[0005] An estimated over 600,000 Americans will die from cancer in 2021, corresponding to more than 1600 deaths per day (Cancer Facts and Figures 2021). The greatest number of deaths are from cancers of the lung, prostate, and colorectum in men, and cancers of the lung, breast, and colorectum in women. Almost one-quarter of all cancer deaths are due to lung cancer, 82% of which is directly caused by cigarette smoking. The 5-year survival rate for lung cancer patients is only about 20%.

[0006] KRAS is mutationally activated in lung cancer, and Glycine-to-Cysteine (G12C) mutations account for the majority of codon 12 mutations associated with cigarette smoking. A significant percentage of colorectal cancers are also driven by KRAS G12C mutations.

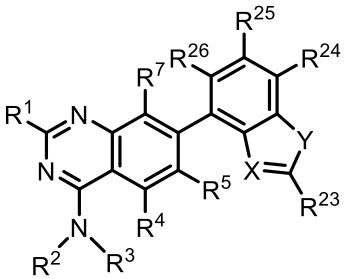
[0007] Early clinical data for allele-specific covalent KRAS G12C inhibitors show some effectiveness, at least in lung cancer. Those KRAS G12C inhibitors (e.g., Amgen Inc.'s sotorasib and Mirati Therapeutics. Inc.'s adagrasib) target inactive (GDP)-bound protein, and their effectiveness is enabled by high (comparable to wild type (WT) KRAS) intrinsic GTP hydrolysis rate of KRAS G12C mutant. Clinical data for these agents have shown that though most patients with KRAS G12C mutant non-small cell lung cancer (NSCLC) experience clinical benefit from selective KRAS G12C inhibition, patients with colorectal cancer bearing the same mutation rarely respond.

[0008] The cause of limited efficacy of KRAS G12C (GDP) inhibitors in colorectal cancers has been investigated. Unlike NSCLC cell lines, KRAS G12C colorectal cancer models have high basal receptor tyrosine kinase (RTK) activation and are responsive to growth factor stimulation. In colorectal cancer lines, KRAS G12C inhibition induces higher phospho-ERK rebound than in NSCLC cells. Also, it has been reported that KRAS G12C-GDP inhibitors induce transcription of new KRAS G12C that is in GTP-bound conformation, and insensitive to KRAS G12C inactive state inhibitors.

[0009] Therefore, there is a need for improved KRAS G12C inhibitors.

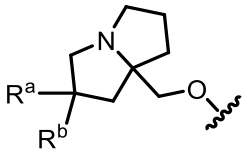
SUMMARY

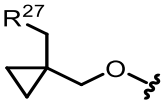
[0009a] In an aspect of the present disclosure, there is provided a compound represented by Formula IA2:



(IA2)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from 

, and 

;

R^2 and R^3, together with the atom to which they are attached, form a 4-8 membered heterocycle that is substituted with one or more E and 0-4 R^{11}, optionally wherein two R^{11} groups, together with the atom or atoms to which they are attached, form a 3-6 membered carbocycle or heterocycle;

R^4 is H;

R^5 is selected from H, -CN, halogen, C_{1-6}alkyl, -OR^{12}, a 3-6 membered carbocycle, a 5-6 membered heteroaryl, phenyl, and a 3-6 membered heterocycle, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}, and wherein any carbocycle, heteroaryl, phenyl, or heterocycle is unsubstituted or substituted with one or more R^{14};

R^7 is selected from halogen, -OR^{12}, -CN, and H;

each R^{11} is independently selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{22}, -CN, -$N(R^{22})_2$, and halogen;

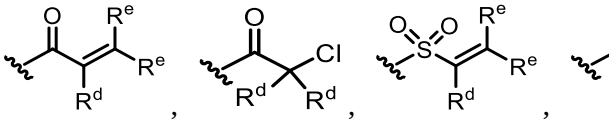
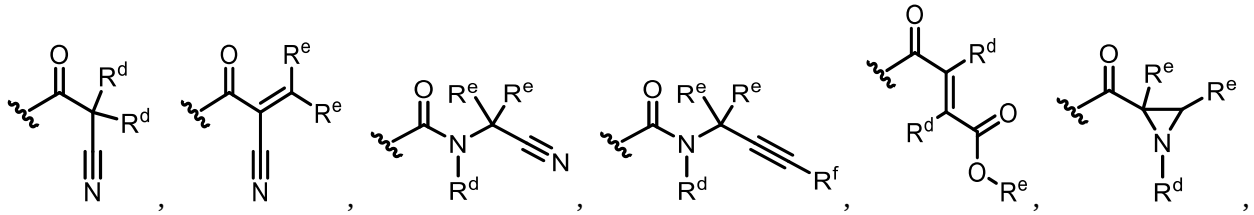
each R^{14} is independently selected from halogen, -CN, -$N(R^{12})_2$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -CN, -NH_2, -NHC_{1-6}alkyl, and halogen;

each R^{22} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

R^{27} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from C_{1-6}alkyl and halogen.

