Non-mutant, *e.g.*, wild type, IDH1 catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate thereby reducing NAD^+ ($NADP^+$) to NADH (NADPH), *e.g.*, in the forward reaction:

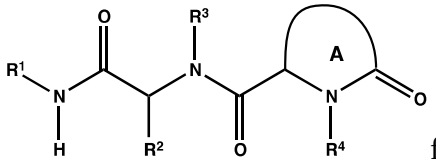
Isocitrate + NAD^+ ($NADP^+$) → α-KG + CO_2 + NADH (NADPH) + H^+.

It has been discovered that mutations of IDH1 present in certain cancer cells result in a new ability of the enzyme to catalyze the NADPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate (2HG). The production of 2HG is believed to contribute to the formation and progression of cancer (Dang, L et al, Nature 2009, 462:739-44).

The inhibition of mutant IDH1 and its neoactivity is therefore a potential therapeutic treatment for cancer. Accordingly, there is an ongoing need for inhibitors of IDH1 mutants having alpha hydroxyl neoactivity.

SUMMARY ~~OF INVENTION~~

Described herein are methods of treating a cancer characterized by the presence of a mutant allele of IDH1 or IDH2. The methods comprise the step of administering to a subject in need thereof a compound of formula I, or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof, wherein:



formula I

R^1 is optionally substituted C_4-C_6 carbocyclyl;

each R^2 and R^3 is independently selected from optionally substituted aryl or optionally substituted heteroaryl;

R^4 is alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, or optionally substituted heteroaralkyl;

ring A is 4-6 membered non-aromatic ring having 0-1 additional heteroatoms selected from N, O or S, wherein ring A is optionally substituted with one or two R^5 groups;

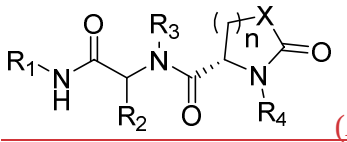
each R^5 is independently halo; $-CF_3$; -CN; $-OR^6$;$-N(R^6)_2$; $-C(O)C_1$-C_4 alkyl; C_1-C_4 haloalkyl; C_1-C_4 alkyl optionally substituted with $-OR^6$ or $-N(R^6)_2$; $-O-C_1$-C_4 alkyl optionally substituted with halo, $-OR^6$ or $-N(R^6)_2$; $-SO_2N(R^6)_2$; $-SO_2(C_1$-C_4 alkyl); $-NR^6SO_2R^6$; C_3-C_5

carbocyclyl optionally substituted with one or two R^6 groups; -O-(C_3-C_6 carbocyclyl optionally substituted with one or two R^6 groups); 5-6 membered heteroaryl; -C_1-C_4 alkyl-C(O)O-C_1-C_4 alkyl; or -C(O)O-C_1-C_4 alkyl;or

each R^6 is independently H or C_1-C_3 alkyl.

The compound of formula I inhibits mutant IDH1/2, particularly mutant IDH1 having alpha hydroxyl neoactivity. Also described herein are pharmaceutical compositions comprising a compound of formula I.

In one aspect, the present disclosure refers to a method of making a compound of structural formula (A) or a pharmaceutically acceptable salt, tautomer or hydrate thereof, wherein:



(A)

R^1 is optionally substituted C_4-C_6 carbocyclyl;

each R^2 and R^3 is independently selected from optionally substituted aryl or optionally substituted heteroaryl;

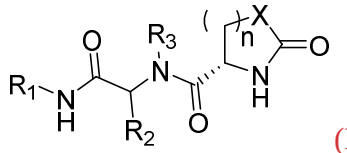
R^4 is optionally substituted aryl or optionally substituted heteroaryl,

n is 1 or 2; and

X is –CH_2-, O, –NH-, –CH(OH)-, or –CH(F)-,

the method comprising:

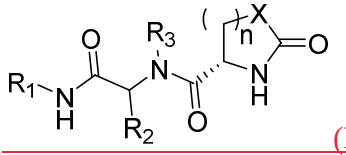
reacting a compound of formula B:



(B)

with R^4-Br under Buchwald conditions to provide the compound of structural formula (A).

