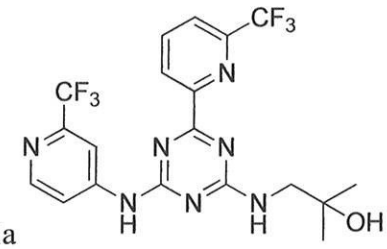
R(-)-2-hydroxyglutarate (2HG). 2HG is not formed by wild-type IDH2. The production of 2HG is believed to contribute to the formation and progression of cancer (Dang, L et al, Nature 2009, 462:739-44).

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.

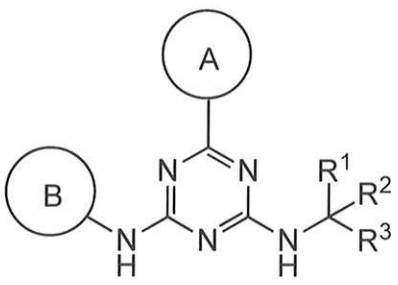
SUMMARY

In a first aspect, there is provided a compound having formula  or a pharmaceutically acceptable salt thereof.

In a second aspect, there is provided a pharmaceutical composition comprising a compound of the first aspect, and a pharmaceutically acceptable carrier.

In a third aspect, there is provided use of a compound of the first aspect 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 NADPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate in a patient.

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;

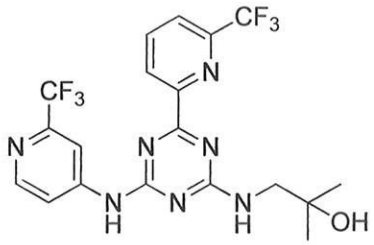
ring B is an optionally substituted 5-6 member monocyclic aryl or monocyclic heteroaryl;

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

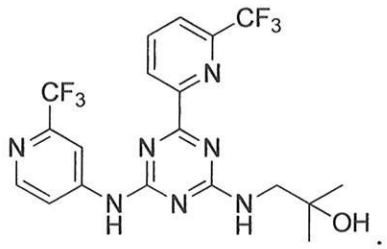
Claims

1. A compound having formula



or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound is:



3. A pharmaceutical composition comprising a compound of claim 1 or 2, and a pharmaceutically acceptable carrier.

4. The composition of claim 3, further comprising a second therapeutic agent useful in the treatment of cancer, characterized by the presence of an isocitrate dehydrogenase 2 mutation.

5. Use of a compound of claim 1 or 2 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 NADPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate in a patient.

6. The use of claim 5, wherein the IDH2 mutation is an IDH2 R140Q or R172K mutation.

7. The use of claim 6, wherein the IDH2 mutation is an IDH2 R140Q mutation.

8. The use of claim 5, wherein the cancer is selected from glioblastoma (or glioma), myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), acute myelogenous leukemia (AML), sarcoma, melanoma, non-small cell lung cancer, chondrosarcoma, cholangiocarcinomas or angioimmunoblastic non-Hodgkin's lymphoma (NHL), each characterized by the presence of an isocitrate dehydrogenase 2 mutation.

9. The use of claims 5, wherein the compound is to be administered in combination with a second therapeutic agent useful in the treatment of cancer, characterized by the presence of an isocitrate dehydrogenase 2 mutation.

10. The use of claim 8, wherein the cancer is an acute myelogenous leukemia characterized by the presence of an isocitrate dehydrogenase 2 mutation.

11. The use of claim 8, wherein the cancer is an acute myelogenous leukemia characterized by the presence of an isocitrate dehydrogenase 2 mutation, wherein the IDH2 mutation results in a new ability of the enzyme to catalyze the reduction of α-ketoglutarate to R(-)-2-hydroxyglutarate.

12. The use of claim 8, wherein the cancer is an acute myelogenous leukemia characterized by the presence of an IDH2 mutation, wherein the IDH2 mutation results in a new ability of the enzyme to catalyze the NADPH-dependent reduction of α-ketoglutarate to R(-)-2-hydroxyglutarate.