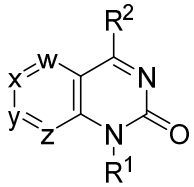
CLAIMS

1. A combination of a methionine adenosyltransferase II alpha (MAT2A) inhibitor and a protein arginine methyltransferase 5 (PRMT5) inhibitor for use in treating cancer in a subject in need thereof, wherein the MAT2A inhibitor is a compound of Formula (I):



(**I**)

or a pharmaceutically acceptable salt thereof;

wherein

w is CR^3 or N; x is CR^4 or N; y is CR^5 or N; and z is CR^6 or N, provided that no more than two of w, x, y, and z can be N, wherein:

R^3 is hydrogen;

R^5 is haloalkyl;

R^4 is hydrogen;

R^6 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfonyl, halo, haloalkyl, haloalkoxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, or dialkylaminocarbonyl;

R^1 is R^7 wherein R^7 is aryl optionally substituted with R^d, R^e, or R^f;

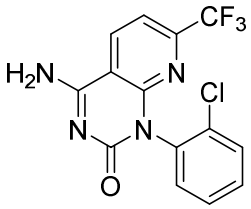
R^2 is $-NR^9R^{10}$;

R^9 is hydrogen or alkyl;

R^{10} is hydrogen or alkyl;

R^d, R^e, and R^f are each independently halo.

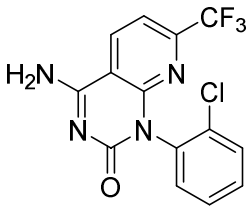
2. The combination for use of claim 1, wherein the MAT2A inhibitor is Compound A:



Compound A

or a pharmaceutically acceptable salt thereof.

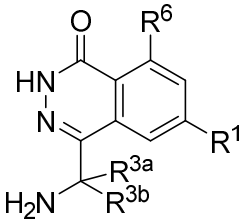
3. The combination for use of claim 1 or claim 2, wherein the MAT2A inhibitor is Compound A:



Compound A.

4. The combination for use of any one of claims 1 to 3, wherein the PRMT5 inhibitor binds in an MTA-uncompetitive or MTA-cooperative manner.

5. The combination for use of any one of claims 1 to 4, wherein the PRMT5 inhibitor is a compound a compound of Formula (III):



(**III**)

or a pharmaceutically acceptable salt thereof;

wherein

R^1 is hydrogen, halogen, hydroxyalkyl, -L-CN, -Y-C_1-C_5alkyl, -Y-cycloalkyl, -Y-heterocyclyl, -Y-aryl, -Y-arC_1-C_3alkyl or -Y-heteroaryl, wherein the cycloalkyl, the heterocyclyl, the aryl, and the heteroaryl portions are each optionally substituted with one or more R^2;

each Y is independently a bond or -NR^4-;

each R^2 is independently hydroxy, halogen, cyano, cyanomethyl, -$(NR^4)_2$, hydroxyalkyl, alkoxy, -SO_2C_1-C_3alkyl, -X-arC_1-C_3alkyl, heteroalkyl, C_2-C_4 alkynyl, -X-haloalkyl, -X-C_1-C_5 alkyl,
-Z-C_1-C_5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5;

each X is independently a bond, O, S, -NR^4- or -NR^4C(O)-

each Z is independently a bond, -SO-, -SO_2-, -CH(OH)- or -C(O)-;

each L is independently a bond or C_1-C_3 alkylene;

R^{3a} and R^{3b} are each independently hydrogen or deuterium, or R^{3a} and R^{3b} together are oxo;

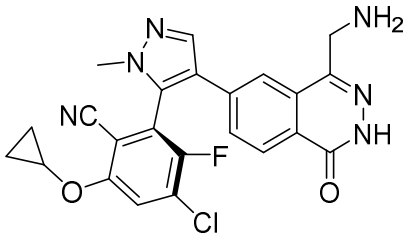
each R^4 is independently hydrogen or C_1- C_3 alkyl;

each R^5 is independently cyano, oxo, halogen, C_1-C_3 alkyl, hydroxyalkyl, alkoxy, -X-haloalkyl, -Z-cycloalkyl, -X-arC_1-C_3alkyl, X-ar C_1-C_3alkyl substituted with cyano -X-L-cycloalkyl,

-X-L-heteroaryl optionally substituted with one or more C_1-C_3alkyl or oxo, or -X-aryl; and

R^6 is hydrogen, halogen, C_1- C_3 alkyl, haloalkyl or alkoxy.

