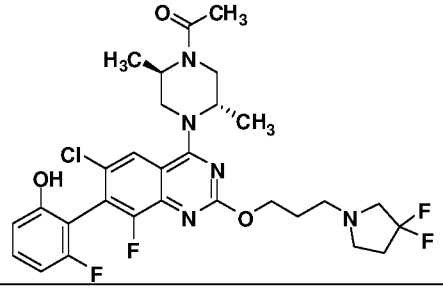
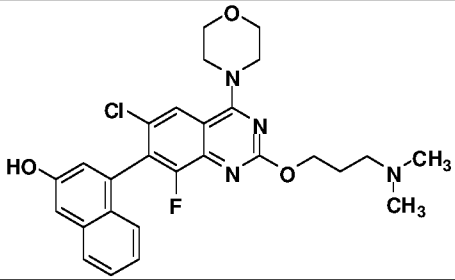
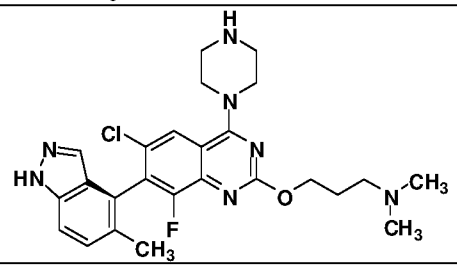
No.	Structure	$[M+H]^+$
99		586.3
100		534.4
101		548.4
102		569.3
103		569.3
104		586.3

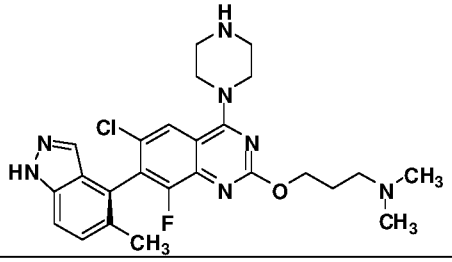
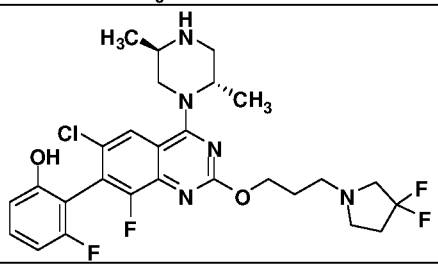
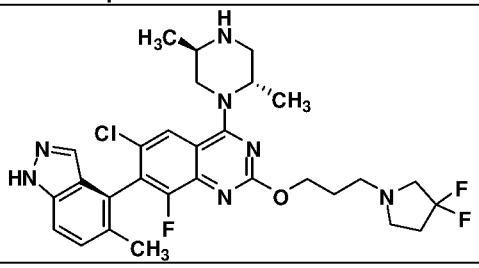
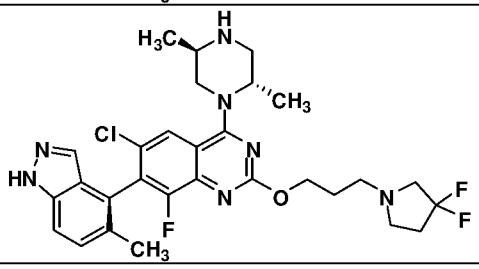
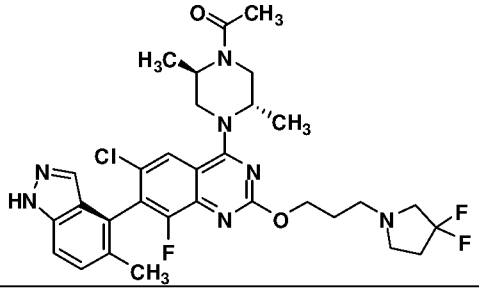
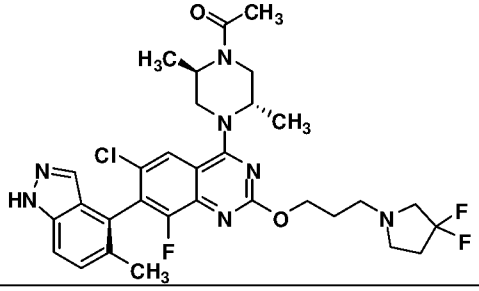
No.	Structure	$[M+H]^+$
105		586.3
106		526.4
107		554.4
108		498.3
109		568.4
110		548.3

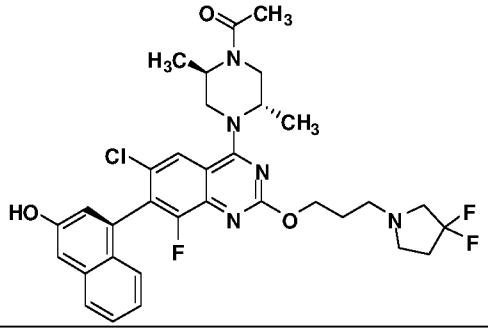
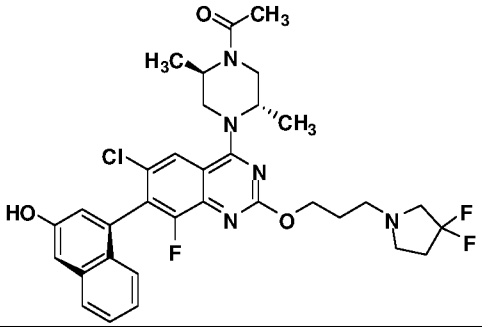
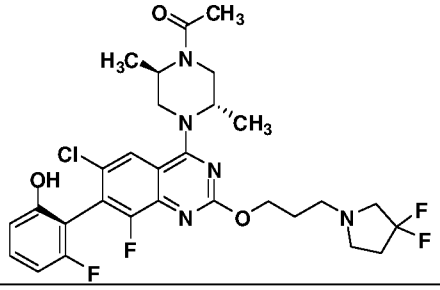
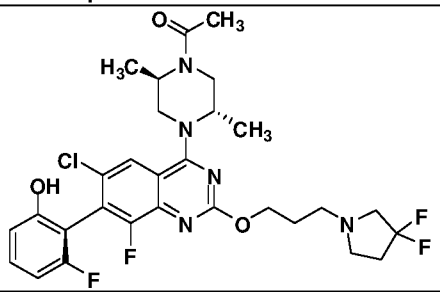
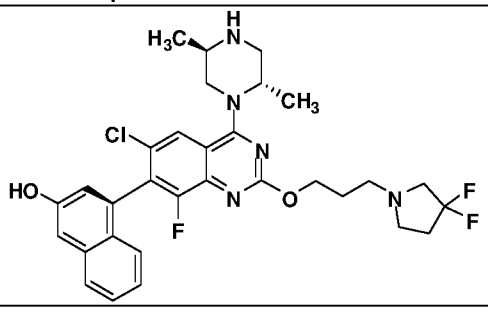
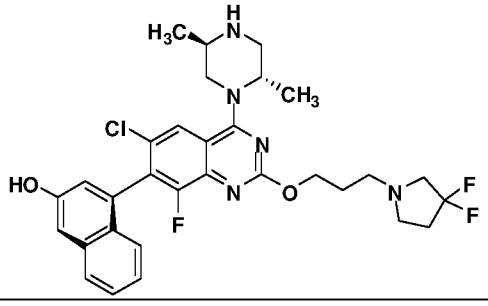
No.	Structure	$[M+H]^+$
111		548.3
112		478.2
113		534.3
114		534.3
115		520.2
116		526.3

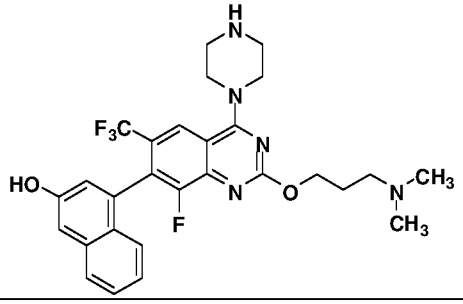
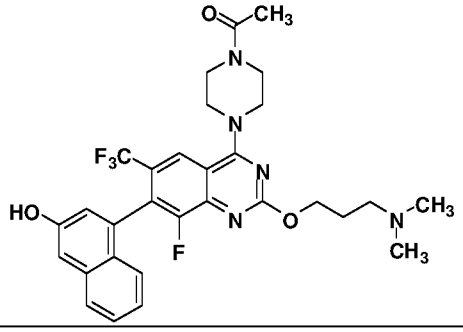
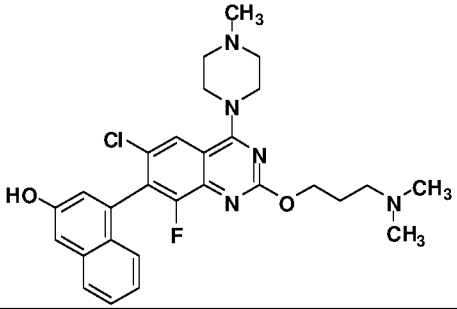
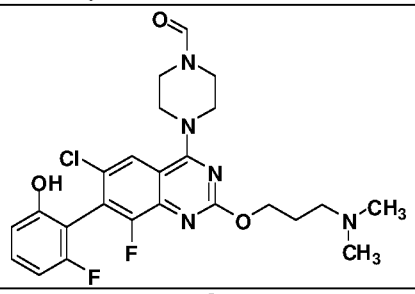
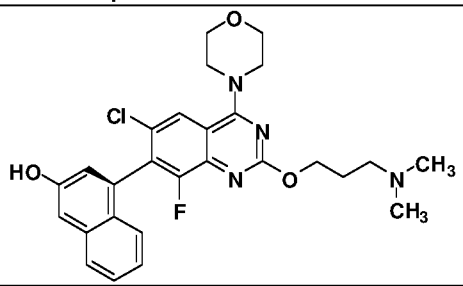
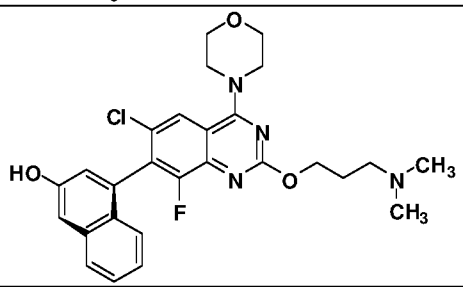
No.	Structure	$[M+H]^+$
117		526.3
118		526.3
119		540.4
120		526.2
121		568.3
122		568.3

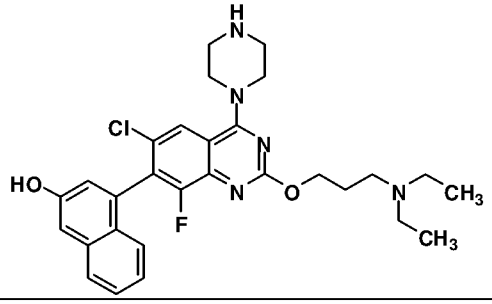
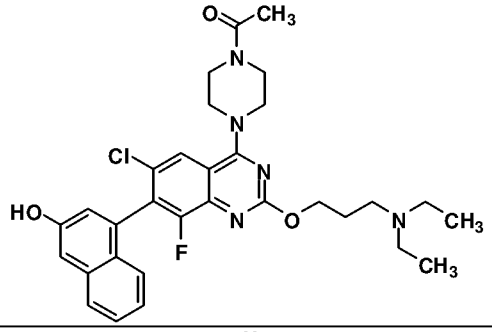
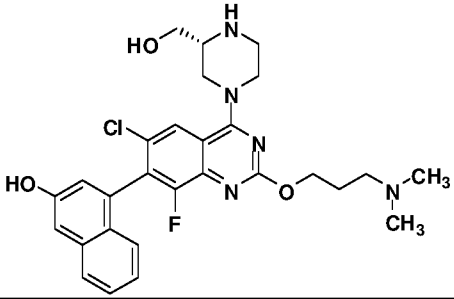
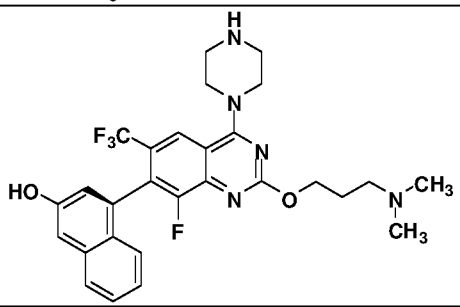
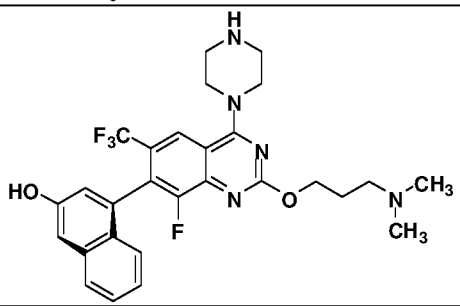
No.	Structure	$[M+H]^+$
123		520.3
124		520.3
125		588.4
126		545.3
127		526.3
128		526.3

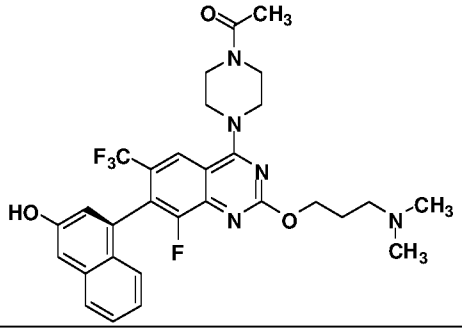
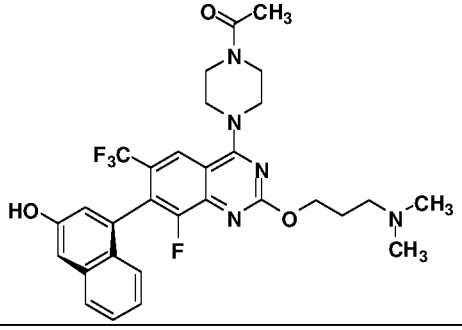
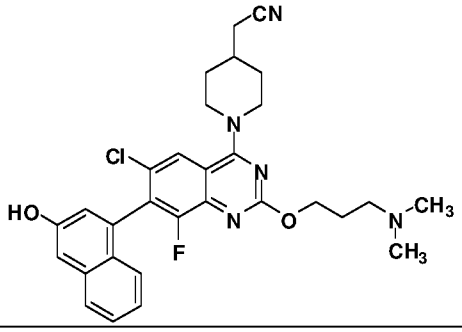
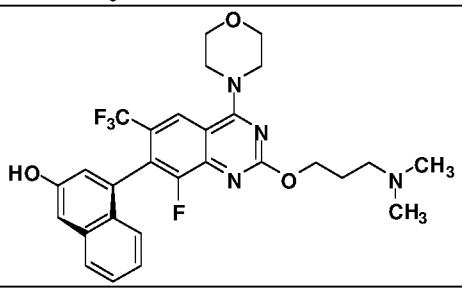
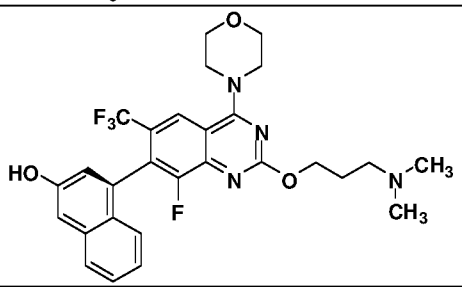
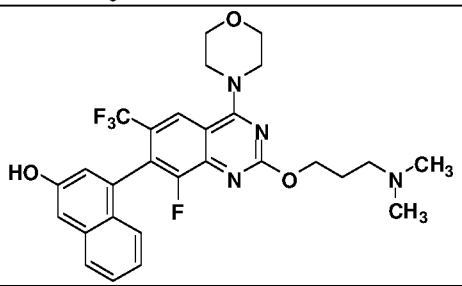
No.	Structure	$[M+H]^+$
129		630.4
130		526.3
131		526.3
132		610.3
133		511.3
134		498.4

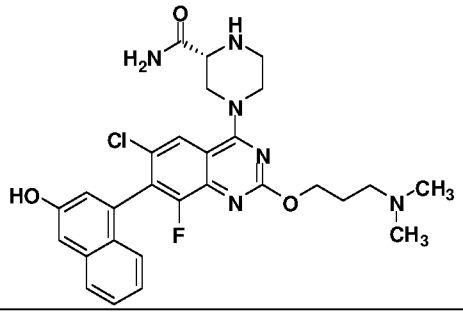
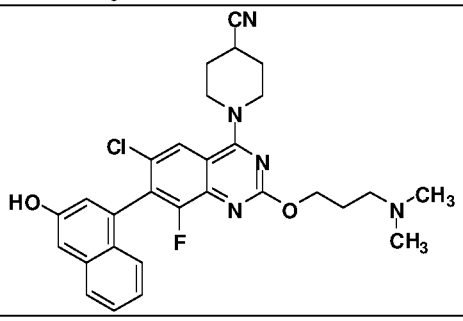
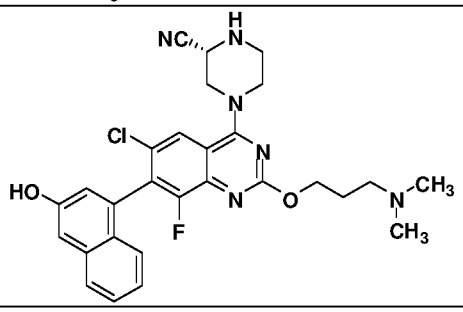
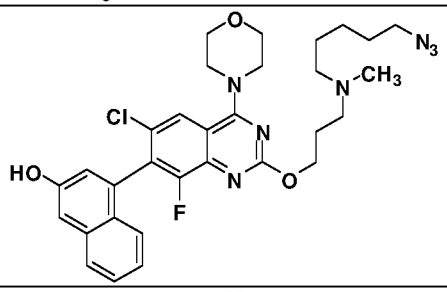
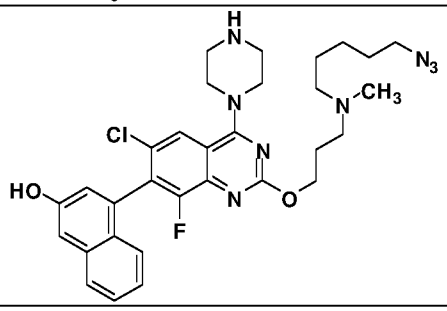
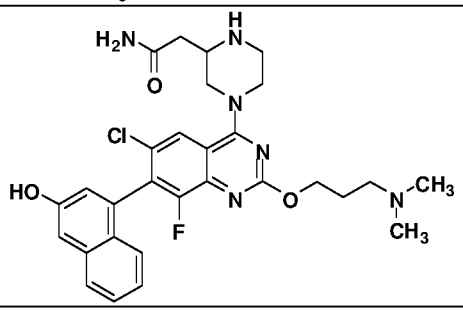
No.	Structure	$[M+H]^+$
135		498.4
136		568.4
137		588.4
138		588.4
139		630.4
140		630.4

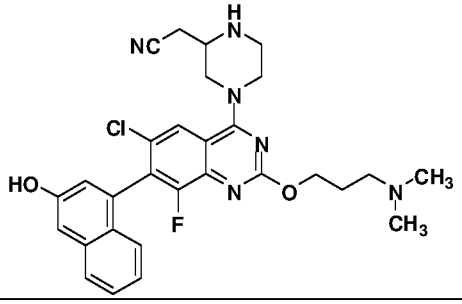
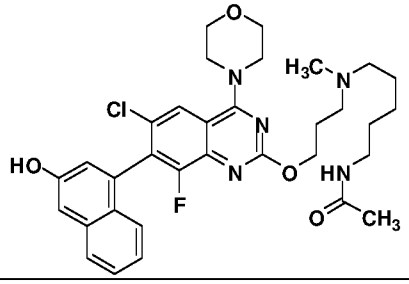
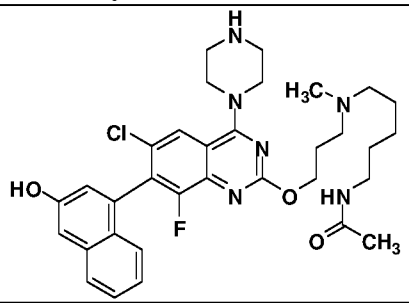
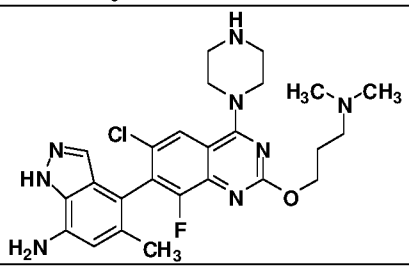
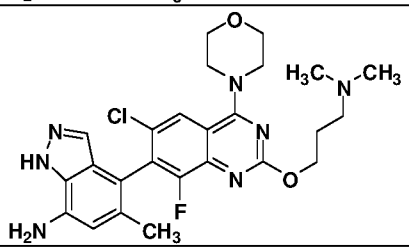
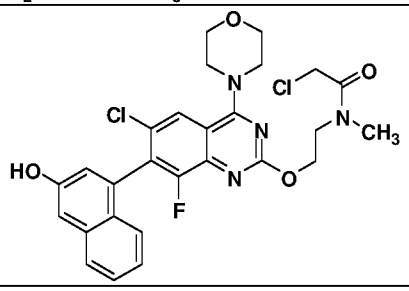
No.	Structure	$[M+H]^+$
141		642.3
142		642.3
143		610.4
144		610.4
145		600.4
146		600.4

