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:

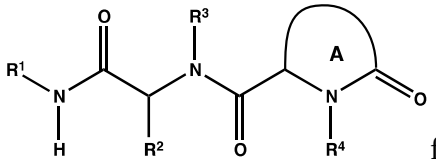
Isocitrate + NAD^+ ($NADP^+$) → α-KG + CO_2 + NADH (NADPH) + H^+.

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

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;

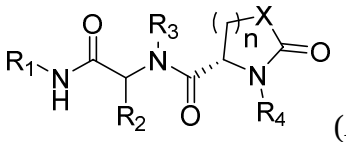
each R^5 is independently halo; $-CF_3$; -CN; $-OR^6$;$-N(R^6)_2$; $-C(O)C_1$-C_4 alkyl; C_1-C_4 haloalkyl; C_1-C_4 alkyl optionally substituted with $-OR^6$ or $-N(R^6)_2$; $-O-C_1$-C_4 alkyl optionally substituted with halo, $-OR^6$ or $-N(R^6)_2$; $-SO_2N(R^6)_2$; $-SO_2(C_1$-C_4 alkyl); $-NR^6SO_2R^6$;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

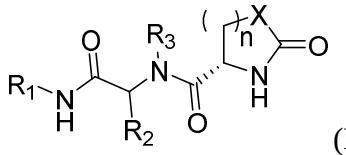
R^4 is optionally substituted aryl or optionally substituted heteroaryl,

n is 1 or 2; and

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

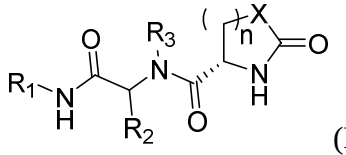
the method comprising:

reacting a compound of formula B:


(B)

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

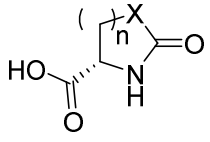
In one aspect, the present disclosure refers to a method of making a compound of structural formula (B) or a pharmaceutically acceptable salt, tautomer, or hydrate thereof,



(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.

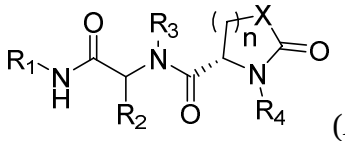
Definitions:

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 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;

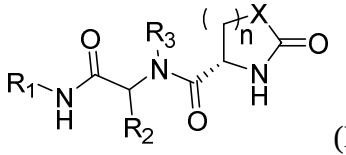
R^4 is optionally substituted aryl or optionally substituted heteroaryl,

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:



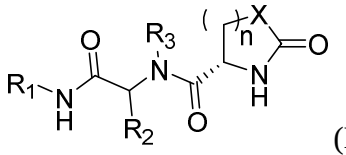
(B)

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.

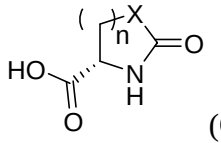
4. A method of making a compound of structural formula (B) or a pharmaceutically acceptable salt, tautomer, or hydrate thereof,



(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.