each E is independently selected from , , and -CN;

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13};

each R^d and R^e is independently selected from halogen, C_{1-6} alkyl, and H;

each R^f is independently selected from C_{1-6} alkyl and H;

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{12})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

[0009b] In another aspect of the present disclosure, there is provided a compound shown in Table 2, Table 3, Table 4, or Table 5, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0009c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a salt (e.g., pharmaceutically acceptable salt) thereof, and a pharmaceutically acceptable excipient.

[0009d] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use as a medicament.

[0009e] In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the treatment of a disease, disorder, or condition.

[0009f] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the manufacture of a medicament.

[0009g] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a salt (e.g., pharmaceutically acceptable salt) thereof, for the manufacture of a medicament for the treatment of a cancer.

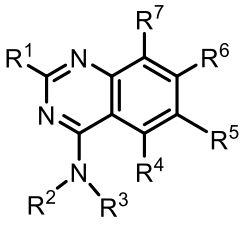
[0009h] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a salt (e.g. pharmaceutically acceptable salt) thereof, in the manufacture of a medicament for contacting a KRAS protein having a G12C mutation with the compound or salt.

[0009i] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a salt (e.g. pharmaceutically acceptable salt) thereof, in the manufacture of a medicament for inhibiting the function of a KRAS protein having a G12C mutation, wherein the KRAS protein is to be contacted with the compound or salt.

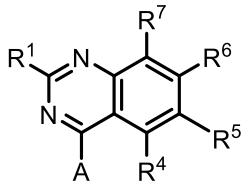
[0009j] In another aspect of the present disclosure, there is provided a compound capable of inhibiting a KRAS protein with a G12C mutation in both its active (GTP-bound) and inactive (GDP-bound) state.

[0010] The present disclosure provides compounds, as well as compositions and kits comprising the same, and methods of using the same in the treatment of diseases and disorders such as cancers. In some examples, the present disclosure provides KRAS G12C inhibitors targeting both active GTP-bound protein and inactive GDP-bound protein, which inhibitors may provide therapeutic advantages over KRAS G12C-GDP inhibitors. In some examples, compounds provided herein have inhibitory activity against a KRAS protein comprising a glycine to cysteine mutation at codon 12 (e.g., a G12C mutation) in both its active and inactive conformations. In some examples, compounds provided herein are useful in the treatment of cancers, such as cancers characterized by a KRAS G12C mutation.

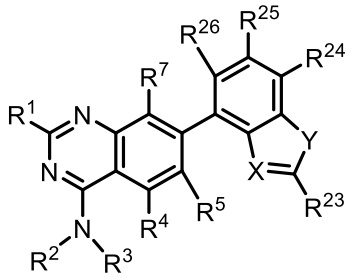
[0011] In an example, the present disclosure provides compositions comprising compounds represented by one of Formulas AA (e.g., Formula IA, IC, ID, or IE), BB (e.g., Formula IB), CC (e.g., Formula IIA, IIC, or IID), and DD (e.g., Formula IIB):



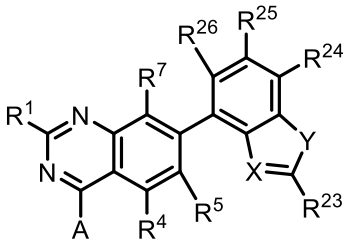
(AA)



(BB)



(CC)



(DD)

or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein A, X, Y, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{23}, R^{24}, R^{25}, and R^{26} are as provided herein. In some examples, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer thereof, can modulate (e.g., inhibit) the activity of a KRAS protein, such as a KRAS protein having a G12C mutation. In some examples, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer thereof, includes an electrophilic moiety E, as provided herein. In some examples, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer thereof, is capable of interacting covalently with a cysteine at the 12 position of the KRAS protein (e.g., a G12C mutation). In some examples, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer thereof, is capable of binding a KRAS protein in an active ("GTP-bound") conformation. In some examples, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer thereof, is capable of binding a KRAS protein in an inactive ("GDP-bound") conformation.

