

alkyl)-, -S(O)₀₋₂-, C(=O), and C₁₋₃ alkylene; and

each **R^{b1}** is independently selected from the group consisting of: C₃₋₁₀ cycloalkyl, 4-10 membered heterocyclyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl, each of which is optionally substituted with 1-3 **R^g**;

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each **R^c** is independently selected from the group consisting of: halo, cyano, -OH, -C₁₋₆ alkoxy, -C₁₋₆ haloalkoxy, -NR^dR^e, C(=O)C₁₋₆ alkyl, C(=O)C₁₋₆ haloalkyl, C(=O)OC₁₋₆ alkyl, C(=O)OC₁₋₆ haloalkyl, C(=O)OH, C(=O)N(**R^f**)₂, S(O)₀₋₂(C₁₋₆ alkyl), S(O)₀₋₂(C₁₋₆ haloalkyl), and S(O)₁₋₂N(**R^f**)₂;

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each **R^d** and **R^e** is independently selected from the group consisting of: H, C(=O)C₁₋₆ alkyl, C(=O)C₁₋₆ haloalkyl, C(=O)OC₁₋₆ alkyl, C(=O)OC₁₋₆ haloalkyl, C(=O)N(**R^f**)₂, S(O)₁₋₂(C₁₋₆ alkyl), S(O)₁₋₂(C₁₋₆ haloalkyl), S(O)₁₋₂N(**R^f**)₂, and C₁₋₆ alkyl optionally substituted with 1-3 **R^h**;

each **R^f** is independently selected from the group consisting of: H and C₁₋₆ alkyl optionally substituted with 1-3 **R^h**;

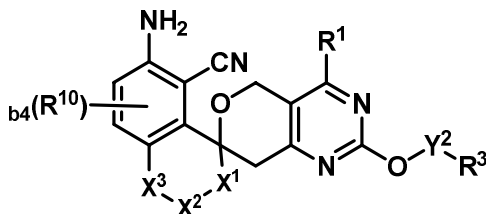
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each **R^g** is independently selected from the group consisting of: **R^h**, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₃₋₅ cycloalkyl, and 4-5 membered heterocyclyl; and

each **R^h** is independently selected from the group consisting of: halo, cyano, -OH, -C₁₋₆ alkoxy, -C₁₋₆ haloalkoxy, -NH₂, -N(H)(C₁₋₃ alkyl), and -N(C₁₋₃ alkyl)₂.

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In one aspect, the present disclosure refers to a compound of Formula (**II-a**):



Formula (**II-a**)

or a pharmaceutically acceptable salt thereof, wherein:

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b4 is 0 or 1;

each **R¹⁰** is independently selected from the group consisting of: -Cl, -F, -CN, and C₁₋₃ alkyl optionally substituted with 1-3 **R^c**;

X^1 is selected from the group consisting of a bond, $S(O)_{0-2}$, CH_2 , CHR^L , $C(R^L)_2$, and O;

X^2 and X^3 are independently selected from the group consisting of: CH_2 , CHR^L , $C(R^L)_2$, O, and $S(O)_{0-2}$, provided that no more than one of X^1 , X^2 , and X^3 is selected from the group consisting of: O and $S(O)_{0-2}$;

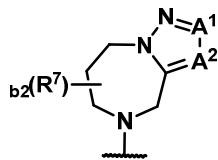
each R^L is independently selected from the group consisting of C_{1-3} alkoxy, -F, CN, and C_{1-3} alkyl optionally substituted with 1-3 R^c ; or

one pair of R^L on the same or different ring carbon atom(s) taken together with the ring atom(s) connecting them form a C_{3-6} cycloalkyl ring;

R^1 is selected from the group consisting of:

(i) a 4-10 membered heterocyclyl optionally substituted with 1-4 R^7 ;

