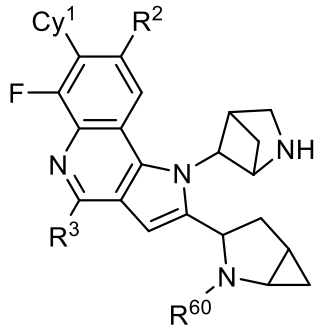
oncogenic driver is further supported by extensive in vivo experimental evidence showing mutant KRAS is required for early tumor onset and maintenance in animal models (A. D. Cox, *et al. Nat. Rev. Drug. Discov.*, **2014**, *13(11)*, 828-51).

Taken together, these findings indicate that KRAS mutations play a critical role in human cancers. Development of inhibitors targeting KRAS, including mutant KRAS, will therefore be useful in the clinical treatment of diseases that are characterized by involvement of KRAS, including diseases characterized by the involvement or presence of a KRAS mutation.

Efficient and scalable synthetic routes are required to prepare KRAS inhibitors. The processes disclosed herein meet this need by providing a scalable synthetic route to prepare chiral KRAS inhibitors.

SUMMARY

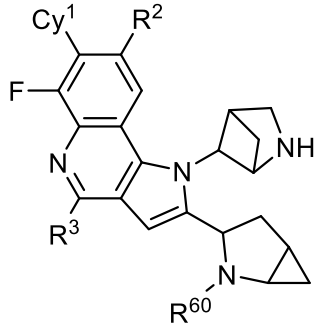
Provided herein are processes for preparing KRAS inhibitors such as compounds of Formula I:



I

or pharmaceutically acceptable salts thereof, wherein the variables are as disclosed herein. Also disclosed are intermediates useful for preparing such KRAS inhibitors and processes of preparing such intermediates.

In one aspect, provided herein is a process for preparing a compound of Formula I:



I

wherein

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

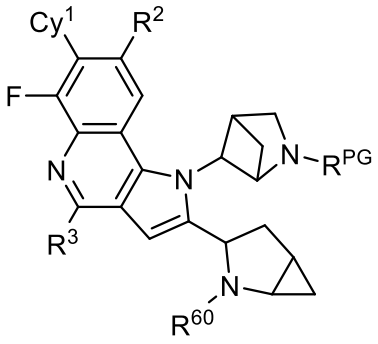
each R^{10} is independently selected from C_{1-3} alkyl and halo;

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

R^{60} is selected from C_{1-3} alkyl, halo, and $C(O)R^{b60}$; and

R^{b60} is selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, and C_{3-6} cycloalkyl;

comprising deprotecting a compound of Formula II:



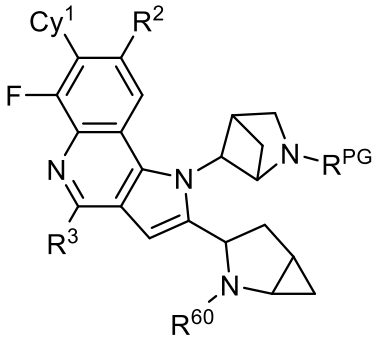
II

wherein

R^{PG} is a nitrogen protecting group;

to produce the compound of Formula I.

In another aspect, provided herein is a process for preparing a compound of Formula II:



II

wherein

R^{PG} is a nitrogen protecting group;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

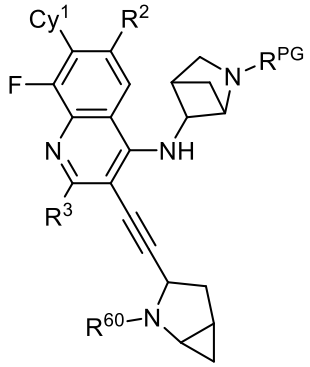
each R^{10} is independently selected from C_{1-3} alkyl and halo;

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

R^{60} is selected from C_{1-3} alkyl, halo, and $C(O)R^{b60}$; and

R^{b60} is selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, and C_{3-6} cycloalkyl;

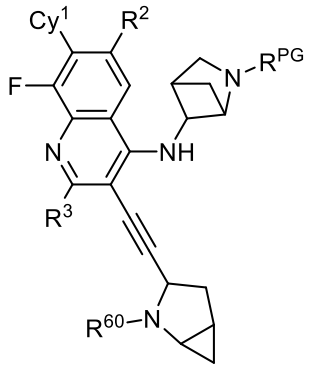
comprising cyclizing a compound of Formula III:



III

to form the compound of Formula II.

