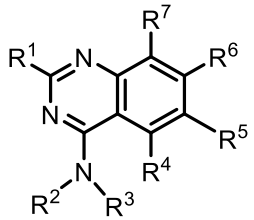
properties. However, they are differentially expressed, and mutated with different frequencies in cancer. *KRAS* is the most frequently mutated oncogene in cancer and *KRAS* mutation is commonly associated with poor prognosis and resistance to therapy. Significant cancer type preferences exist among the RAS genes. *KRAS* mutations predominate in lung, colorectal, and pancreatic cancer, whereas *NRAS* mutations predominate in cutaneous melanomas and acute myelogenous leukemia, and *HRAS* mutations are found in bladder and head and neck squamous cell carcinomas.

[0005] KRAS is mutationally activated in 94% of pancreatic cancers. Pancreatic cancer (e.g., pancreatic ductal adenocarcinoma (PDAC)) became the third leading cause of cancer deaths in the United States in 2016. With a continued increase in incidence, pancreatic cancer is projected to become the second leading cause of cancer death by 2020. With no biomarkers for early detection, late onset of symptoms when the cancer has already reached the metastatic state, and the 5-year survival rate of 8%, pancreatic cancer is the deadliest cancer in the US.

[0006] KRAS mutations are the initiating genetic step in pancreatic cancer; however, continued mutant KRAS function is required to maintain the growth of PDAC. RNA interference-mediated KRAS inactivation in KRAS G12D-driven PDAC showed rapid regression of tumor growth. These data support the significance of mutant KRAS as a therapeutic target in PDAC. Since 40% of PDACs are driven by KRAS G12D mutant, inhibitors targeting this mutation are highly desirable. KRAS G12D mutation also occurs in high frequency in lung and colorectal cancers, making KRAS G12D desirable therapeutic target for direct G12D allele-specific inhibitors.

SUMMARY

[0006a] In a first aspect of the present disclosure, there is provided a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from -OR^8, a 4-6 membered heterocycle comprising a nitrogen atom, and H, wherein the heterocycle is unsubstituted or substituted with one or more R^{16};

R^2 is selected from H, a 3-6 membered carbocycle, and C_{1-6} alkyl, wherein the 3-6 membered carbocycle or the C_{1-6} alkyl is unsubstituted or substituted with one or more R^{13};

R^3 is selected from C_{1-6} alkyl, a carbocycle, and a heterocycle, wherein any C_{1-6}alkyl is substituted with one or more R^9, and wherein the carbocycle or heterocycle is unsubstituted or substituted with one or more R^{10};

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

R^4 is selected from H, halogen, -OR^{12}, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, a 3-6 membered carbocycle, 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 and heterocycle is unsubstituted or substituted with one or more R^{14};

R^5 is selected from H, halogen, -OR^{12}, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, a 5-6 membered heteroaryl, and phenyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}, and wherein any carbocycle, heterocycle, heteroaryl, and phenyl is unsubstituted or substituted with one or more R^{14};

R^6 is a bicyclic heteroaryl that is unsubstituted or substituted with one or more R^{15};

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

R^8 is selected from heterocycle and alkylheterocycle, any of which is unsubstituted or substituted with one or more R^{16}, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6} alkyl;

each R^9 is independently selected from -$N(R^{17})_2$, -$N(R^{17})C(O)C_{1-6}$alkyl, and -OR^{17}, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{18};

each R^{10} is independently selected from halogen, -$N(R^{19})_2$, -$C(O)R^{19}$, -$C(O)N(R^{19})_2$, -$C(O)(C_{1-6}alkyl)N(R^{19})_2$, -$(C_{1-6}alkyl)C(O)N(R^{19})_2$, -$C(NR^{19})NR^{19}CN$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

each R^{11} is independently selected from $-N(R^{19})_2$, $-C(O)R^{19}$, $-C(O)N(R^{19})_2$, $-C(O)(C_{1-6}alkyl)N(R^{19})_2$, $-(C_{1-6}alkyl)C(O)N(R^{19})_2$, $-C(NR^{19})NR^{19}CN$, and $C_{1-6}alkyl$, 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, $-OR^{12}$, -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^{15} is independently selected from halogen, $-OR^{12}$, -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^{16} is independently selected from halogen, $-N(R^{12})_2$, $C_{1-6}alkyl$, $-OR^{12}$, and 3-6 membered heterocycle, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{13};

each R^{17} is independently selected from C_{1-6} alkyl and H;

each R^{18} is independently selected from -OH, $-OC_{1-6}alkyl$, -CN, $-NH_2$, $-NHC_{1-6}alkyl$, and halogen;

each R^{19} is independently selected from C_{1-6} alkyl, 3-6 membered heterocycle, and H, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{21};

each R^{20} is independently selected from -OH, $-OC_{1-6}alkyl$, -CN, $-NH_2$, $-NHC_{1-6}alkyl$, halogen, and 3-6 membered carbocycle;

each R^{21} is independently selected from -OH, $-OC_{1-6}alkyl$, -CN, $-NH_2$, $-NHC_{1-6}alkyl$, and halogen; and

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

[0006b] In another aspect of the present disclosure, there is provided a compound selected from any one of Tables 2-9, or a pharmaceutically acceptable salt thereof.

[0006c] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0006d] In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use as a medicament.

[0006e] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament.

[0006f] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12D mutation.

[0006g] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease, disorder, or condition.

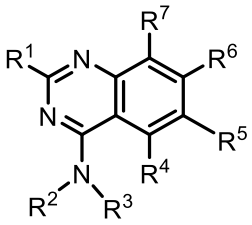
[0006h] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, wherein the medicament is to be administered to a subject in need thereof.

[0006i] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament.

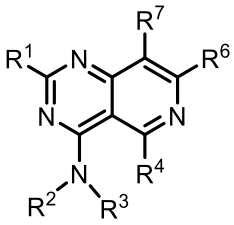
[0006j] In a further aspect of the present disclosure, there is provided a non-therapeutic method, comprising contacting a KRAS protein with a compound as disclosed herein, or a pharmaceutically acceptable salt thereof.

[0006k] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for contacting a KRAS protein.

[0007] In an ~~aspect~~example, the present disclosure provides compositions comprising compounds represented by Formula I or Formula II:



(I)



(II)

or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as provided herein. In some ~~embodiment~~examples, a compound provided herein, or a

salt, ester, tautomer, zwitterionic form, or stereoisomer thereof, can modulate the activity of a KRAS protein, such as a KRAS protein having a G12D mutation.

[0008] In another ~~aspect~~example, the present disclosure provides a pharmaceutical composition comprising a compound represented by Formula I or Formula II, together with a pharmaceutically acceptable carrier.