(ii) an 8-12 membered bicyclic heterocyclyl, wherein the heterocyclyl comprises an endocyclic group selected from the group consisting of $C(=O)NH$ and $S(O)_2NH$, and wherein the heterocyclyl is further optionally substituted with 1-3 R^7 at one or more ring carbon atoms; and



(iii) , wherein b_2 is 0, 1, 2, or 3; and A^1 and A^2 are independently selected from the group consisting of: N, CH, and CR^7 ;

each R^7 is independently selected from the group consisting of R^a and R^b ;

Y^2 is a bond or a straight-chain C_{1-6} alkylene optionally substituted with 1-6 R^Y ;

each R^Y is independently selected from the group consisting of: halo, cyano, -OH, oxo, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl, and C_{1-6} haloalkyl, or

one pair of R^Y on the same or different carbon atom(s) taken together with the atom(s) connecting them forms a C_{3-6} cycloalkyl ring or 4-6 membered heterocyclyl ring, each of which is optionally substituted with 1-3 independently selected C_{1-3} alkyl;

R^3 is selected from the group consisting of:

(a) 4-15 membered heterocyclyl optionally substituted with 1-6 substituents independently selected from the group consisting of: R^a and R^b ; and

(b) $-NR^dR^e$;

each **R^a** is independently selected from the group consisting of:

- (a) halo;
- (b) cyano;
- (c) -OH;
- (d) oxo;
- (e) -C₁₋₆ alkoxy;
- (f) -C₁₋₆ haloalkoxy;
- (g) -NR^dR^e;
- (h) C(=O)C₁₋₆ alkyl;
- (i) C(=O)C₁₋₆ haloalkyl;
- (j) C(=O)OH;
- (k) C(=O)OC₁₋₆ alkyl;
- (l) C(=O)OC₁₋₆ haloalkyl;
- (m) C(=O)N(R^f)₂;
- (n) S(O)₀₋₂(C₁₋₆ alkyl);
- (o) S(O)₀₋₂(C₁₋₆ haloalkyl);
- (p) S(O)₁₋₂N(R^f)₂; and
- (q) C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl, each optionally substituted with 1-6 **R^c**;

each **R^b** is independently selected from the group consisting of: -(L^b)_b-R^{b1} and -R^{b1},

wherein:

b is 1, 2, or 3;

each -L^b is independently selected from the group consisting of: -O-, -N(H)-, -N(C₁₋₃ alkyl)-, -S(O)₀₋₂-, C(=O), and C₁₋₃ alkylene; and

each **R^{b1}** is independently selected from the group consisting of: C₃₋₁₀ cycloalkyl, 4-10 membered heterocyclyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl, each of which is optionally substituted with 1-3 **R^g**;

each **R^c** is independently selected from the group consisting of: halo, cyano, -OH, -C₁₋₆ alkoxy, -C₁₋₆ haloalkoxy, -NR^dR^e, C(=O)C₁₋₆ alkyl, C(=O)C₁₋₆ haloalkyl, C(=O)OC₁₋₆ alkyl, C(=O)OC₁₋₆ haloalkyl, C(=O)OH, C(=O)N(R^f)₂, S(O)₀₋₂(C₁₋₆ alkyl), S(O)₀₋₂(C₁₋₆ haloalkyl), and S(O)₁₋₂N(R^f)₂;

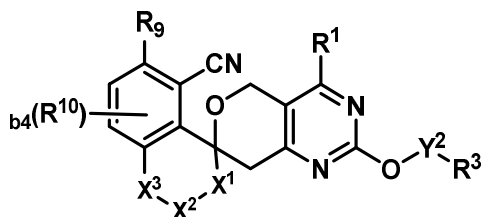
each **R^d** and **R^e** is independently selected from the group consisting of: H, C(=O)C₁₋₆ alkyl, C(=O)C₁₋₆ haloalkyl, C(=O)OC₁₋₆ alkyl, C(=O)OC₁₋₆ haloalkyl, C(=O)N(**R^f**)₂, S(O)₁₋₂(C₁₋₆ alkyl), S(O)₁₋₂(C₁₋₆ haloalkyl), S(O)₁₋₂N(**R^f**)₂, and C₁₋₆ alkyl optionally substituted with 1-3 **R^h**;

