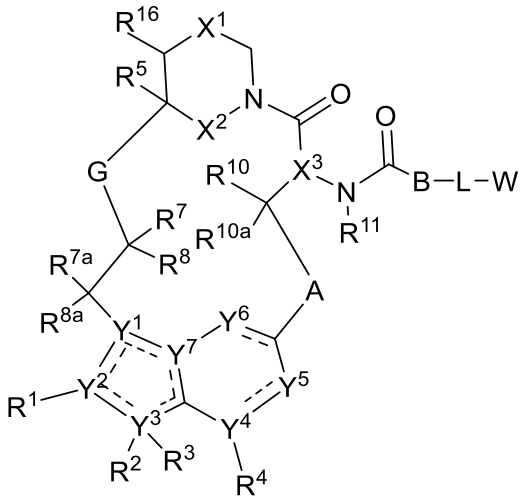
some ~~embodiments~~examples, the inhibitors of Ras described herein induce a new binding pocket in Ras by driving formation of a high affinity tri-complex between the Ras protein and the widely expressed cytosolic chaperone, cyclophilin A (CYPA). Without being bound by theory, the inventors believe that one way the inhibitory effect on Ras is effected by compounds of the disclosure~~invention~~ 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 ~~some embodiments~~an aspect, 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, $S(O)_2R'$, 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 $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

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, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally 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 $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally

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 another aspec, 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 ~~invention~~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 ~~embodiments~~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 ~~invention~~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 ~~invention~~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 a Ras protein related disorder.

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