[0012] In another example, the present disclosure provides a pharmaceutical composition comprising a compound provided herein (e.g., a compound represented by one of Formulas AA, BB, CC, and DD, or any other formula set forth herein), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, together with a pharmaceutically acceptable carrier.

[0013] In a further example, the present disclosure provides a method of inhibition of KRAS activity in a human or animal subject for the treatment of a disease such as cancer, including pancreatic cancer (e.g., pancreatic ductal adenocarcinoma (PDAC)), colorectal cancer, and lung cancer, using, e.g., a compound provided herein (e.g., a compound represented by one of Formulas AA, BB, CC, and DD, or any other formula set forth herein), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, or a pharmaceutical composition comprising the same.

[0014] In another example, the present disclosure provides a use of a compound provided herein (e.g., a compound represented by one of Formulas AA, BB, CC, and DD, or any other formula set forth herein), or a salt, ester, tautomer, zwitterionic form, or stereoisomer thereof, in the manufacture of a medicament for the treatment of a disease, disorder, or condition (e.g., a cancer) ameliorated, treated, inhibited, or reduced by inhibition of KRAS, including KRAS having a G12C mutation. In some examples, the disease, disorder, or condition is pancreatic cancer (e.g., pancreatic ductal adenocarcinoma (PDAC)), colorectal cancer, or lung cancer.

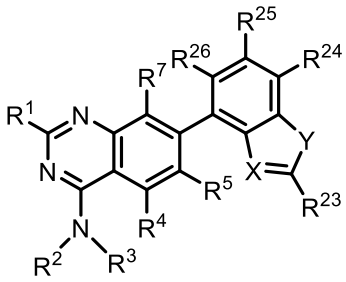
[0015] In a further example, the present disclosure provides a compound as provided herein (e.g., a compound represented by one of Formulas AA, BB, CC, and DD, or any other formula set forth herein), or a salt, ester, tautomer, zwitterionic form, or stereoisomer thereof, for use as a medicament. In some examples, the medicament is used in the treatment of a disease, disorder, or condition (e.g., a cancer). In some examples, the disease, disorder, or condition is pancreatic cancer (e.g., pancreatic ductal adenocarcinoma (PDAC)), colorectal cancer, or lung cancer.

DETAILED DESCRIPTION

[0016] The present disclosure provides compounds (e.g., compounds of Formulas IA, IA1, IA2, IB, IC, IC1, IC2, IC3, IC4, IC5, IC6, ID, ID1, IE, II, IIA, IIA1, IIA2, IIB, IIC, and IID), which compounds may possess useful KRAS inhibitory activity, and may be used in the treatment or prophylaxis of a disease, disorder, or condition in which KRAS plays an active role. In particular, certain compounds provided herein may possess useful inhibitory activity of KRAS having a G12C mutation, which KRAS protein is in an active (GTP-bound) or inactive (GDP-bound) conformation. Certain compounds provided herein may be capable of inhibiting both active and inactive forms of KRAS. The present disclosure also provides pharmaceutical compositions comprising one or more compounds provided herein together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. The present disclosure also provides methods for inhibiting KRAS, including KRAS having a G12C mutation, which KRAS is in an active or inactive conformation. In an aspect, the present disclosure

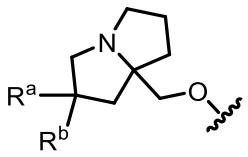
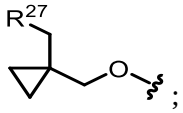
Claims

1. A compound represented by Formula IA2:



(IA2)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from  , and  ;

R^2 and R^3, together with the atom to which they are attached, form a 4-8 membered heterocycle that is substituted with one or more E and 0-4 R^{11}, optionally wherein two R^{11} groups, together with the atom or atoms to which they are attached, form a 3-6 membered carbocycle or heterocycle;

R^4 is H;

R^5 is selected from H, -CN, halogen, C_{1-6}alkyl, -OR^{12}, a 3-6 membered carbocycle, a 5-6 membered heteroaryl, phenyl, and a 3-6 membered heterocycle, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}, and wherein any carbocycle, heteroaryl, phenyl, or heterocycle is unsubstituted or substituted with one or more R^{14};