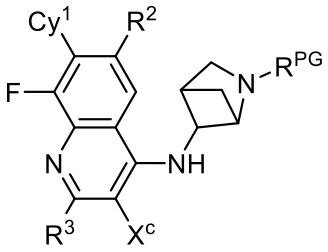
In another aspect, provided herein is a process of preparing a compound of Formula III:



III

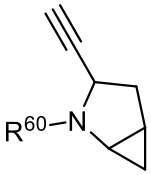
comprising

coupling a compound of Formula IV:



IV

with a compound of Formula V:



V

to form the compound of Formula III

wherein

X^c is Cl, Br, or I;

R^{PG} is a nitrogen protecting group;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

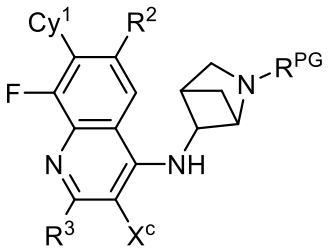
each R^{10} is independently selected from C_{1-3} alkyl and halo;

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

R^{60} is selected from C_{1-3} alkyl, halo, and $C(O)R^{b60}$; and

R^{b60} is selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, and C_{3-6} cycloalkyl.

In another aspect, provided herein is a process of preparing a compound of Formula IV:



IV

wherein

X^c is Cl, Br, or I;

R^{PG} is a nitrogen protecting group;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

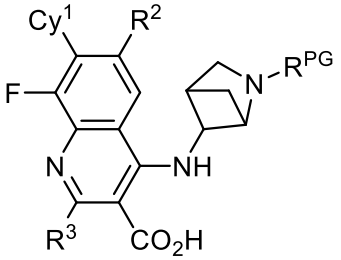
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

comprising halogenating a compound of Formula VI:

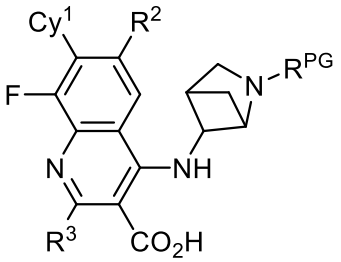


VI

wherein

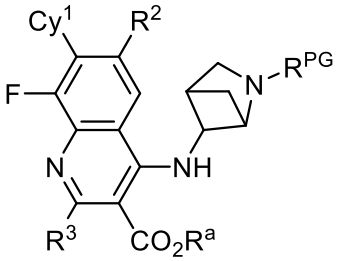
to form the compound of Formula IV.

In another aspect, provided herein is a process of preparing a compound of Formula VI:



VI

comprising hydrolyzing a compound of Formula VII:



VII

wherein

R^a is C_{1-3} alkyl;

R^{PG} is a nitrogen protecting group;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

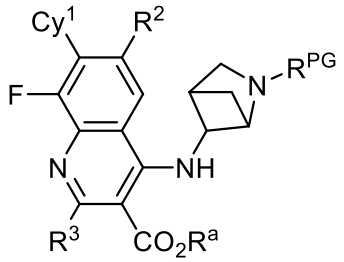
R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

to form the compound of Formula VI.

In another aspect, provided herein is a process of preparing a compound of Formula VII:



VII

wherein

R^a is C_{1-3} alkyl;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

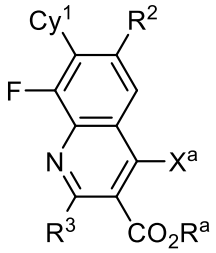
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

comprising reacting a compound of Formula VIII:

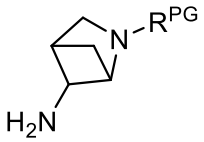


VIII

wherein

X^a is halo or OH;

with a compound of Formula IX:



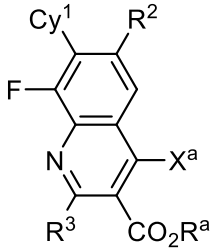
IX

wherein

R^{PG} is a nitrogen protecting group;

to form the compound of Formula VII.