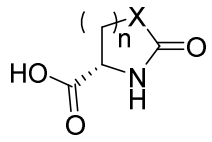
In one aspect, the present disclosure refers to a method of making a compound of structural formula (B) or a pharmaceutically acceptable salt, tautomer, or hydrate thereof,



(B)

the method comprising:

reacting a compound of structural formula (C):



(C)

with R^1NC, R^2CHO and R^3-NH_2 under Ugi coupling reaction conditions to provide the compound of structural formula (B).

DETAILED DESCRIPTION OF THE INVENTION

The details of construction and the arrangement of components set forth in the following description or illustrated in the drawings are not meant to be limiting. Other embodiments and different ways to practice the invention are expressly included. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing", "involving", and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

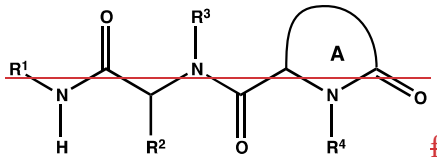
Definitions:

The term "halo" or "halogen" refers to any radical of fluorine, chlorine, bromine or iodine.

The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C_1-C_{12} alkyl indicates that the group may have from 1 to 12 (inclusive) carbon atoms in it. The term "haloalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by halo, and includes alkyl moieties in which all hydrogens have been replaced by halo (e.g., perfluoroalkyl). The terms "arylalkyl" or "aralkyl" refer to an alkyl moiety in which an alkyl hydrogen atom is replaced by an aryl group. Arylalkyl or aralkyl includes groups in which more than one hydrogen atom has been replaced by an aryl group. Examples of "arylalkyl" or "aralkyl" include benzyl, 2-phenylethyl, 3-phenylpropyl, 9-fluorenyl, benzhydryl, and trityl groups. The terms "heteroarylalkyl" or "heteroaralkyl" refer to an alkyl moiety in which an alkyl hydrogen atom is

Claims

1. A compound of formula I or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof, wherein:



formula I

R^1 is optionally substituted C_4-C_6 carbocyclyl;

each R^2 and R^3 is independently selected from optionally substituted aryl or optionally substituted heteroaryl;

R^4 is alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, or optionally substituted heteroaralkyl;

ring A is 4-6 membered non-aromatic ring having 0-1 additional heteroatoms selected from N, O or S, wherein ring A is optionally substituted with one or two R^5 groups;

each R^5 is independently halo; $-CF_3$; $-CN$; $-OR^6$; $-N(R^6)_2$; $-C(O)C_1$-C_4 alkyl; C_1-C_4 haloalkyl; C_1-C_4 alkyl optionally substituted with $-OR^6$ or $-N(R^6)_2$; $-O$-C_1-C_4 alkyl optionally substituted with halo, $-OR^6$ or $-N(R^6)_2$; $-SO_2N(R^6)_2$; $-SO_2(C_1$-C_4 alkyl); $-NR^6SO_2R^6$; C_3-C_5 carbocyclyl optionally substituted with one or two R^6 groups; $-O$-(C_3-C_6 carbocyclyl optionally substituted with one or two R^6 groups); 5-6 membered heteroaryl; $-C_1$-C_4 alkyl-$C(O)O$-C_1-C_4 alkyl; or $-C(O)O$-C_1-C_4 alkyl; or

each R^6 is independently H or C_1-C_3 alkyl.

2. The compound of claim 1, wherein:

R^1 is C_4-C_6 carbocyclyl optionally substituted with one to three R^7 groups;

each R^2 and R^3 is independently selected from aryl or heteroaryl, wherein said aryl or heteroaryl is independently optionally substituted with one to three R^7 groups;

R^4 is alkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl, wherein said aryl, heteroaryl, aralkyl, and heteroaralkyl are each independently optionally substituted with one to three R^7 groups;

