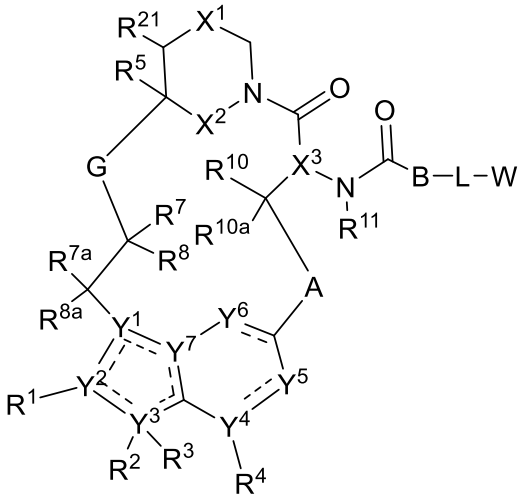
a widely expressed cytosolic chaperone (presenter protein) in the cell (e.g., cyclophilin A). More specifically, in some examples~~embodiments~~, the inhibitors of Ras described herein induce a new binding pocket in Ras by driving formation of a high affinity tri-complex, or conjugate, between the Ras 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 ~~invention~~ disclosure and the complexes, or conjugates, 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)-, >C=C$R^9R^{9'}$, or >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 a cross-linking group comprising a vinyl ketone, a vinyl sulfone, an ynone, a haloacetal, or an alkynyl sulfone;

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 H, 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; or

R^9 and $R^{9'}$, combined with the atoms to which they are attached, form a 3 to 6-membered cycloalkyl or a 3 to 6-membered heterocycloalkyl;

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; and

R^{21} is hydrogen or C_1-C_3 alkyl (e.g., methyl).

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

Also provided are pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

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 ~~F~~further provided ~~is~~ a conjugate, or salt thereof, comprising the structure of Formula IV:

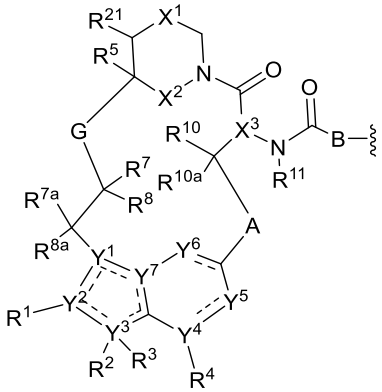
M-L-P

Formula IV

wherein L is a linker;

P is a monovalent organic moiety; and

M has the structure of Formula V:



Formula V

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 6-membered heteroarylene;

B is absent, -CH(R^9)-, >C=C$R^9R^{9'}$, or >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-

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 H, 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; or

R^9 and $R^{9'}$, combined with the atoms to which they are attached, form a 3 to 6-membered cycloalkyl or a 3 to 6-membered heterocycloalkyl;

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; and

R^{21} is H or C_1-C_3 alkyl.

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.

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

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.

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 disclosure~~invention~~.

Brief Description of the Drawings

FIG. 1A and FIG. 1B: These figures illustrate a matched pair analysis of potencies of certain compounds of the present invention (Formula BB) (points on the right) and corresponding compounds of Formula AA (points on the left) wherein a H is replaced with (*S*)Me in the context of two different cell-