No.	Structure	$[M+H]^+$
147		544.3
148		86.4
149		524.3
150		506.3
151		511.3
152		511.3

No.	Structure	$[M+H]^+$
153		538.3
154		580.3
155		542.3
156		544.3
157		544.3

No.	Structure	$[M+H]^+$
158		586.4
159		586.4
160		548.3
161		545.3
162		545.3
163		545.3

No.	Structure	$[M+H]^+$
164		553.3
165		534.4
166		535.4
167		608.4
168		607.4
169		567.4

No.	Structure	$[M+H]^+$
170		549.4
171		624.3
172		623.3
173		513.3
174		514.3
175		559.2

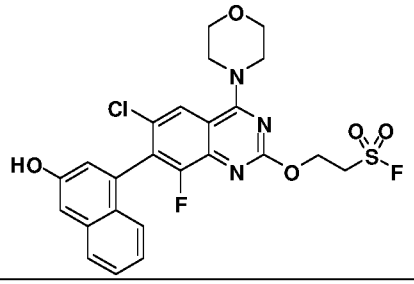
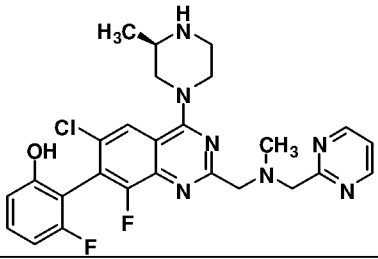
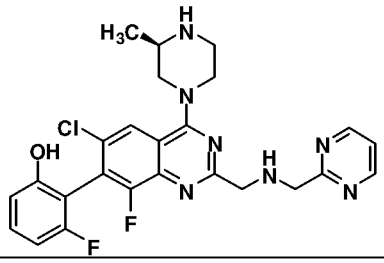
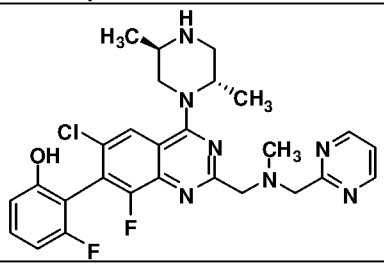
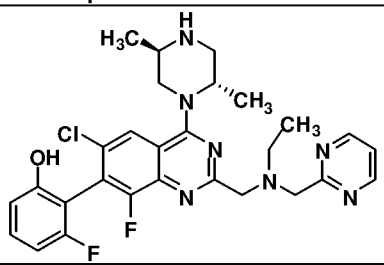
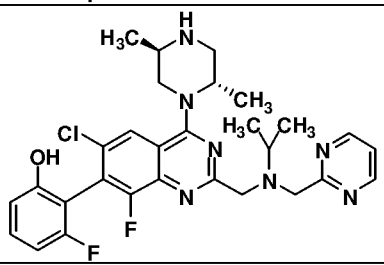
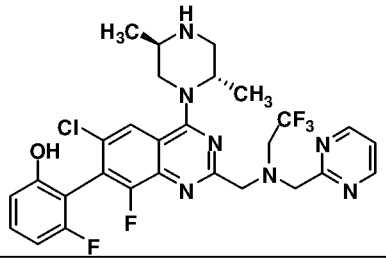
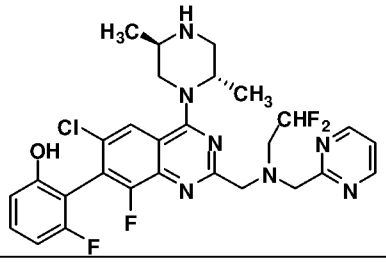
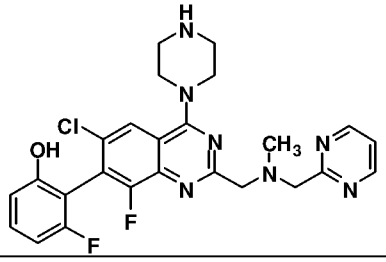
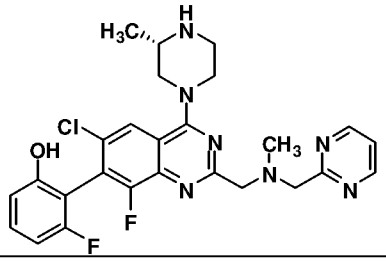
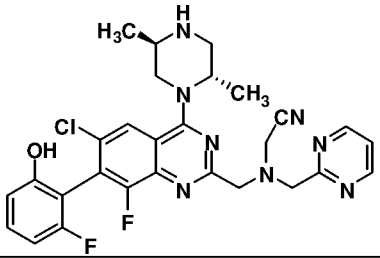
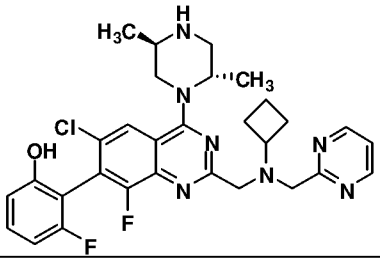
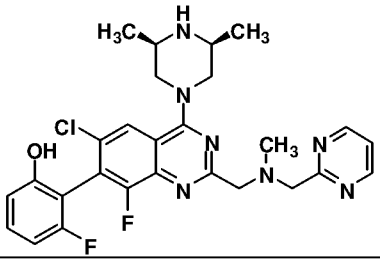
No.	Structure	$[M+H]^+$
176		536.3

Table 2

No.	Structure	$[M+H]^+$
68		525.6
69		512.2
70		540.2
71		554.2
72		568.2

No.	Structure	$[M+H]^+$
73		608.2
74		590.2
75		512.2
76		526.1
77		565.1
78		580.2
79		539.7

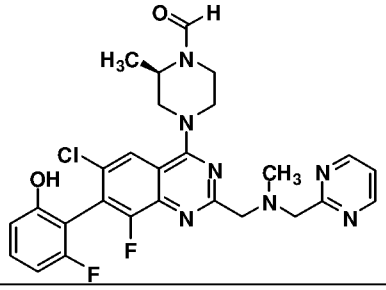
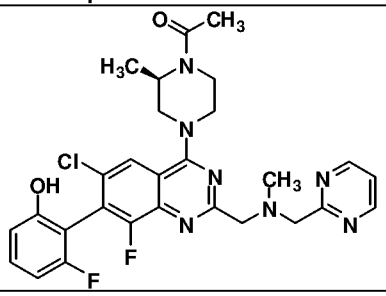
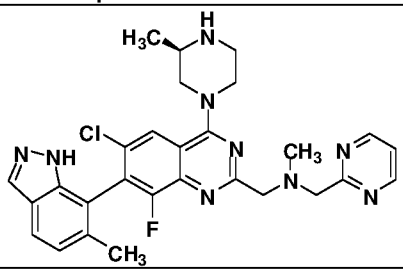
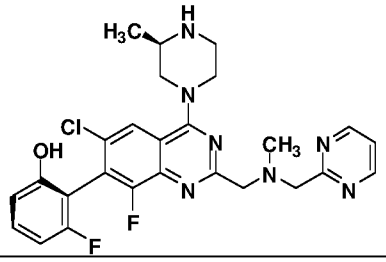
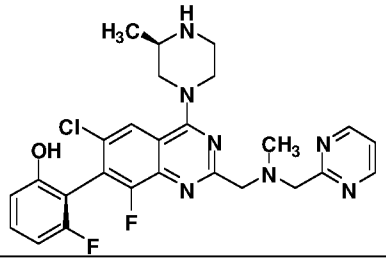
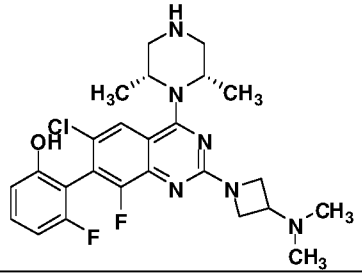
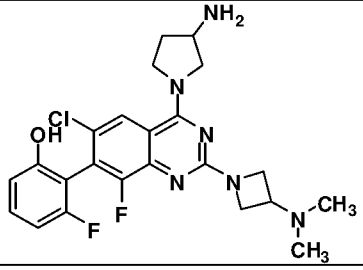
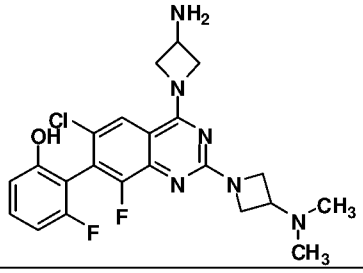
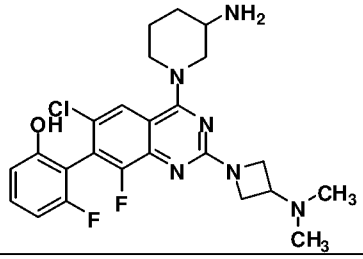
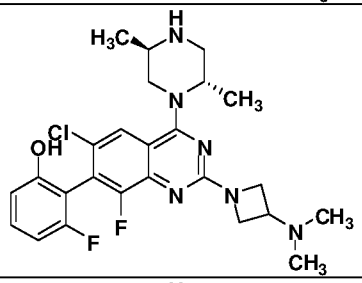
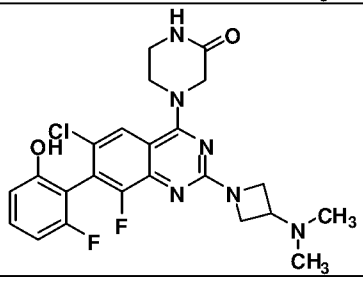
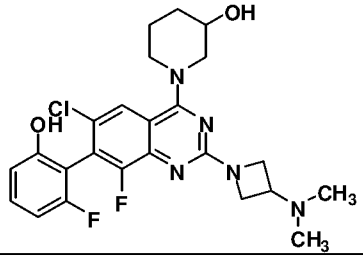
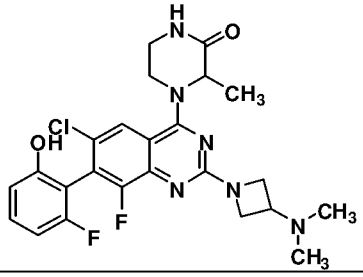
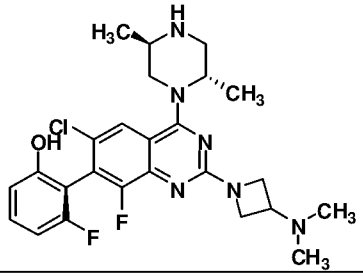
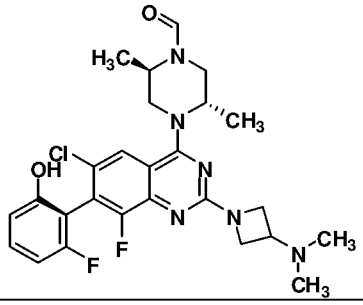
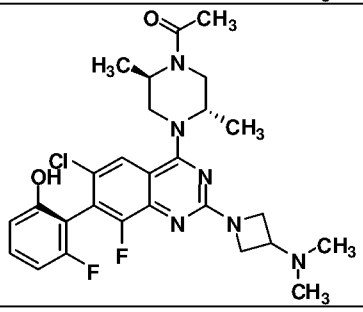
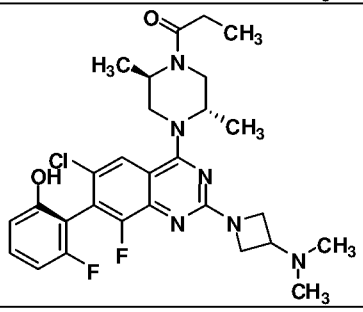
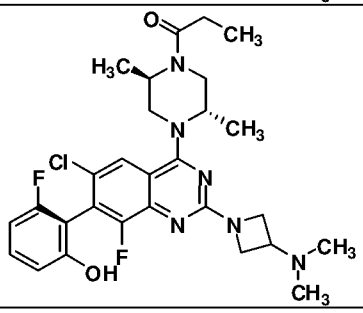
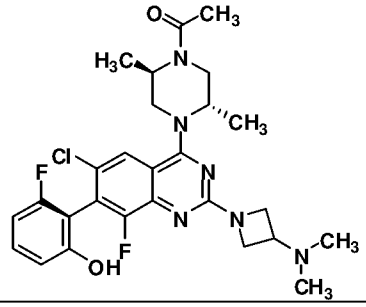
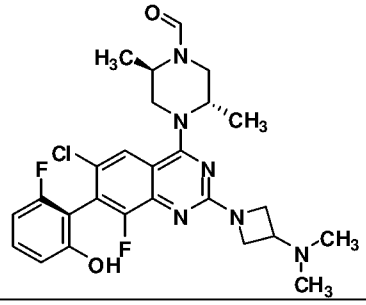
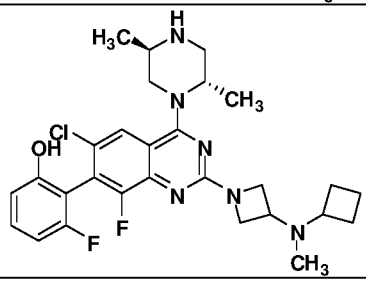
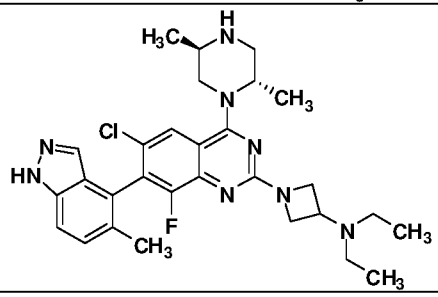
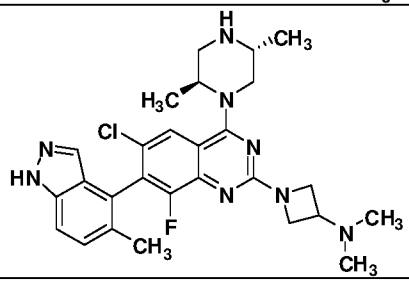
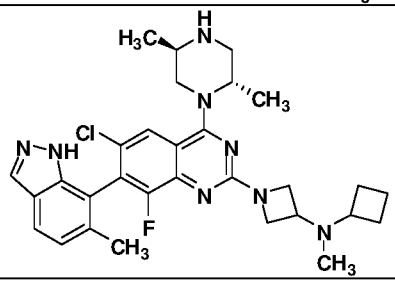
No.	Structure	$[M+H]^+$
80		553.7
81		567.7
82		545.4
83		525.7
84		525.7

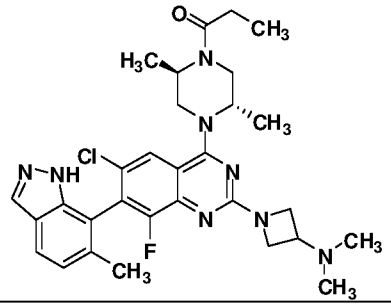
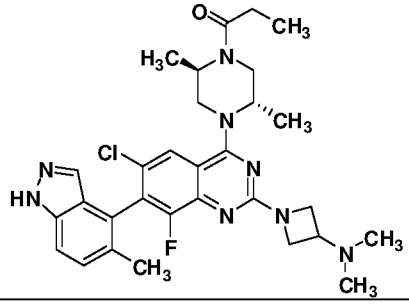
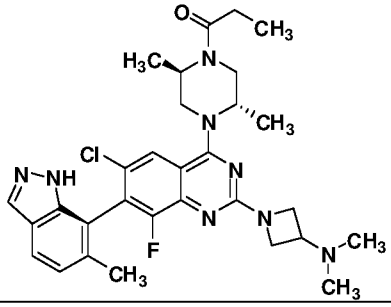
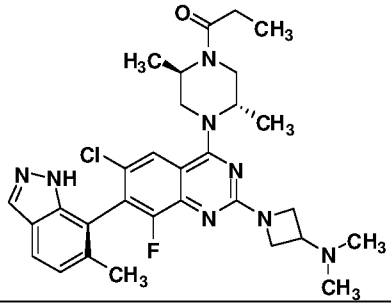
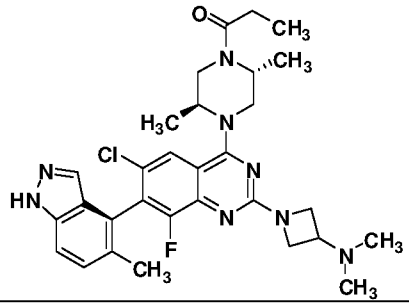
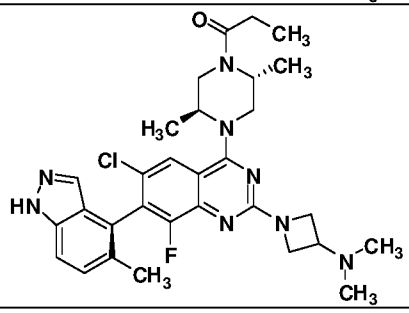
Table 3

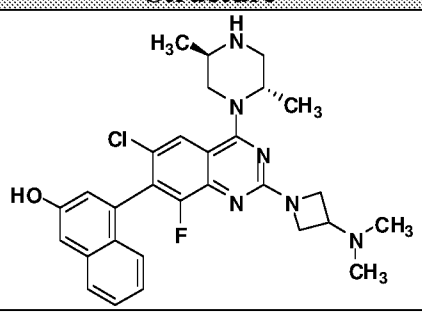
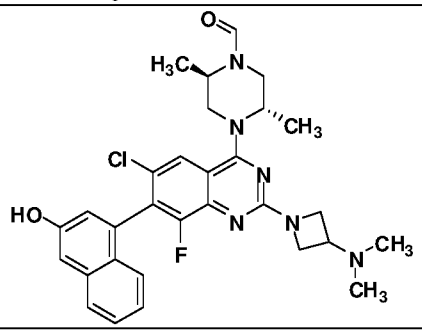
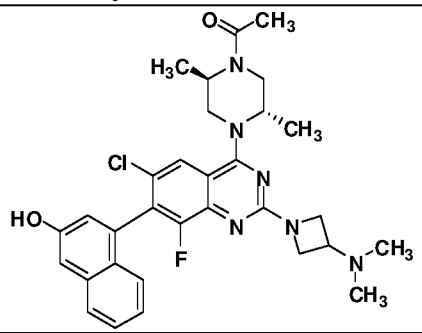
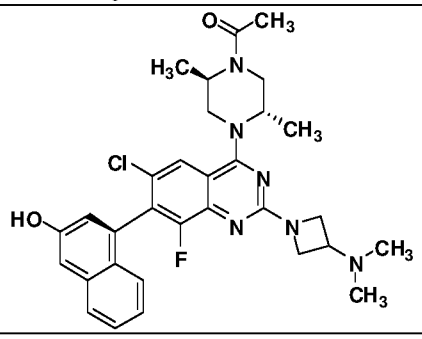
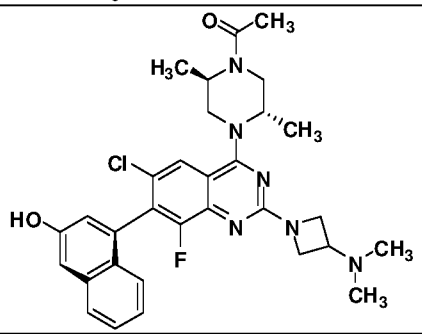
No.	Structure	$[M+H]^+$
300		503.25