[0009] In a further ~~aspect~~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.

[0010] In another ~~aspect~~example, the present disclosure provides a use of a compound provided 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 G12D mutation. In some ~~embodiment~~examples, the disease, disorder, or condition is pancreatic cancer (e.g., pancreatic ductal adenocarcinoma (PDAC)), colorectal cancer, or lung cancer.

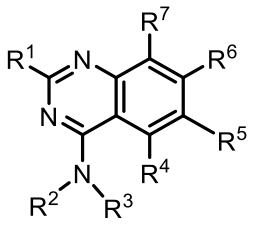
[0011] In a further ~~aspect~~example, the present disclosure provides a compound as provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer thereof, for use as a medicament. In some ~~embodiment~~examples, the medicament is used in the treatment of a disease, disorder, or condition (e.g., a cancer). In some ~~embodiment~~examples, the disease, disorder, or condition is pancreatic cancer (e.g., pancreatic ductal adenocarcinoma (PDAC)), colorectal cancer, or lung cancer.

DETAILED DESCRIPTION

[0012] The present disclosure provides compounds of Formulas I and II, 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 G12D mutation, which KRAS protein is in an active (GTP-bound) or inactive (GDP-bound) conformation. The present disclosure also provides pharmaceutical compositions comprising one or more compounds provided herein together with a pharmaceutically acceptable carrier, as well as methods

CLAIMS

1. A compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from -OR^8, a 4-6 membered heterocycle comprising a nitrogen atom, and H, wherein the heterocycle is unsubstituted or substituted with one or more R^{16};

R^2 is selected from H, a 3-6 membered carbocycle, and C_{1-6} alkyl, wherein the 3-6 membered carbocycle or the C_{1-6} alkyl is unsubstituted or substituted with one or more R^{13};

R^3 is selected from C_{1-6} alkyl, a carbocycle, and a heterocycle, wherein any C_{1-6}alkyl is substituted with one or more R^9, and wherein the carbocycle or heterocycle is unsubstituted or substituted with one or more R^{10};

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

R^4 is selected from H, halogen, -OR^{12}, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, a 3-6 membered carbocycle, 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 and heterocycle is unsubstituted or substituted with one or more R^{14};

R^5 is selected from H, halogen, -OR^{12}, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, a 5-6 membered heteroaryl, and phenyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}, and wherein any carbocycle, heterocycle, heteroaryl, and phenyl is unsubstituted or substituted with one or more R^{14};

R^6 is a ~~phenyl, monocyclic heteroaryl, bicyclic aryl, or~~ bicyclic heteroaryl~~, wherein any phenyl, monocyclic heteroaryl, bicyclic aryl, and bicyclic heteroaryl~~ that is unsubstituted or substituted with one or more R^{15};

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

R^8 is selected from heterocycle and alkylheterocycle, any of which is unsubstituted or substituted with one or more R^{16}, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6} alkyl;

each R^9 is independently selected from -$N(R^{17})_2$, -$N(R^{17})C(O)C_{1-6}$alkyl, and -OR^{17}, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{18};

each R^{10} is independently selected from halogen, -$N(R^{19})_2$, -$C(O)R^{19}$, -$C(O)N(R^{19})_2$, -$C(O)(C_{1-6}$alkyl$)N(R^{19})_2$, -$(C_{1-6}$alkyl$)C(O)N(R^{19})_2$, -$C(NR^{19})NR^{19}CN$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

each R^{11} is independently selected from -$N(R^{19})_2$, -$C(O)R^{19}$, -$C(O)N(R^{19})_2$, -$C(O)(C_{1-6}$alkyl$)N(R^{19})_2$, -$(C_{1-6}$alkyl$)C(O)N(R^{19})_2$, -$C(NR^{19})NR^{19}CN$, and 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, -OR^{12}, -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^{15} is independently selected from halogen, -OR^{12}, -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^{16} is independently selected from halogen, -$N(R^{12})_2$, C_{1-6}alkyl, -OR^{12}, and 3-6 membered heterocycle, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{17} is independently selected from C_{1-6} alkyl and H;

each R^{18} is independently selected from -OH, -OC_{1-6}alkyl, -CN, -NH_2, -NHC_{1-6}alkyl, and halogen;

each R^{19} is independently selected from C_{1-6} alkyl, 3-6 membered heterocycle, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{21};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -CN, -NH_2, -NHC_{1-6}alkyl, halogen, and 3-6 membered carbocycle;

each R^{21} is independently selected from -OH, -OC_{1-6}alkyl, -CN, -NH_2, -NHC_{1-6}alkyl, and halogen; and

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

2. The compound of claim 1, wherein R^1 is –OR^8.

3. The compound of claim 1 or 2, wherein R^8 is a heterocycle, wherein the heterocycle is unsubstituted or substituted with one or more R^{16}.

4. The compound of any one of claims 1-3, wherein R^8 is a 4-8 membered heterocycle having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the heterocycle is unsubstituted or substituted with one or more R^{16}.

5. The compound of claim 1 or 2, wherein R^8 is an alkylheterocycle, wherein the alkylheterocycle is unsubstituted or substituted with one or more R^{16}.

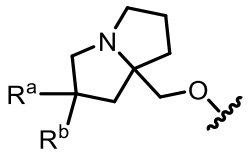
6. The compound of claim 5, wherein the alkylheterocycle is –CH_2(heterocycle), wherein the heterocycle is unsubstituted or substituted with one or more R^{16}.

7. The compound of claim 5 or 6, wherein the heterocycle of the alkylheterocycle is a 4-8 membered heterocycle having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and the heterocycle is unsubstituted or substituted with one or more R^{16}.

8. The compound of any one of claims 1-7, wherein R^8 is substituted with one or more R^{16}.

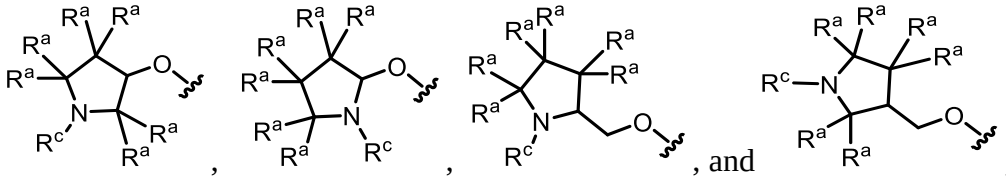
9. The compound of any one of claims 1-8, wherein each R^{16} is independently selected from halogen, C_{1-6}alkyl, and -OR^{12}, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

10. The compound of any one of claims 1, 2, and 5-9, wherein –OR^8 is:



wherein 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}.

