

**BENZISOTHIAZOLE, ISOTHIAZOLO[3,4-B]PYRIDINE, QUINAZOLINE,
PHTHALAZINE, PYRIDO[2,3-D]PYRIDAZINE AND PYRIDO[2,3-D]PYRIMIDINE
DERIVATIVES AS KRAS G12C INHIBITORS FOR TREATING LUNG,
PANCREATIC OR COLORECTAL CANCER
RELATED APPLICATIONS**

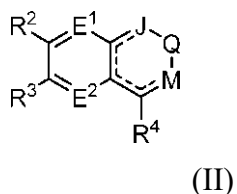
This application claims the benefit of U.S. Provisional patent application 62/438,334 filed on December 22, 2016, which specification is hereby incorporated herein by reference in its entirety for all purposes.

BACKGROUND

[0001] KRAS gene mutations are common in pancreatic cancer, lung adenocarcinoma, colorectal cancer, gall bladder cancer, thyroid cancer, and bile duct cancer. KRAS mutations are also observed in about 25% of patients with NSCLC, and some studies have indicated that KRAS mutations are a negative prognostic factor in patients with NSCLC. Recently, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations have been found to confer resistance to epidermal growth factor receptor (EGFR) targeted therapies in colorectal cancer; accordingly, the mutational status of KRAS can provide important information prior to the prescription of TKI therapy. Taken together, there is a need for new medical treatments for patients with pancreatic cancer, lung adenocarcinoma, or colorectal cancer, especially those who have been diagnosed to have such cancers characterized by a KRAS mutation, and including those who have progressed after chemotherapy.

SUMMARY

[0001a] In one aspect, the present disclosure refers to a compound having a structure of formula (II)



wherein

E¹ and E² are each independently N or CR¹;

J is NR¹⁰;

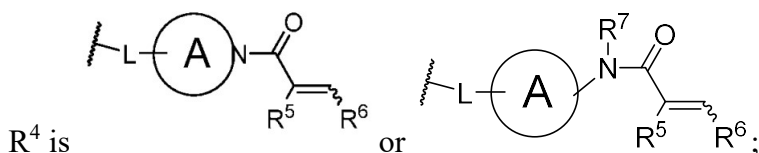
M is N;

$\equiv$ is a single or double bond as necessary to give every atom its normal valence;

R^1 is independently H, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, $NH-C_{1-4}$ alkyl, $N(C_{1-4}$ alkyl)₂, cyano, or halo;

R^2 is halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR' , $N(R')$ ₂, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{0-3} alkylene- C_{3-14} cycloalkyl, C_{0-3} alkylene- C_{2-14} heterocycloalkyl, aryl, heteroaryl, C_{0-3} alkylene- C_{6-14} aryl, or C_{0-3} alkylene- C_{2-14} heteroaryl, and each R' is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-14} cycloalkyl, C_{3-14} heterocycloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R^3 is halo, C_{1-3} alkyl, C_{1-2} haloalkyl, C_{1-3} alkoxy, C_{3-4} cycloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, or heteroaryl;



ring A is a monocyclic 4-7 membered ring or a bicyclic, bridged, fused, or spiro 6-11 membered ring;

L is a bond, C_{1-6} alkylene, $-O-C_{0-5}$ alkylene, $-S-C_{0-5}$ alkylene, or $-NH-C_{0-5}$ alkylene, and for C_{2-6} alkylene, $-O-C_{2-5}$ alkylene, $-S-C_{2-5}$ alkylene, or $-NH-C_{2-5}$ alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^5 and R^6 are each independently H, halo, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} alkylene- $O-C_{1-6}$ alkyl, C_{1-6} alkylene-OH, C_{1-6} haloalkyl, C_{1-6} alkyleneamine, C_{0-6} alkylene-amide, C_{0-3} alkylene- $C(O)OH$, C_{1-6} alkylene- $C(O)OC_{1-4}$ alkyl, C_{1-6} alkylene-O-aryl, C_{0-3} alkylene- $C(O)C_{1-4}$ alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_{0-3} alkylene- C_{3-14} cycloalkyl, C_{0-3} alkylene- C_{2-14} heterocycloalkyl, C_{0-3} alkylene- C_{6-14} aryl, C_{0-3} alkylene- C_{2-14} heteroaryl, or cyano, or R^5 and R^6 , together with the atoms to which they are attached, form a 4-6 membered ring;