In another aspect, provided herein is a process of preparing a compound of Formula VIII:



VIII

wherein

R^a is C_{1-3} alkyl;

X^a is halo or OH;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

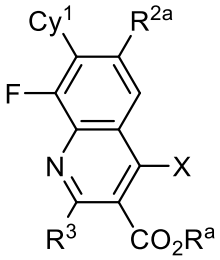
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

comprising reducing a compound of Formula X:



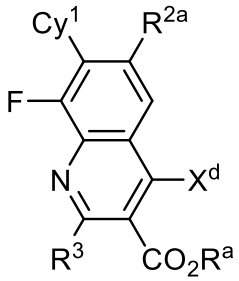
X

wherein

R^{2a} is selected from C_{2-4} alkyl and C_{2-4} alkenyl, both of which are optionally substituted with CN;

to form the compound of Formula VIII.

In another aspect, provided herein is a process of preparing a compound of Formula X-A:



X-A

wherein

R^a is C_{1-3} alkyl;

X^d is halo;

R^{2a} is selected from C_{2-4} alkyl and C_{2-4} alkenyl, both of which are optionally substituted with CN;

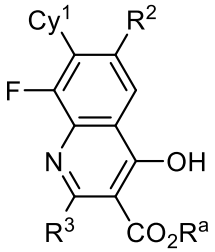
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

comprising halodehydroxylating a compound of Formula XI:



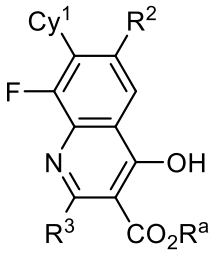
XI

to form the compound of Formula X;

wherein

R^2 is selected from C_{2-4} alkyl and C_{2-4} alkenyl, both of which are optionally substituted with CN.

In another aspect, provided herein is a process of preparing a compound of Formula XI:



XI

wherein

R^a is C_{1-3} alkyl;

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

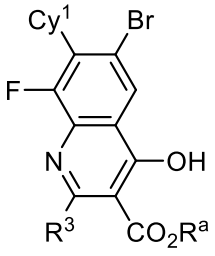
R^2 is selected from C_{2-4} alkenyl optionally substituted with CN;

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

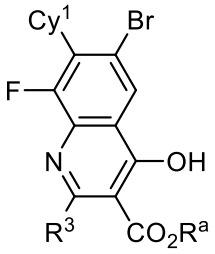
comprising coupling a compound of Formula XII:



XII

with an alkene form the compound of Formula XI.

In another aspect, provided herein is a process of preparing a compound of Formula XII:



XII

wherein

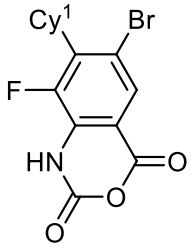
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo;

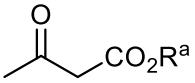
each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

comprising reacting a compound of Formula XIII:



XIII

with a compound of Formula XIV:

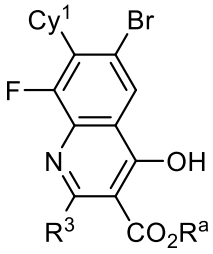


XIV;

wherein R^a is C_{1-3} alkyl;

to form the compound of Formula XII.

In another aspect, provided herein is a process of preparing a compound of Formula XII:



XII

wherein

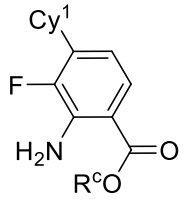
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo;

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

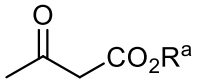
comprising reacting a compound of Formula XIII:



XIIIa

wherein R^c is C_{1-3} alkyl;

with a compound of Formula XIV:

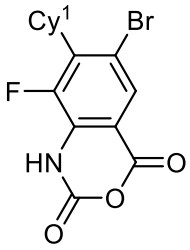


XIV;

wherein R^a is C_{1-3} alkyl;

to form the compound of Formula XII.

In another aspect, provided herein is a process of preparing a compound of Formula XIII:



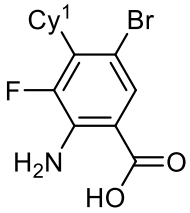
XIII

wherein

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10}; and

each R^{10} is independently selected from C_{1-3} alkyl and halo;

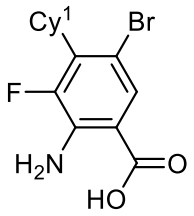
comprising carbonylating a compound of Formula XV:



XV

to form the compound of Formula XIII.