11. The compound of any one of claims 1-9, wherein –OR^8 is selected from:



wherein:

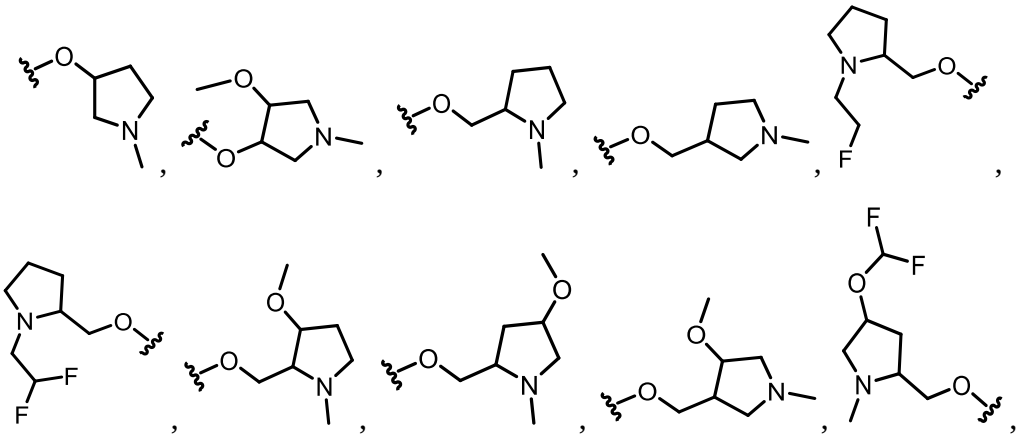
each R^a is independently selected from halogen, C_{1-6} alkyl, -OR^{12}, and H; and

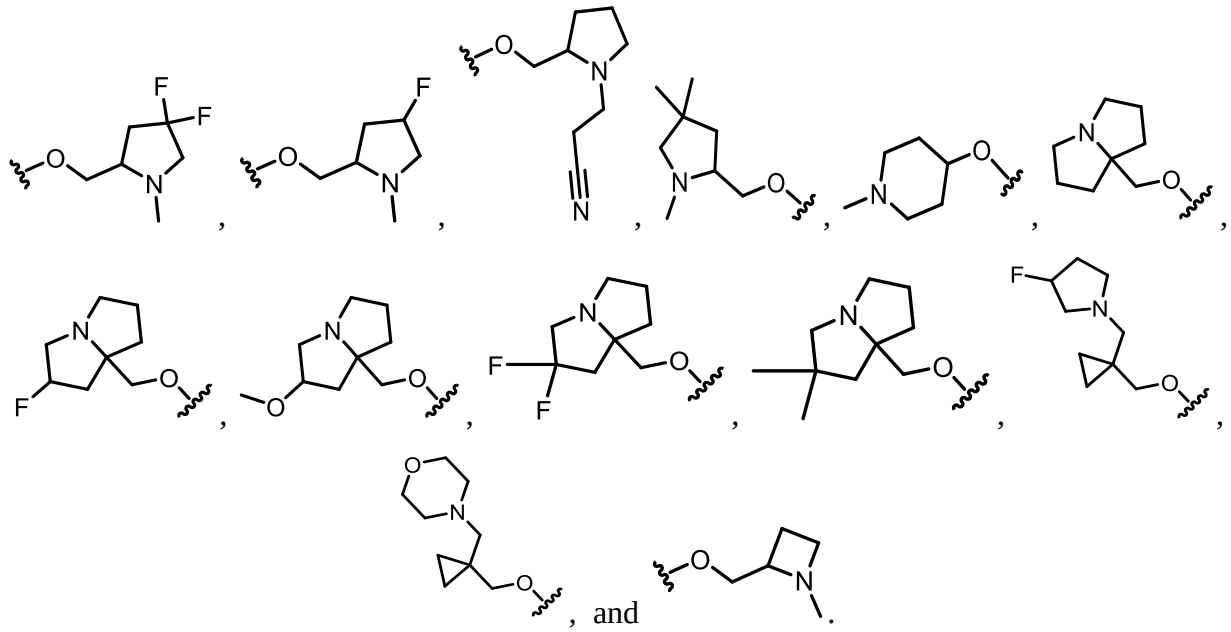
R^c is selected from C_{1-6} alkyl,

wherein a C_{1-6} alkyl of a R^a or R^c is unsubstituted or is substituted with one or more R^{13}.

12. The compound of claim 11, wherein one R^a is selected from halogen, C_{1-6} alkyl, and -OR^{12}, and the other R^a's are H.

13. The compound of claim 1, wherein –OR^8 is selected from:





14. The compound of claim 1, wherein R^1 is a 4-6 membered heterocycle comprising a nitrogen atom, wherein the heterocycle is unsubstituted or substituted with one or more R^{16}.

15. The compound of claim 1 or 14, wherein each R^{16} is independently selected from -$N(R^{12})_2$, $C_{1\text{-}6}$alkyl, and 3-6 membered heterocycle.

16. The compound of any one of claim 1, 14, and 15, wherein R^1 is selected from:



17. The compound of claim 1, wherein R^1 is H.

18. The compound of any one of claims 1-17, wherein R^2 is H.

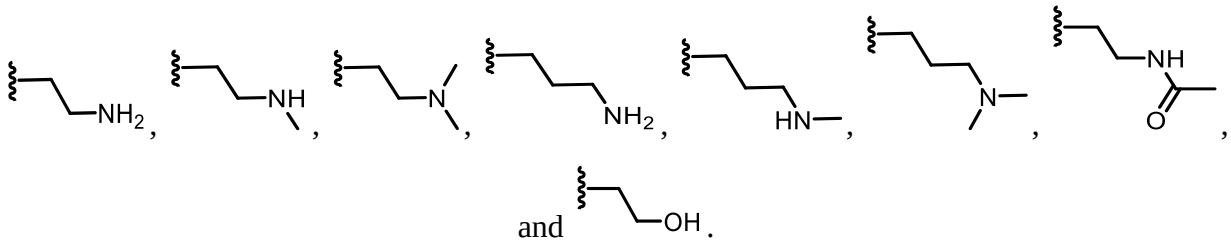
19. The compound of any one of claims 1-17, wherein R^2 is $C_{1\text{-}6}$ alkyl, unsubstituted or substituted with one or more R^{13}.

20. The compound of any one of claims 1-17, wherein R^2 is a 3-6 membered carbocycle.

21. The compound of any one of claim 1-20, wherein R^3 is C_{1-6}alkyl substituted with one or more R^9.

22. The compound of claim 21, wherein R^9 is $-N(R^{17})_2$.

23. The compound of claim 1 or 21, wherein R^3 is selected from:



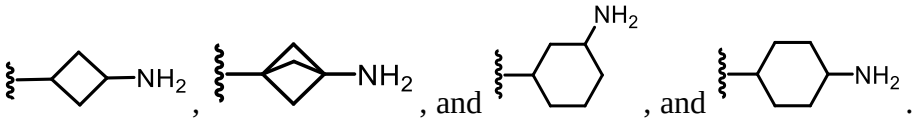
and .