R^7 is selected from halogen, -OR^{12}, -CN, and H;

each R^{11} is independently selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{22}, -CN, -$N(R^{22})_2$, and halogen;

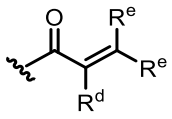
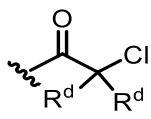
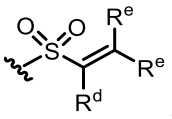
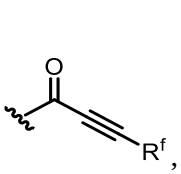
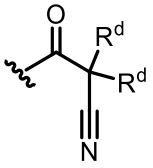
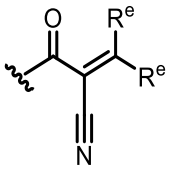
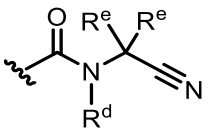
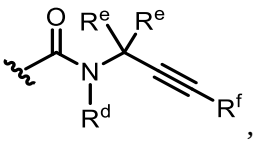
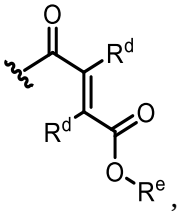
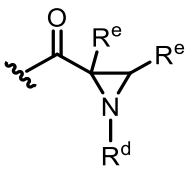
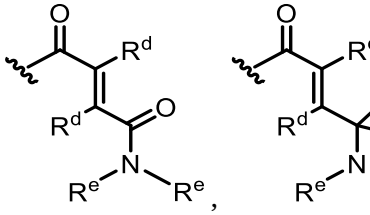
each R^{14} is independently selected from halogen, -CN, -$N(R^{12})_2$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -CN, -NH_2, -NHC_{1-6}alkyl, and halogen;

each R^{22} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

R^{27} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each E is independently selected from , , , , , , , , , , , and -CN;

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13};

each R^d and R^e is independently selected from halogen, C_{1-6} alkyl, and H;

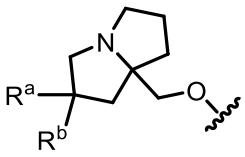
each R^f is independently selected from C_{1-6} alkyl and H;

X is selected from N and C-CN;

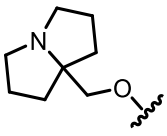
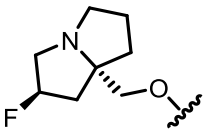
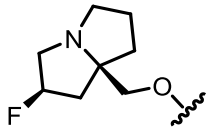
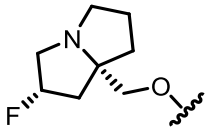
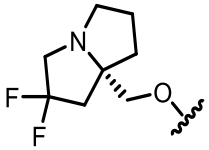
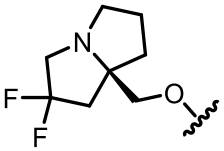
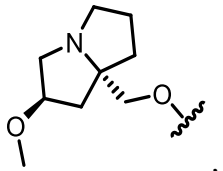
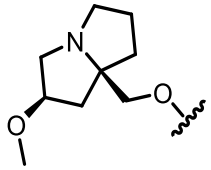
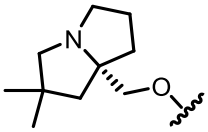
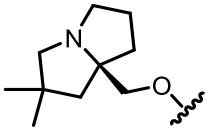
Y is selected from O and S;

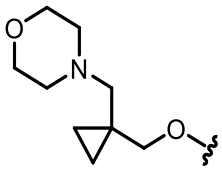
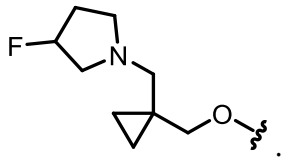
R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{12})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

2. The compound of claim 1, wherein R^1 is selected from .

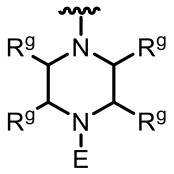
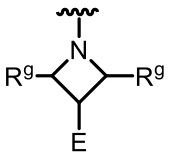
3. The compound of claim 2, wherein R^a is a halogen and/or wherein R^b is a halogen.