In another aspect, provided herein is a process of preparing a compound of Formula XV:



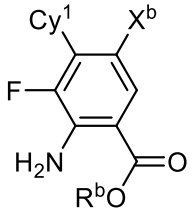
XV

wherein

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

comprising hydrolyzing a compound of Formula XVI:



XVI

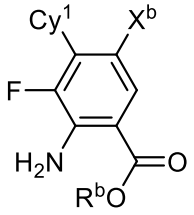
wherein

X^b is Cl, Br, or I;

R^b is C_{1-3} alkyl;

to form the compound of Formula XV.

In another aspect, provided herein is a process of preparing a compound of Formula XVI:



XVI

wherein

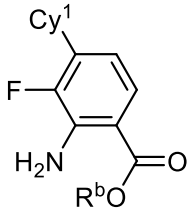
X^b is Cl, Br, or I;

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

R^b is C_{1-3} alkyl;

comprising halogenating a compound of Formula XVII:

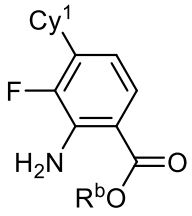


XVII

wherein

to form the compound of Formula XVI.

In another aspect, provided herein is a process of preparing a compound of Formula XVII:



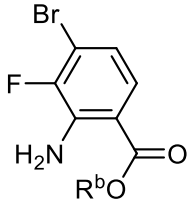
XVII

wherein

R^b is C_{1-3} alkyl;

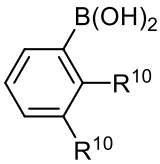
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

comprising coupling a compound of Formula XVIII:



XVIII

with a compound of Formula XIX:



XIX

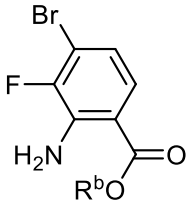
or an ester thereof;

wherein

each R^{10} is independently selected from C_{1-3} alkyl and halo;

in the presence of a palladium catalyst to form the compound of Formula XVII.

In another aspect, provided herein is a process of preparing a compound of Formula XVII:

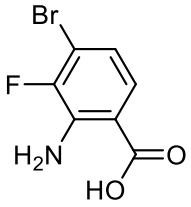


XVIII

wherein

R^b is C_{1-3} alkyl;

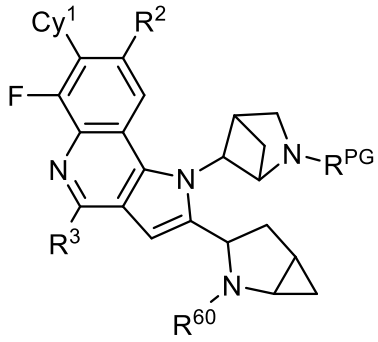
comprising esterifying a compound of Formula XX:



XX

to form the compound of Formula XVIII.

In another aspect, provided herein is a compound of Formula II:



II

wherein

R^{PG} is a nitrogen protecting group;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

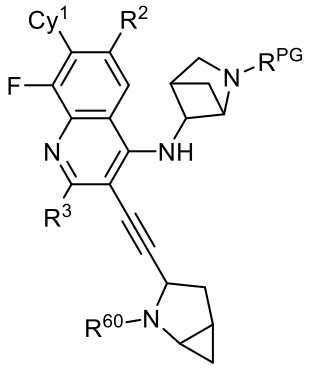
each R^{10} is independently selected from C_{1-3} alkyl and halo;

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

R^{60} is selected from C_{1-3} alkyl, halo, and $C(O)R^{b60}$; and

R^{b60} is selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, and C_{3-6} cycloalkyl.

In another aspect, provided herein is a compound of Formula III:



III

wherein

R^{PG} is a nitrogen protecting group;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

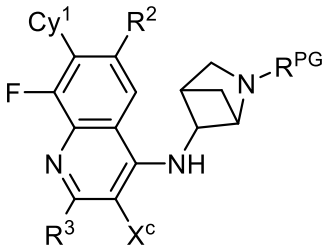
each R^{10} is independently selected from C_{1-3} alkyl and halo;

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D;

R^{60} is selected from C_{1-3} alkyl, halo, and $C(O)R^{b60}$; and

R^{b60} is selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, and C_{3-6} cycloalkyl.

In another aspect, provided herein is a compound of Formula IV:



IV

wherein

X^c is Cl, Br, or I;

R^{PG} is a nitrogen protecting group;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

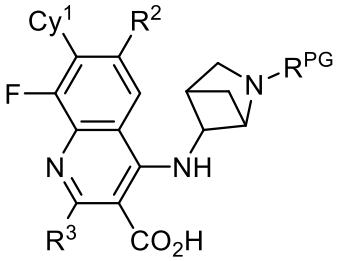
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D.