24. The compound of any one of claims 1-20, wherein R^3 is a carbocycle, unsubstituted or substituted with one or more R^{10}.

25. The compound of claim 24, wherein R^3 is a 4-6 membered carbocycle, unsubstituted or substituted with one or more R^{10}.

26. The compound of claim 24 or 25, wherein R^{10} is $-N(R^{19})_2$, wherein each R^{19} is independently selected from unsubstituted or substituted C_{1-6} alkyl and H.

27. The compound of any one of claims 1, 25, and 26, wherein R^3 is selected from:



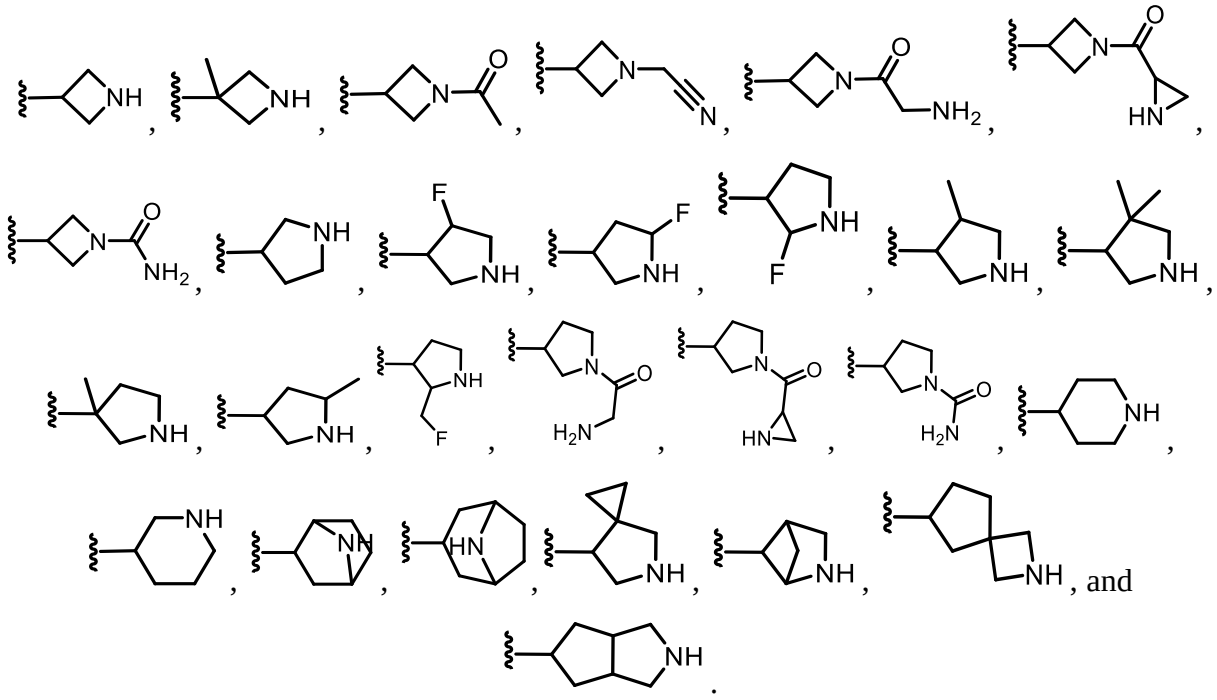
, and , and .

28. The compound of any one of claims 1-20, wherein R^3 is a heterocycle, unsubstituted or substituted with one or more R^{10}.

29. The compound of claim 28, wherein R^3 is a 4-8 membered heterocycle having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the heterocycle is unsubstituted or substituted with one or more R^{10}.

30. The compound of claim 28 or 29, wherein each R^{10} is independently selected from halogen, $-N(R^{19})_2$, $-C(O)R^{19}$, $-C(O)N(R^{19})_2$, $-C(O)(C_{1-6}alkyl)N(R^{19})_2$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}.

31. The compound of any one of claims 1 and 28-30, wherein R^3 is selected from:



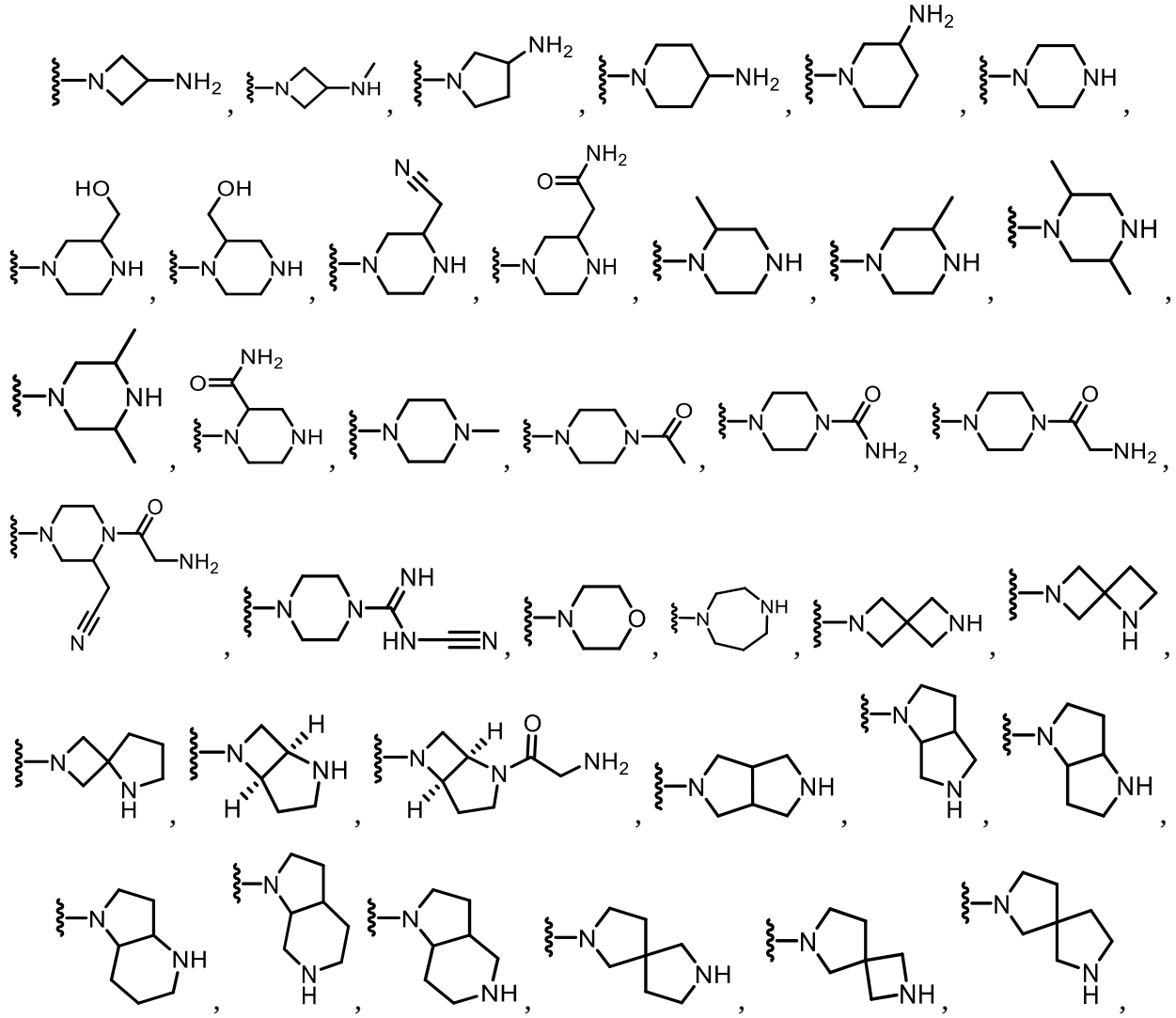
32. The compound of any one of claims 1-20, wherein R^2 and R^3, together with the atom to which they are attached, form a heterocycle that is unsubstituted or substituted with one or more R^{11}.