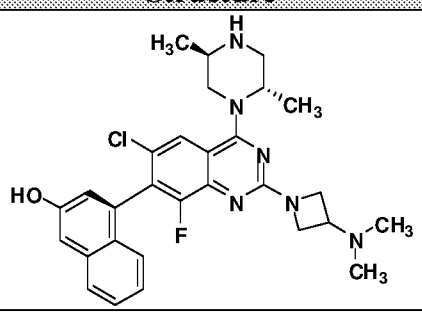
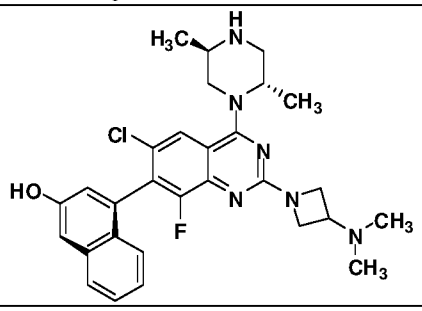
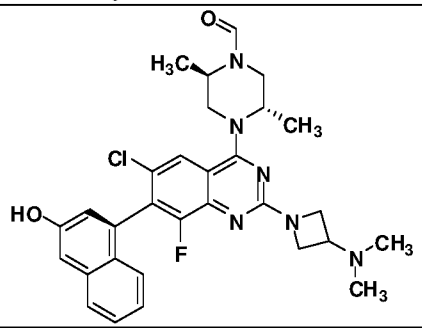
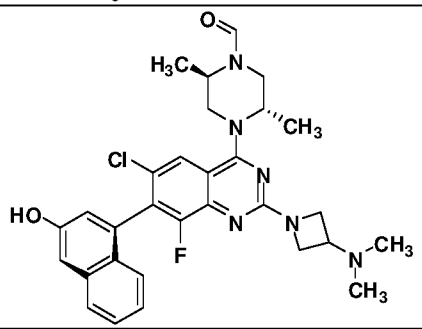
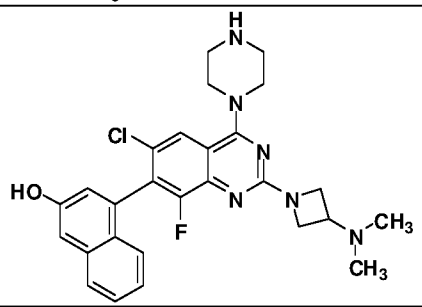
No.	Structure	$[M+H]^+$
301		475.30
302		461.20
303		489.30
304		503.25
305		489.20
306		490.2

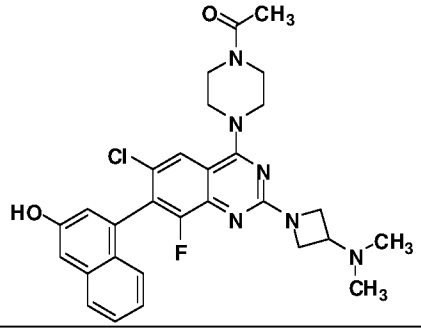
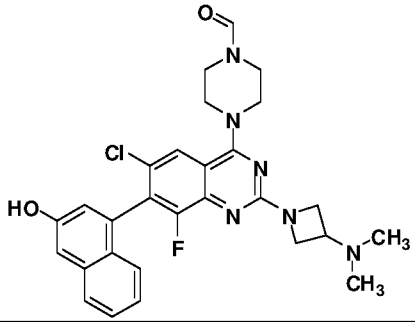
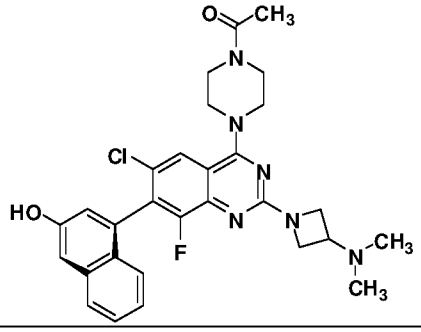
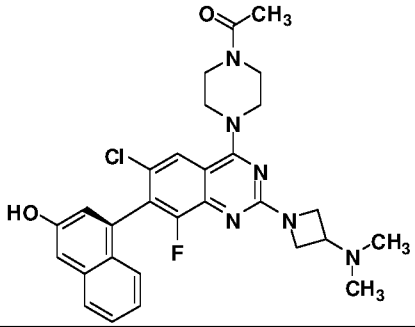
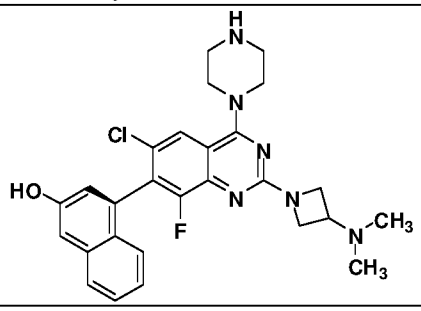
No.	Structure	$[M+H]^+$
307		503.25
308		503.2
309		531.2
310		545.2
311		559.2
312		559.2

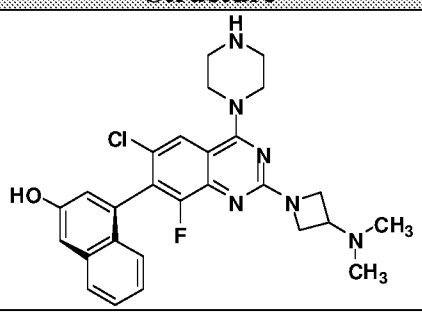
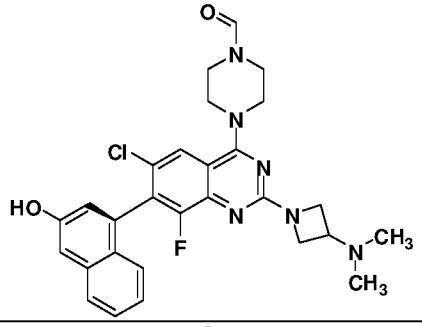
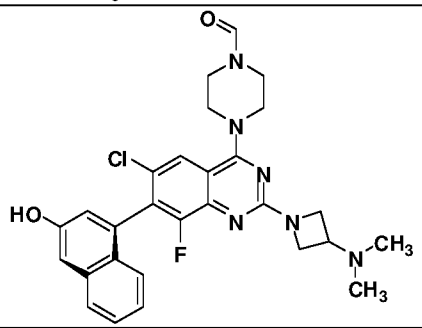
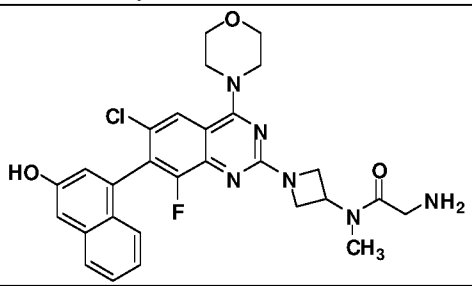
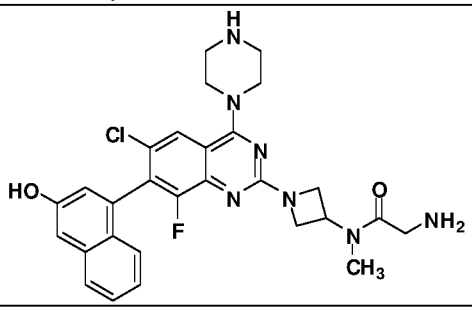
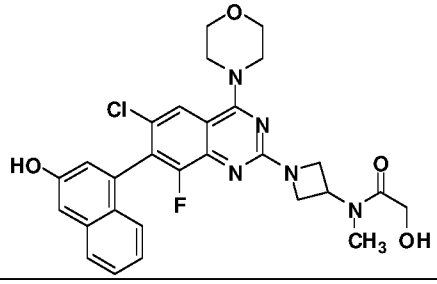
No.	Structure	$[M+H]^+$
313		545.2
314		531.2
315		542.7
316		550.7
317		522.8
318		563.3

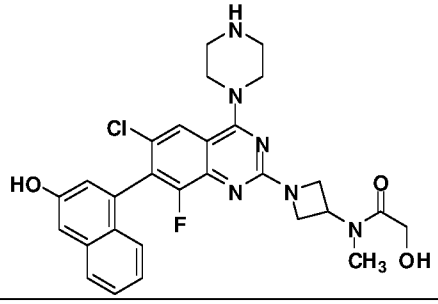
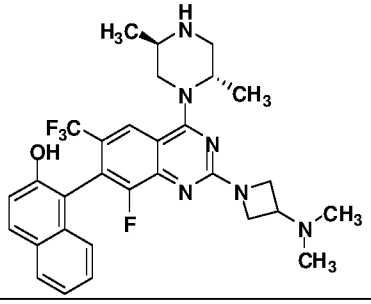
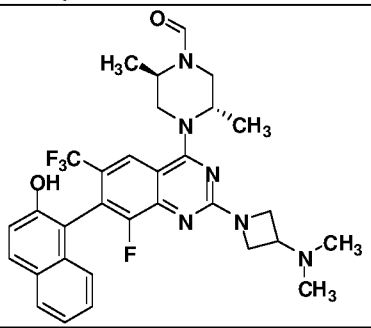
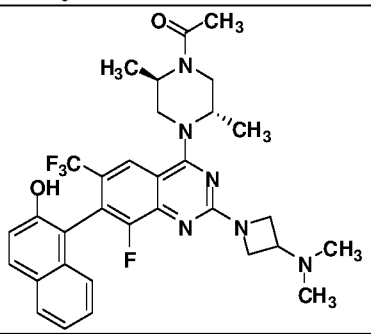
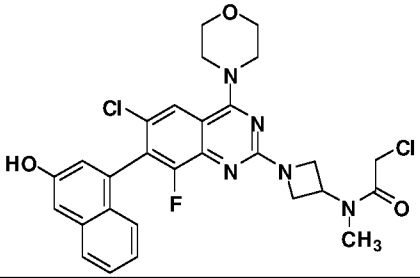
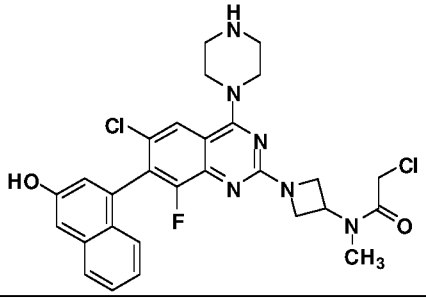
No.	Structure	$[M+H]^+$
319		578.2
320		579.3
321		579.4
322		579.3
323		579.4
324		579.4

No.	Structure	$[M+H]^+$
325		535.4
326		563.4
327		577.4
328		577.4
329		577.4

No.	Structure	$[M+H]^+$
330		535.3
331		535.3
332		563.3
333		563.3
334		507.3

No.	Structure	$[M+H]^+$
335		549.4
336		535.3
337		549.3
338		549.3
339		507.3

No.	Structure	$[M+H]^+$
340		507.3
341		535.3
342		535.3
343		551.3
344		550.3
345		552.4

No.	Structure	$[M+H]^+$
346		551.3
347		
348		
349		
350		570.3
351		569.3

[0197] Pharmaceutical Compositions

[0198] Other embodiments are directed to pharmaceutical compositions. The pharmaceutical composition comprises any one (or more) of the foregoing compounds and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated for oral administration. In other embodiments, the pharmaceutical composition is formulated for injection. In still more embodiments, the pharmaceutical compositions comprise a compound as disclosed herein and an additional therapeutic agent (e.g., anticancer agent). Non-limiting examples of such therapeutic agents are described herein below.

[0199] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[0200] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

[0201] The compounds according to the disclosure are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that are used in some embodiments. An exemplary dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[0202] In some embodiments, a compound of the disclosure is administered in a single dose. Typically, such administration will be by injection, e.g., intravenous injection, in order to introduce the agent quickly. However, other routes are used as appropriate. In some

embodiments, a single dose of a compound of the disclosure is used for treatment of an acute condition.

[0203] In some embodiments, a compound of the disclosure is administered in multiple doses. In some embodiments, dosing is about once, twice, three times, four times, five times, six times, or more than six times per day. In other embodiments, dosing is about once a month, once every two weeks, once a week, or once every other day. In another embodiment a compound of the disclosure and another agent are administered together about once per day to about 6 times per day. In another embodiment the administration of a compound of the disclosure and an agent continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[0204] Administration of the compounds of the disclosure may continue as long as necessary. In some embodiments, a compound of the disclosure is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, a compound of the disclosure is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, a compound of the disclosure is administered chronically on an ongoing basis, e.g., for the treatment of chronic effects.

[0205] In some embodiments, the compounds of the disclosure are administered in dosages. It is known in the art that due to intersubject variability in compound pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy. Dosing for a compound of the disclosure may be found by routine experimentation in light of the instant disclosure.

[0206] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

[0207] Provided herein are pharmaceutical compositions comprising a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) and a pharmaceutically acceptable diluent(s),

excipient(s), or carrier(s). In certain embodiments, the compounds described are administered as pharmaceutical compositions in which compounds of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) are mixed with other active ingredients, as in combination therapy. Encompassed herein are all combinations of actives set forth in the combination therapies section below and throughout this disclosure. In specific embodiments, the pharmaceutical compositions include one or more compounds of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C).

[0208] A pharmaceutical composition, as used herein, refers to a mixture of a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds provided herein are administered in a pharmaceutical composition to a mammal having a disease, disorder or medical condition to be treated. In specific embodiments, the mammal is a human. In certain embodiments, therapeutically effective amounts vary depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds described herein are used singly or in combination with one or more therapeutic agents as components of mixtures.

[0209] In one embodiment, one or more compounds of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) is formulated in an aqueous solutions. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, one or more compound described herein is/are formulated for transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated. In still other embodiments wherein the compounds described herein are formulated for other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions. In specific embodiments, such solutions include physiologically compatible buffers and/or excipients.

[0210] In another embodiment, compounds described herein are formulated for oral administration. Compounds described herein are formulated by combining the active compounds with, e.g., pharmaceutically acceptable carriers or excipients. In various embodiments, the compounds described herein are formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

[0211] In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0212] In one embodiment, dosage forms, such as dragee cores and tablets, are provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

[0213] In certain embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated into other oral dosage forms. Oral dosage forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules, contain one or more active compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

[0214] In other embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated for buccal or sublingual administration. Formulations suitable for buccal or sublingual administration include, by way of example only, tablets, lozenges, or gels. In still other embodiments, the compounds described herein are formulated for parental injection, including formulations suitable for bolus injection or continuous infusion. In specific

embodiments, formulations for injection are presented in unit dosage form (e.g., in ampoules) or in multi-dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical compositions are formulated in a form suitable for parenteral injection as sterile suspensions, solutions or emulsions in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. In additional embodiments, suspensions of the active compounds (e.g., compounds of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C)) are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension contains suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, in other embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0215] In still other embodiments, the compounds of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) are administered topically. The compounds described herein are formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compositions optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0216] In yet other embodiments, the compounds of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) are formulated for transdermal administration. In specific embodiments, transdermal formulations employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. In various embodiments, such patches are constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. In additional embodiments, the transdermal delivery of a compound described herein is accomplished by means of iontophoretic patches and the like. In certain embodiments, transdermal patches provide controlled delivery of a compound described herein. In specific embodiments, the rate of absorption is slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. In alternative embodiments, absorption enhancers are used to increase absorption. Absorption

enhancers or carriers include absorbable pharmaceutically acceptable solvents that assist passage through the skin. For example, in one embodiment, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[0217] In other embodiments, the compounds of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) are formulated for administration by inhalation. Various forms suitable for administration by inhalation include, but are not limited to, aerosols, mists or powders. Pharmaceutical compositions of any compound described herein are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In specific embodiments, the dosage unit of a pressurized aerosol is determined by providing a valve to deliver a metered amount. In certain embodiments, capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator are formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0218] In still other embodiments, the compounds of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

[0219] In certain embodiments, pharmaceutical compositions are formulated in any conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are optionally used as suitable. Pharmaceutical compositions comprising a compound described herein are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0220] Pharmaceutical compositions include at least one pharmaceutically acceptable carrier,

diluent or excipient and at least one compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C), described herein as an active ingredient. The active ingredient is in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of N-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. All tautomers of the compounds described herein are included within the scope of the compounds presented herein. Additionally, the compounds described herein encompass unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

[0221] Methods for the preparation of compositions comprising the compounds described herein include formulating the compounds with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions and creams. The form of the pharmaceutical compositions described herein include liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions also optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

[0222] In some embodiments, pharmaceutical composition comprising at least one compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) illustratively takes the form of a liquid where the agents are present in solution, in suspension or both. Typically when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

[0223] In certain embodiments, useful aqueous suspensions contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers, e.g., hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked

carboxyl-containing polymers. Certain pharmaceutical compositions described herein comprise a mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[0224] Useful pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C). The term "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, e.g., polyethylene glycol 400, and glycol ethers.

[0225] Furthermore, useful pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[0226] Additionally, useful compositions also, optionally, include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[0227] Other useful pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[0228] Still other useful compositions include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

[0229] Still other useful compositions include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

[0230] In certain embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

[0231] In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or carriers useful herein. In certain embodiments, organic solvents such as N-methylpyrrolidone are also employed. In additional embodiments, the compounds described herein are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are useful herein. In some embodiments, sustained-release capsules release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

[0232] In certain embodiments, the formulations described herein comprise one or more antioxidants, metal chelating agents, thiol containing compounds and/or other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

[0233] In some embodiments, the concentration of one or more compounds provided in the pharmaceutical compositions of the present disclosure is less than 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%,14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v or v/v.

[0234] In some embodiments, the concentration of one or more compounds of the disclosure is greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%,

6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 125% , 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v, or v/v.

[0235] In some embodiments, the concentration of one or more compounds of the disclosure is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40 %, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, approximately 1% to approximately 10% w/w, w/v or v/v.

[0236] In some embodiments, the concentration of one or more compounds of the disclosure is in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

[0237] In some embodiments, the amount of one or more compounds of the disclosure is equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

[0238] In some embodiments, the amount of one or more compounds of the disclosure is more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g,

0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, , 0.15 g, 0.2 g, , 0.25 g, 0.3 g, , 0.35 g, 0.4 g, , 0.45 g, 0.5 g, 0.55 g, 0.6 g, , 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5g, 7 g, 7.5g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g.

[0239] In some embodiments, the amount of one or more compounds of the disclosure is in the range of 0.0001-10 g, 0.0005-9 g, 0.001-8 g, 0.005-7 g, 0.01-6 g, 0.05-5 g, 0.1-4 g, 0.5-4 g, or 1-3 g.

[0240] Kits/Articles of Manufacture

[0241] For use in the therapeutic applications described herein, kits and articles of manufacture are also provided. In some embodiments, such kits comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers are formed from a variety of materials such as glass or plastic.

[0242] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include those found in, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. For example, the container(s) includes one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[0243] For example, a kit typically includes one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included. A label is optionally on or associated with the container. For example, a label is on a container when letters, numbers or other characters forming the label are attached, molded or

etched into the container itself, a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In addition, a label is used to indicate that the contents are to be used for a specific therapeutic application. In addition, the label indicates directions for use of the contents, such as in the methods described herein. In certain embodiments, the pharmaceutical compositions is presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack for example contains metal or plastic foil, such as a blister pack. Or, the pack or dispenser device is accompanied by instructions for administration. Or, the pack or dispenser is accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0244] Methods

[0245] The present disclosure provides a method of inhibiting Ras-mediated cell signaling comprising contacting a cell with an effective amount of one or more compounds disclosed herein. Inhibition of Ras-mediated signal transduction can be assessed and demonstrated by a wide variety of ways known in the art. Non-limiting examples include a showing of (a) a decrease in GTPase activity of Ras; (b) a decrease in GTP binding affinity or an increase in GDP binding affinity; (c) an increase in K off of GTP or a decrease in K off of GDP; (d) a decrease in the levels of signaling transduction molecules downstream in the Ras pathway, such as a decrease in pMEK level; and/or (e) a decrease in binding of Ras complex to downstream signaling molecules including but not limited to Raf. Kits and commercially available assays can be utilized for determining one or more of the above.