each **R^f** is independently selected from the group consisting of: H and C₁₋₆ alkyl optionally substituted with 1-3 **R^h**;

each **R^g** is independently selected from the group consisting of: **R^h**, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₃₋₅ cycloalkyl, and 4-5 membered heterocyclyl; and

each **R^h** is independently selected from the group consisting of: halo, cyano, -OH, -C₁₋₆ alkoxy, -C₁₋₆ haloalkoxy, -NH₂, -N(H)(C₁₋₃ alkyl), and -N(C₁₋₃ alkyl)₂.

Also provided herein are compounds of Formula (III):



Formula (III)

or pharmaceutically acceptable salts thereof, wherein:

R¹ is selected from the group consisting of:

(i) a 4-10 membered heterocyclyl optionally substituted with 1-4 **R⁷**;

(ii) an 8-12 membered bicyclic heterocyclyl, wherein the heterocyclyl comprises an endocyclic group selected from the group consisting of C(=O)NH and S(O)₂NH, and wherein the heterocyclyl is further optionally substituted with 1-3 **R⁷** at one or more ring carbon atoms;

Formula (IV-a), (IV-b), (IV-c), (IV-a1), (IV-b1), (IV-a2), or (IV-b2)), or Formula (V) (e.g., Formula (V-a) or (V-b), (V-a1), (V-c), (V-d), (V-b1), (V-a2), or (V-b2)), or Formula (VI) (e.g., Formula (VI-a), (VI-b), (VI-c), (VI-d), or (VI-e))), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In one aspect, the present disclosure refers to a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein, for use in therapy.

In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a KRas-associated cancer.

Provided herein are methods for treating cancer in a subject in need thereof, the methods comprising administering to the subject a therapeutically effective amount of a compound of Formula (A) (e.g., Formula (I) (e.g., Formula (I-a1), (I-a2), (I-a3), (I-a4), (I-a5), (I-b1), (I-b2), (I-b3), (I-b4), (I-b5), or (I-c1)), Formula (II) (e.g., Formula (II-a), (II-b), (II-a1), (II-b1), (II-a2), or (II-b2)), Formula (III) (e.g., Formula (III-1) or (III-2)), Formula (IV) (e.g., Formula (IV-a), (IV-b), (IV-c), (IV-a1), (IV-b1), (IV-a2), or (IV-b2)), or Formula (V) (e.g., Formula (V-a) or (V-b), (V-a1), (V-c), (V-d), (V-b1), (V-a2), or (V-b2)), or Formula (VI) (e.g., Formula (VI-a), (VI-b), (VI-c), (VI-d), or (VI-e))), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Also provided herein are methods for treating cancer in a subject in need thereof, the methods comprising (a) determining that the cancer has a KRas dysregulation (e.g., a KRas mutation (e.g., a KRas G12D mutation, a KRas G12R mutation, or a KRas G12V mutation)); and (b) administering to the subject a therapeutically effective amount of a compound of Formula (A) (e.g., Formula (I) (e.g., Formula (I-a1), (I-a2), (I-a3), (I-a4), (I-a5), (I-b1), (I-b2), (I-b3), (I-b4), (I-b5), or (I-c1)), Formula (II) (e.g., Formula (II-a), (II-b), (II-a1), (II-b1), (II-a2), or (II-b2)), Formula (III) (e.g., Formula (III-1) or (III-2)), Formula (IV) (e.g., Formula (IV-a), (IV-b), (IV-c), (IV-a1), (IV-b1), (IV-a2), or (IV-b2)), or Formula (V) (e.g., Formula (V-a) or (V-b), (V-a1), (V-c), (V-d), (V-b1), (V-a2), or (V-b2)), or Formula (VI) (e.g., Formula (VI-a), (VI-b), (VI-c), (VI-d), or (VI-e))), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Provided herein are methods of treating a KRas-associated disease or disorder (e.g., a mutant KRas-associated disease or disorder (e.g., a KRas G12D-associated cancer, a KRas G12R-associated cancer, or a KRas G12V-associated cancer)) in a subject, the methods comprising administering to a subject identified or diagnosed as having a KRas-associated disease or disorder a therapeutically effective amount of a compound of Formula (A) (e.g., Formula (I) (e.g., Formula (I-a1), (I-a2), (I-a3), (I-a4), (I-a5), (I-b1), (I-b2), (I-b3), (I-b4), (I-b5), or (I-c1)), Formula (II) (e.g., Formula (II-a), (II-b), (II-a1), (II-b1), (II-a2), or (II-b2)), Formula (III) (e.g., Formula (III-1) or (III-2)), Formula (IV) (e.g., Formula (IV-a), (IV-b), (IV-c), (IV-a1), (IV-b1), (IV-a2), or (IV-b2)), or Formula (V) (e.g., Formula (V-a) or (V-