4. The compound of claim 2, wherein R^1 is selected from , , , , , , , , , and .

5. The compound of claim 1, wherein R^1 is selected from  and .

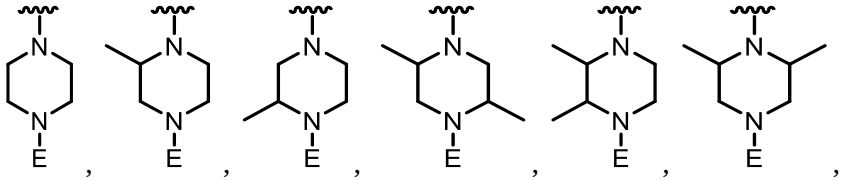
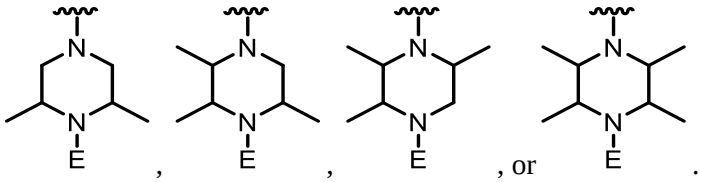
6. The compound of any one of claims 1-5, wherein R^2 and R^3, together with the atom to which they are attached, form a piperazinyl ring that is substituted with one or more E and 0-4 R^{11}, optionally wherein two R^{11} groups, together with the atom or atoms to which they are attached, form a 3-6 membered carbocycle or heterocycle.

7. The compound of claim 6, wherein R^2 and R^3, together with the atom to which they are attached, form a piperazinyl ring that is substituted with one or more E and 1-2 R^{11}, and R^{11} is $C_{1\text{-}6}$ alkyl.

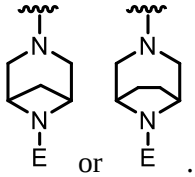
8. The compound of claim 1, wherein R^2 and R^3, together with the atom to which they are attached, form the structure  or , wherein each R^g is independently selected from $C_{1\text{-}6}$alkyl and H, wherein any $C_{1\text{-}6}$alkyl is unsubstituted or substituted with one or more R^{20}, optionally wherein two R^g groups, together with the atoms to which they are attached, form a 3-6 membered carbocycle or heterocycle.

9. The compound of claim 8, wherein at least one R^g is $C_{1\text{-}6}$alkyl that is unsubstituted or substituted with one or more R^{20}.

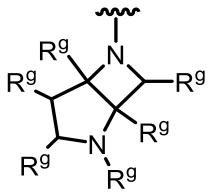
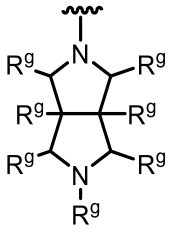
10. The compound of claim 9, wherein one or two R^g groups are methyl.

11. The compound of claim 8, wherein R^2 and R^3, together with the atom to which they are attached, form the structure , , or .

12. The compound of claim 1, wherein R^2 and R^3, together with the atom to which they are attached, form a bridged piperazinyl ring that is substituted with one or more E and 0-4 R^{11}.

13. The compound of claim 12, wherein R^2 and R^3, together with the atom to which they are attached, form the structure  or .

14. The compound of claim 1, wherein R^2 and R^3, together with the atom to which they are attached, form a 4-8 membered bicyclic heterocycle comprising a fused ring system that is substituted with one or more E and 0-4 R^{11}.

15. The compound of claim 14, wherein R^2 and R^3, together with the atom to which they are attached, form a structure selected from:  and , wherein each R^g is independently selected from $C_{1\text{-}6}$alkyl, H, and E, wherein at least one R^g is E, and wherein any $C_{1\text{-}6}$alkyl is unsubstituted or substituted with one or more R^{20}.

16. The compound of any one of claims 1-15, wherein R^4 is H.

17. The compound of any one of claims 1-16, wherein R^5 is a halogen.

18. The compound of claim 17, wherein R^5 is Cl.

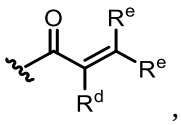
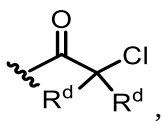
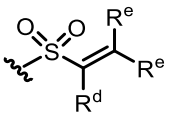
19. The compound of any one of claims 1-16, wherein R^5 is selected from $C_{1\text{-}6}$alkyl that is unsubstituted or substituted with one or more R^{13}.

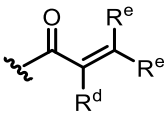
20. The compound of claim 19, wherein R^5 is $C_{1\text{-}6}$alkyl that is substituted with one or more halogens.