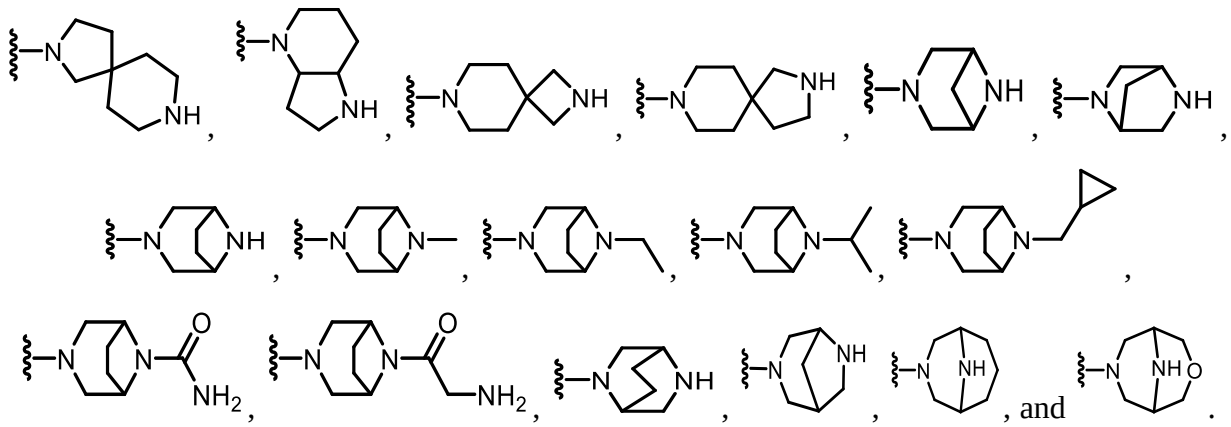
33. The compound of claim 32, wherein R^2 and R^3, together with the atom to which they are attached, form a 4-9 membered heterocycle having 0-2 additional heteroatoms independently

selected from nitrogen, oxygen, and sulfur, wherein the heterocycle is unsubstituted or substituted with one or more R^{11}.

34. The compound of any one of claims 1, 32, and 33, wherein each R^{11} is independently selected from $-N(R^{19})_2$, $-C(O)R^{19}$, $-C(O)N(R^{19})_2$, $-C(O)(C_{1-6}alkyl)N(R^{19})_2$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}.

35. The compound of any one of claims 1, 32, and 33, wherein R^2 and R^3, together with the atom to which they are attached, form a heterocycle selected from:





~~36. The compound of any one of claims 1-35, wherein R^6 is a bicyclic aryl or bicyclic heteroaryl, wherein the aryl or heteroaryl are unsubstituted or substituted with one or more R^{15}.~~

3637. The compound of any one of claims 1-3536, wherein R^6 is a 9-10 membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur that is unsubstituted or substituted with one or more R^{15}.

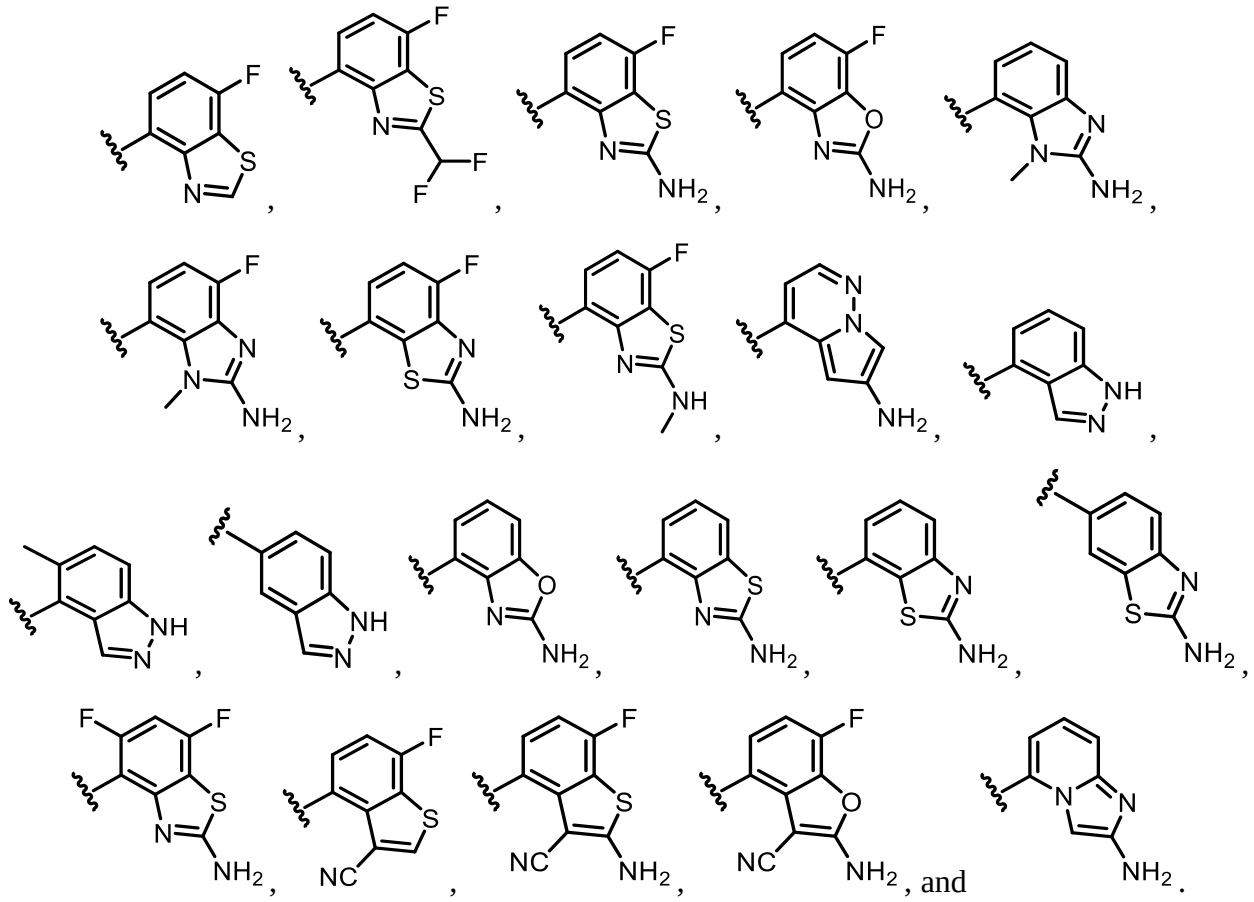
378. The compound of claim 3637, wherein R^6 is substituted with one or more R^{15}.