determining that the cancer in the subject has a KRas dysregulation (e.g., a KRas mutation (e.g., a KRas G12D mutation, a KRas G12R mutation, or a KRas G12V mutation)); and administering to the subject a therapeutically effective amount of a compound of Formula (A) (e.g., Formula (I) (e.g., Formula (I-a1), (I-a2), (I-a3), (I-a4), (I-a5), (I-b1), (I-b2), (I-b3), (I-b4), (I-b5), or (I-c1)), Formula (II) (e.g., Formula (II-a), (II-b), (II-a1), (II-b1), (II-a2), or (II-b2)), Formula (III) (e.g., Formula (III-1) or (III-2)), Formula (IV) (e.g., Formula (IV-a), (IV-b), (IV-c), (IV-a1), (IV-b1), (IV-a2), or (IV-b2)), or Formula (V) (e.g., Formula (V-a) or (V-b), (V-a1), (V-c), (V-d), (V-b1), (V-a2), or (V-b2)), or Formula (VI) (e.g., Formula (VI-a), (VI-b), (VI-c), (VI-d), or (VI-e))), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

To facilitate understanding of the disclosure set forth herein, a number of terms are provided. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties. In the case of conflict between the present disclosure and any content incorporated by reference, the present disclosure controls.

The details of one or more examples of the disclosure are set forth in the accompanying drawings and the description below. Other features and advantages of the disclosure will be apparent from the description and drawings, and from the claims.

DETAILED DESCRIPTION

This disclosure provides compounds of Formula (A) (e.g., Formula (I) (e.g., Formula (I-a1), (I-a2), (I-a3), (I-a4), (I-a5), (I-b1), (I-b2), (I-b3), (I-b4), (I-b5), or (I-c1)), Formula (II) (e.g., Formula (II-a), (II-b), (II-a1), (II-b1), (II-a2), or (II-b2)), Formula (III) (e.g., Formula (III-1) or (III-2)), Formula (IV) (e.g., Formula (IV-a), (IV-b), (IV-c), (IV-a1), (IV-b1), (IV-a2), or (IV-b2)), or Formula (V) (e.g., Formula (V-a) or (V-b), (V-a1), (V-c), (V-d), (V-b1), (V-a2), or (V-b2)), or Formula (VI) (e.g., Formula (VI-a), (VI-b), (VI-c), (VI-d), or (VI-e))), or pharmaceutically acceptable salts thereof, that inhibit a KRas protein (e.g., a dysregulated KRas protein, such as a mutant KRas protein). These compounds are useful, e.g., for treating a disease, disorder, or condition associated with a KRas dysregulation (e.g., a KRas