R^7 is H or C_{1-8} alkyl, or R^7 and R^5 , together with the atoms to which they are attached, form a 4-6 membered ring;

Q is $C=O$;

R¹⁰ is C₁₋₈alkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₃₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₃₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₃₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine; or
a pharmaceutically acceptable salt thereof,

wherein

an alkyl, alkylene, alkenyl, alkynyl or alkoxy group is optionally substituted with one or more groups independently selected from halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, nitro, cyano, alkylamino, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -NC, amino, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀heterocycloalkyl, C₅₋₁₀aryl, and C₅₋₁₀heteroaryl;

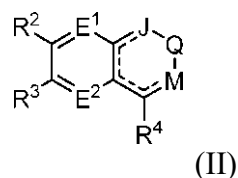
an aryl group is unsubstituted or optionally substituted with one or more groups independently selected from halo, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -CF₃, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀heterocycloalkyl, C₅₋₁₀aryl, and C₅₋₁₀heteroaryl;

a cycloalkyl or heterocycloalkyl group is unsubstituted or optionally substituted with one or more groups selected from halo, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, amino, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀heterocycloalkyl, C₅₋₁₀aryl, and C₅₋₁₀heteroaryl; and

a heteroaryl group is unsubstituted or optionally substituted with one or more substituents selected from halo, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, amino, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀heterocycloalkyl, C₅₋₁₀aryl, and C₅₋₁₀heteroaryl.

What is Claimed:

1. A compound having a structure of formula (II)



wherein

E^1 and E^2 are each independently N or CR^1 ;

J is NR^{10} ;

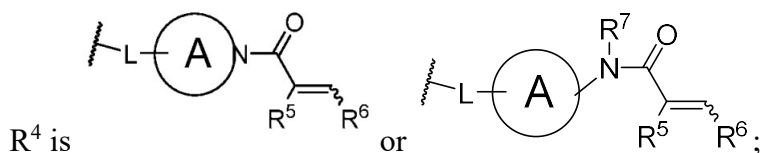
M is N;

$\equiv$ is a single or double bond as necessary to give every atom its normal valence;

R^1 is independently H, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, $NH-C_{1-4}$ alkyl, $N(C_{1-4}alkyl)_2$, cyano, or halo;

R^2 is halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR' , $N(R')_2$, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{0-3} alkylene- C_{3-14} cycloalkyl, C_{0-3} alkylene- C_{2-14} heterocycloalkyl, aryl, heteroaryl, C_{0-3} alkylene- C_{6-14} aryl, or C_{0-3} alkylene- C_{2-14} heteroaryl, and each R' is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-14} cycloalkyl, C_{3-14} heterocycloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R^3 is halo, C_{1-3} alkyl, C_{1-2} haloalkyl, C_{1-3} alkoxy, C_{3-4} cycloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, or heteroaryl;



ring A is a monocyclic 4-7 membered ring or a bicyclic, bridged, fused, or spiro 6-11 membered ring;

L is a bond, C_{1-6} alkylene, $-O-C_{0-5}$ alkylene, $-S-C_{0-5}$ alkylene, or $-NH-C_{0-5}$ alkylene, and for C_{2-6} alkylene, $-O-C_{2-5}$ alkylene, $-S-C_{2-5}$ alkylene, or $-NH-C_{2-5}$ alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^5 and R^6 are each independently H, halo, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} alkylene- $O-C_{1-6}$ alkyl, C_{1-6} alkylene-OH, C_{1-6} haloalkyl, C_{1-6} alkyleneamine, C_{0-6} alkylene-amide, C_{0-}

₃alkylene-C(O)OH, C₁₋₆alkylene-C(O)OC₁₋₄alkyl, C₁₋₆alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4-6 membered ring;