[0246] The disclosure also provides methods of using the compounds or pharmaceutical compositions of the present disclosure to treat disease conditions, including but not limited to conditions implicated by K-Ras, H-Ras or N-Ras mutation, H-Ras mutation and/or N-Ras mutation (*e.g.*, cancer).

[0247] The disclosure also provides methods of using the compounds or pharmaceutical compositions of the present disclosure to treat disease conditions, including but not limited to conditions implicated by G12C G12D, G12S, G12V, and/or G13D mutations in K-Ras, H-Ras and/or N-Ras, (*e.g.*, cancer).

[0248] In some embodiments, a method for treatment of cancer is provided, the method comprising administering an effective amount of any of the foregoing pharmaceutical compositions comprising a compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) to a subject in need thereof. In some embodiments, the cancer is mediated by a K-Ras, H-Ras or N-Ras G12C mutation. In other embodiments, the cancer is pancreatic cancer, colon cancer, MYH associated polyposis, colorectal cancer or lung cancer.

[0249] In some embodiments the disclosure provides method of treating a disorder in a subject in need thereof, wherein the said method comprises determining if the subject has a K-Ras, H-Ras or N-Ras G12C mutation and if the subject is determined to have the K-Ras, H-Ras or N-Ras G12C mutation, then administering to the subject a therapeutically effective dose of at least one compound of Formula (I), (I-A), (I-B), (I-C), (II), (II-A), (II-B) or (II-C) or a pharmaceutically acceptable salt, ester, prodrug, tautomer, solvate, hydrate or derivative thereof.

[0250] The disclosed compounds strongly inhibit anchorage-independent cell growth and therefore have the potential to inhibit tumor metastasis. Accordingly, in another embodiment the disclosure provides a method for inhibiting tumor metastasis, the method comprising administering an effective amount a pharmaceutical composition of comprising any of the compounds disclosed herein and a pharmaceutically acceptable carrier to a subject in need thereof.

[0251] Ras mutations including but not limited to K-Ras, H-Ras or N-Ras mutations have also been identified in hematological malignancies (e.g., cancers that affect blood, bone marrow and/or lymph nodes). Accordingly, certain embodiments are directed to administration of a disclosed compounds (e.g., in the form of a pharmaceutical composition) to a patient in need of treatment of a hematological malignancy. Such malignancies include, but are not limited to leukemias and lymphomas. For example, the presently disclosed compounds can be used for treatment of diseases such as Acute lymphoblastic leukemia (ALL), Acute myelogenous leukemia (AML), Chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Chronic myelogenous leukemia (CML), Acute monocytic leukemia (AMoL) and/ or other leukemias. In other embodiments, the compounds are useful for treatment of lymphomas such as all subtypes of Hodgkins lymphoma or non-Hodgkins lymphoma.

[0252] Determining whether a tumor or cancer comprises a Ras mutation including but not limited to a K-Ras, H-Ras or N-Ras mutation can be undertaken by assessing the nucleotide sequence encoding the Ras protein, by assessing the amino acid sequence of Ras protein, or by assessing the characteristics of a putative Ras mutant protein. The sequence of wild-type human Ras proteins including but not limited to K-Ras, H-Ras or N-Ras is known in the art, (e.g.

Accession No. NP203524).

[0253] Methods for detecting a mutation in a Ras nucleotide sequence including but not limited to K-Ras, H-Ras or N-Ras nucleotide sequence are known by those of skill in the art. These methods include, but are not limited to, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays, polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) assays, real-time PCR assays, PCR sequencing, mutant allele-specific PCR amplification (MASA) assays, direct sequencing, primer extension reactions, electrophoresis, oligonucleotide ligation assays, hybridization assays, TaqMan assays, SNP genotyping assays, high resolution melting assays and microarray analyses. In some embodiments, samples are evaluated for Ras mutations including but not limited to K-Ras, H-Ras or N-Ras mutations by real-time PCR. In real-time PCR, fluorescent probes specific for the Ras mutation including but not limited to K-Ras, H-Ras or N-Ras mutation are used. When a mutation is present, the probe binds and fluorescence is detected. In some embodiments, the Ras mutation including but not limited to a K-Ras, H-Ras or N-Ras mutation is identified using a direct sequencing method of specific regions (e.g., exon 2 and/or exon 3) in the Ras gene or corresponding K-Ras, H-Ras or N-Ras gene, for example. This technique will identify all possible mutations in the region sequenced.

[0254] Methods for detecting a mutation in a Ras protein including but not limited to a K-Ras, H-Ras or N-Ras protein are known by those of skill in the art. These methods include, but are not limited to, detection of a K-Ras, H-Ras or N-Ras mutant using a binding agent (e.g., an antibody) specific for the mutant protein, protein electrophoresis and Western blotting, and direct peptide sequencing.

[0255] Methods for determining whether a tumor or cancer comprises a Ras mutation including but not limited to a K-Ras, H-Ras or N-Ras mutation can use a variety of samples. In some embodiments, the sample is taken from a subject having a tumor or cancer. In some embodiments, the sample is taken from a subject having a cancer or tumor. In some embodiments, the sample is a fresh tumor/cancer sample. In some embodiments, the sample is a frozen tumor/cancer sample. In some embodiments, the sample is a formalin-fixed paraffin-embedded sample. In some embodiments, the sample is processed to a cell lysate. In some embodiments, the sample is processed to DNA or RNA.

[0256] The disclosure also relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. In some embodiments, said method relates to the treatment

of cancer such as acute myeloid leukemia, cancer in adolescents, adrenocortical carcinoma childhood, AIDS-related cancers (e.g. Lymphoma and Kaposi's Sarcoma), anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myleoproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer (NSCLC), oral cancer, lip and oral cavity cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or Viral-Induced cancer. In some embodiments, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

[0257] In certain particular embodiments, the disclosure relates to methods for treatment of lung

cancers, the methods comprise administering an effective amount of any of the above described compound (or a pharmaceutical composition comprising the same) to a subject in need thereof. In certain embodiments the lung cancer is a non-small cell lung carcinoma (NSCLC), for example adenocarcinoma, squamous-cell lung carcinoma or large-cell lung carcinoma. In other embodiments, the lung cancer is a small cell lung carcinoma. Other lung cancers treatable with the disclosed compounds include, but are not limited to, glandular tumors, carcinoid tumors and undifferentiated carcinomas.

[0258] Subjects that can be treated with compounds of the disclosure, or pharmaceutically acceptable salt, ester, prodrug, solvate, tautomer, hydrate or derivative of said compounds, according to the methods of this disclosure include, for example, subjects that have been diagnosed as having acute myeloid leukemia, acute myeloid leukemia, cancer in adolescents, adrenocortical carcinoma childhood, AIDS-related cancers (e.g. Lymphoma and Kaposi's Sarcoma), anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myleoproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer,lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/ myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer (NSCLC), oral cancer, lip and oral cavity cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal

cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or Viral-Induced cancer. In some embodiments subjects that are treated with the compounds of the disclosure include subjects that have been diagnosed as having a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

[0259] The disclosure further provides methods of modulating a mutant Ras including but not limited to a mutant K-Ras, H-Ras or N-Ras protein activity by contacting the protein with an effective amount of a compound of the disclosure. Modulation can be inhibiting or activating protein activity. In some embodiments, the disclosure provides methods of inhibiting protein activity by contacting the mutant Ras protein (for example, a Mutant K-Ras, H-Ras or N-Ras protein) with an effective amount of a compound of the disclosure in solution. In some embodiments, the disclosure provides methods of inhibiting the mutant Ras protein activity by contacting a cell, tissue, organ that express the protein of interest. In some embodiments, the disclosure provides methods of inhibiting protein activity in a subject including but not limited to rodents and mammal (e.g., human) by administering into the subject an effective amount of a compound of the disclosure. In some embodiments, the percentage modulation exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%. In some embodiments, the percentage of inhibiting exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%.

[0260] In some embodiments, the disclosure provides methods of inhibiting Ras activity including but not limited to K-Ras, H-Ras or N-Ras mutant activity in a cell by contacting said cell with an amount of a compound of the disclosure sufficient to inhibit the activity of Ras or a K-Ras, H-Ras or N-Ras mutant in said cell. In some embodiments, the disclosure provides methods of inhibiting Ras or mutant K-Ras, H-Ras or N-Ras activity in a tissue by contacting said tissue with an amount of a compound of the disclosure sufficient to inhibit the activity of mutant Ras or including but not limited to mutant K-Ras, H-Ras or N-Ras in said tissue. In some embodiments, the disclosure provides methods of inhibiting Ras including but not limited to mutant K-Ras, H-Ras or N-Ras activity in an organism by contacting said organism with an amount of a compound of the disclosure sufficient to inhibit the activity of Ras including but not

limited to mutant K-Ras, H-Ras or N-Ras in said organism. In some embodiments, the disclosure provides methods of inhibiting Ras including but not limited to mutant K-Ras, H-Ras or N-Ras activity in an animal by contacting said animal with an amount of a compound of the disclosure sufficient to inhibit the activity of Ras including but not limited to mutant K-Ras, H-Ras or N-Ras in said animal. In some embodiments, the disclosure provides methods of inhibiting Ras including but not limited to mutant K-Ras, H-Ras or N-Ras activity in a mammal by contacting said mammal with an amount of a compound of the disclosure sufficient to inhibit the activity of Ras including but not limited to mutant K-Ras, H-Ras or N-Ras in said mammal. In some embodiments, the disclosure provides methods of inhibiting Ras including but not limited to mutant K-Ras, H-Ras or N-Ras activity in a human by contacting said human with an amount of a compound of the disclosure sufficient to inhibit the activity of Ras including but not limited to mutant K-Ras, H-Ras or N-Ras in said human. The present disclosure provides methods of treating a disease mediated by Ras including but not limited to mutant K-Ras, H-Ras or N-Ras activity in a subject in need of such treatment.

[0261] The present disclosure also provides methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in combination with a compound of the present disclosure, or a pharmaceutically acceptable salt, ester, prodrug, solvate, tautomer, hydrate or derivative thereof. In one aspect, such therapy includes but is not limited to the combination of one or more compounds of the disclosure with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic or additive therapeutic effect.

[0262] Many chemotherapeutics are presently known in the art and can be used in combination with the compounds of the disclosure. In some embodiments, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

[0263] Non-limiting examples are chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules such as Gleevec® (Imatinib Mesylate), Velcade® (bortezomib), Casodex (bicalutamide), Iressa® (gefitinib), and Adriamycin as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CYTOXANTM); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as

chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, CasodexTM, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK.RTM.; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (“Ara-C”); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (TAXOLTM, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERETM, Rhone-Poulenc Rorer, Antony, France); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, (NolvadexTM), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS

2000; difluoromethylornithine (DMFO). Where desired, the compounds or pharmaceutical composition of the present disclosure can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin®, Avastin®, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, ABVD, AVICINE, Abagovomab, Acridine carboxamide, Adecatumumab, 17-N-Allylamino-17-demethoxygeldanamycin, Alpharadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastic, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Biricodar, Brostallicin, Bryostatin, Buthionine sulfoximine, CBV (chemotherapy), Calyculin, cell-cycle nonspecific antineoplastic agents, Dichloroacetic acid, Discodermolide, Elsamitrucin, Enocitabine, Epothilone, Eribulin, Everolimus, Exatecan, Exisulind, Ferruginol, Forodesine, Fosfestrol, ICE chemotherapy regimen, IT-101, Imexon, Imiquimod, Indolocarbazole, Irofulven, Laniquidar, Larotaxel, Lenalidomide, Lucanthone, Lurtotecan, Mafosfamide, Mitozolomide, Nafoxidine, Nedaplatin, Olaparib, Ortataxel, PAC-1, Pawpaw, Pixantrone, Proteasome inhibitor, Rebeccamycin, Resiquimod, Rubitecan, SN-38, Salinosporamide A, Sapacitabine, Stanford V, Swainsonine, Talaporfin, Tariquidar, Tegafur-uracil, Temodar, Tesetaxel, Triplatin tetranitrate, Tris(2-chloroethyl)amine, Troxacitabine, Uramustine, Vadimezan, Vinflunine, ZD6126 or Zosuquidar.

[0264] This disclosure further relates to a method for using the compounds or pharmaceutical compositions provided herein, in combination with radiation therapy for inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the disclosure in this combination therapy can be determined as described herein.

[0265] Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (e.g. At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm-153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner of the present disclosure include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta

particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

[0266] Without being limited by any theory, the compounds of the present disclosure can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, this disclosure further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of a compound of the present disclosure or pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof, which amount is effective is sensitizing abnormal cells to treatment with radiation. The amount of the compound, salt, or solvate in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein.

[0267] The compounds or pharmaceutical compositions of the disclosure can be used in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, antiproliferative agents, glycolysis inhibitors, or autophagy inhibitors.

[0268] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound of the disclosure and pharmaceutical compositions described herein. Anti-angiogenesis agents include, for example, rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Examples of useful COX-II inhibitors include CELEBREXTM (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24,1996), WO 96/27583 (published March 7,1996), European Patent Application No. 97304971.1 (filed July 8,1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26,1998), WO 98/03516 (published January 29,1998), WO 98/34918 (published August 13,1998), WO 98/34915 (published August 13,1998), WO 98/33768 (published August 6,1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13,1994), European Patent Publication 931, 788 (published July 28,1999), WO 90/05719 (published May 31,1990), WO 99/52910 (published October 21,1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17,1999), PCT International Application No. PCT/IB98/01113 (filed July 21,1998), European Patent

Application No. 99302232.1 (filed March 25,1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12,1999), United States Patent 5,863, 949 (issued January 26,1999), United States Patent 5,861, 510 (issued January 19,1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (i. e., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-ll, MMP-12, andMMP-13). Some specific examples of MMP inhibitors useful in the disclosure are AG-3340, RO 32-3555, and RS 13-0830.

[0269] Autophagy inhibitors include, but are not limited to chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4-imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNA that inhibits expression of proteins including but not limited to ATG5 (which are implicated in autophagy), may also be used.

[0270] The disclosure also relates to a method of and to a pharmaceutical composition for treating a cardiovascular disease in a mammal which comprises an amount of a compound of the disclosure, or a pharmaceutically acceptable salt, ester, prodrug, solvate, tautomer, hydrate or derivative thereof, or an isotopically-labeled derivative thereof, and an amount of one or more therapeutic agents use for the treatment of cardiovascular diseases.

[0271] Exemplary agents for use in cardiovascular disease applications are anti-thrombotic agents, e.g., prostacyclin and salicylates, thrombolytic agents, e.g., streptokinase, urokinase, tissue plasminogen activator (TPA) and anisoylated plasminogen-streptokinase activator complex (APSAC), anti-platelets agents, e.g., acetyl-salicylic acid (ASA) and clopidrogel, vasodilating agents, e.g., nitrates, calcium channel blocking drugs, anti-proliferative agents, e.g., colchicine and alkylating agents, intercalating agents, growth modulating factors such as interleukins, transformation growth factor-beta and congeners of platelet derived growth factor, monoclonal antibodies directed against growth factors, anti-inflammatory agents, both steroidal and non-steroidal, and other agents that can modulate vessel tone, function, arteriosclerosis, and the healing response to vessel or organ injury post intervention. Antibiotics can also be included in combinations or coatings comprised by the disclosure. Moreover, a coating can be used to effect therapeutic delivery focally within the vessel wall. By incorporation of the active agent in

a swellable polymer, the active agent will be released upon swelling of the polymer.

[0272] In some embodiments, the compounds described herein are formulated or administered in conjunction with liquid or solid tissue barriers also known as lubricants. Examples of tissue barriers include, but are not limited to, polysaccharides, polyglycans, seprafilm, interceed and hyaluronic acid.

[0273] In some embodiments, medicaments which are administered in conjunction with the compounds described herein include any suitable drugs usefully delivered by inhalation for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; anti-infectives, e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines or pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutalin, isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments are used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimize the activity and/or stability of the medicament.

[0274] Other exemplary therapeutic agents useful for a combination therapy include but are not limited to agents as described above, radiation therapy, hormone antagonists, hormones and their releasing factors, thyroid and antithyroid drugs, estrogens and progestins, androgens, adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones, insulin, oral hypoglycemic agents, and the pharmacology of the endocrine pancreas, agents affecting calcification and bone turnover: calcium, phosphate, parathyroid hormone, vitamin D, calcitonin, vitamins such as water-soluble vitamins, vitamin B complex, ascorbic acid, fat-soluble vitamins, vitamins A, K, and E, growth factors, cytokines, chemokines, muscarinic receptor agonists and antagonists; anticholinesterase agents; agents acting at the neuromuscular junction and/or autonomic ganglia; catecholamines, sympathomimetic drugs, and adrenergic receptor agonists or antagonists; and 5-

hydroxytryptamine (5-HT, serotonin) receptor agonists and antagonists.

[0275] Therapeutic agents can also include agents for pain and inflammation such as histamine and histamine antagonists, bradykinin and bradykinin antagonists, 5-hydroxytryptamine (serotonin), lipid substances that are generated by biotransformation of the products of the selective hydrolysis of membrane phospholipids, eicosanoids, prostaglandins, thromboxanes, leukotrienes, aspirin, nonsteroidal anti-inflammatory agents, analgesic-antipyretic agents, agents that inhibit the synthesis of prostaglandins and thromboxanes, selective inhibitors of the inducible cyclooxygenase, selective inhibitors of the inducible cyclooxygenase-2, autacoids, paracrine hormones, somatostatin, gastrin, cytokines that mediate interactions involved in humoral and cellular immune responses, lipid-derived autacoids, eicosanoids, β-adrenergic agonists, ipratropium, glucocorticoids, methylxanthines, sodium channel blockers, opioid receptor agonists, calcium channel blockers, membrane stabilizers and leukotriene inhibitors.

[0276] Additional therapeutic agents contemplated herein include diuretics, vasopressin, agents affecting the renal conservation of water, rennin, angiotensin, agents useful in the treatment of myocardial ischemia, anti-hypertensive agents, angiotensin converting enzyme inhibitors, β-adrenergic receptor antagonists, agents for the treatment of hypercholesterolemia, and agents for the treatment of dyslipidemia.

[0277] Other therapeutic agents contemplated include drugs used for control of gastric acidity, agents for the treatment of peptic ulcers, agents for the treatment of gastroesophageal reflux disease, prokinetic agents, antiemetics, agents used in irritable bowel syndrome, agents used for diarrhea, agents used for constipation, agents used for inflammatory bowel disease, agents used for biliary disease, agents used for pancreatic disease. Therapeutic agents used to treat protozoan infections, drugs used to treat Malaria, Amebiasis, Giardiasis, Trichomoniasis, Trypanosomiasis, and/or Leishmaniasis, and/or drugs used in the chemotherapy of helminthiasis. Other therapeutic agents include antimicrobial agents, sulfonamides, trimethoprim-sulfamethoxazole quinolones, and agents for urinary tract infections, penicillins, cephalosporins, and other, β-lactam antibiotics, an agent comprising an aminoglycoside, protein synthesis inhibitors, drugs used in the chemotherapy of tuberculosis, mycobacterium avium complex disease, and leprosy, antifungal agents, antiviral agents including nonretroviral agents and antiretroviral agents.

[0278] Examples of therapeutic antibodies that can be combined with a compound of the disclosure include but are not limited to anti-receptor tyrosine kinase antibodies (cetuximab, panitumumab, trastuzumab), anti CD20 antibodies (rituximab, tositumomab), and other antibodies such as alemtuzumab, bevacizumab, and gemtuzumab.

[0279] Moreover, therapeutic agents used for immunomodulation, such as immunomodulators,

immunosuppressive agents, tolerogens, and immunostimulants are contemplated by the methods herein. In addition, therapeutic agents acting on the blood and the blood-forming organs, hematopoietic agents, growth factors, minerals, and vitamins, anticoagulant, thrombolytic, and antiplatelet drugs.