In another aspect, provided herein is a compound of Formula VI:



VI

wherein

R^{PG} is a nitrogen protecting group;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

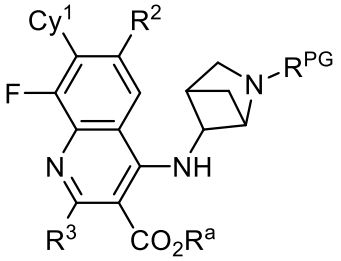
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D.

In another aspect, provided herein is a compound of Formula VII:



VII

wherein

R^a is C_{1-3} alkyl;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

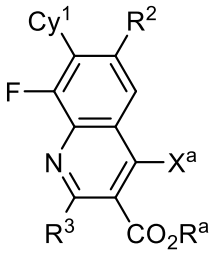
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D.

In another aspect, provided herein is a compound of Formula VIII:



VIII

wherein

X^a is halo or OH;

R^a is C_{1-3} alkyl;

R^2 is selected from C_{2-4} alkyl optionally substituted with CN;

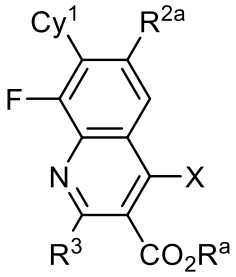
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D.

In another aspect, provided herein is a compound of Formula X:



X

wherein

R^a is C_{1-3} alkyl;

X is halo;

R^{2a} is selected from C_{2-4} alkyl and C_{2-4} alkenyl, both of which are optionally substituted with CN;

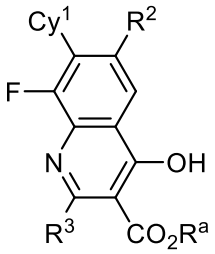
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D.

In another aspect, provided herein is a compound of Formula XI:



XI

wherein

R^a is C_{1-3} alkyl;

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

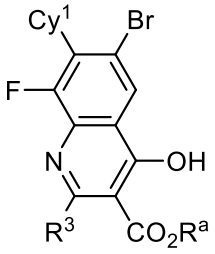
R^2 is selected from C_{2-4} alkenyl optionally substituted with CN;

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D.

In another aspect, provided herein is a compound of Formula XII:



XII

wherein

R^a is C_{1-3} alkyl;

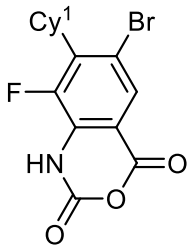
Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from R^{30};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

each R^{30} is independently selected from C_{1-3} alkyl, halo, and D.

In another aspect, provided herein is a compound of Formula XIII:



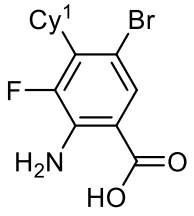
XIII

wherein

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10}; and

each R^{10} is independently selected from C_{1-3} alkyl and halo.

In another aspect, provided herein is a compound of Formula XV:



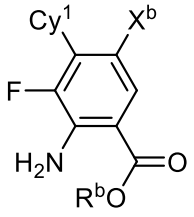
XV

wherein

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10}; and

each R^{10} is independently selected from C_{1-3} alkyl and halo.

In another aspect, provided herein is a compound of Formula XVI:



XVI

wherein

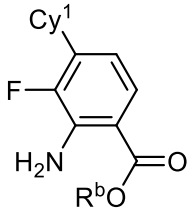
X^b is Cl, Br, or I;

R^b is C_{1-3} alkyl;

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10}; and

each R^{10} is independently selected from C_{1-3} alkyl and halo.

In another aspect, provided herein is a compound of Formula XVII:



XVII

wherein

Cy^1 is phenyl; wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R^{10};

each R^{10} is independently selected from C_{1-3} alkyl and halo; and

R^b is C_{1-3} alkyl.

DETAILED DESCRIPTION

Provided herein are processes for preparing potent and selective KRAS inhibitors and pharmaceutically acceptable salts thereof. An example of such a compound is 3-(1-((1*R*,4*R*,5*S*)-2-azabicyclo[2.1.1]hexan-5-yl)-2-((1*R*,3*R*,5*R*)-2-(cyclopropanecarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-7-(2,3-dichlorophenyl)-6-fluoro-4-methyl-1*H*-pyrrolo[3,2-*c*]quinolin-8-yl)propanenitrile (Compound 1*):