R⁷ is H or C₁₋₈alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4-6 membered ring;

Q is C=O;

R¹⁰ is C₁₋₈alkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₃₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₃₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine; or

a pharmaceutically acceptable salt thereof;

wherein

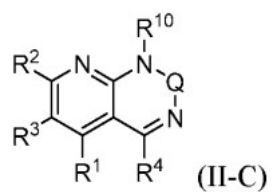
an alkyl, alkylene, alkenyl, alkynyl or alkoxy group is optionally substituted with one or more groups independently selected from halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, nitro, cyano, alkylamino, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -NC, amino, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃-C₁₀cycloalkyl, C₃-C₁₀heterocycloalkyl, C₅-C₁₀aryl, and C₅-C₁₀heteroaryl;

an aryl group is unsubstituted or optionally substituted with one or more groups independently selected from halo, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -CF₃, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃-C₁₀cycloalkyl, C₃-C₁₀heterocycloalkyl, C₅-C₁₀aryl, and C₅-C₁₀heteroaryl;

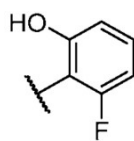
a cycloalkyl or heterocycloalkyl group is unsubstituted or optionally substituted with one or more groups selected from halo, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, amino, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃-C₁₀cycloalkyl, C₃-C₁₀heterocycloalkyl, C₅-C₁₀aryl, and C₅-C₁₀heteroaryl; and

a heteroaryl group is unsubstituted or optionally substituted with one or more substituents selected from halo, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, amino, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃-C₁₀cycloalkyl, C₃-C₁₀heterocycloalkyl, C₅-C₁₀aryl, and C₅-C₁₀heteroaryl.

2. The compound of claim 1, wherein E¹ is N and E² is CR¹.
3. The compound of claim 1 or claim 2, wherein the compound is in the form of formula (II-C)



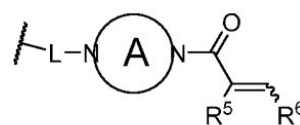
4. The compound of any one of claims 1 to 3, wherein R¹⁰ is C₀₋₃alkylene-C₃₋₁₄heteroaryl.
5. The compound of any one of claims 1 to 4, wherein R¹⁰ comprises ortho-substituted C₃₋₁₄heteroaryl.
6. The compound of claim 5, wherein the ortho-substituted C₃₋₁₄heteroaryl comprises one or two ortho-substituents independently selected from the group consisting of methyl, ethyl, isopropyl and cyclopropyl.
7. The compound of any one of claims 1 to 6, wherein R¹ is H.
8. The compound of any one of claims 1 to 7, wherein R² is aryl.
9. The compound of claim 8, wherein R² is phenyl.
10. The compound of claim 8, wherein R² is phenyl substituted with one or more groups independently selected from halo and -OH.



11. The compound of claim 8, wherein R^2 is .

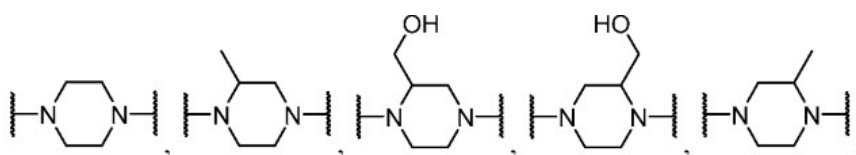
12. The compound of any one of claims 1 to 11, wherein R^3 is halo.