[0280] For treating renal carcinoma, one may combine a compound of the present disclosure with sorafenib and/or avastin. For treating an endometrial disorder, one may combine a compound of the present disclosure with doxorubincin, taxotere (taxol), and/or cisplatin (carboplatin). For treating ovarian cancer, one may combine a compound of the present disclosure with cisplatin (carboplatin), taxotere, doxorubincin, topotecan, and/or tamoxifen. For treating breast cancer, one may combine a compound of the present disclosure with taxotere (taxol), gemcitabine (capecitabine), tamoxifen, letrozole, tarceva, lapatinib, PD0325901, avastin, herceptin, OSI-906, and/or OSI-930. For treating lung cancer, one may combine a compound of the present disclosure with taxotere (taxol), gemcitabine, cisplatin, pemetrexed, Tarceva, PD0325901, and/or avastin.

[0281] Further therapeutic agents that can be combined with a compound of the disclosure are found in Goodman and Gilman's "The Pharmacological Basis of Therapeutics" Tenth Edition edited by Hardman, Limbird and Gilman or the Physician's Desk Reference, both of which are incorporated herein by reference in their entirety.

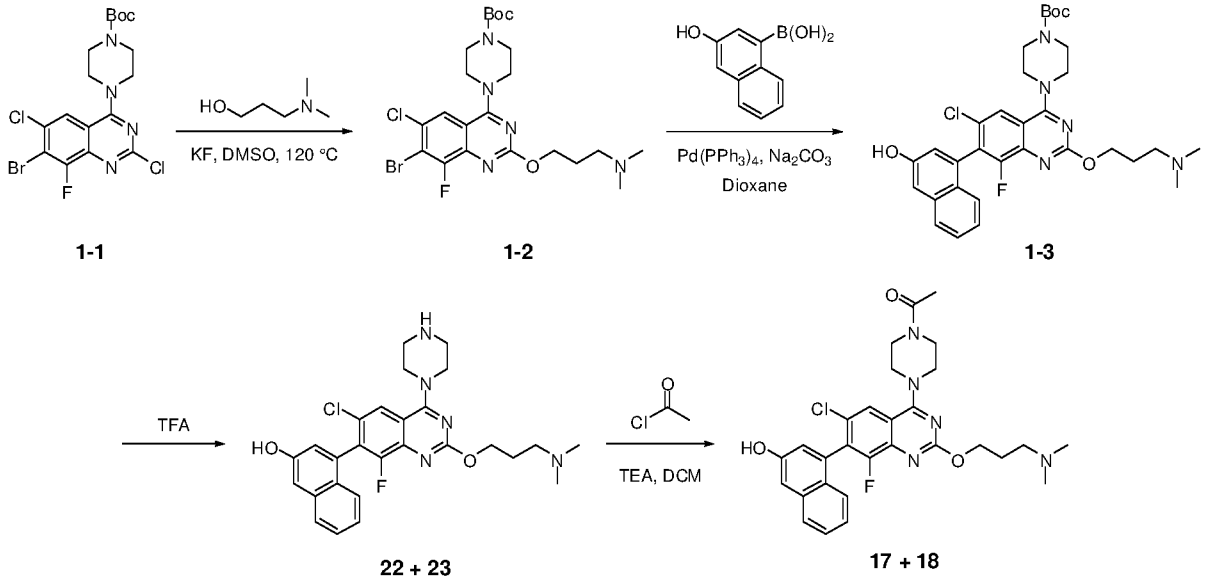
[0282] The compounds described herein can be used in combination with the agents disclosed herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments the one or more compounds of the disclosure will be co-administered with other agents as described above. When used in combination therapy, the compounds described herein are administered with the second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of the disclosure and any of the agents described above can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound of the present disclosure can be administered just followed by and any of the agents described above, or vice versa. In some embodiments of the separate administration protocol, a compound of the disclosure and any of the agents described above are administered a few minutes apart, or a few hours apart, or a few days apart.

[0283] The following examples are given for the purpose of illustrating various embodiments of

the disclosure and are not meant to limit the present disclosure in any fashion. The present examples, along with the methods and compositions described herein, are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the disclosure. Changes therein and other uses which are encompassed within the spirit of the disclosure as defined by the scope of the claims will occur to those skilled in the art.

EXAMPLES

[0284] Example 1: Synthesis of Compounds 22, 23, 17 and 18.



[0285] Step A: Preparation of 2-Amino-4-bromo-5-chloro-3-fluorobenzoic acid. To a solution of 2-amino-4-bromo-3-fluorobenzoic acid (17 g, 72.6 mmol) in DMF (200 mL) at room temperature was added NCS (10.2 g, 76.2 mmol). The resulting mixture was stirred at 70 °C for 16 h. The mixture was allowed to cool to room temperature and poured into cold brine. The precipitate was collected by filtration, rinsed with water and dried to afford the desired product as a white solid (14.6 g, 75% yield). ESI-MS *m/z*: 269.8 $[M+H]^+$.

[0286] Step B: Preparation of 7-Bromo-6-chloro-8-fluoroquinazoline-2,4(1H,3H)-dione. A mixture of 2-amino-4-bromo-5-chloro-3-fluorobenzoic acid (23.3 g, 110 mmol) and urea (68 g, 1100 mmol) was stirred at 200 °C for 4 h. The mixture was allowed to cool to room temperature. The solid was rinsed with boiling water 3 times, collected by filtration and dried to afford the desired product (24 g, 74% yield) as a gray solid.

[0287] Step C: Preparation of 7-Bromo-2,4,6-trichloro-8-fluoroquinazoline. The mixture of 7-bromo-6-chloro-8-fluoroquinazoline-2,4(1H,3H)-dione (14 g, 48 mmol) in $POCl_3$ (200 mL) and DIPEA (20 mL) was stirred at reflux for 16 h. The mixture was allowed to cool to room temperature and then concentrated *in vacuo* to remove $POCl_3$. The residue was purified by flash column chromatography on silica gel (2% ethyl acetate / petroleum ether) and then washed with

HCl (1M) to afford the product (9 g, 57% yield) as a yellow solid.

[0288] Step D: Preparation of tert-Butyl 4-(7-bromo-2,6-dichloro-8-fluoroquinazolin-4-yl)piperazine-1-carboxylate (Compound 1-1). To a solution of 7-bromo-2,4,6-trichloro-8-fluoroquinazoline (9 g, 27.3 mmol) and Et_3N (11.4 mL, 82 mmol) in 1,4-dioxane (60 mL) at room temperature was added tert-butyl piperazine-1-carboxylate (5.07 g, 27.3 mmol), and the resulting mixture was stirred at 50 °C for 20 min. The mixture was allowed to cool to room temperature and partitioned between water and dichloromethane. The organic layer was washed with 1N HCl, water, saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was triturated with a mixture of petroleum ether/ ethyl acetate = 5:1 to afford the desired product (12 g, 91.5% yield) as a light yellow solid. ESI-MS *m/z*: 447.2 $[M+H]^+$. ^1H-NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, J = 1.8 Hz, 1H), 3.90-3.87 (m, 4H), 3.67-3.64 (m, 4H), 1.49 (s, 9H).

[0289] Step E: Preparation of tert-butyl 4-(7-bromo-6-chloro-2-(3-(dimethylamino)propoxy)-8-fluoroquinazolin-4-yl)piperazine-1-carboxylate (Compound 1-2). To a solution of tert-butyl 4-(7-bromo-2,6-dichloro-8-fluoroquinazolin-4-yl)piperazine-1-carboxylate (1.21 g, 2.5 mmol) and DIPEA (968 mg, 7.5 mmol) in DMSO (30 mL) at room temperature was added 3-(dimethylamino)propan-1-ol (516 mg, 5.0 mmol), and the resulting mixture was stirred at 130 °C for 3 h under N_2. The mixture was allowed to cool to room temperature and partitioned between water and EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was triturated with a mixture of petroleum ether/ ethyl acetate to afford the desired product (825 mg, 60.2% yield). ESI-MS *m/z*: 548.15 $[M+H]^+$.

[0290] Step F: Preparation of tert-butyl 4-(6-chloro-2-(3-(dimethylamino)propoxy)-8-fluoro-7-(3-hydroxynaphthalen-1-yl)quinazolin-4-yl)piperazine-1-carboxylate (Compound 1-3). To a stirred solution of tert-butyl 4-(7-bromo-6-chloro-2-(3-(dimethylamino)propoxy)-8-fluoroquinazolin-4-yl)piperazine-1-carboxylate (825 mg, 1.5 mmol) in 1,4-dioxane/H_2O (20 mL / 5mL), 3-hydroxynaphthalen-1-yl-1-boronic acid (846 mg, 4.5 mmol), Tetrakis(triphenylphosphine)palladium (173 mg, 0.15 mmol) and Na_2CO_3 (477 mg, 4.5 mmol) were added. The mixture was degassed and back-filled with N_2 several cycles and then stirred at 100 °C overnight. The mixture was partitioned between water and ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the desired product (539 mg, 58.9% yield). ESI-MS *m/z*: 610.35 $[M+H]^+$.

[0291] Step G: Preparation of 4-(6-chloro-2-(3-(dimethylamino)propoxy)-8-fluoro-4-(piperazin-1-yl)quinazolin-7-yl)naphthalen-2-ol (Compounds 22 and 23). A solution of tert-butyl 4-(6-

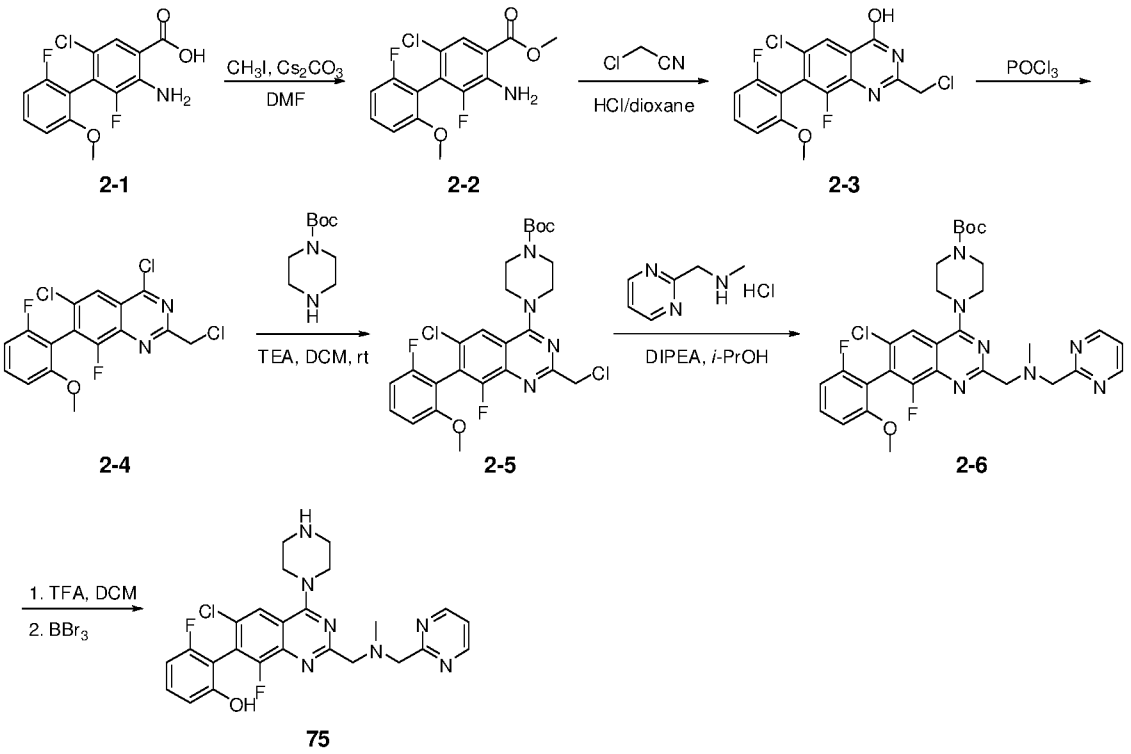
chloro-2-(3-(dimethylamino)propoxy)-8-fluoro-7-(3-hydroxynaphthalen-1-yl)quinazolin-4-yl)piperazine-1-carboxylate (300 mg, 0.492 mmol) in HCl/CH_3OH (15 mL) was stirred at RT for 1 h. The mixture was concentrated *in vacuo*. The residue was diluted with NH_3/CH_3OH and the solution was concentrated *in vacuo*. The residue was purified by prep-TLC to afford the desired product (230 mg, 95% yield). ESI-MS *m/z*: 510.20 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.07 (s, 1H),7.96 (s, 1H), 7.80-7.82 (d, J = 8.0 Hz, 1H),7.42-7.46 (m, 1H), 7.29-7.30 (d, J = 2.4 Hz, 1H), 7.21-7.23 (m, 2H), 7.07-7.08 (d, J = 2.4 Hz,1H), 4.36-4.39 (m, 2H), 3.84(m, 4H), 3.02-3.03 (m, 4H), 2.46-2.48 (m, 2H), 2.23 (s, 6H),1.89-1.96 (m, 2H).

[0292] The two atropisomers were separated by chiral SFC separation using a CHIRALPAK AD-H column (50 × 250 mm, 5 μm) on preparative SFC-200 (Thar, Waters) instrument eluting with CO_2/methanol (50:50) at a flow rate of 130 g/min to afford Compounds 22 and 23, respectively.

[0293] Step H: Preparation of 1-(4-(6-chloro-2-(3-(dimethylamino)propoxy)-8-fluoro-7-(3-hydroxynaphthalen-1-yl)quinazolin-4-yl)piperazin-1-yl)ethanone (Compounds 17 and 18). To a solution of 4-(6-chloro-2-(3-(dimethylamino)propoxy)-8-fluoro-4-(piperazin-1-yl)quinazolin-7-yl)naphthalen-2-ol (125 mg, 0.246 mmol) and Et_3N (124 mg, 1.23 mmol) in DCM (8 mL) at 0 °C, acetyl chloride (23 mg, 0.295 mmol) was added and the resulting mixture was stirred at 0 °C for 3 h. The mixture was allowed to cool to room temperature and partitioned between water and dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford the desired product (14 mg, 10% yield). ESI-MS *m/z*: 552.30 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.24 (s, 1H), 8.01 (s, 1H), 7.80-7.82 (d, J = 8.4 Hz, 1H), 7.43-7.46 (m, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.21-7.22 (m, 2H), 7.07-7.08 (d, J = 2.0 Hz, 1H), 4.36-4.39 (m, 2H), 3.86-3.93 (m, 8H), 2.54-2.57 (m, 2H), 2.29 (s, 6H), 2.07 (s, 3H),1.93-1.98 (m, 2H).

[0294] The two atropisomers were separated by chiral SFC separation using a CHIRALPAK AD-H column (50 × 250 mm, 5 μm) on preparative SFC-200 (Thar, Waters) instrument eluting with CO_2/methanol (50:50) at a flow rate of 130 g/min to afford Compounds 17 and 18, respectively.

[0295] Example 2: Synthesis of Compound 75.



[0296] Step A: Preparation of 3-Amino-2,2'-difluoro-6'-methoxy-[1,1'-biphenyl]-4-carboxylic acid. To a stirred solution of 2-amino-4-bromo-3-fluorobenzoic acid (10 g, 43 mmol) in 1,4-dioxane (400 mL) and water (100 mL), 2-fluoro-6-methoxyphenylboronic acid (36 g, 213 mmol), tetrakis(triphenylphosphine)palladium (2.5 g, 2.15 mmol) and Na_2CO_3 (27 g, 258 mmol), were added. The mixture was degassed and back-filled with nitrogen several times, and then stirred at 100 °C overnight. The mixture was allowed to cool to RT and partitioned between water and ethyl acetate. The organic layer was discarded, and 1M HCl solution was added to the aqueous phase to adjust pH <3. The aqueous phase was extracted with ethyl acetate (200 mL x 2), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired product (11 g, 92% yield). ESI-MS *m/z*: 280.1 $[M+H]^+$.

[0297] Step B: Preparation of 3-Amino-6-chloro-2,2'-difluoro-6'-methoxy-[1,1'-biphenyl]-4-carboxylic acid (Compound 2-1). To a solution of 3-amino-2,2'-difluoro-6'-methoxy-[1,1'-biphenyl]-4-carboxylic acid (11 g, 39.6 mmol) in N,N-dimethylformamide (100 mL) at RT, N-chlorosuccinimide (5.27 g, 39.6 mmol) was added and the resulting mixture was stirred at 100 °C for 1 h. The mixture was allowed to cool to RT, and then slowly added to H_2O (300 mL). The mixture was filtered and the cake was dried to afford the desired product (11.5 g, 93.1% yield).

[0298] Step C: Preparation of Methyl 3-amino-6-chloro-2,2'-difluoro-6'-methoxy-[1,1'-biphenyl]-4-carboxylate (Compond 2-2). 3-Amino-6-chloro-2,2'-difluoro-6'-methoxy-[1,1'-biphenyl] -4-carboxylic acid (7.8 g, 29.2 mmol) and Cs_2CO_3 (28.5 g, 9.62 mmol) were dissolved in DMF (80 mL), CH_3I (4.15 g, 29.2 mmol) was added and the resulting mixture was stirred at

RT overnight. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FC to afford the desired product (5.87 g, 61.3% yield) as an yellow solid.

[0299] Step D: Preparation of 6-chloro-2-(chloromethyl)-8-fluoro-7-(2-fluoro-6-methoxyphenyl)quinazolin-4-ol (Compound 2-3). Methyl 3-amino-6-chloro-2,2'-difluoro-6'-methoxy-[1,1'-biphenyl]-4-carboxylate (5.87 g, 20.9 mmol) and 2-chloroacetonitrile (7.89 g, 104 mmol) were dissolved in 1,4-dioxane (100 mL), and HCl gas was vapored into the solution for 1 h. The resultant solution was stirred at rt for 16 h. H_2O was added and the product extracted with ethyl acetate. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by by flash column chromatography on silica gel to afford the desire product (7.34 g, 94.7% yield). ESI-MS *m/z*: 370.95 $[M+H]^+$.

[0300] Step E: Preparation of 4,6-Dichloro-2-(chloromethyl)-8-fluoro-7-(2-fluoro-6-methoxyphenyl)quinazoline (Compound 2-4). 6-Chloro-2-(chloromethyl)-8-fluoro-7-(2-fluoro-6-methoxyphenyl)quinazolin-4-ol (7.34 g, 19.8 mmol) was dissolved in $POCl_3$ (50 mL), and DIPEA (5 mL) was added. The resulting solution was stirred at 110 °C for 16 h. The mixture was concentrated and diluted with ethyl acetate. The organic layer was concentrated *in vacuo*. The residue was purified by by flash column chromatography on silica gel to afford the desired product (6.4 g, 83% yield).

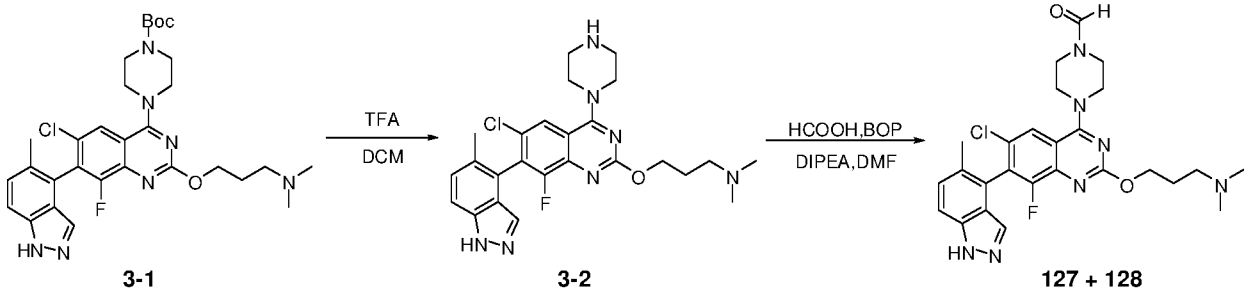
[0301] Step F: Preparation of tert-Butyl 4-(6-chloro-2-(chloromethyl)-8-fluoro-7-(2-fluoro-6-methoxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate (Compound 2-5). A solution of 4,6-dichloro-2-(chloromethyl)-8-fluoro-7-(2-fluoro-6-methoxyphenyl)quinazoline (200 mg, 0.51 mmol) and tert-butyl piperazine-1-carboxylate (115 mg, 0.616 mmol) in DCM (15 mL) was stirred at RT overnight. The mixture was partitioned between water and DCM. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the desired product (200 mg, 72.2% yield).

[0302] Step G: Preparation of tert-Butyl 4- (6-chloro-8-fluoro-7- (2-fluoro-6-methoxyphenyl)-2-((pyrimidin-2-ylmethylamino)methyl)quinazolin-4-yl) piperazine–1-carboxylate (Compound 2-6). To a solution of tert-butyl 4-(6-chloro-2-(chloromethyl)-8-fluoro-7-(2-fluoro-6-methoxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate (200 mg, 0.37 mmol) and DIPEA (239 mg, 1.85 mmol) in *i*-PrOH (15 mL) at room temperature, N-methyl(pyrimidin-2-yl)methanamine hydrochloride (71 mg, 0.445 mmol) was added and the resulting mixture was stirred at reflux overnight. The mixture was allowed to cool to room temperature and concentrated *in vacuo*. The residue was partitioned between water and ethyl acetate. The organic layer was washed with

brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by by flash column chromatography on silica gel to afford the desired product (169 mg, 72.8% yield). ESI-MS *m/z*: 626.30 $[M+H]^+$.

[0303] Step H: Preparation of 2-(6-Chloro-8-fluoro-2-((methyl(pyrimidin-2-ylmethyl)amino)methyl)-4-(piperazin-1-yl)quinazolin-7-yl)-3-fluorophenol (Compound 75). To a stirred solution of tert-butyl 4-(6-chloro-8-fluoro-7-(2-fluoro-6-methoxyphenyl)-2-((pyrimidin-2-ylmethylamino)methyl)quinazolin–4-yl) piperazine–1-carboxylate (169 mg, 0.269 mmol) in dichloromethane (15 mL), was added TFA (5 mL). The mixture was stirred at RT for 2 h and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in dichloromethane (20 mL) and cooled to -78 °C. To this mixture, BBr_3 (673 mg, 2.69 mmol) was added and the resulting mixture was stirred for 2 h. The mixture was poured to ice water and extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-TLC to afford the desired product (6 mg, 4.3% yield). ESI-MS *m/z*: 512.2 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.77-8.81 (s, 2H), 8.00 (s, 1H), 7.32-7.38 (m, 2H), 6.73-6.82 (m, 2H), 4.06-4.23 (m, 8H), 3.16-3.23 (m, 4H), 2.64 (s, 3H).

[0304] Example 3: Synthesis of Compounds 127 and 128.



[0305] Compound 3-1 was prepared following the procedure for the synthesis of Compound 1-3 in Example 1, except that (5-methyl-1H-indazol-4-yl)boronic acid was used instead of (3-hydroxynaphthalen-1-yl)boronic acid in the Suzuki coupling step.

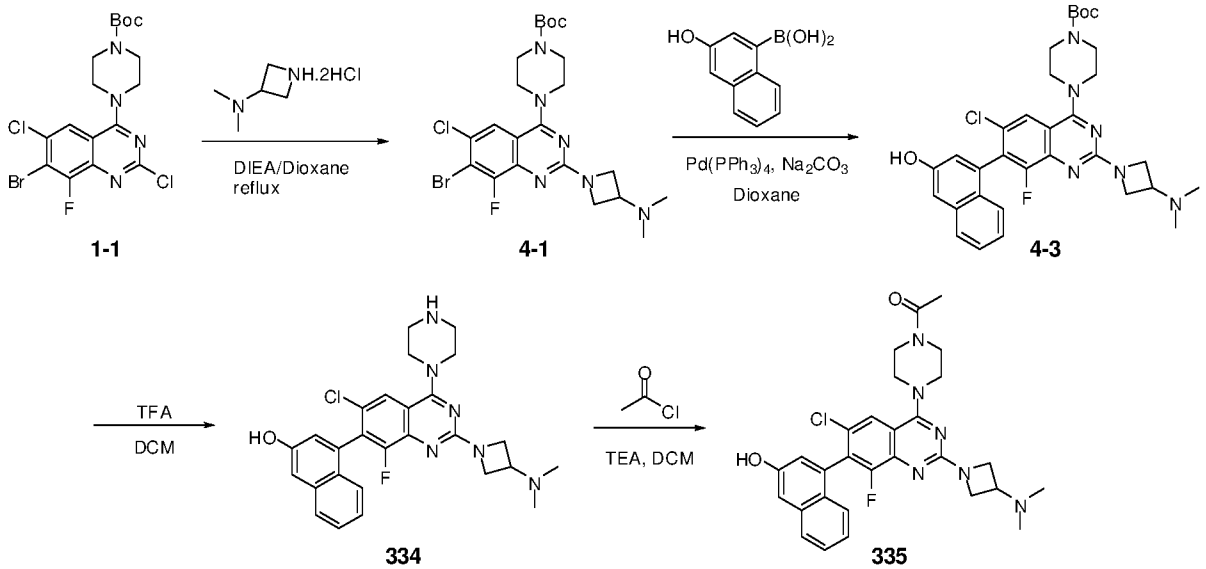
[0306] Step A: Preparation of 3-(6-Chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)-4-(piperazin-1-yl)quinazolin-2-yloxy)-N,N-dimethylpropan-1-amine (Compound 3-2). A mixture of tert-butyl 4-(6-chloro-2-(3-(dimethylamino)propoxy)-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)piperazine-1-carboxylate (580 mg, 0.97 mmol) in HCl/CH_3OH (15 mL) was stirred at RT for 2 h. The mixture was concentrated in vacuo and the residue was diluted with NH_3/CH_3OH. The mixture was concentrated *in vacuo* to afford the crude product which was used in the next step directly. ESI-MS *m/z*: 498.30 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.20 (s, 1H), 7.96 (s,

1H), 7.56-7.59 (m, 2H), 7.37-7.40 (d, J = 8.8 Hz,1H), 4.35-4.39 (m, 2H), 3.80-3.82 (m, 4H), 2.96-3.00 (m, 4H), 2.42-2.45 (m, 2H), 2.16 (s, 6H), 1.87-1.94 (m, 2H).

[0307] Step B: Preparation of 4-(6-Chloro-2-(3-(dimethylamino)propoxy)-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)piperazine-1-carbaldehyde (Compounds 127 and 128). To a solution of 3-(6-chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)-4-(piperazin-1-yl)quinazolin-2-yloxy)-N,N-dimethylpropan-1-amine (150 mg, 0.30 mmol) and formic acid (21 mg, 0.45 mmol) in DMF (15 mL) at room temperature, BOP (200 mg, 0.45 mmol) and DIPEA (116 mg, 0.90 mmol) were added and the resulting mixture was stirred at RT overnight. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-TLC to afford the desired product (35 mg, 22% yield). ESI-MS *m/z*: 526.25 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.20 (s, 1H), 8.14 (s, 1H), 7.96-8.03 (m, 2H), 7.53-7.61 (m, 2H), 7.39-7.41 (d, J = 8.8 Hz,1H), 4.42-4.45 (m, 2H), 3.80-3.87 (m, 4H), 3.64 (m, 4H), 3.17-3.21 (m, 2H), 2.78 (s, 6H), 2.12-2.17 (m, 5H).

[0308] The two atropisomers were separated by chiral SFC separation using a CHIRALPAK AD-H column (50 × 250 mm, 5 μm) on preparative SFC-200 (Thar, Waters) instrument eluting with CO_2/methanol (50:50) at a flow rate of 130 g/min to afford compounds 127 and 128 respectively.

[0309] Example 4: Synthesis of Compounds 334 and 335.



[0310] Step A: Preparation of tert-Butyl 4-(7-bromo-6-chloro-2-(3-(dimethylamino)azetidin-1-yl)-8-fluoroquinazolin-4-yl)piperazine-1-carboxylate (Compound 4-1). To a solution of tert-butyl 4-(7-bromo-2,6-dichloro-8-fluoroquinazolin-4-yl)piperazine-1-carboxylate (1.0 g, 2.08 mmol) and DIPEA (1.34 g, 10.4 mmol) in *i*-PrOH (100 mL) at room temperature, N,N-

dimethylazetidin-3-amine dihydrochloride (4.29 g, 2.49 mmol) was added and the resulting mixture was stirred at 100 °C overnight. The mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the desired product (1.12 g, 100% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, J = 1.8 Hz, 1H), 3.90-3.87 (m, 4H), 3.67-3.64 (m, 4H), 1.49 (s, 9H).

[0311] Step B: Preparation of tert-Butyl 4-(6-chloro-2-(3-(dimethylamino)azetidin-1-yl)-8-fluoro-7-(3-hydroxynaphthalen -1-yl)quinazolin-4-yl)piperazine-1-carboxylate (Compound 4-3). To a stirred solution of tert-butyl 4-(7-bromo-6-chloro-2-(3-(dimethylamino)azetidin-1-yl)-8-fluoroquinazolin-4-yl)piperazine-1-carboxylate (1.12 g, 2.08 mmol) in 1,4-dioxane/H_2O (20 mL / 5mL), 3-hydroxynaphthalen-1-yl-1-boronic acid (895 mg, 4.79 mmol), Tetrakis(triphenylphosphine)palladium (276 mg, 0.23 mmol) and Na_2CO_3 (1.0 g, 9.5 mmol) were added. The mixture was degassed and back-filled with N_2 several cycles and then stirred at 100 °C overnight. The mixture was partitioned between water and ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the desired product (1.0 g, 79% yield).

[0312] Step C: Preparation of 4-(6-Chloro-2-(3-(dimethylamino)azetidin-1-yl)-8-fluoro-4-(piperazin-1-yl)quinazolin-7-yl)naphthalen-2-ol (Compound 334). To a solution of tert-butyl 4-(6-chloro-2-(3-(dimethylamino)azetidin-1-yl)-8-fluoro-7-(3-hydroxynaphthalen-1-yl)quinazolin-4-yl)piperazine-1-carboxylate (1.0 g, 1.65 mmol) in DCM (15 mL) at RT, was added TFA (10 mL) and the resulting mixture was stirred for 1 h. The mixture was concentrated *in vacuo*. The residue was partitioned between sat $NaHCO_3$ solution and ethyl acetate. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the desired product (665 mg, 79% yield). ESI-MS *m/z*: 507.30 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.02 (s, 1H), 7.79-7.81 (d, J = 8.4 Hz, 1H), 7.75 (s, 1H), 7.41-7.45 (m, 1H), 7.26-7.27 (d, J = 2.4 Hz, 1H), 7.21-7.22 (d, J = 4.0 Hz, 1H), 7.03-7.04 (d, J = 2.4 Hz, 1H), 4.08-4.12 (m, 2H), 3.85-3.89 (m, 2H), 3.67 (m, 4H), 3.11-3.14 (m, 1H), 2.92 (m, 4H), 2.11 (s, 6H).

[0313] Step D: Preparation of 1-(4-(6-Chloro-2-(3-(dimethylamino)azetidin-1-yl)-8-fluoro-7-(3-hydroxynaphthalen-1-yl)quinazolin-4-yl)piperazin-1-yl)ethanone (Compound 335). To a solution of 4-(6-chloro-2-(3-(dimethylamino)azetidin-1-yl)-8-fluoro-4-(piperazin-1-yl)quinazolin-7-yl)naphthalen-2-ol (110 mg, 0.22 mmol) in 2 N NaOH/THF (10 mL/10mL) at 0 °C, acetyl chloride (34 mg, 0.43 mmol) was added and the resulting mixture was stirred at RT for 1 h. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with

brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-TLC to afford the desired product (14 mg, 10% yield). ESI-MS *m/z*: 549.35 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-*d6*) δ: 10.01 (s, 1H), 7.79-7.83 (m, 2H), 7.42-7.46 (m, 1H), 7.27 (d, J = 2.4 Hz, 1H), 7.21-7.22 (d, J = 3.2 Hz, 2H), 7.04 (d, J = 2.5 Hz, 1H), 4.10-4.14 (m, 2H), 3.87-3.91 (m, 2H), 3.68-3.79 (m, 8H), 3.15 (m, 1H), 2.13 (s, 6H), 2.07 (s,3H).

[0314] Example 5: *Biochemical and Cellular Assays of the Compounds.*

[0315] Inhibition of Cell Growth: The ability of a compound disclosed herein to inhibit Ras-mediated cell growth is assessed and demonstrated as follows. Cells expressing a wildtype or a mutant Ras are plated in white, clear bottom 96-well plates at a density of 5,000 cells per well. Cells are allowed to attach for about 2 hours after plating before a compound disclosed herein is added. After a certain time (e.g., 24 hours, 48 hours, or 72 hours of cell growth), cell proliferation is determined by measuring total ATP content using the Cell Titer Glo reagent (Promega) according to manufacturer's instructions. Proliferation EC50s are determined by analyzing 8 point compound dose responses at half-log intervals decreasing from 100 μM.

[0316] Inhibition of Ras-mediated signaling transduction: The ability of a compound disclosed herein to inhibit Ras-mediated signaling is assessed and demonstrated as follows. Cells expressing wild type or a mutant Ras (such as G12C, G12D, G12V, or G12A) are treated with or without (control cells) a subject compound. Inhibition of Ras signaling by one or more subject compounds is demonstrated by a decrease in the steady-state level of phosphorylated MEK, phosphorylated ERK, phosphorylated RSK, and/or Raf binding in cells treated with the one or more of the subject compounds as compared to the control cells.

[0317] Inhibition of Ras-mediated signaling transduction: The ability of a compound disclosed herein to inhibit Ras-mediated signaling is assessed and demonstrated as follows. Cells expressing wild type or a mutant Ras (such as G12C, G12D, G12V, or G12A) are treated with or without (control cells) a subject compound. Inhibition of Ras signaling by one or more subject compounds is demonstrated by a decrease in binding of Ras complex to downstream signaling molecules (for example Raf) in cells treated with the one or more of the subject compounds as compared to the control cells.

[0318] A compound of Table 1, Table 2 or Table 3 is tested according to the above procedures. The compound of Table 1, Table 2 or Table 3 is expected to inhibit Ras-mediated signaling transduction by one or more of the procedures described herein.

[0319] Example 6: *Assessing inhibition of cell proliferation by a compound disclosed herein*

[0320] Two cancer cell lines, NCI H441 (human lung adenenocarcinoma cells comprising a G12V mutation) and MIA paca-2 (human pancreatic carcinoma comprising a G12C mutation)

are used in this experiment. Both the cell lines are treated with a compound of Table 1, Table 2 or Table 3 at a concentration of 100 μM, 30 μM, 10 μM and 3 μM, and cell potency is measured as described in Example 5.

[0321] Example 7: *Comparison of cell proliferation inhibition by a compound disclosed herein*

[0322] Three cell lines, NCI H441 (human lung adenenocarcinoma cells), NCI 1568 (lung adenenocarcinoma cells) and MIA paca-2 (human pancreatic carcinoma) are used in this experiment. Both the cell lines are treated with a compound of Table 1, Table 2 or Table 3 at a concentration of 100 μM, 30 μM, 10 μM and 3 μM, and cell potency is measured.

[0323] Example 8: *SOS-mediated nucleotide exchange assays.*

[0324] GDP-loaded, hexahistidine tagged, truncated (1-169) KRAS proteins (WT or G12D) were used (stored in protein dilution buffer [20 mM HEPES pH=7.5, 150 NaCl, 1 mM $MgCl_2$]). 1 μL of the respective KRAS protein (1.88 μM stock, 0.125 μM final) was mixed with 10 μL of assay buffer (30 mM TRIS pH=7.5, 1.5 mM $MgCl_2$, 0.135 μM Bodipy-GDP [20 mM TRIS pH=7.5, 1.0 mM $MgCl_2$, 0.09 μM final]) and 1 μL of 15X compound stock in 30% DMSO (final DMSO conc. 2%). After 30 min incubation at room temperature, the exchange reaction was initiated by addition of 3 μL SOS(cat) (catalytic domain, 2.5 μM stock in protein dilution buffer, 0.5 μM final). The assay was carried out in black low-volume plates (Corning #4514) and fluorescence was monitored (485nm excitation and 510nm emission) for 45 minutes after initiation at 60-s intervals.

[0325] For data analysis, relative fluorescence values for each sample after subtracting the background values (before SOS addition) were plotted in graph pad. Rates were then calculated by fitting the data by non-linear regression (one phase association curve). Typically, 6 dilutions per compound (3-fold series, starting at 60 μM final) were measured. Calculated rates vs compound concentrations were fitted by non-linear regression (log(inhibitor) vs response-Variable slope (four parameters) fit) to determine IC_{50} values.

[0326] Table 4 shows biological activities of selected compounds in an SOS-mediated nucleotide exchange assay. Compound numbers correspond to the numbers and structures provided in Tables 1, 2 and 3 and Examples 1-4.

Table 4

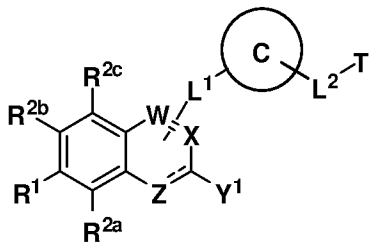
	Less than 15 μM (++)	Greater than 15 μM (+)
Kras WT IC_{50} (μM)	18, 151, 158, 162, 170	22, 97, 108, 112, 120, 134, 147, 155, 156, 164, 165, 166, 171, 172, 173, 175, 176, 330, 339, 344, 346, 350, 351
Kras G12D IC_{50} (μM)	22, 155, 156, 169, 172, 334, 339, 344	18, 97, 108, 112, 120, 134, 151, 158, 162, 164, 165, 166, 167, 168, 170, 171, 173, 174, 175, 176, 330, 346, 350, 351

[0327] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I),

or a salt or prodrug thereof, wherein:

R^1, R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen and R^{50};

W and X are each independently selected from N, NR^5 and CR^6;

Z is selected from bond, N, and CR^6;

Y^1 is selected from $-OR^{55}$; and alkyl, alkenyl, alkynyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with $-OR^{55}$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, $-OS(O)-$, $-S(O)O-$, $-S(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, $-N(R^{51})S(O)N(R^{51})-$; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

═══ indicates a single or double bond such that all valences are satisfied;

R^5 is independently selected at each occurrence from R^{51};

R^6 is independently selected at each occurrence from hydrogen, R^{50}, and a bond to L^1;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, -

$NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{55} is selected from:

alkyl, alkenyl, and alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{55} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, -

$NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

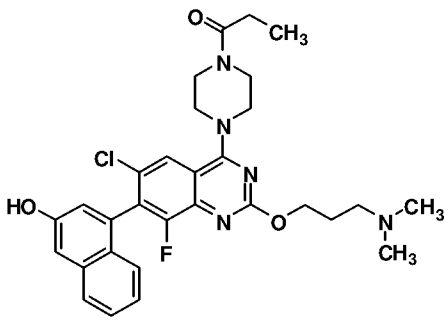
R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH);

wherein one of W, X and Z is CR^6 where R^6 is a bond to L^1; and

wherein the compound of Formula (I) is not: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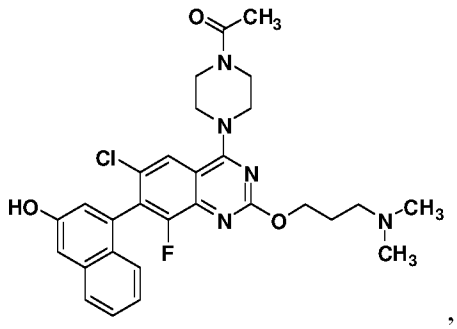
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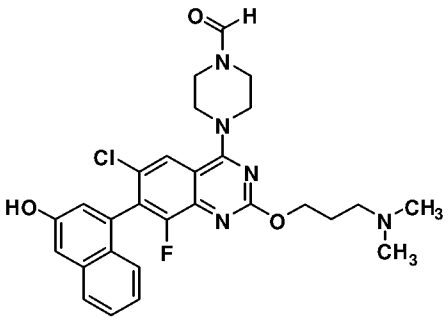
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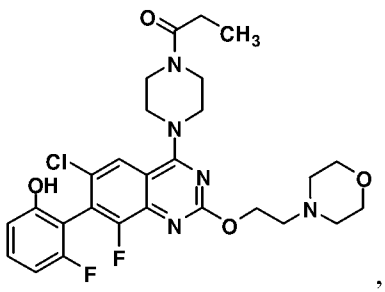
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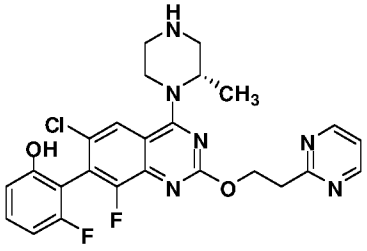
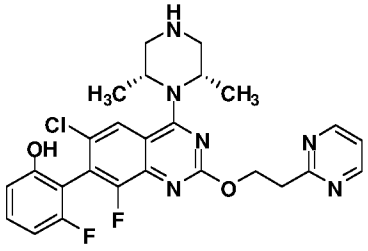

, or

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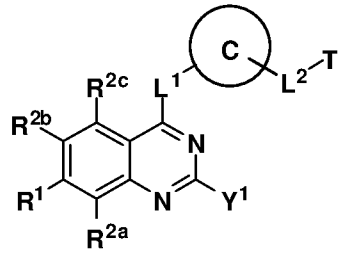
2. The compound of claim 1, represented by Formula (I-A):



(I-A), or a salt or prodrug thereof.

