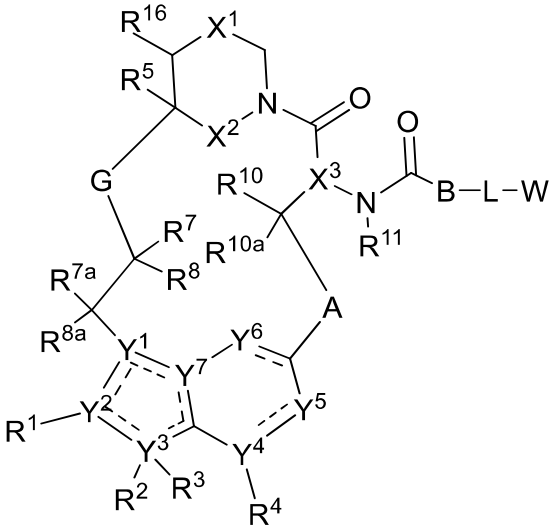
some examples, the inhibitors of Ras described herein induce a new binding pocket in Ras by driving formation of a high affinity tri-complex between the Ras protein and the widely expressed cytosolic chaperone, cyclophilin A (CYPA). Without being bound by theory, the inventors believe that one way the inhibitory effect on Ras is effected by compounds of the disclosure and the complexes they form is by steric occlusion of the interaction site between Ras and downstream effector molecules, such as RAF and PI3K, which are required for propagating the oncogenic signal.

As such, in an example, the disclosure features a compound, or pharmaceutically acceptable salt thereof, of structural Formula I:



Formula I

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is absent, -CH(R^9)-, or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is hydrogen, cyano, S(O)$_2$R', optionally substituted amino, optionally substituted amido, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or S(O)$_n$;

substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

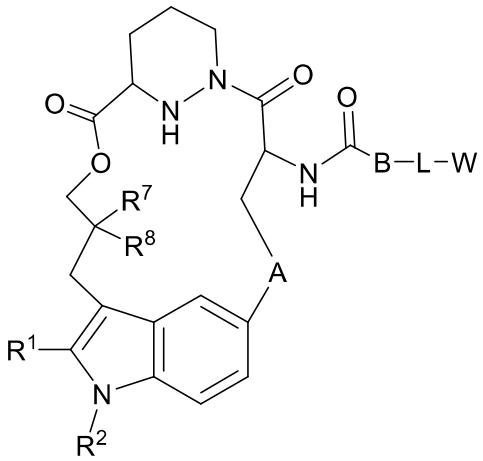
R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo;

R^{11} is hydrogen or C_1-C_3 alkyl.Also provided are pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient; and

R^{16} is hydrogen or C_1-C_3 alkyl (e.g., methyl).

In an aspect, there is provided a compound, or pharmaceutically acceptable salt thereof, having the structure of Formula If:



Formula If

wherein A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, optionally

substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or 3 to 8-membered heteroaryl;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

R^7 is C_1-C_3 alkyl;

R^8 is C_1-C_3 alkyl; and

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, of Table 1 or 2.

In another aspect, there is provided a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, as defined above and a pharmaceutically acceptable excipient

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, as defined above or a pharmaceutical composition as defined above, for use as a medicament.

Also provided is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt thereof, as defined above or a pharmaceutical composition as defined above, in the manufacture of a medicament for the treatment of cancer.

In some examples, a method is provided of treating a Ras protein-related disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

Further provided is a method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

It is specifically contemplated that any limitation discussed with respect to one example of the disclosure may apply to any other example of the disclosure. Furthermore, any compound or composition of the disclosure may be used in any method of the disclosure, and any method of the disclosure may be used to produce or to utilize any compound or composition of the disclosure.