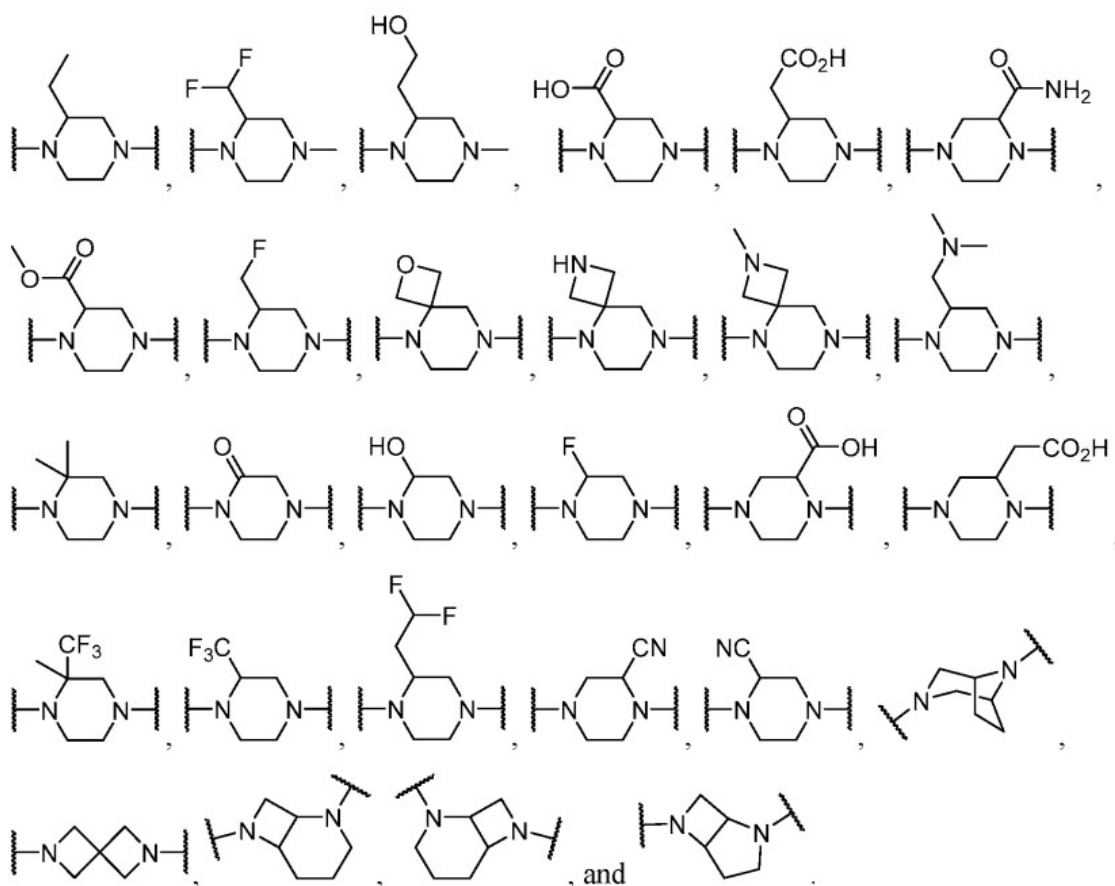
13. The compound of claim 12, wherein R^3 is F.

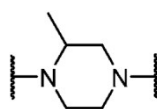
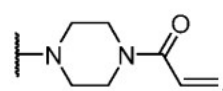