389. The compound of claim 3738, wherein each R^{15} is independently selected from halogen, -CN, and $-N(R^{12})_2$.

3940. The compound of claim 37 or 38~~ or 39~~, wherein at least one R^{15} is $-N(R^{12})_2$.

4041. The compound of any one of claims 37-3938~~-40~~, wherein at least one R^{15} is a halogen.

4142. The compound of any one of claims 1~~, 36, and~~ or 37, wherein R^6 is selected from:



~~43. The compound of claim 42, wherein R^6 is naphthyl substituted with one or more R^{15}.~~

~~44. The compound of any one of claims 1-35, wherein R^6 is phenyl or monocyclic heteroaryl, wherein the phenyl or heteroaryl are unsubstituted or substituted with one or more R^{15}.~~

42~~45~~. The compound of any one of claims 1-41~~44~~, wherein R^4 is H.

43~~46~~. The compound of any one of claims 1-41~~44~~, wherein R^4 is $-OR^{12}$.

44~~47~~. The compound of any one of claims 1-43~~46~~, wherein R^5 is selected from H, halogen, $-OR^{12}$, -CN, C_{1-6}alkyl, C_{2-6}alkynyl, a 3-6 membered carbocycle, a 5-6 membered heteroaryl, and

phenyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}, and wherein any carbocycle, heteroaryl, and phenyl is unsubstituted or substituted with one or more R^{14}.

4548. The compound of claim 4447, wherein R^5 is H.

4649. The compound of claim 4447, wherein R^5 is a halogen.

4750. The compound of claim 4447, wherein R^5 is C_{1-6}alkyl, unsubstituted or substituted with one or more R^{13}.

4851. The compound of claim 4447, wherein R^5 is selected from a 3-6 membered carbocycle, a 5-6 membered heteroaryl, and phenyl, wherein any carbocycle, heteroaryl, and phenyl is unsubstituted or substituted with one or more R^{14}.

4952. The compound of any one of claims 1-4851, wherein R^7 is a halogen.

5053. The compound of any one of claims 1-4851, wherein R^7 is -CN.

5154. The compound of any one of claims 1-5053, wherein:

R^2 is selected from H and C_{1-6} alkyl;

R^5 is selected from halogen, -OR^{12}, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, a 3-6 membered carbocycle, 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 and heterocycle is unsubstituted or substituted with one or more R^{14};

R^6 is a bicyclic heteroaryl substituted with one or more R^{15};

R^8 is selected from heterocycle and alkylheterocycle, any of which is unsubstituted or substituted with one or more R^{16};

each R^{10} is independently selected from -$N(R^{19})_2$, -$C(O)R^{19}$, -$C(O)N(R^{19})_2$, -$C(O)(C_{1-6}$alkyl$)N(R^{19})_2$, -$(C_{1-6}$alkyl$)C(O)N(R^{19})_2$, -$C(NR^{19})NR^{19}$CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

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

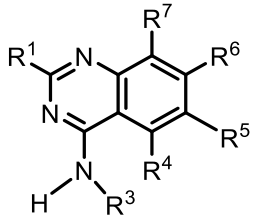
each R^{15} is independently selected from halogen, $N(R^{12})_2$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{16} is independently selected from halogen, $-N(R^{12})_2$, C_{1-6}alkyl, and $-OR^{12}$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{19} is independently selected from C_{1-6} alkyl and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{21}; and

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

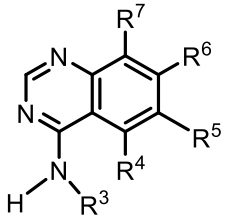
5255. The compound of any one of claims 1-5154, wherein the compound is of Formula IA:



(IA)

or a pharmaceutically acceptable salt thereof.

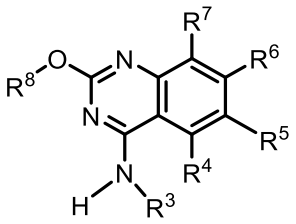
5356. The compound of claim 5255, wherein the compound is of Formula IA1:



(IA1)

or a pharmaceutically acceptable salt thereof.

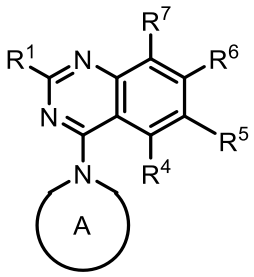
5457. The compound of claim 5255, wherein the compound is of Formula IA2:



(IA2)

or a pharmaceutically acceptable salt thereof.

5558. The compound of any one of claims 1-5154, wherein the compound is of Formula IB:

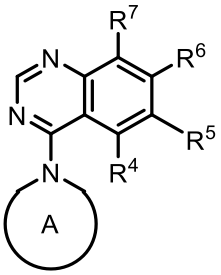


(IB)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a heterocycle that is unsubstituted or substituted with one or more R^{11}.

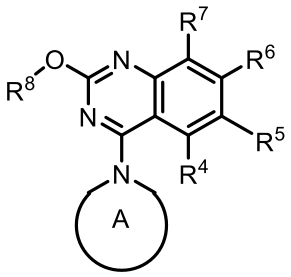
5659. The compound of claim 5558, wherein the compound is of Formula IB1:



(IB1)

or a pharmaceutically acceptable salt thereof.