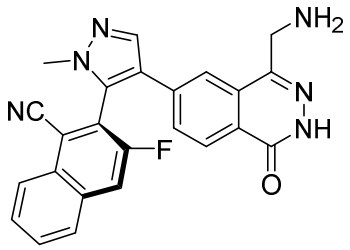
6. The combination for use of any one of claims 1 to 5, wherein the PRMT5 inhibitor is Compound C:



Compound C

or a pharmaceutically acceptable salt thereof.

7. The combination for use of any one of claims 1 to 5, wherein the PRMT5 inhibitor is Compound B:

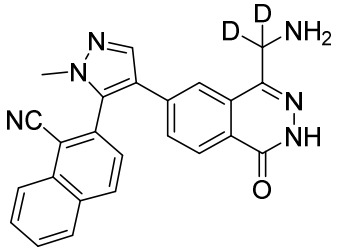


Compound B

or a pharmaceutically acceptable salt thereof.

8. The combination for use of claim 7, wherein Compound B is Compound B HCl.

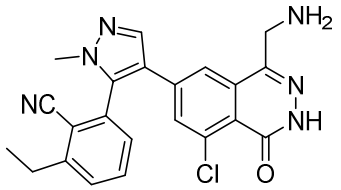
9. The combination for use of any one of claims 1 to 5, wherein the PRMT5 inhibitor is Compound D:



Compound D

or a pharmaceutically acceptable salt thereof.

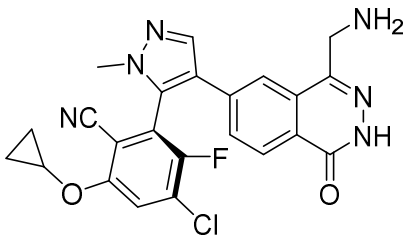
10. The combination for use of any one of claims 1 to 5, wherein the PRMT5 inhibitor is Compound E:



Compound E

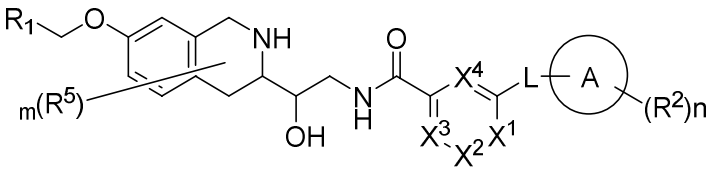
or a pharmaceutically acceptable salt thereof.

11. The combination for use of any one of claims 1 to 10, wherein the PRMT5 inhibitor is Compound C:



Compound C.

12. The combination for use of any one of claims 1 to 3, wherein the PRMT5 inhibitor is a compound a compound of Formula (II):



(**II**)

or a pharmaceutically acceptable salt thereof;

wherein

X^1, X^2, X^3, and X^4 are each independently N or CR^X;

L is a bond, -C(=O)-, -NH- or -O-;

Ring A is a carbocycle, heterocycle or a 5-6 membered monocyclic heteroaryl;

R^1 is a 5-6 membered heteroaryl substituted with 0-3 instances of R^4;

each R^2 is independently selected from =O, halo, -CN, -C_1-C_6 alkyl, -C_1-C_6 heteroalkyl, -C_1-C_6 haloalkyl, -C_3-C_9 carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, -OR^3, -$N(R^3)_2$, -$C(=O)R^3$, -

$C(=O)OR^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)0R^3$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$,$-S(=O)R^3$, $-S(=O)_2R^3$, $-SR^3$, $-S(=O)(=NR^3)R^3$, $-NR^3S(=O)_2R^3$ and $-S(=O)_2N(R^3)_2$;

each R^3 is independently selected from H, C_1-C_6 alkyl, -C_1-C_6 heteroalkyl, C_3-C_9 carbocyclyl, 3-7 membered heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, 5-6 membered heteroaryl, arylalkyl and heteroarylalkyl wherein each alkyl, carbocyclyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted;

each R^4 is independently selected from =O, halo, -CN, -C_1-C_6 alkyl, -C_1-C_6 heteroalkyl, -C_1-C_6 haloalkyl, -C_3-C_9 carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, cycloalkylalkyl, $-OR^3$, $-N(R^3)_2$, $-C(=O)R^3$, $-C(=O)OR^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$,$-S(=O)R^3$, $-S(=O)_2R^3$, $-SR^3$, $-S(=O)(=NR^3)R^3$, $-NR^3S(=O)_2R^3$ and $-S(=O)_2N(R^3)_2$;