21. The compound of claim 20, wherein R^5 is $-CHF_2$ or $-CF_3$.

22. The compound of any one of claims 1-21, wherein R^7 is a halogen.

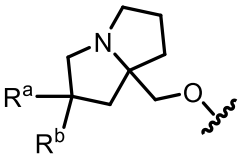
23. The compound of claim 22, wherein R^7 is F.

24. The compound of any one of claims 1-23, wherein each E is independently selected from , , and .

25. The compound of claim 24, wherein each E is .

26. The compound of claim 25, wherein each R^d and R^e is H.

27. The compound of any one of claims 1-26, wherein:

R^1 is ;

R^2 and R^3, together with the atom to which they are attached, form a 4-8 membered heterocycle that is substituted with one or more E and 0-4 R^{11}; and

R^5 is selected from halogen and C_{1-6}alkyl, wherein C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

28. A compound shown in Table 2, Table 3, Table 4, or Table 5, or a salt (e.g., pharmaceutically acceptable salt) thereof.

29. A pharmaceutical composition comprising a compound of any one of claims 1-28, or a salt (e.g., pharmaceutically acceptable salt) thereof, and a pharmaceutically acceptable excipient.

30. A compound of any one of claims 1-28, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use as a medicament.

31. The compound for use of claim 30, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12C mutation.

32. The compound for use of claim 30 or 31, wherein the medicament is useful in the prevention or treatment of a cancer.

33. The compound for use of claim 32, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

34. A compound of any one of claims 1-28, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the treatment of a disease, disorder, or condition.

35. The compound for use of claim 34, wherein the disease, disorder, or condition is a cancer.

36. The compound for use of claim 35, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

37. A compound of any one of claims 1-28, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the manufacture of a medicament.

38. The compound for use of claim 37, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12C mutation.

39. The compound for use of claim 37 or 38, wherein the medicament is useful in the treatment of a cancer.

40. The compound for use of claim 39, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

41. Use of a compound of any one of claims 1-28, or a salt (e.g., pharmaceutically acceptable salt) thereof, for the manufacture of a medicament for the treatment of a cancer.

42. The use of claim 41, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

43. Use of a compound of any one of claims 1-28, or a salt (e.g. pharmaceutically acceptable salt) thereof, in the manufacture of a medicament for contacting a KRAS protein having a G12C mutation with the compound or salt.

44. Use of a compound of any one of claims 1-28, or a salt (e.g. pharmaceutically acceptable salt) thereof, in the manufacture of a medicament for inhibiting the function of a KRAS protein having a G12C mutation, wherein the KRAS protein is to be contacted with the compound or salt.

45. The use of claim 43 or 44, wherein the KRAS protein is in an active (GTP-bound) state.

46. The use of claim 43 or 44, wherein the KRAS protein is in an inactive (GDP-bound) state.

47. The use of any one of claims 43-46, wherein the KRAS protein is located within a cell.

48. A compound capable of inhibiting a KRAS protein with a G12C mutation in both its active (GTP-bound) and inactive (GDP-bound) state.

49. The compound of claim 48, wherein the compound:

(i) demonstrates modification of $\geq$ 70%, 50% $\leq$ modification <70%, or 10%$\leq$ modification <50% of GppNHp-KRAS G12C, GTP-KRAS G12C, or GDP-KRAS G12C in the assay of Biological Example 1 (e.g., a Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS) analysis of covalent modification of Cys12 in GppNHp, GTP or GDP-loaded KRAS4b (amino acids 1-169) G12C/C118S);

(ii) has IC_{50} $\leq$0.5 μM, 0.5 μM< IC_{50} $\leq$5 μM, or 5 μM< IC_{50} $\leq$20 μM in the assay of Biological Example 2 (e.g., a protein:protein interaction (PPI) Homogenous Time Resolved Fluorescence (HTRF) analysis of Avi-KRAS G12C Q25A (amino acids 1-169) GppNHp/3xFLAG-PI3K CA (157-299), Avi-KRAS G12C (amino acids 1-169) GppNHp/RAF1 RBD-3xFLAG (52-151)); and/or

(iii) has IC_{50} ≤0.1 μM; B: 0.1 μM< IC_{50} ≤1 μM; C: IC_{50}>1 μM in the assay of Biological Example 3 (e.g., cell-based pERK).

50. The compound of claim 48 or 49, wherein the compound is capable of irreversibly binding the KRAS protein.

51. The compound of any one of claims 48-50, wherein the compound is capable of reversibly binding the KRAS protein.

52. The compound of any one of claims 48-51, wherein the compound is a compound according to any one of claims 1-28.