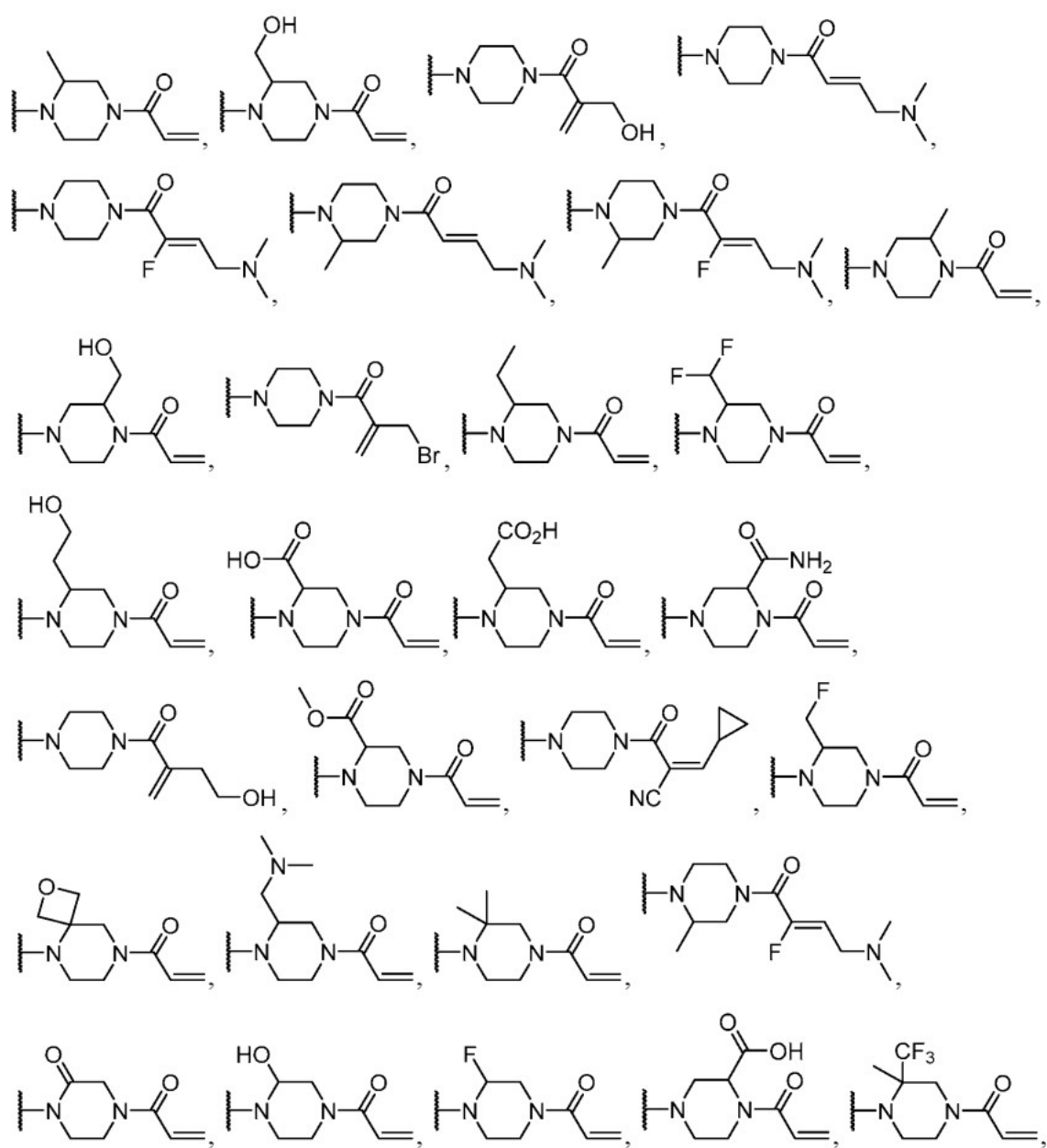
14. The compound of any one of claims 1 to 13, wherein R^4 is