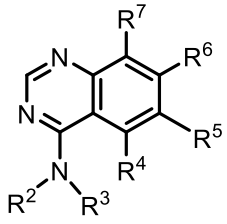
6057. The compound of claim 5558, wherein the compound is of Formula IB2:



(IB2)

or a pharmaceutically acceptable salt thereof.

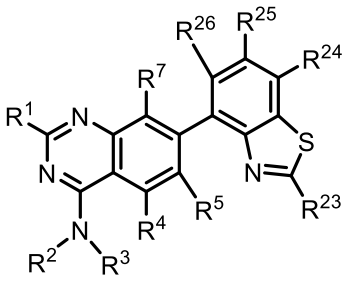
~~61~~58. The compound of any one of claims 1-~~51~~54, wherein the compound is of Formula IC:



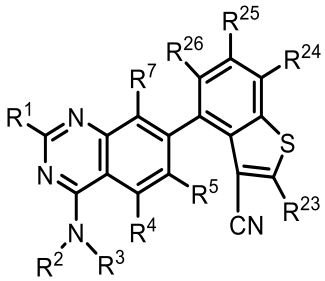
(IC)

or a pharmaceutically acceptable salt thereof.

~~59~~62. The compound of any one of claims 1-~~51~~54, wherein the compound is of Formula ID or ID':



(ID) or



(ID')

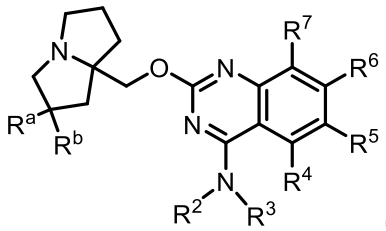
or a pharmaceutically acceptable salt thereof, wherein:

R^{23} is selected from -N(R^{12})$_2$ and C_{1-6}alkyl-N(R^{12})$_2$; 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^{11}.

~~60~~63. The compound of any one of claims 1-~~51~~54, wherein the compound is of Formula IE:

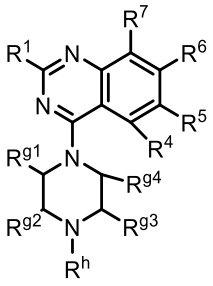


(IE)

or a pharmaceutically acceptable salt thereof, wherein:

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

6164. The compound of any one of claims 1-5154, wherein the compound is of Formula IF:



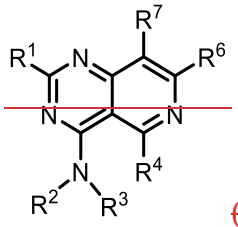
(IF)

or a pharmaceutically acceptable salt thereof, wherein:

R^{g1}, R^{g2}, R^{g3}, and R^{g4} are each independently selected from H and $C_{1\text{-}6}$alkyl; or (a) R^{g1} and R^{g3} or (b) R^{g2} and R^{g3} join together to form a second ring containing 4-6 members, and any of R^{g1}, R^{g2}, R^{g3}, and R^{g4} that are not part of the second ring are independently selected from H and $C_{1\text{-}6}$alkyl, wherein any $C_{1\text{-}6}$alkyl is unsubstituted or substituted with one or more R^{13}; and

R^h is selected from H, $C_{1\text{-}6}$alkyl, -$C(O)NH_2$, and -$C(O)C_{1\text{-}6}$alkylNH_2.

~~65. A compound according to Formula II:~~



~~(II)~~

~~or a pharmaceutically acceptable salt thereof, wherein:~~

R^1 is selected from $-OR^8$, a 4-6 membered heterocycle comprising a nitrogen atom, and H, wherein the heterocycle is unsubstituted or substituted with one or more R^{16};

R^2 is selected from H, a 3-6 membered carbocycle, and C_{1-6} alkyl, wherein the 3-6 membered carbocycle or the C_{1-6} alkyl is unsubstituted or substituted with one or more R^{13};

R^3 is selected from C_{1-6} alkyl, a carbocycle, and a heterocycle, wherein any C_{1-6}alkyl is substituted with one or more R^9, and wherein the carbocycle or heterocycle is unsubstituted or substituted with one or more R^{10};

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

R^4 is selected from H, halogen, $-OR^{12}$, $-CN$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, a 3-6 membered carbocycle, 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 and heterocycle is unsubstituted or substituted with one or more R^{14};

R^6 is a phenyl, monocyclic heteroaryl, bicyclic aryl, or bicyclic heteroaryl, wherein any phenyl, monocyclic heteroaryl, bicyclic aryl, and bicyclic heteroaryl is unsubstituted or substituted with one or more R^{15};

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

R^8 is selected from heterocycle and alkylheterocycle, any of which is unsubstituted or substituted with one or more R^{16}, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6} alkyl;

each R^9 is independently selected from $-N(R^{17})_2$, $-N(R^{17})C(O)C_{1-6}$alkyl, and $-OR^{17}$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{18};

each R^{10} is independently selected from halogen, $-N(R^{19})_2$, $-C(O)R^{19}$, $-C(O)N(R^{19})_2$, $-C(O)(C_{1-6}$alkyl$)N(R^{19})_2$, $-(C_{1-6}$alkyl$)C(O)N(R^{19})_2$, $-C(NR^{19})NR^{19}CN$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

each R^{11} is independently selected from $-N(R^{19})_2$, $-C(O)R^{19}$, $-C(O)N(R^{19})_2$, $-C(O)(C_{1-6}$alkyl$)N(R^{19})_2$, $-(C_{1-6}$alkyl$)C(O)N(R^{19})_2$, $-C(NR^{19})NR^{19}CN$, and 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, -OR^{12}, -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^{15} is independently selected from halogen, -OR^{12}, -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^{16} is independently selected from halogen, -$N(R^{12})_2$, C_{1-6}alkyl, -OR^{12}, and 3-6 membered heterocycle, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{17} is independently selected from C_{1-6} alkyl and H;

each R^{18} is independently selected from -OH, -OC_{1-6}alkyl, -CN, -NH_2, -NHC_{1-6}alkyl, and halogen;

each R^{19} is independently selected from C_{1-6} alkyl, 3-6 membered heterocycle, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{21};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -CN, -NH_2, -NHC_{1-6}alkyl, and halogen, and 3-6 membered carbocycle;

each R^{21} is independently selected from -OH, -OC_{1-6}alkyl, -CN, -NH_2, -NHC_{1-6}alkyl, and halogen; and

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

66. The compound of claim 65, wherein R^1 is -OR^8.

67. The compound of claim 65 or 66, wherein R^8 is a heterocycle, wherein the heterocycle is unsubstituted or substituted with one or more R^{16}.