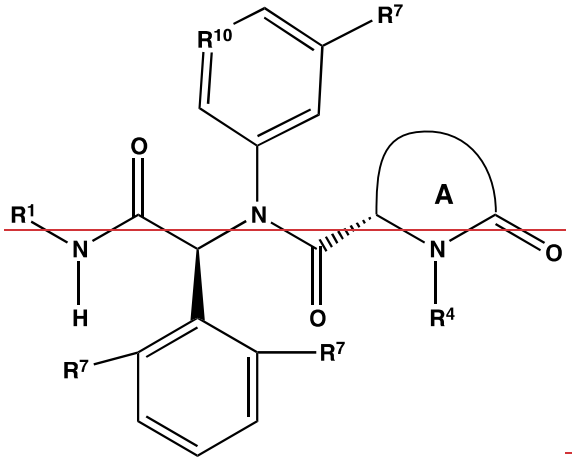
ring A is 4-6 membered non-aromatic ring having 0-1 additional heteroatoms selected from N, O or S, wherein ring A is optionally substituted with one or two R^5 groups;

each R^5 and R^7 is independently halo; CF_3; CN; OR^6; $N(R^6)_2$; $C(O)C_1$-C_4 alkyl; C_1-C_4 haloalkyl; C_1-C_4 alkyl optionally substituted with OR^6 or $N(R^6)_2$; O C_1-C_4 alkyl optionally substituted with halo, OR^6 or $N(R^6)_2$; $SO_2N(R^6)_2$; S(O) C_{1-4} alkyl; $SO_2(C_1$-C_4 alkyl); $NR^6SO_2R^6$; C_3-C_5 carbocyclyl optionally substituted with one or two R^6 groups; O (C_3-C_6 carbocyclyl optionally substituted with one or two R^6 groups); 5-6 membered heteroaryl; C_1-C_4 alkyl C(O)O C_1-C_4 alkyl; or C(O)O C_1-C_4 alkyl; or

each R^6 is independently H or C_1-C_4 alkyl.

3. The compound of claim 1 or 2, wherein each R^2 and R^3 is independently aryl optionally substituted with one to three R^7 groups.

4. The compound of claim 1 having formula II a,

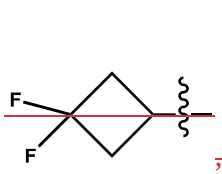
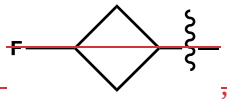
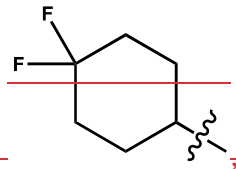
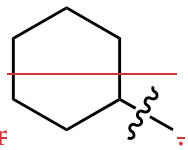


formula II a

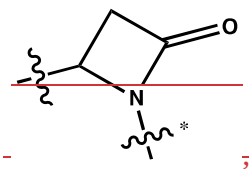
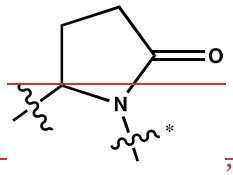
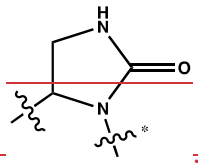
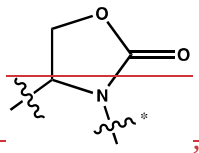
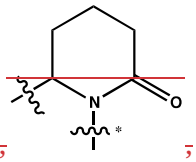
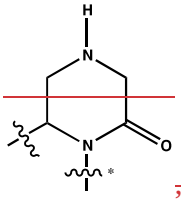
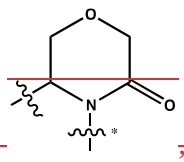
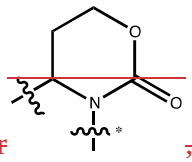
wherein R^{10} is CR^{11} or N; and R^{11} is F, SO_2NH_2, SO_2CH_3, S(O)CH_3, CN, methoxy, OCH_2OH, CH_2OH, $SO_2N(CH_3)_2$, SO_2NHCH_3, $NHSO_2CH_3$, CH_2CH_2OH, $N(CH_3)_2$, t-butyl, cyclopropyl, $C(OH)(CH_3)_2$, OCF_3, $OCHF_2$, O-cyclopropyl, 1-methyl-cyclopropyl, or pyrazolyl.

5. The compound of any one of claims 1-4, wherein R^1 is C_4 or C_6 cycloalkyl optionally substituted with one to two R^7 groups and R^7 associated with R^1 is halo.