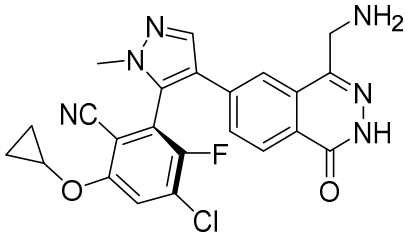
each R^x is independently selected from hydrogen, halo, -CN, -C_1-C_6 alkyl, -C_1-C_6 heteroalkyl, -C_1-C_6 haloalkyl, -C_3-C_9 carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, cycloalkylalkyl, $-OR^3$, $-N(R^3)_2$, $-C(=O)R^3$, $-C(=O)OR^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)0R^3$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$,$-S(=O)R^3$, $-S(=O)_2R^3$, $-SR^3$, $-S(=O)(=NR^3)R^3$, $-NR^3S(=O)_2R^3$ and $-S(=O)_2N(R^3)_2$ wherein each alkyl, carbocyclyl, heterocyclyl, heterocyclylalkyl, cycloalkylalkyl is optionally substituted;

each R^5 is independently selected from =O, halo, -CN, -C_1-C_6 alkyl, -C_1-C_6 heteroalkyl, -C_1-C_6 haloalkyl, -C_3-C_9 carbocyclyl, 3-10 membered heterocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, $-OR^3$, $-N(R^3)_2$, $-C(=O)R^3$, $-C(=O)OR^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)0R^3$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$,$-S(=O)R^3$, $-S(=O)_2R^3$, $-SR^3$, $-S(=O)(=NR^3)R^3$, $-NR^3S(=O)_2R^3$, $-S(=O)_2N(R^3)_2$, or two R^5 can be taken together with the atoms to which they are attached to form a -C_3-C_9 carbocyclyl or a 3-10 membered heterocyclyl;

m is 0, 1, 2 or 3; and

n is 0, 1, 2 or 3.

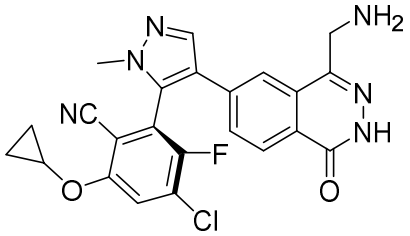
13. A combination of a protein arginine methyltransferase 5 (PRMT5) inhibitor and a methionine adenosyltransferase II alpha (MAT2A) inhibitor for use in treating cancer in a subject in need thereof, wherein PRMT5 inhibitor is Compound C:



Compound C

or a pharmaceutically acceptable salt thereof.

14. The combination for use of claim 13, wherein the PRMT5 inhibitor is Compound C:



Compound C.

15. The combination for use of any one of claims 1 to 14, wherein the cancer is characterized by a reduction or absence of MTAP gene expression, an absence of the MTAP gene, a reduced function of MTAP protein, a reduced level of MTAP protein, a MTA accumulation, an absence of MTAP protein, or a combination thereof.

16. The combination for use of any one of claims 1 to 15, wherein the cancer is selected from the group consisting of leukemia, glioma, melanoma, pancreatic cancer, non-small cell lung cancer, bladder cancer, astrocytoma, osteosarcoma, head and neck cancer, myxoid chondrosarcoma, ovarian cancer, endometrial cancer, breast cancer, soft tissue sarcoma, non-Hodgkin lymphoma, lung cancer, esophageal cancer, gastric cancer, kidney cancer, hepatocellular carcinoma, myelomas, glioblastoma, uterine cancer, and mesothelioma.

17. The combination for use of any one of claims 1 to 16, wherein the cancer is a solid tumor.

18. The combination for use of any one of claims 1 to 17, wherein MAT2A inhibitor and PRMT5 inhibitor are administered concurrently or sequentially.