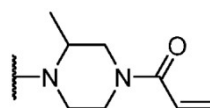
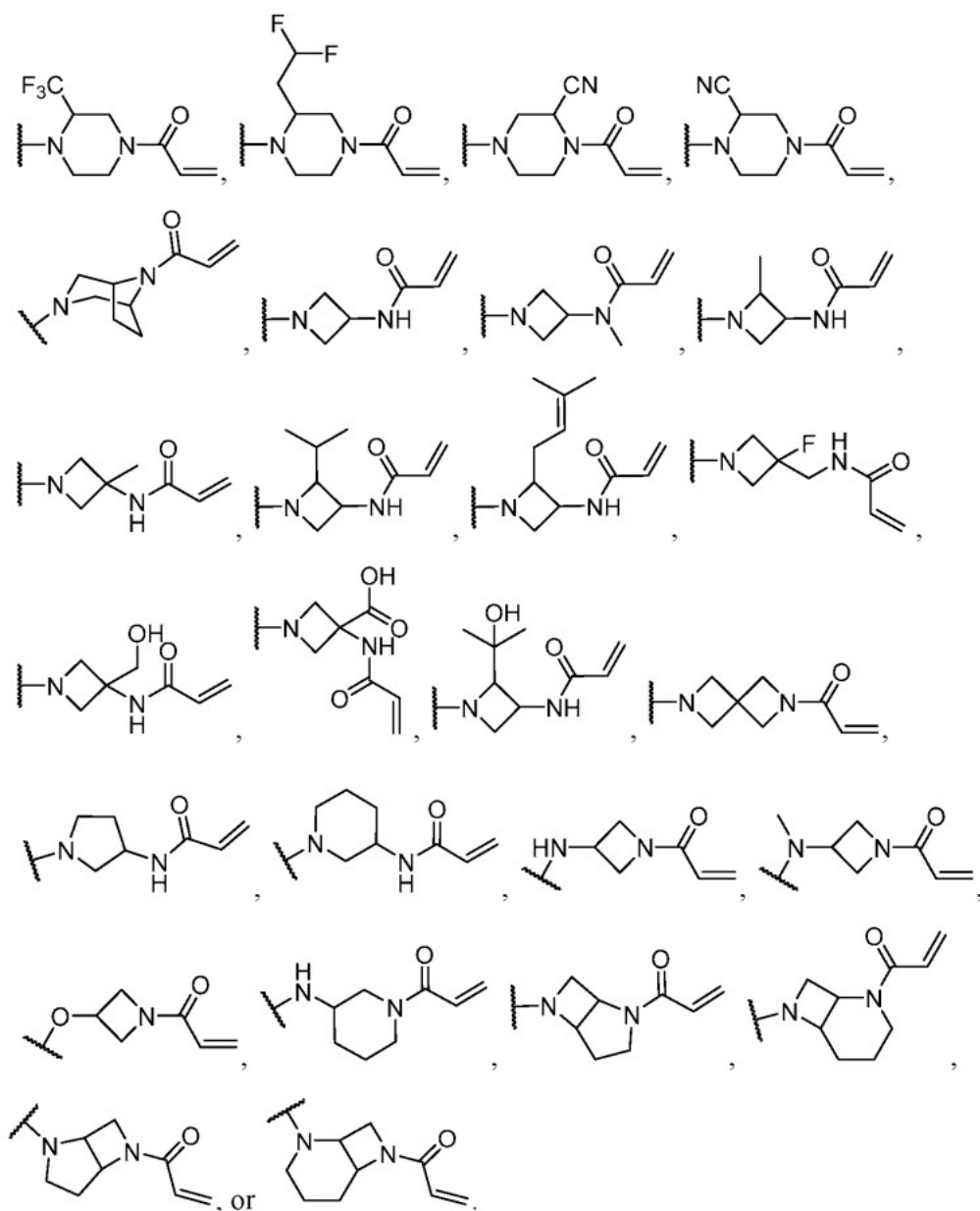
15. The compound of any one of claims 1 to 14, wherein ring A is selected from the group consisting of





16. The compound of claim 15, wherein ring A is .
17. The compound of any one of claims 1 to 15, wherein ring A comprises piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl.
18. The compound of any one of claims 1 to 17, wherein L is a bond.
19. The compound of any one of claims 1 to 18, wherein each of R⁵ and R⁶ is H.
20. The compound of any one of claims 1 to 13, 18 and 19, wherein R⁴ is .





21. The compound of claim 20, wherein R^4 is .
22. A pharmaceutical formulation comprising the compound of any one claims 1 to 21 and a pharmaceutically acceptable excipient.

23. An in vitro method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of any one of claims 1 to 21 or the pharmaceutical formulation of claim 22.
24. Use of a compound of any one of claims 1 to 21 or the pharmaceutical formulation of claim 22 in the manufacture of a medicament for treating cancer.
25. The use of claim 24, wherein the cancer is lung cancer, pancreatic cancer, or colorectal cancer.
26. The use of claim 24, wherein the cancer is non-small cell lung cancer, small intestine cancer, appendix cancer, colorectal cancer, endometrial cancer, pancreatic cancer, skin cancer, gastric cancer, nasal cavity cancer, or bile duct cancer.
27. The use of claim 25, wherein the cancer is non-small cell lung cancer.
28. The use of claim 25, wherein the cancer is colorectal cancer.
29. The use of any one of claims 24 to 28, wherein the cancer is mediated by a KRAS G12C mutation.