Brief Description of the Figures

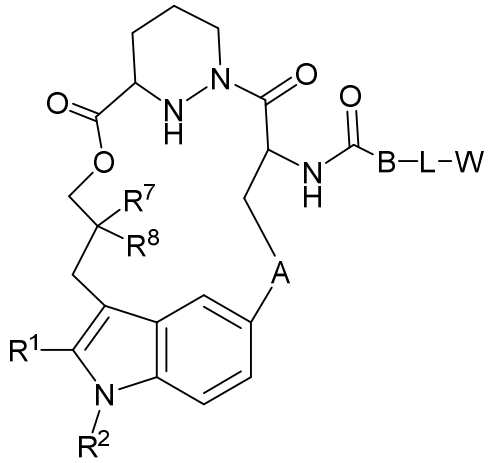
FIG. 1A: A compound of the present invention, Compound A, exhibits PK-dependent RAS pathway modulation in a Capan-2 CDX model (PDAC, KRAS G12V/WT). Single dose compared to twice administered PK/PD measurement of Compound A. Second dose of Compound A delivered 8 hours following first dose, depicted by black arrow. All dose levels well tolerated. Tumor DUSP6 mRNA

expression as percent of control graphed as bars on left y-axis. Dotted line indicates return to control level of DUSP6. Unbound plasma PK (nM) graphed as lines, plotted in Log10 scale on right y-axis. N = 3/time point. Error bars represent standard error of the mean.

FIG. 1B: Combinatorial anti-tumor activity with a compound of the present invention, Compound A, and upstream SHP2 inhibition in a Capan-2 CDX model (PDAC, KRAS G12V/WT). Capan-2 cells were implanted in 50% Matrigel. Animals were randomized and treatment was initiated at average tumor

Claims

1. A compound, or pharmaceutically acceptable salt thereof, having the structure of Formula If:



Formula If

wherein A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or 3 to 8-membered heteroaryl;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

R^7 is C_1-C_3 alkyl;

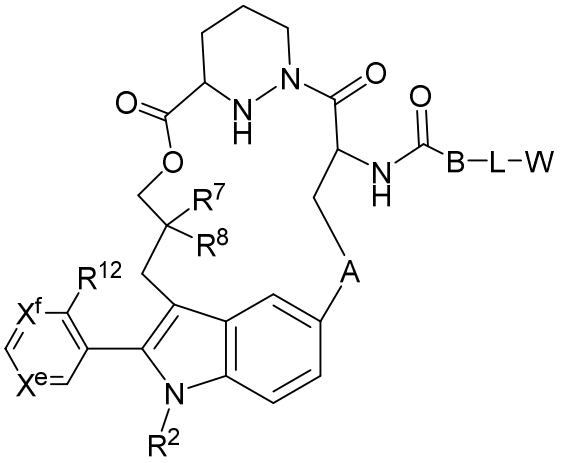
R^8 is C_1-C_3 alkyl; and

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

2. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein R^1 is 5 to 10-membered heteroaryl.

3. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein R^1 is optionally substituted 6-membered aryl or optionally substituted 6-membered heteroaryl.

4. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 3, wherein the compound has the structure of Formula Ig:



Formula Ig

wherein A is, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or 3 to 8-membered heteroaryl;

R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

R^7 is C_1-C_3 alkyl;

R^8 is C_1-C_3 alkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

X^e is N, CH, or CR^{17};

X^f is N or CH;

R^{12} is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl.

5. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 4, wherein A is optionally substituted 6-membered arylene.

6. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 4, wherein A is optionally substituted 5 to 6-membered heteroarylene.

7. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 6, wherein B is -CHR^9-.

8. The compound, or pharmaceutically acceptable salt thereof, of claim 7, wherein R^9 is optionally substituted C_1-C_6 alkyl or optionally substituted 3 to 6-membered cycloalkyl.

9. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 6, wherein B is optionally substituted 6-membered arylene.

10. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 9, wherein the linker is the structure of Formula II:

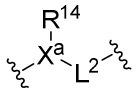
$$A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h\text{-}(D^1)\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$$

Formula II

where A^1 is a bond between the linker and B; A^2 is a bond between W and the linker; B^1, B^2, B^3, and B^4 each, independently, is selected from optionally substituted C_1-C_2 alkylene, optionally substituted C_1-C_3 heteroalkylene, O, S, and NR^N; R^N is hydrogen, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_3 cycloalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted C_1-C_7 heteroalkyl; C^1 and C^2 are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; f, g, h, i, j, and k are each, independently, 0 or 1; and D^1 is optionally substituted C_1-C_{10} alkylene, optionally substituted C_2-C_{10} alkenylene, optionally substituted C_2-C_{10} alkynylene, optionally substituted 3 to 14-membered heterocycloalkylene, optionally substituted 5 to 10-membered heteroarylene, optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 6 to 10-membered arylene, optionally substituted C_2-C_{10} polyethylene glycolene, or optionally substituted C_1-C_{10} heteroalkylene, or a chemical bond linking A^1-$(B^1)_f$-$(C^1)_g$-$(B^2)_h$- to -$(B^3)_i$-$(C^2)_j$-$(B^4)_k$–A^2.

11. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 10, wherein the linker is acyclic.

12. The compound, or a pharmaceutically acceptable salt thereof, of claim 11, wherein the linker has the structure of Formula IIa:



Formula IIa

wherein X^a is absent or N;

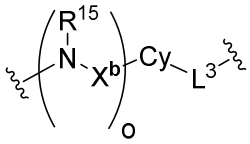
R^{14} is absent, hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_3 cycloalkyl; and

L^2 is absent, -C(O)-, -SO_2-, optionally substituted C_1-C_4 alkylene or optionally substituted C_1-C_4 heteroalkylene,

wherein at least one of X^a, R^{14}, or L^2 is present.

13. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 10, wherein the linker is or comprises a cyclic group.

14. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 10, wherein the linker has the structure of Formula IIb:



Formula IIb

wherein o is 0 or 1;

X^b is C(O) or SO_2;

R^{15} is hydrogen or optionally substituted C_1-C_6 alkyl;

Cy is optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 3 to 8-membered heterocycloalkylene, optionally substituted 6-10 membered arylene, or optionally substituted 5 to 10-membered heteroarylene; and

L^3 is absent, -C(O)-, -SO_2-, optionally substituted C_1-C_4 alkylene or optionally substituted C_1-C_4 heteroalkylene.

15. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is hydrogen.

16. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is optionally substituted amino.

17. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is optionally substituted amido.

18. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is optionally substituted C_1-C_4 alkoxy.

19. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is optionally substituted C_1-C_4 alkyl.

20. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is optionally substituted C_1-C_4 hydroxyalkyl.

21. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is optionally substituted C_1-C_4 aminoalkyl.

22. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is optionally substituted C_1-C_4 haloalkyl.

23. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is optionally substituted C_1-C_4 guanidinoalkyl.

24. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W optionally substituted 3 to 11-membered heterocycloalkyl.

25. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is 3 to 8-membered cycloalkyl.

26. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is optionally substituted 3 to 8-membered heteroaryl.

27. The compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, wherein W is optionally substituted 6- to 10-membered aryl.

28. A compound, or a pharmaceutically acceptable salt thereof, of Table 1 or 2.

29. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 28 and a pharmaceutically acceptable excipient.

30. A compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 28 or a pharmaceutical composition of claim 29, for use as a medicament.

31. Use of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 28 or a pharmaceutical composition of claim 29, in the manufacture of a medicament for the treatment of cancer.

32. The use of claim 31, wherein the cancer is pancreatic cancer, colorectal cancer, non-small cell lung cancer, gastric cancer, esophageal cancer, ovarian cancer or uterine cancer.

33. The use of claim 32, wherein the cancer comprises a Ras mutation.

34. The use of claim 33, wherein the Ras mutation is at position 12, 13 or 61.

35. The use of claim 33, wherein the Ras mutation is K-Ras G12C, K-Ras G12D, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G13D, or K-Ras Q61L.

36. The use of any one of claims 31 to 35, wherein the treatment of cancer further comprises an additional anticancer therapy to be administered.

37. The use of claim 36, wherein the additional anticancer therapy is an EGFR inhibitor, a second Ras inhibitor, a SHP2 inhibitor, a SOS1 inhibitor, a Raf inhibitor, a MEK inhibitor, an ERK

inhibitor, a PI3K inhibitor, a PTEN inhibitor, an AKT inhibitor, an mTORC1 inhibitor, a BRAF inhibitor, a PD-L1 inhibitor, a PD-1 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, or a combination thereof.

38. The use of claim 36 or 37, wherein the additional anticancer therapy is a SHP2 inhibitor.