6. The compound of claim 5, wherein R^1 is

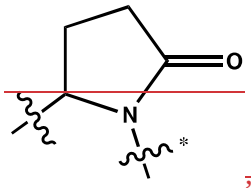
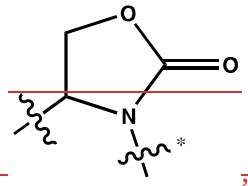
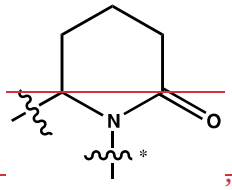
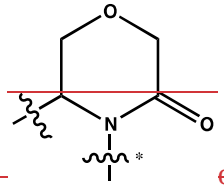
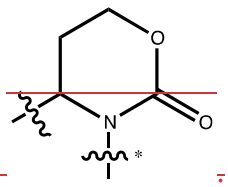





7. The compound of claim 5, wherein ring A is:

, wherein denotes ring A's attachment to the amide moiety of formula and denotes ring A's attachment to R^4; and each member of ring A is optionally substituted with one or two R^5 groups.

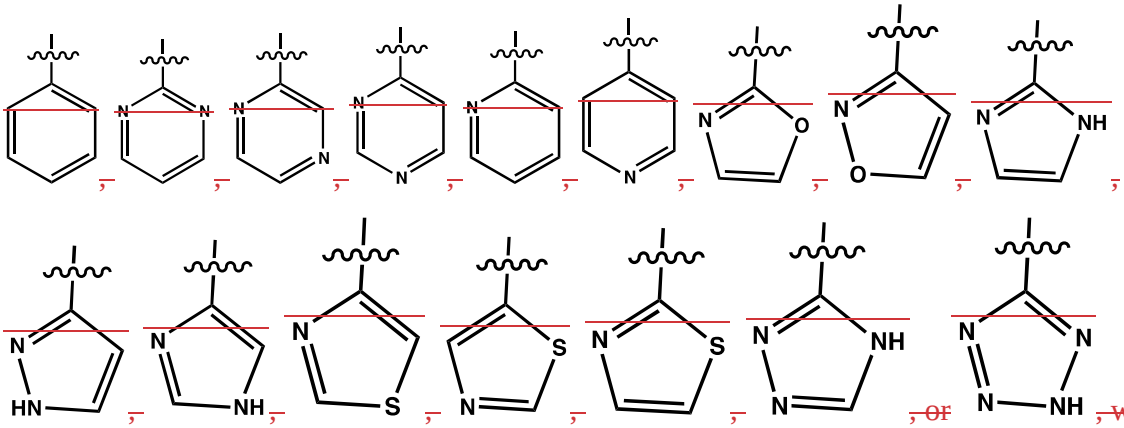
8. The compound of claim 7, wherein ring A is:

or .

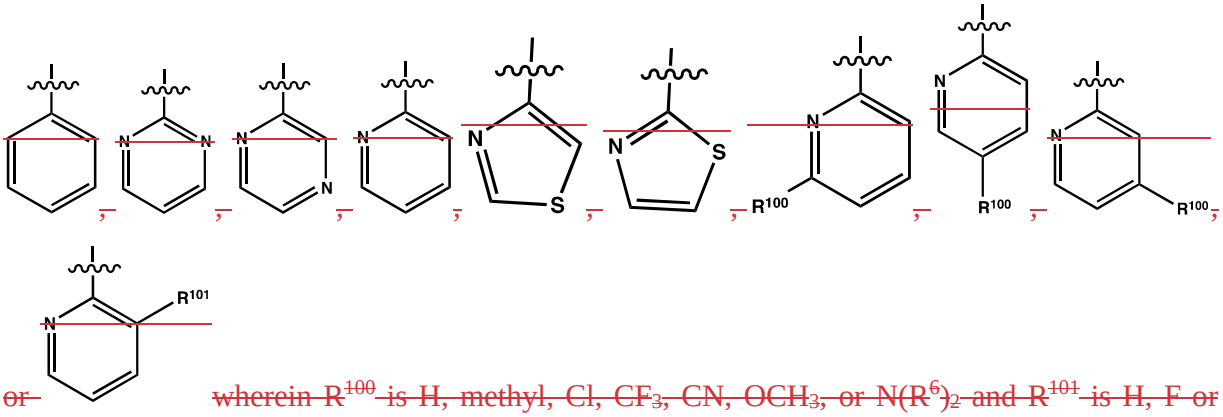
9. The compound of claim 7, wherein R^4 is aryl or heteroaryl, each aryl or heteroaryl is optionally substituted with one to three R^7 groups.

10. The compound of claim 9, wherein R^4 is:



, wherein each member of R^4 is optionally substituted with one or two R^7 groups and each R^7 is independently F, Cl, methyl, CF_3, CN, OMe, or $N(R^6)_2$.

11. The compound of claim 10, wherein R^4 is:



wherein R^{100} is H, methyl, Cl, CF_3, CN, OCH_3, or $N(R^6)_2$ and R^{101} is H, F or methyl.

12. The compound is selected from any one of compounds from Table 1.

13. A pharmaceutical composition comprising a compound of any one of claims 1 to 12; and a pharmaceutically acceptable carrier.

14. The composition of claim 13, further comprising a second therapeutic agent useful in the treatment of cancer.

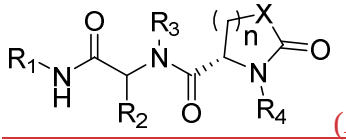
~~15. A method of treating a cancer characterized by the presence of an IDH1 mutation, wherein the IDH1 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate in a patient, comprising the step of administering to the patient in need thereof a composition of claim 13.~~

~~16. The method of claim 15, wherein the IDH1 mutation is an IDH1 R132H or R132C mutation.~~

~~17. The method of claim 15, wherein the cancer is selected from glioma (glioblastoma), acute myelogenous leukemia, melanoma, non-small cell lung cancer (NSCLC), cholangiocarcinomas, chondrosarcoma, myelodysplastic syndromes (MDS), myeloproliferative neoplasm (MPN), colon cancer in a patient.~~

~~18. The method of claim 17, further comprising administering to the patient in need thereof a second therapeutic agent useful in the treatment of cancer.~~

1. A method of making a compound of structural formula (A) or a pharmaceutically acceptable salt, tautomer or hydrate thereof, wherein:



(A)

R^1 is optionally substituted C_4-C_6 carbocyclyl;

each R^2 and R^3 is independently selected from optionally substituted aryl or optionally substituted heteroaryl;

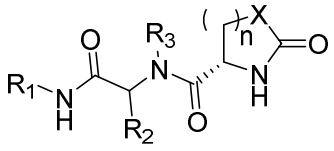
R^4 is optionally substituted aryl or optionally substituted heteroaryl,

n is 1 or 2; and

X is $–CH_2$-, O, –NH-, –CH(OH)-, or –CH(F)-,

the method comprising:

reacting a compound of formula B:



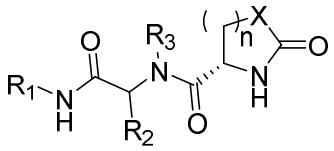
(B)

with R^4-Br under Buchwald conditions to provide the compound of structural formula (A).

2. The method of claim 1 wherein the Buchwald conditions comprise use of a palladium catalyst, a ligand and a base in an organic solvent.

3. The method of claim 2 wherein the solvent is dioxane, the palladium catalyst is $Pd_2(dba)_3$, the ligand is Xantphos and the base is cesium carbonate.

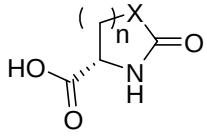
4. A method of making a compound of structural formula (B) or a pharmaceutically acceptable salt, tautomer, or hydrate thereof,



(B)

the method comprising:

reacting a compound of structural formula (C):



(C)

with R^1NC, R^2CHO and R^3-NH_2 under Ugi coupling reaction conditions to provide the compound of structural formula (B).

5. The method of claim 4 wherein the Ugi coupling takes place in a solvent.

6. The method of claim 5 wherein the solvent is methanol.