3. The compound of claim 1 or 2, wherein Y^1 is $-OR^{55}$.

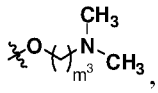
4. The compound of any one of the preceding claims, wherein R^{55} is selected from:

alkyl, alkenyl, and alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

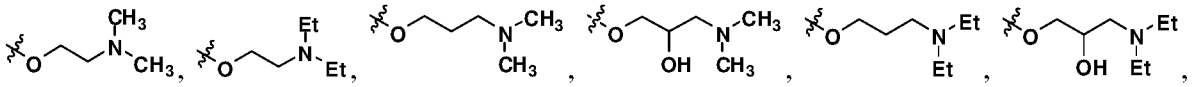
wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle is independently optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl.

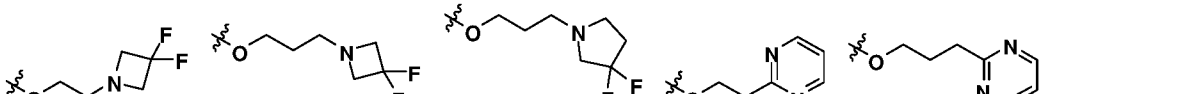
5. The compound of any one of the preceding claims, wherein R^{55} is selected from C_{1-4} alkyl substituted with $-N(R^{52})_2$, $-NR^{53}R^{54}$, or 3- to 12-membered heterocycle; and 3- to 12-membered heterocycle, wherein each 3- to 12-membered heterocycle is optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl.

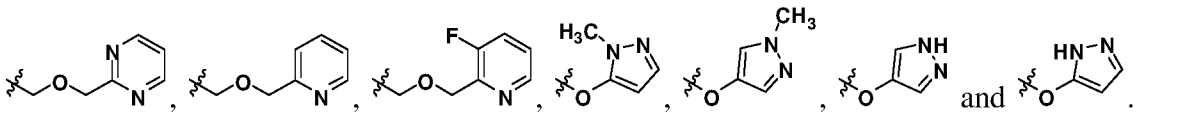
6. The compound of any one of the preceding claims, wherein Y^1 is  , wherein m^3 is an integer from 1 to 6.

7. The compound of claim 6, wherein m^3 is 2 or 3.

8. The compound of claim 1 or 2, wherein Y^1 is selected from:

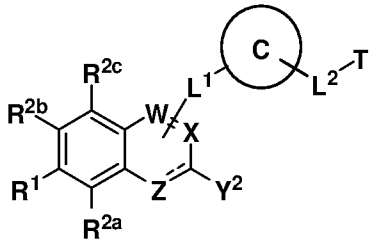






and .

9. A compound of Formula (II):



(II),

or a salt or prodrug thereof, wherein:

R^1, R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen and R^{50};

W and X are each independently selected from N, NR^5 and CR^6;

Z is selected from bond, N, and CR^6;

Y^2 is selected from $-N(R^{56})_2$; and alkyl, alkenyl, alkynyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with $-N(R^{56})_2$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, $-OS(O)-$, $-S(O)O-$, -S(O)-, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, $-N(R^{51})S(O)N(R^{51})-$; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

═══ indicates a single or double bond such that all valences are satisfied;

R^5 is independently selected at each occurrence from R^{51};

R^6 is independently selected at each occurrence from hydrogen, R^{50}, and a bond to L^1;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, -

$NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in

R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{56} is independently selected at each occurrence from:

hydrogen;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, -

$C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl,

or two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50}; and

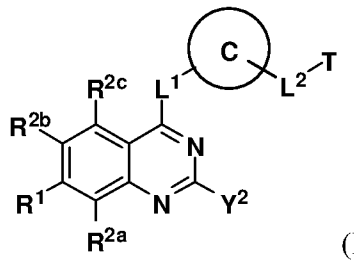
R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH);

wherein one of W, X and Z is CR^6 where R^6 is a bond to L^1.

10. The compound of claim 9, represented by Formula (II-A):



(II-A), or a salt or prodrug thereof.

11. The compound of claim 9 or 10, wherein Y^2 is C_{1-4} alkyl substituted with $-N(R^{56})_2$, and wherein at least one R^{56} is not hydrogen.

12. The compound of any one of claims 9 to 11, wherein R^{56} is independently selected at each occurrence from:

hydrogen;

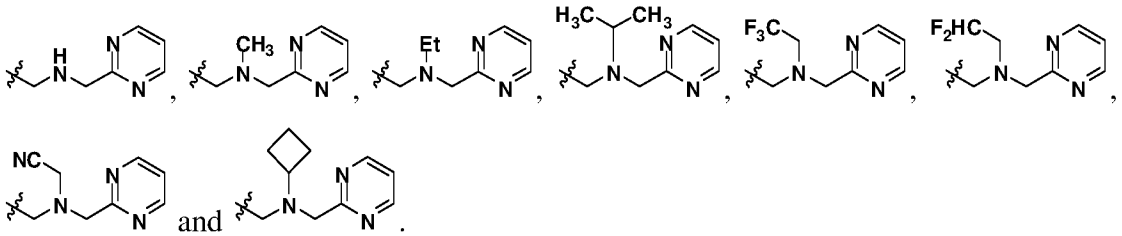
C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle is independently optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl.

13. The compound of any one of claims 9 to 12, wherein R^{56} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl substituted with one or more substituents selected from halogen, -CN, $-N(R^{52})_2$, $-NR^{53}R^{54}$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle is optionally substituted with one or more substituents selected from halogen, =O, C_{1-6} alkyl, and C_{1-6} haloalkyl.

14. The compound of any one of claims 9 to 13, wherein Y^2 is selected from:



and

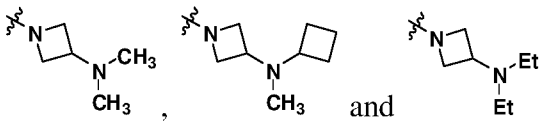
.

15. The compound of claim 9 or 10, wherein Y^2 is $-N(R^{56})_2$ and the two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a heterocycle, wherein the heterocycle is optionally substituted with one or more R^{50}.

16. The compound of claim 9 or 10, wherein Y^2 is $-N(R^{56})_2$ and the two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered heterocycle, wherein the heterocycle is substituted with $-N(R^{52})_2$ or $-NR^{53}R^{54}$.

17. The compound of claim 15 or 16, wherein Y^2 is azetidinyl, optionally substituted with one or more R^{50}.

18. The compound of claim 17, wherein Y^2 is selected from:



and

.

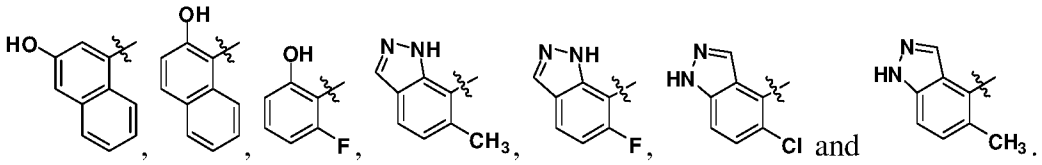
19. The compound of any one of the preceding claims, wherein R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

20. The compound of claim 19, wherein R^1 is selected from monocyclic aryl, bicyclic aryl, monocyclic heteroaryl, and bicyclic heteroaryl.

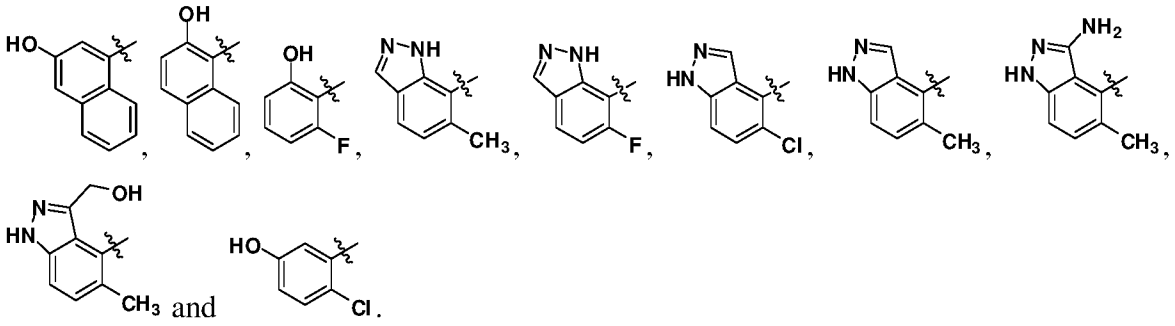
21. The compound of claim 19, wherein R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl.

22. The compound of any one of the preceding claims, wherein R^1 is substituted with one or more substituents selected from halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl.

23. The compound of any one of the preceding claims, wherein R^1 is selected from:



24. The compound of any one of claims 1 to 22, wherein R^1 is selected from:



25. The compound of any one of the preceding claims, wherein R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen, halogen, -OH, $-OCH_3$, C_{1-4} alkyl, and C_{1-4} haloalkyl.

26. The compound of any one of the preceding claims, wherein R^{2a} and R^{2b} are each independently selected from halogen.

27. The compound of any one of the preceding claims, wherein R^{2a} is fluorine.

28. The compound of any one of the preceding claims, wherein R^{2b} is chlorine.

29. The compound of any one of the preceding claims, wherein R^{2c} is hydrogen.

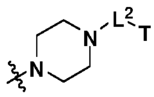
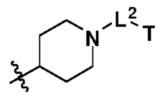
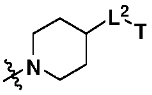
30. The compound of any one of the preceding claims, wherein C is 5- to 8-membered heterocycle, optionally substituted with one or more R^{57}.

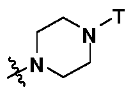
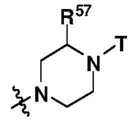
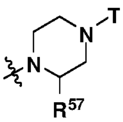
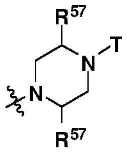
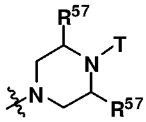
31. The compound of claim 30, wherein C is 6-membered monocyclic heterocycle, optionally substituted with one or more R^{57}.

32. The compound of claim 30 or 31, wherein the heterocycle comprises at least one nitrogen atom.

33. The compound of claim 32, wherein C is selected from morpholinyl, piperidinylene and piperazinylene, optionally substituted with one or more R^{57}.

34. The compound of claim 32, wherein C is selected from piperidinylene and piperazinylene, optionally substituted with one or more R^{57}.

35. The compound of claim 34, wherein C is selected from  ,  , and  , optionally substituted with one or more R^{57}.

36. The compound of claim 35, wherein C is selected from  ,  ,  ,  , and  .

37. The compound of any one of the preceding claims, wherein R^{57} is independently selected at each occurrence from C_{1-6} alkyl.

38. The compound of claim 37, wherein R^{57} is CH_3.

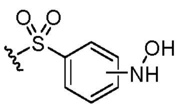
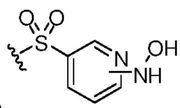
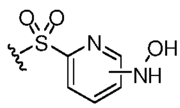
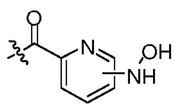
39. The compound of any one of the preceding claims, wherein T is capable of forming a complex with a metal ion that is complexed with the Ras protein.

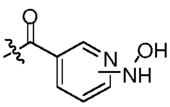
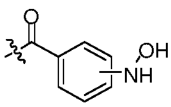
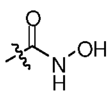
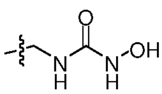
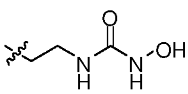
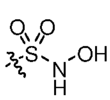
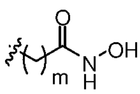
40. The compound of any one of claims 1 to 38, wherein T is capable of forming an interaction with a mutation residue in the Ras protein.

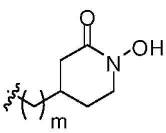
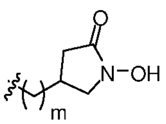
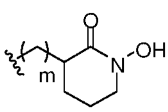
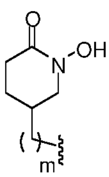
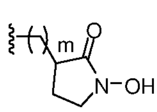
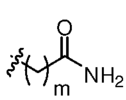
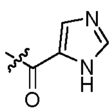
41. The compound of claim 40, wherein the mutation residue is G12D.

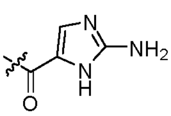
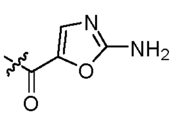
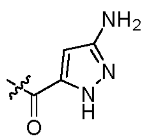
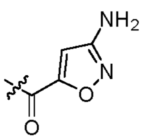
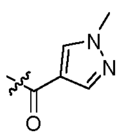
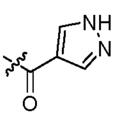
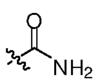
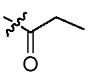
42. The compound of claim 40, wherein the mutation residue is G12A, G12C, G12D, G12S or G12V.

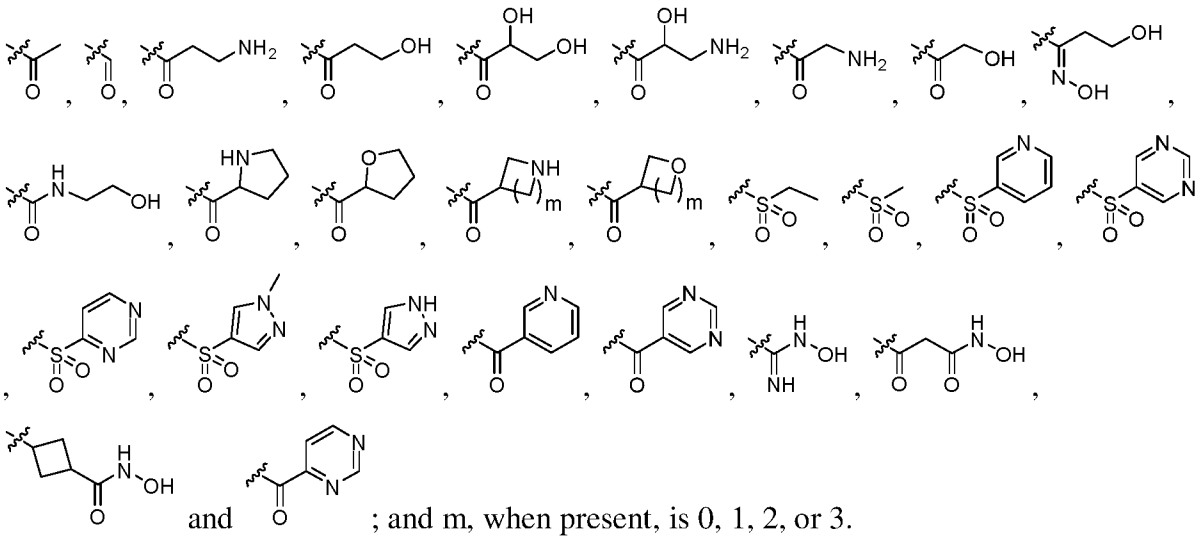
43. The compound of any one of the preceding claims, wherein T is selected from:

-H, $-NH_2$, -OH, $-NH(C_{1-6}$ alkyl),  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,  ,



and ; and m, when present, is 0, 1, 2, or 3.

44. The compound of any one of claims 1 to 36, wherein T is selected from R^{57}.

45. The compound of claim 44, wherein T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O.

46. The compound of claim 45, wherein T is selected from hydrogen, $-CH_3$, -C(O)H, $-C(O)CH_3$, and $-C(O)CH_2CH_3$.

47. The compound of any one of claims 1 to 36, wherein:

T is selected from hydrogen, C_{1-10} alkyl, C_{1-10} alkyl substituted with one or more R^{52}, $-C(O)R^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-C(S)N(R^{52})_2$, $-C(S)NR^{53}R^{54}$, $-NR^{52}C(S)R^{52}$, $-S(O)_2N(R^{52})_2$, $-S(O)_2NR^{53}R^{54}$, $-NR^{52}S(O)_2R^{52}$, $-C(NR^{52})N(R^{52})_2$, $-C(NR^{52})NR^{53}R^{54}$, and $-NR^{52}C(NR^{52})R^{52}$; and

R^{52} is independently selected at each occurrence from:

hydrogen; and

C_{1-20} alkyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle.

48. The compound of any one of the preceding claims, wherein L^1 is selected from bond and $-N(R^{51})-$.

49. The compound of claim 48, wherein L^1 is a bond.

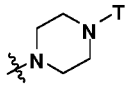
50. The compound of any one of the preceding claims, wherein L^2 is a bond.

51. The compound of any one of claims 1 to 18, wherein:

R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl, optionally substituted with one or more substituents selected from halogen, -OH, and $-CH_3$;

R^{2a} and R^{2b} are each independently selected from halogen;

R^{2c} is hydrogen;

C is  , optionally substituted with one or more R^{57};

T is selected from hydrogen; and C_{1-6} alkyl, optionally substituted with =O; and

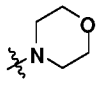
L^1 and L^2 are each a bond.

52. The compound of any one of claims 1 to 18, wherein:

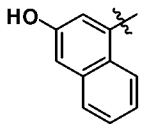
R^1 is selected from phenyl, naphthyl, indazolyl, and quinolinyl, optionally substituted with one or more substituents selected from halogen, -OH, and $-CH_3$;

R^{2a} and R^{2b} are each independently selected from halogen;

R^{2c} is hydrogen;

C is  , optionally substituted with one or more R^{57}; and

L^1 is a bond.

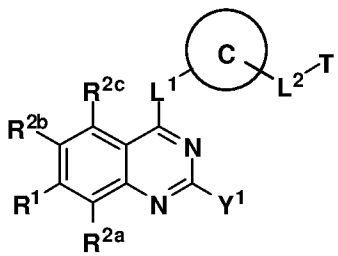
53. The compound of claim 51 or 52, wherein R^1 is  .

