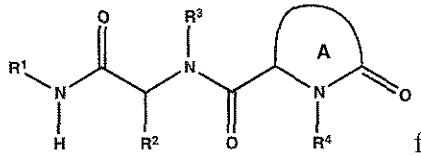
Claims

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;

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

2. The compound of claim 1 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof, 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;

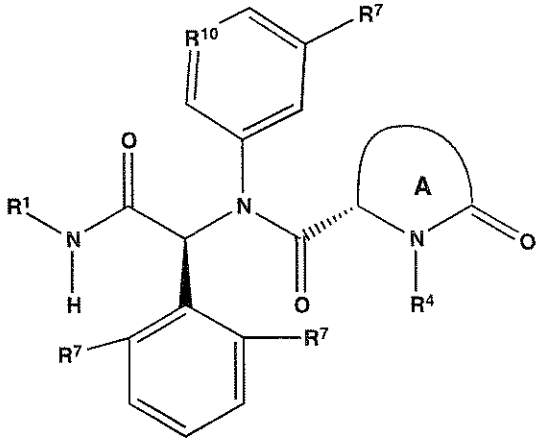
each R^5 and R^7 is independently halo; $-CF_3$; -CN; $-OR^6$;$-N(R^6)_2$; $-C(O)C_1$-C_4 alkyl; C_1-C_4 haloalkyl; C_1-C_4 alkyl optionally substituted with $-OR^6$ or $-N(R^6)_2$; $-O-C_1$-C_4 alkyl optionally

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;

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

3. The compound of claim 1 or 2 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof, 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 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof having formula II-a,

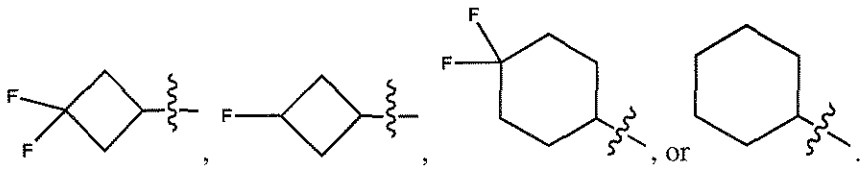


formula II-a

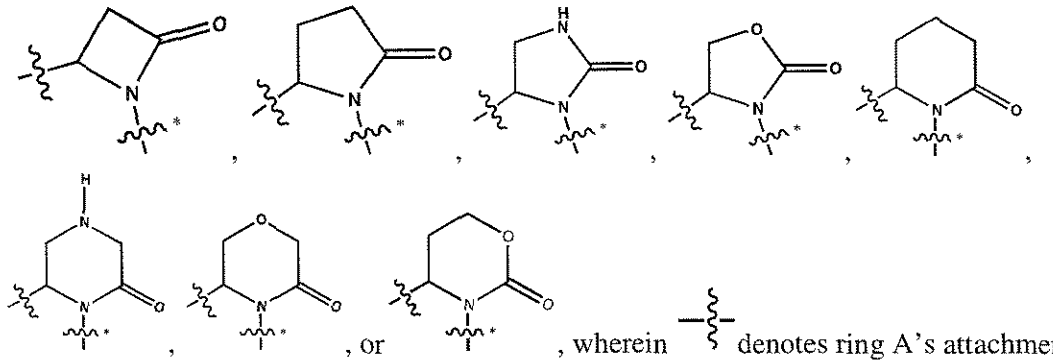
wherein R^{10} is CR^{11} or N; and R^{11} is -F, $-SO_2NH_2$, $-SO_2CH_3$, $-S(O)CH_3$, -CN, methoxy, $-OCH_2OH$, $-CH_2OH$, $-SO_2N(CH_3)_2$, $-SO_2NHCH_3$, $-NHSO_2CH_3$, $-CH_2CH_2OH$, $-N(CH_3)_2$, t-butyl, cyclopropyl, $-C(OH)(CH_3)_2$, $-OCF_3$, $-OCHF_2$, -O-cyclopropyl, -1-methyl-cyclopropyl,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

5. The compound of any one of claims 1-4 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof , 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 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof, wherein R^1 is