68. The compound of claim 65 or 66, wherein R^8 is an alkylheterocycle, wherein the alkylheterocycle is unsubstituted or substituted with one or more R^{16}.

69. The compound of claim 68, wherein the alkylheterocycle is $-CH_2$(heterocycle), wherein the heterocycle is unsubstituted or substituted with one or more R^{16}.

70. The compound of any one of claims 65-69, wherein each R^{16} is independently selected from halogen, C_{1-6}alkyl, and $-OR^{12}$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

71. The compound of claim 65, wherein R^1 is a 4-6 membered heterocycle comprising a nitrogen atom, wherein the heterocycle is unsubstituted or substituted with one or more R^{16}.

72. The compound of claim 65 or 71, wherein each R^{16} is independently selected from $-N(R^{12})_2$, C_{1-6}alkyl, and 3-6 membered heterocycle.

73. The compound of claim 65, wherein R^1 is H.

74. The compound of any one of claims 65-73, wherein R^2 is H.

75. The compound of any one of claims 65-73, wherein R^2 is C_{1-6} alkyl, unsubstituted or substituted with one or more R^{13}.

76. The compound of any one of claims 65-73, wherein R^2 is a 3-6 membered carbocycle.

77. The compound of any one of claim 65-76, wherein R^3 is C_{1-6}alkyl substituted with one or more R^9.

78. The compound of claim 77, wherein R^9 is $-N(R^{17})_2$.

79. The compound of any one of claims 65-76, wherein R^3 is a carbocycle, unsubstituted or substituted with one or more R^{10}.

80. The compound of any one of claims 65-76, wherein R^3 is a heterocycle, unsubstituted or substituted with one or more R^{10}.

81. The compound of any one of claims 65-76, wherein R^2 and R^3, together with the atom to which they are attached, form a heterocycle that is unsubstituted or substituted with one or more R^{11}.

82. The compound of any one of claims 65-81, wherein R^6 is a bicyclic aryl or bicyclic heteroaryl, wherein the aryl or heteroaryl are unsubstituted or substituted with one or more R^{15}.

83. The compound of claim 82, wherein each R^{15} is independently selected from halogen, -CN, and $-N(R^{12})_2$.

84. The compound of any one of claims 65-83, wherein R^4 is H.

85. The compound of any one of claims 65-84, wherein R^7 is a halogen.

86. The compound of any one of claim 65-85, wherein:

R^2 is selected from H and C_{1-6}alkyl;

R^6 is a bicyclic heteroaryl substituted with one or more R^{15};

R^8 is selected from heterocycle and alkylheterocycle, any of which is unsubstituted or substituted with one or more R^{16};

each R^{10} is independently selected from $-N(R^{19})_2$, $-C(O)R^{19}$, $-C(O)N(R^{19})_2$, $-C(O)(C_{1-6}$alkyl$)N(R^{19})_2$, $-(C_{1-6}$alkyl$)C(O)N(R^{19})_2$, $-C(NR^{19})NR^{19}$CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

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

each R^{15} is independently selected from halogen, $N(R^{12})_2$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

~~each R^{16} is independently selected from halogen, $-N(R^{12})_2$, C_{1-6}alkyl, and $-OR^{12}$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};~~

~~each R^{19} is independently selected from C_{1-6} alkyl and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{21}; and~~

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

~~87~~62. A compound selected from any one of Tables 2-9, or a pharmaceutically acceptable salt thereof.

~~88~~63. A pharmaceutical composition comprising a compound of any one of claims 1-62~~87~~, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

64~~89~~. A compound of any one of claims 1-62~~87~~, or a pharmaceutically acceptable salt thereof, for use as a medicament.

~~90~~65. A compound of any one of claims 1-62~~87~~, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament.

~~91~~66. ~~The compound of claim 89 or 90, wherein the medicament is useful in~~ Use of a compound of any one of claims 1-62, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12D mutation.

~~92~~67. The ~~compound~~ use of ~~any one of claims 89-91~~claim 66, wherein the medicament is useful in the treatment of a cancer.

~~93~~68. Use of a~~A~~ compound of any one of claims 1-62~~87~~, or a pharmaceutically acceptable salt thereof, ~~for use~~ in the manufacture of a medicament for the treatment of a disease, disorder, or condition.

~~94~~69. The ~~compound~~ use of claim 68~~93~~, wherein the disease, disorder, or condition is a cancer.

70~~95~~. The ~~compound~~ use of claim ~~92 or 94~~67 or 69, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

71~~96~~. ~~A method, comprising administering a therapeutically effective amount~~Use of a compound of any one of claims 1-62~~87~~, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, wherein the medicament is to be administered to a subject in need thereof.

72~~97~~. The ~~method~~ use of claim 71~~96~~, wherein the subject has a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12D mutation.

73~~98~~. The ~~method~~ use of claim ~~96 or 97~~71 or 72, wherein the subject has a cancer.

~~99~~74. The ~~method~~ use of claim 73~~98~~, wherein the subject was previously diagnosed with the cancer.

~~100~~75. The ~~method~~ use of claim 73~~98~~, wherein the subject has previously undergone a treatment regimen for the cancer.

~~101~~76. The ~~method~~ use of claim 73~~98~~, wherein the subject has previously entered remission from the cancer.

~~102~~77. The ~~method~~ use of any one of claims 73-76~~98-101~~, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

78~~103~~. The ~~method~~ use of any one of claims ~~98-102~~73-77, wherein the compound or pharmaceutically acceptable salt thereof is to be administered in combination with an additional therapeutic agent.

~~104~~79. Use of a compound of any one of claims 1-~~87~~62, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament.

~~105~~80. The use of claim ~~104~~79, wherein the medicament is for treating cancer.

~~106~~81. The use of claim 80~~105~~, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

~~107~~82. A non-therapeutic method, comprising contacting a KRAS protein with a compound of any one of claims 1-~~87~~62, or a pharmaceutically acceptable salt thereof.

83. Use of a compound of any one of claims 1-62, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for contacting a KRAS protein.

~~108~~84. The method of claim ~~107~~82, or use of claim 83, wherein contacting the KRAS protein with the compound modulates KRAS.

~~109~~85. The method of claim ~~107 or 108~~82 or 84, or use of claim 83 or 84, wherein the KRAS protein has a G12D mutation.

~~110~~86. The method of any one of claims ~~107-109~~82, 84-85, or use of any one of claims 83-85, wherein the KRAS protein is in an active state.

~~111~~87. The method of any one of claims ~~107-109~~82, 84-85, or use of any one of claims 83-85, wherein the KRAS protein is in an inactive state.