54. The compound of any one of claims 51 to 53, wherein R^{57} is $-CH_3$.

55. The compound of any one of claims 51 to 54, wherein T is hydrogen.

56. A substantially pure atropisomer of the compound of any one of claims 1 to 55.

57. A stereoisomer of a compound of Formula (I-A):



(I-A),

or a salt or prodrug thereof, wherein:

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with one or more substituents independently selected from halogen, -OH, $-OR^{52}$, $-NH_2$, -NHMe, $-NMe_2$, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from hydrogen, halogen, -OH, $-OR^{52}$, C_{1-4} alkyl, and C_{1-4} haloalkyl, wherein at least one of R^{2a} and R^{2b} is not hydrogen;

R^{2c} is selected from hydrogen, halogen, -OH, $-OR^{52}$, C_{1-4} alkyl, and C_{1-4} haloalkyl;

and

Y^1 is selected from $-OR^{55}$; and C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, each of which is substituted with $-OR^{55}$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, -OS(O)-, -S(O)O-, -S(O)-, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, $-N(R^{51})S(O)N(R^{51})-$; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in

R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{55} is selected from:

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

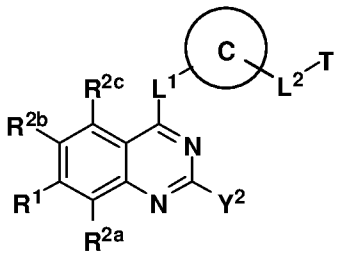
wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{55} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, -C(O)OH, -C(O)H, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

58. A stereoisomer of a compound of Formula (II-A):



(II-A),

or a salt or prodrug thereof, wherein:

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with one or more substituents independently selected from halogen, -OH, $-OR^{52}$, $-NH_2$, -NHMe, $-NMe_2$, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from hydrogen, halogen, -OH, $-OR^{52}$, C_{1-4} alkyl, and C_{1-4} haloalkyl, wherein at least one of R^{2a} and R^{2b} is not hydrogen;

R^{2c} is selected from hydrogen, halogen, -OH, $-OR^{52}$, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

Y^2 is selected from $-N(R^{56})_2$; and C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, each of which is substituted with $-N(R^{56})_2$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, $-OS(O)-$, $-S(O)O-$, $-S(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, $-N(R^{51})S(O)N(R^{51})-$; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$,

$-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{56} is independently selected at each occurrence from:

hydrogen;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, -

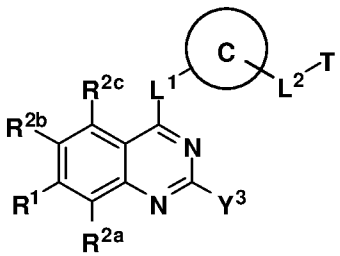
$NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

R^{57} is independently selected at each occurrence from:

halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl$)$, $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl$)$, $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

59. A stereoisomer of a compound of Formula (III-A):



(III-A),

or a salt or prodrug thereof, wherein:

R^1 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with one or more substituents independently selected from halogen, -OH, $-OR^{52}$, $-NH_2$, -NHMe, $-NMe_2$, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

R^{2a} and R^{2b} are each independently selected from hydrogen, halogen, -OH, $-OR^{52}$, C_{1-4} alkyl, and C_{1-4} haloalkyl, wherein at least one of R^{2a} and R^{2b} is not hydrogen;

R^{2c} is selected from hydrogen, halogen, -OH, $-OR^{52}$, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

Y^3 is selected from $-OR^{55}$, $-N(R^{56})_2$; and C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, each of which is substituted with $-OR^{55}$ or $-N(R^{56})_2$ and optionally futher substituted with one or more R^{50};

L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, -OS(O)-, -S(O)O-, -S(O)-, $-OS(O)_2-$, -

$S(O)_2O$-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})S(O)$-, -$S(O)N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, -$N(R^{51})S(O)N(R^{51})$-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50};

L^2 is selected from bond and alkylene;

C is selected from 3- to 12-membered heterocycle, optionally substituted with one or more R^{57};

T is hydrogen or a polar group capable of forming a complex with a Ras protein via an interaction other than one resulting in a covalent bond with the cysteine residue at position 12 of a K-Ras, H-Ras or N-Ras G12C mutant protein;

R^{50} is independently selected at each occurrence from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{1-6} alkyl, C_{1-6}

haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $-CN$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $=O$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{55} is selected from:

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, -

$NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{55} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{56} is independently selected at each occurrence from:

hydrogen;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, -

$C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl,

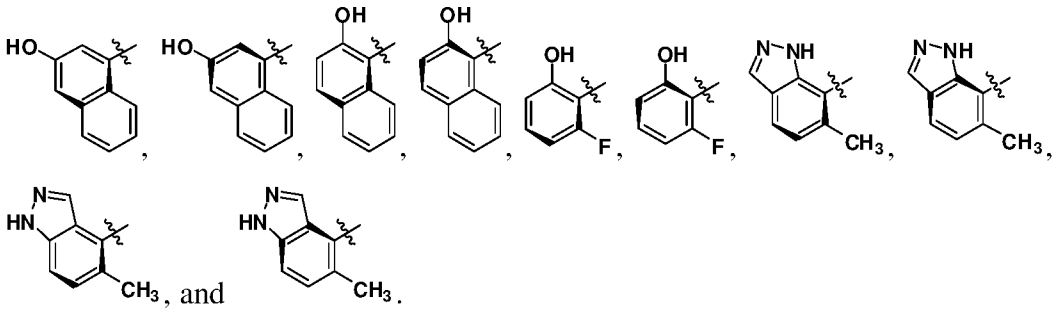
or two R^{56} groups are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50}; and

R^{57} is independently selected at each occurrence from:

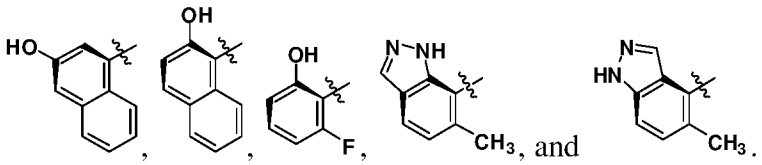
halogen, -CN, -OH, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, =N(OH); and

C_{1-10} alkyl, optionally substituted at each occurrence with one or more substituents selected from -CN, -OH, $-NH_2$, -OMe, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)OH$, $-C(O)H$, $-C(O)C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, =O, and =N(OH).

60. The compound of any one of claims 57 to 59, wherein R^1 is selected from:



61. The compound of claim 60, wherein R^1 is selected from:



62. The compound of any one of claims 57 to 61, wherein the stereoisomer is an atropisomer.

63. The compound of any one of claims 57 to 62, wherein the stereoisomer is provided in at least 90% enantiomeric excess.

64. The compound of any one of claims 57 to 62, wherein the stereoisomer is provided in at least 90% diastereomeric excess.

65. The compound of claim 1 or 9, wherein the compound is selected from a compound in Table 1, Table 2 or Table 3.

66. A pharmaceutical composition comprising a compound of any one of claims 1 to 65 and a pharmaceutically acceptable carrier.

67. The pharmaceutical composition of claim 66, wherein the pharmaceutical composition is formulated for oral administration.

68. The pharmaceutical composition of claim 66, wherein the pharmaceutical composition is formulated for injection.

69. A method for treatment of cancer, the method comprising administering an effective amount of the pharmaceutical composition of claim 66 to a subject in need thereof.

70. The method of claim 69, wherein the cancer is mediated by a K-Ras, H-Ras, or N-Ras mutant protein.

71. The method of claim 69, wherein the cancer is a hematological cancer, pancreatic cancer, MYH associated polyposis, colorectal cancer or lung cancer.

72. A method for regulating activity of a K-Ras, H-Ras or N-Ras mutant protein, the method comprising contacting the Ras mutant protein with the compound of any one of claims 1 to 65.

73. A method for inhibiting proliferation of a cell population, the method comprising contacting the cell population with the compound of any one of claims 1 to 65.

74. The method of claim 73, wherein inhibition of proliferation is measured as a decrease in cell viability of the cell population.

75. A method for treating a disorder mediated by a K-Ras, H-Ras or N-Ras mutant protein in a subject in need thereof, the method comprising:

determining if the subject has a K-Ras, H-Ras or N-Ras mutation; and

if the subject is determined to have the K-Ras, H-Ras or N-Ras mutation, then administering to the subject a therapeutically effective amount of the pharmaceutical composition of claim 66.

76. The method of claim 75, wherein the disorder is a cancer.

77. The method of claim 76, wherein the cancer is a hematological cancer, pancreatic cancer, MYH associated polyposis, colorectal cancer or lung cancer.

78. A method for inhibiting tumor metastasis, the method comprising administering an effective amount of the pharmaceutical composition of claim 66 to a subject in need thereof.

79. The method of claim 78, further comprising administering a second anti-cancer agent.

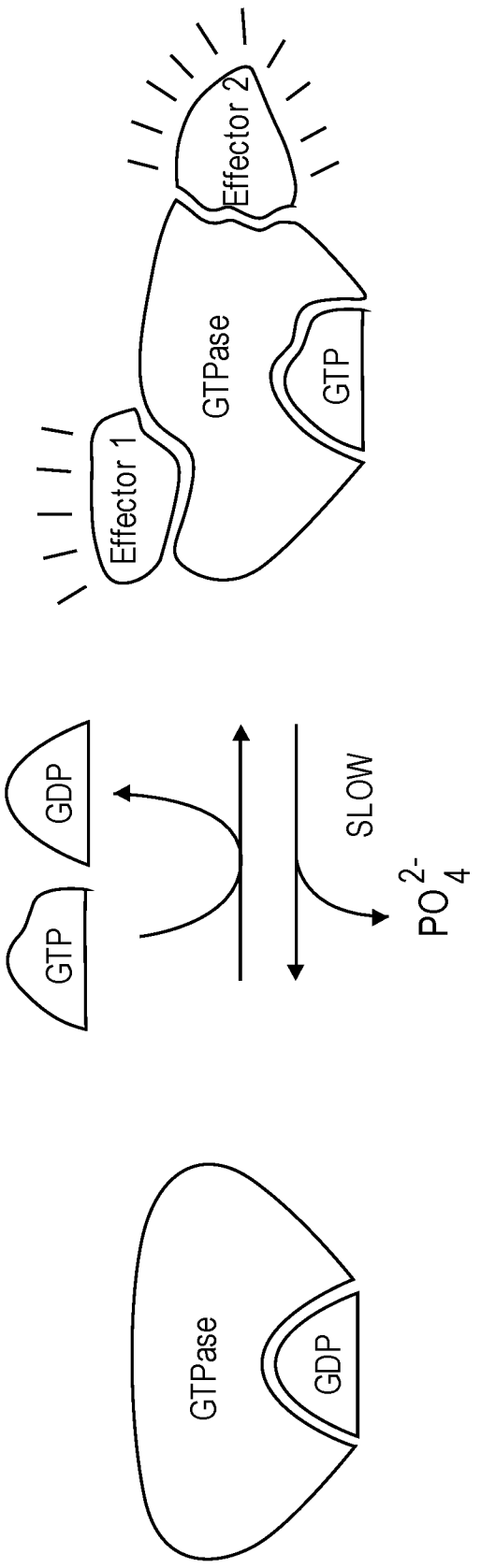

Effector 2
GTPase
GTP
Effector 1
GDP
GTP
SLOW
PO_4^{2-}
GTPase
GDP

FIG. 1

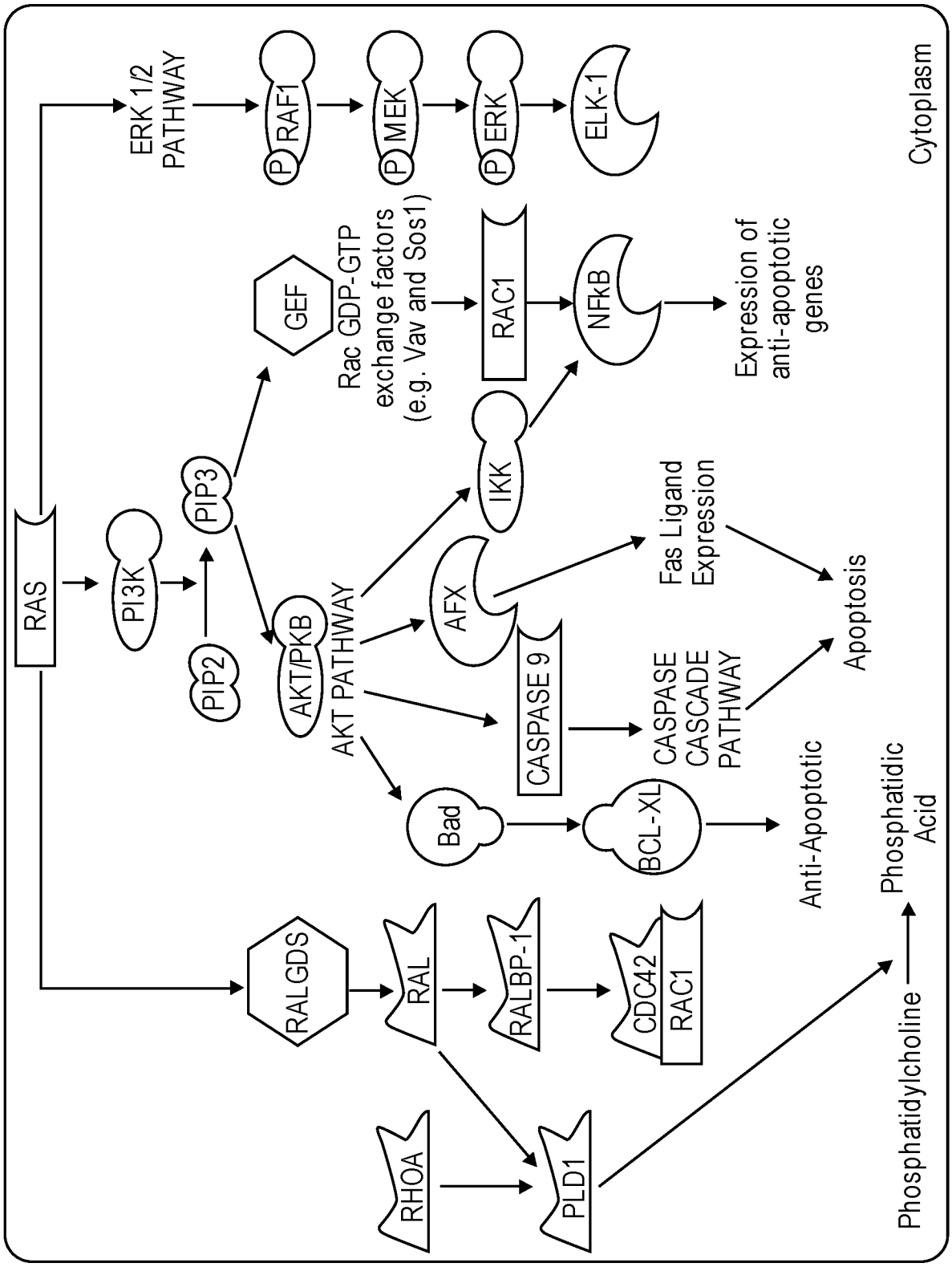

Cytoplasm
ERK 1/2 PATHWAY
RAF1
MEK
ERK
ELK-1
RAS
PI3K
PIP3
PIP2
GEF
Rac GDP-GTP exchange factors (e.g. Vav and Sos1)
RAC1
NFkB
Expression of anti-apoptotic genes
IKK
AKT/PKB
AKT PATHWAY
AFX
Fas Ligand Expression
CASPASE 9
CASPASE CASCADE PATHWAY
Apoptosis
Bad
BCL-XL
Anti-Apoptotic
RALGDS
RAL
RALBP-1
CDC42
RAC1
RHOA
PLD1
Phosphatidylcholine
Phosphatidic Acid

FIG. 2

Oncogene	Tumor Type	Cumulative Mutation Frequency (All Tumors)
Bcr-Abl	90% CML	< 1%
EGFR	10% NSCLC	< 5%
ALK	5% NSCLC	< 1%
B-Raf	66% Melanoma	< 5%
Flt3	25% AML	< 1%
PI3Kα	25% Breast; 25% Endometrial, 15% CRC	15-20%
K-Ras	> 80% Pancreatic; >40% colon >20% lung	~20%

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/24839

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-7, 12-14, 17-56, 62-64 and 66-79
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
--see supplemental page--

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1 and 3/1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/24839

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C11D 3/50, C07D 239/74 (2017.01)
CPC - C07D 239/26, A61K 2800/10, C11D 3/50, A61Q 13/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2013/0012489 A1 (Mederski et al.) 10 January 2013 (10.01.2013); para [0227]	1, 3/1
A	US 2015/0239900 A1 (Li et al.) 27 August 2015 (27.08.2015); para [0347]	1, 3/1
A	"Pubchem CID 10375614" Create Date: 25 October 2006 (25.10.2006) Date Accessed: 08 August 2017 (08.08.2017); pg. 3	1, 3/1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 August 2017	16 AUG 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/24839

--continued from Box No. III--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-3, 8, 57, 59(in part), (60-61)/(57, 59), and 65(in part), directed to compounds having the general formula of claim 1, formula (I). The compound of formula (I) will be searched to the extent that it encompasses the first species of claim 1, represented by the first formula of claim 1, formula (I), wherein R1, R2a, R2b and R2c are hydrogen; W is CR6 and X is N; Z is a bond; Y1 is OR55; L1 is a bond; L2 is a bond; C is a 3 membered heterocycle; T is hydrogen; dashed line is a single bond such that all valencies are satisfied; R6 is a bond to L1; R55 is alkyl, wherein one of W, X and Z is CR6 where R6 is a bond to L1. It is believed that claims 1 and 3/1 read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, represented by the first formula of claim 1, wherein R1, R2a, R2b and R2c are hydrogen; W is CR6 and X is N; Z is a bond; Y1 is OR55; L1 is a bond; L2 is a bond; C is a 3 membered heterocycle; T is hydrogen; dashed line is a single bond such that all valencies are satisfied; R6 is a bond to L1; R55 is alkyl substituted with one substituent which is -N(R52)2, wherein R52 is C1 alkyl, wherein one of W, X and Z is CR6 where R6 is a bond to L1 (i.e., claims 1 and (3, 8)/1).

Group II+: Claims 9-11, 15-16, 58, 59(in part), (60-61)/(58-59), and 65(in part), directed to compounds having the general formula of claim 9, formula II. The compound of formula (II) will be searched to the extent that it encompasses the first species of claim 9, represented by the first formula of claim 9, formula (II), wherein R1, R2a, R2b and R2c are hydrogen; W is CR6 and X is N; Z is a bond; Y2 is NR(56)2; L1 is a bond; L2 is a bond; C is a 3 membered heterocycle; T is hydrogen; dashed line is a single bond such that all valencies are satisfied; R6 is a bond to L1; R56 is hydrogen, wherein one of W, X and Z is CR6 where R6 is a bond to L1. It is believed that claim 9 reads on this first named invention, and thus this claim will be searched without fee. Applicant is invited to elect additional compounds of claim 9, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 9, formula (II), wherein R1, R2a, R2b and R2c are hydrogen; W is CR6 and X is N; Z is a bond; Y2 is C1 alkyl substituted with -N(R56)2, wherein one R56 is hydrogen and the other R56 is halogen; L1 is a bond; L2 is a bond; C is a 3 membered heterocycle; T is hydrogen; dashed line is a single bond such that all valencies are satisfied; R6 is a bond to L1; wherein one of W, X and Z is CR6 where R6 is a bond to L1 (i.e., claims 9-10).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of formula in claim 1, which is not required by any other invention of Group I+ or II+.

Group II+ includes the technical feature of a unique compound of formula in claim 9, which is not required by any other invention of Group II+ or I+.

Common technical features:

The inventions of Group I+ share the technical feature of compound of formula I in claim 1.

The inventions of Group II+ share the technical feature of compound of formula II in claim 9.

The inventions of Group I+ and II+ share the technical feature of the core structure of a compound of formula I and II in claim 1 and claim 9; respectively, without a substituent Y1 or Y2.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 2013/0012489 A1 to Mederski et al. (hereinafter Mederski). Mederski teaches the compound of formula I wherein R1 is R50, wherein R50 is 6 membered heterocycle; R2a, R2b and R2c are hydrogen; W is CR6 and X is N; Z is N; Y1 is OR55; L1 is a bond; L2 is a bond; C is a 6 membered heterocycle; T is hydrogen; dashed line is a double bond such that all valencies are satisfied; R6 is a bond to L1; R55 is alkyl, wherein one of W, X and Z is CR6 where R6 is a bond to L1 (para [0227]: Table 2, compound 39). Mederski further discloses a compound of formula II wherein R1 is R50, wherein R50 is 6 membered heterocycle; R2a, R2b and R2c are hydrogen; W is CR6 and X is N; Z is N; Y2 is N(R56)2; L1 is a bond; L2 is a bond; C is a 6 membered heterocycle; T is hydrogen; dashed line is a double bond such that all valencies are satisfied; R6 is a bond to L1; R56 is hydrogen, wherein one of W, X and Z is CR6 where R6 is a bond to L1 (para [0227]: Table 2, compound 57).

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ or II+. The inventions of Group I+ and II+ thus lack unity under PCT Rule 13.