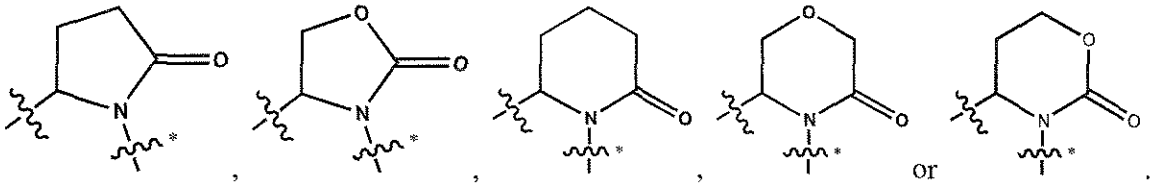


7. The compound of claim 5 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof, wherein ring A is:



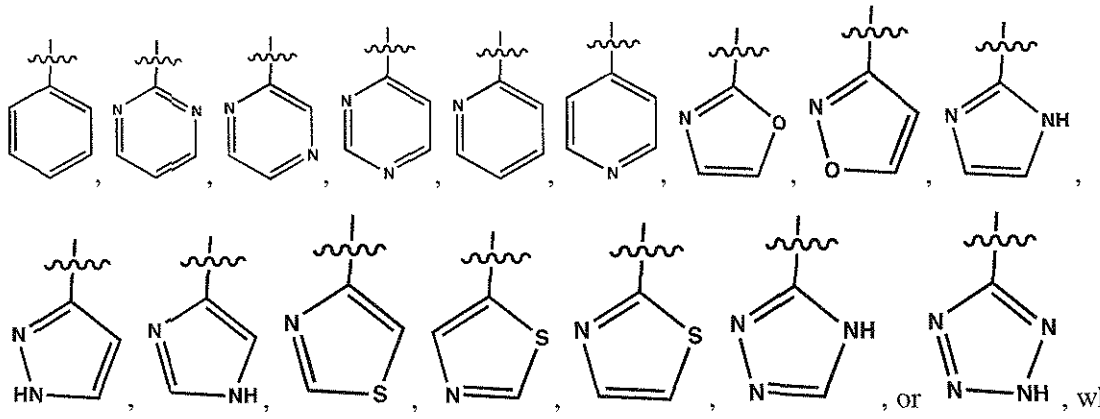
, wherein denotes ring A's attachment to the amide moiety of formula and  denotes ring A's attachment to R^4; and each member of ring A is optionally substituted with one or two R^5 groups.

8. The compound of claim 7 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof, wherein ring A is:



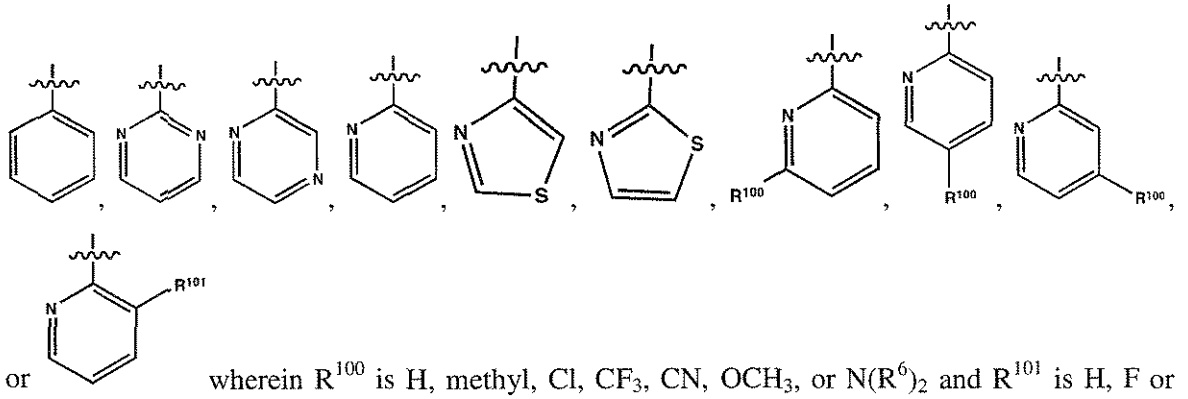
9. The compound of claim 7 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof, wherein R^4 is aryl or heteroaryl, each aryl or heteroaryl is optionally substituted with one to three R^7 groups.

10. The compound of claim 9 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof, wherein R^4 is:



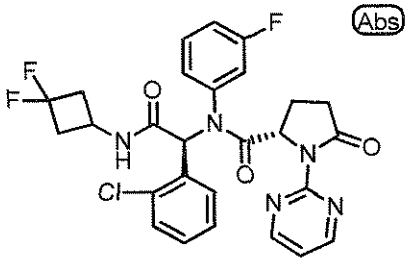
each member of R^4 is optionally substituted with one or two R^7 groups and each R^7 is independently F, Cl, methyl, CF_3, CN, OMe, or $N(R^6)_2$.

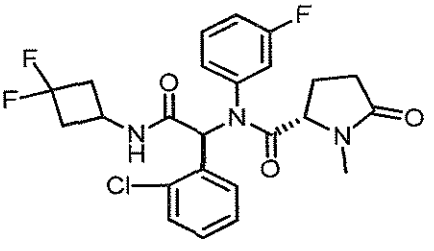
11. The compound of claim 10 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof, wherein R^4 is:

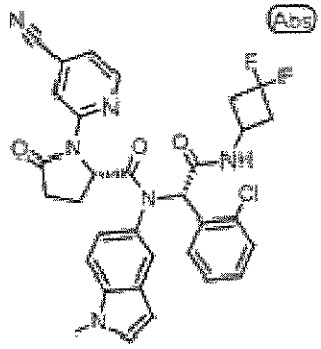


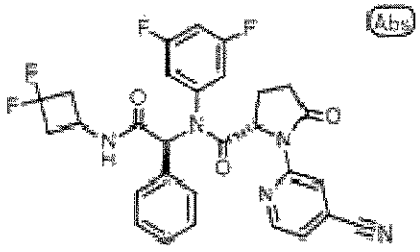
wherein R^{100} is H, methyl, Cl, CF_3, CN, OCH_3, or $N(R^6)_2$ and R^{101} is H, F or methyl.

