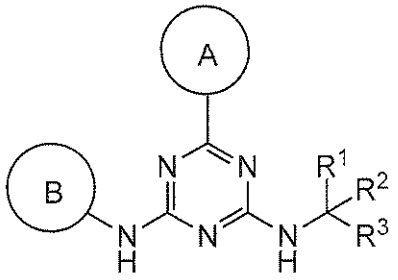
R(-)-2-hydroxyglutarate (2HG). 2HG is not formed by wild-type IDH2. The production of 2HG is believed to contribute to the formation and progression of cancer (Dang, L et al, Nature 2009, 462:739-44).

The inhibition of mutant IDH2 and its neoactivity is therefore a potential therapeutic treatment for cancer. Accordingly, there is an ongoing need for inhibitors of IDH2 mutants having alpha hydroxyl neoactivity.

SUMMARY ~~OF INVENTION~~

Described herein are compounds of Structural Formula I, or a pharmaceutically acceptable salt or hydrate thereof:



(I), wherein:

ring A is an optionally substituted 5-6 member monocyclic aryl or monocyclic heteroaryl;

ring B is an optionally substituted 5-6 member monocyclic aryl or monocyclic heteroaryl;

R^1 and R^3 are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -O-C_1-C_4 alkyl, and CN, wherein any alkyl portion of R^1 is optionally substituted with -OH, NH_2, NH(C_1-C_4 alkyl), or N(C_1-C_4 alkyl)$_2$;

R^2 is selected from: -(C_1-C_6 alkyl), -(C_2-C_6 alkenyl or alkynyl), -(C_1-C_6 alkylene)-N(R^6)-(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)(R^6), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1-2}$-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1-2}$-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-S(O)$_{1-2}$-N(R^6)(R^6), -(C_1-C_4 alkylene)-S(O)$_{1-2}$-N(R^6)-(C_1-C_6 alkylene)-Q, -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)- (C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6

(E)-3-(4-((4-((3-(diethylamino)propyl)amino)-6-phenyl-1,3,5-triazin-2-yl)amino)-2-methoxyphenyl)-2-phenylacrylonitrile ,

4-((4-((furan-2-ylmethyl)amino)-6-(pyridin-4-yl)-1,3,5-triazin-2-yl)amino)phenol, 3-(4-((5-aminopentyl)amino)-6-((3-fluorophenyl)amino)-1,3,5-triazin-2-yl)phenol,

N^2,6-bis(3-fluorophenyl)-N^4-(piperidin-3-yl)-1,3,5-triazine-2,4-diamine,

N^2-butyl-6-phenyl-N^4-(p-tolyl)-1,3,5-triazine-2,4-diamine, N^2-cyclohexyl-N^4,6-diphenyl-1,3,5-triazine-2,4-diamine,

(R)-3-((4-(3-chlorophenyl)-6-(pyrrolidin-3-ylamino)-1,3,5-triazin-2-yl)amino)-4-methylbenzamide,

2-chloro-4-(methylsulfonyl)-N-[4-(phenylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-benzamide,

N^2-(2-methoxyethyl)-*N*^{4}-phenyl-6-[5-[6-(2,2,2-trifluoroethoxy)-3-pyridinyl]-1,2,4-oxadiazol-3-yl]-1,3,5-triazine-2,4-diamine,

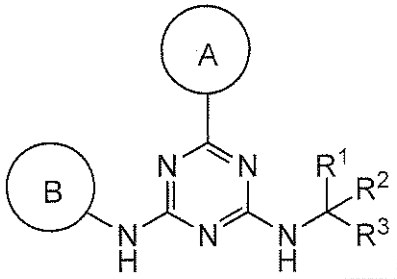
N^2-(2-furanylmethyl)-6-phenyl-N^4-[3-(trifluoromethyl)phenyl]-1,3,5-triazine-2,4-diamine,

6-(3-methoxyphenyl)-*N*^{2}-methyl-*N*^{4}-(3-nitrophenyl)-1,3,5-triazine-2,4-diamine,

N^2-butyl-*N*^{4}-(4-methylphenyl)-6-phenyl-1,3,5-triazine-2,4-diamine, and

4-[[4-(5-chloro-2-methylphenyl)-6-(methylamino)]-1,3,5-triazin-2-yl]amino-benzenemethanol.

In an aspect, there is provided a compound having Formula I or a pharmaceutically acceptable salt or hydrate thereof:



(I), wherein:

ring A is an optionally substituted ring selected from phenyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and thiazolyl;

ring B is an optionally substituted 5-6 member monocyclic aryl or monocyclic heteroaryl;

R^1 and R^3 are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -O-C_1-C_4 alkyl, and CN, wherein any alkyl portion of R^1 is optionally substituted with -OH, NH_2, $NH(C_1$-C_4 alkyl), or $N(C_1$-C_4 alkyl)$_2$;

R^2 is selected from: -(C_1-C_6 alkyl), -(C_2-C_6 alkenyl or alkynyl), -(C_1-C_6 alkylene)-$N(R^6)$-(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-$N(R^6)$-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-$N(R^6)(R^6)$, -(C_1-C_6 alkylene)-$N(R^6)$-$S(O)_{1-2}$-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-$N(R^6)$-$S(O)_{1-2}$-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-$S(O)_{1-2}$-$N(R^6)(R^6)$, -(C_1-C_4 alkylene)-$S(O)_{1-2}$-$N(R^6)$-(C_1-C_6 alkylene)-Q, -$C(O)N(R^6)$-(C_1-C_6 alkylene)-C(O)- (C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -$C(O)N(R^6)$-(C_1-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-$C(O)N(R^6)$-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-$C(O)N(R^6)$-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-$N(R^6)C(O)$-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-$N(R^6)C(O)$-(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-$S(O)_{0-2}$-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-$S(O)_{0-2}$-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-$N(R^6)$-C(O)-$N(R^6)$-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-Q, wherein:

any alkyl or alkylene moiety present in R^2 is optionally substituted with one or more -OH, -O(C_1-C_4 alkyl) or halo;

any terminal methyl moiety present in R^2 is optionally replaced with $-CH_2OH$, CF_3, $-CH_2F$, $-CH_2Cl$, $C(O)CH_3$, $C(O)CF_3$, CN, or CO_2H;

each R^6 is independently selected from hydrogen and C_1-C_6 alkyl; and

Q is selected from aryl, pyrazolyl, carbocyclyl and heterocyclyl, any of which is optionally substituted; or

R^1 and R^3 are optionally taken together with the carbon atom to which they are attached to form C(=O), or

R^1 and R^2 are optionally taken together to form substituted carbocyclyl, or optionally substituted heterocyclyl, wherein:

a. when ring A is unsubstituted phenyl, and ring B is phenyl substituted by methoxy or ethoxy; then said phenyl of ring B is not further substituted by oxazolyl;

b. when ring A is optionally substituted phenyl or optionally substituted pyridyl and ring B is optionally substituted phenyl; then the portion of the compound represented by -NH-C(R^1)(R^2)(R^3) is not -NH(CH_2)-aryl;

c. when ring A is optionally substituted phenyl, and ring B is optionally substituted phenyl or pyrrolyl; then the portion of the compound represented by -NH-C(R^1)(R^2)(R^3) is not -NH(CH_2)C(O)NH_2;

d. when ring A is phenyl substituted with 2 or more hydroxyl or methoxy, and ring B is optionally substituted phenyl; then the portion of the compound represented by -NH-C(R^1)(R^2)(R^3) is not -NH-cycloheptyl;

e. when ring A is optionally substituted phenyl and ring B is optionally substituted phenyl; then R^1 and R^3 do not form 2,2,6,6,-tetramethylpiperidin-4-yl;

f. when ring A and ring B are optionally substituted phenyl; then the portion of the compound represented by -NH-C(R^1)(R^2)(R^3) is not cysteine, optionally substituted phenylalanine or leucine or methyl ester thereof;

g. when ring A is phenyl or pyridin-3-yl optionally substituted with one or more substituents selected from halo, methyl or CF_3, and ring B is phenyl optionally substituted with one or more substituents selected from halo, methyl, CF_3, methoxy, or CH=C(phenyl)CN; then the portion of the compound represented by -NHC(R^1)(R^2)(R^3) is other than -NH(C_1-C_8 alkylene)-N(R^a)(R^a), -NH-1-(aminomethyl)cyclopentylmethyl, -NH-4-(aminomethyl)cyclohexylmethyl, wherein each R^a is hydrogen, C_1-C_4 alkyl or two R^as are taken together with the nitrogen to which they are commonly bound to form morpholin-4-yl or pipieridin-1-yl;

h. when ring A is phenyl, 4-chlorophenyl or 4-methyl phenyl and ring B is 4-chlorophenyl or 3,4-dichlorophenyl; then the portion of the compound represented by -NHC(R^1)(R^2)(R^3) is not -NH-isopropyl;

i. when ring A is unsubstituted phenyl and the portion of the compound represented by -NHC(R^1)(R^2)(R^3) is -NH-$CH_2CH_2N(CH_3)_2$, -NH-CH_2CH_2-morpholin-4-yl or -NH-CH_2CH_2OH; then ring B is other than oxadiazole, imidazole, thiazole or oxazole each of which is substituted with -C(O)NHR^b, wherein R^b is isopropyl, cyclopropyl or 2-chloro-6-methylphenyl;

j. when ring A is phenyl substituted with SO_2OH or SO_2Na and ring B is phenyl, or when ring B is phenyl substituted with SO_2OH and ring B is substituted phenyl; then the portion of the compound represented by -NHC(R^1)(R^2)(R^3) is not -$NH(CH_2)_2OH$ or -$NH(CH_2)CH(OH)CH_3$; and

k. the compound is other than:

(E)-3-(4-((4-((3-(diethylamino)propyl)amino)-6-phenyl-1,3,5-triazin-2-yl)amino)-2-methoxyphenyl)-2-phenylacrylonitrile ,

4-((4-((furan-2-ylmethyl)amino)-6-(pyridin-4-yl)-1,3,5-triazin-2-yl)amino)phenol,

3-(4-((5-aminopentyl)amino)-6-((3-fluorophenyl)amino)-1,3,5-triazin-2-yl)phenol,

N^2,6-bis(3-fluorophenyl)-N^4-(piperidin-3-yl)-1,3,5-triazine-2,4-diamine,

N^2-butyl-6-phenyl-N^4-(p-tolyl)-1,3,5-triazine-2,4-diamine, N^2-cyclohexyl-N^4,6-diphenyl-1,3,5-triazine-2,4-diamine,

(R)-3-((4-(3-chlorophenyl)-6-(pyrrolidin-3-ylamino)-1,3,5-triazin-2-yl)amino)-4-methylbenzamide,

2-chloro-4-(methylsulfonyl)-N-[4-(phenylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-benzamide,

N^2-(2-methoxyethyl)-N^4-phenyl-6-[5-[6-(2,2,2-trifluoroethoxy)-3-pyridinyl]-1,2,4-oxadiazol-3-yl]-1,3,5-triazine-2,4-diamine,

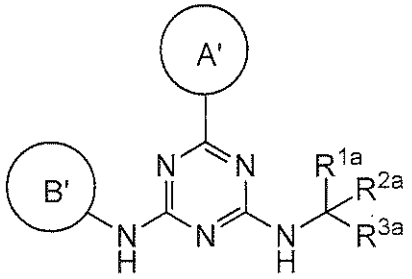
N^2-(2-furanylmethyl)-6-phenyl-N^4-[3-(trifluoromethyl)phenyl]-1,3,5-triazine-2,4-diamine,

6-(3-methoxyphenyl)-N^2-methyl-N^4-(3-nitrophenyl)-1,3,5-triazine-2,4-diamine,

N^2-butyl-N^4-(4-methylphenyl)-6-phenyl-1,3,5-triazine-2,4-diamine, and

4-[[4-(5-chloro-2-methylphenyl)-6-(methylamino)]-1,3,5-triazin-2-yl]amino-benzenemethanol.

In another aspect, there is provided a compound having Structural Formula II:



(II), or a pharmaceutically acceptable salt thereof, wherein:

Ring A' is selected from phenyl and pyridin-2-yl, wherein ring A' is optionally substituted with one or two substituents independently selected from chloro, fluoro, $-CF_3$, $-CHF_2$, $-CH_3$, $-CH_2CH_3$, $-CF_2CH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-NH_2$, $-NH(CH_3)$, and $-N(CH_3)_2$;

Ring B' is selected from pyridin-3-yl, pyridin-4-yl, isoxazoly-4-yl, isoxazol-3-yl, thiazol-5-yl, pyrimidin-5-yl and pyrazol-4-yl, wherein ring B' is optionally substituted with one to two substituents independently selected from halo; -CN; -OH; C_1-C_4 alkyl optionally substituted with halo, CN or -OH; $-S(O)_2$-C_1-C_4 alkyl; -S(O)-C_1-C_4 alkyl; $-S(O)_2$-NH-C_1-C_4 alkyl; $-S(O)_2$-$N(C_1$-C_4 alkyl$)_2$; $-S(O)_2$-azetidin-1-yl; -O-C_1-C_4 alkyl; $-CH_2$-O-CH_3, morpholin-4-yl, cyclopropyl, $-S(O)_2$-NH-cyclopropyl; -C(O)-O-CH_3; and

$-C(R^{1a})(R^{2a})(R^{3a})$ is selected from C_1-C_6 alkyl optionally substituted with halo or -OH; -(C_0-C_1 alkylene)-cycloalkyl, wherein the alkylene is optionally substituted with methyl and the cycloalkyl is optionally substituted with halo, $-OCH_3$ or methyl; saturated heterocyclyl optionally substituted with halo or methyl; -C(O)-O-C_1-C_6 alkyl; -C(O)-(C_0-C_1 alkylene)-cyclopropyl; and C(O)-benzyl.

The compound of Formula I or II or as described in any one of the embodiments herein inhibits mutant IDH2, particularly mutant IDH2 having alpha hydroxyl neoactivity.

In another aspect, there is provided a pharmaceutical composition comprising a compound of Formula I as described herein, and a pharmaceutically acceptable carrier. Also described herein are ~~pharmaceutical compositions comprising a compound of Formula I and~~ methods of using such compositions to treat cancers characterized by the presence of a mutant IDH2. In another aspect, there is provided the use of a composition as described herein in the manufacture of a medicament for treating a cancer characterized by the presence of an IDH2

mutation, wherein the IDH2 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.

DETAILED DESCRIPTION

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.