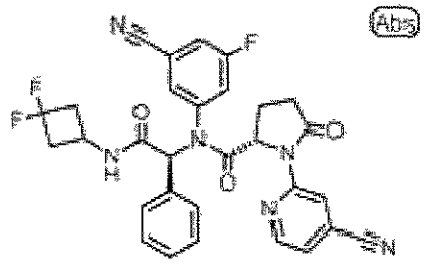
12. The compound of claim 1 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof selected from:

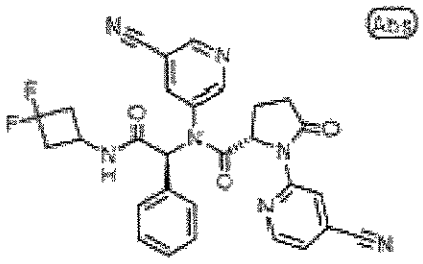






,


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or


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13. A pharmaceutical composition comprising a compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof; and a pharmaceutically acceptable carrier.

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

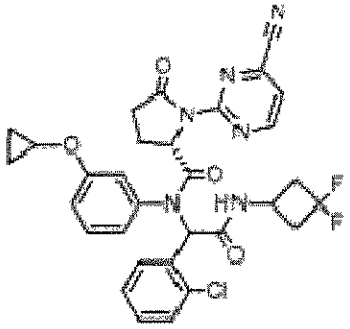
15. Use of a composition of claim 13 in the manufacture of a medicament for treating a cancer characterized by the presence of an IDH1 mutation, wherein the IDH1 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate in a patient.

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

17. The use 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), and colon cancer in a patient.

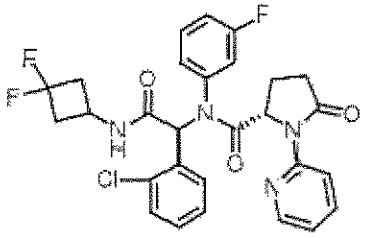
18. The use of claim 17, wherein the medicament is to be administered with a second therapeutic agent useful in the treatment of cancer.

19. The compound of claim 1, which is



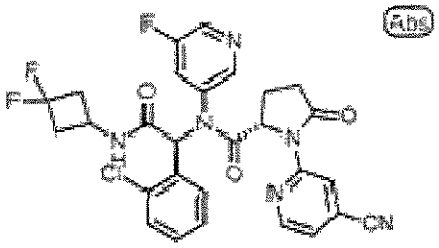
, or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof.

20. The compound of claim 1, which is



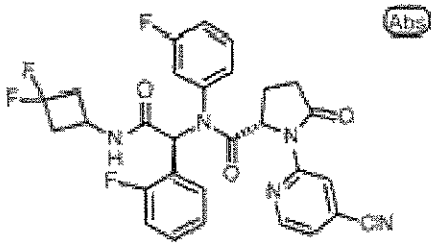
, or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof.

21. The compound of claim 1, which is



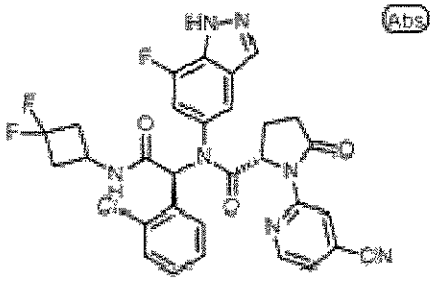
, or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof.

22. The compound of claim 1, which is



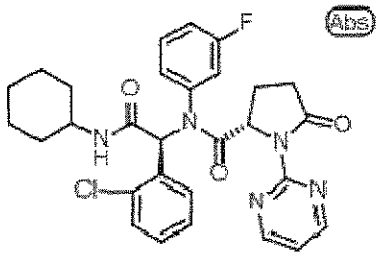
, or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof.

23. The compound of claims 1, which is



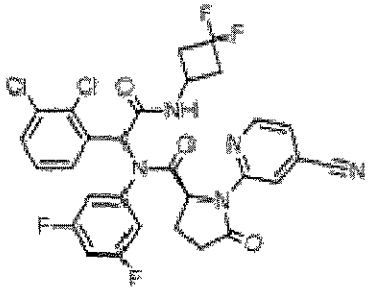
, or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof.

24. The compound of claim 1, which is



, or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof.

25. The compound of claim 1, which is



, or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof.