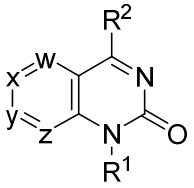
CLAIMS

1. A methionine adenosyltransferase II alpha (MAT2A) inhibitor for use in treating cancer in a subject in need thereof, wherein the MAT2A inhibitor is administered in combination with a protein arginine methyltransferase 5 (PRMT5) inhibitor; and 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, alkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, halo, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyloxy, cyano, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, hydroxyalkyl, hydroxyalkoxy, hydroxyalkylamino, alkoxyalkyl, alkoxyalkoxy, alkoxyalkylamino, aminoalkyl, aminoalkoxy, aminoalkylamino, heteroaryl, heteroaryloxy, heteroaralkyloxy, heteroarylamino, heterocyclyl, heterocyclyloxy, heterocyclylamino, heterocyclylalkyloxy, heterocyclyloxyalkoxy, or heterocyclyloxyalkylamino, wherein heterocyclyl or heteroaryl, by itself or as part of another group, is unsubstituted or substituted with R^a, R^b, and/or R^c independently selected from alkyl, cycloalkyl, haloalkyl, haloalkoxy, alkoxy, hydroxy, halo, cyano, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, or aminoalkyl;

R^5 is alkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, halo, haloalkyl, haloalkoxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, hydroxyalkyl, hydroxyalkoxy, hydroxyalkylamino, alkoxyalkyl, alkoxyalkoxy, alkoxyalkylamino, aminoalkyl, aminoalkoxy, aminoalkylamino, heteroaryl, heteroaryloxy, heteroarylamino, heterocyclyl, heterocyclyloxy, heterocyclylamino, heterocyclyloxyalkoxy, or heterocyclyloxyalkylamino, wherein heterocyclyl or heteroaryl, by itself or as part of another group, is unsubstituted or substituted with R^a, R^b, and/or R^c independently selected from alkyl, cycloalkyl, haloalkyl, haloalkoxy, alkoxy, hydroxy, halo, cyano, hydroxyalkyl, alkoxyalkyl, or aminoalkyl;

R^4 and R^6 are independently 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 cycloalkyl, bridged cycloalkyl, fused cycloalkyl, spirocycloalkyl, aryl, heteroaryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, and morpholinyl, bridged heterocyclyl, fused heterocyclyl, or spiroheterocyclyl, wherein aryl, heteroaryl, or heterocyclyl is unsubstituted or substituted with R^d, R^e, and/or R^f;

R^2 is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl, aminosulfonylalkyl, -O-R^8, -NR^9R^{10}, or -X^b-R^{11};

R^8 is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, cycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, bridged cycloalkyl, bridged cycloalkylalkyl, fused cycloalkyl, spirocycloalkyl, spirocycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, heterocyclyloxyalkyl, fused heterocyclyl, fused heterocyclylalkyl, bridged heterocyclyl, bridged heterocyclylalkyl, spiroheterocyclyl, or spiroheterocyclylalkyl, wherein aryl, heteroaryl, or heterocyclyl, by itself or as part of another group, is unsubstituted or substituted with R^g, R^h, and/or R^i;

R^9 is hydrogen, alkyl, deuteroalkyl, or cycloalkyl;

R^{10} is hydrogen, alkyl, deuteroalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, haloalkoxyalkyl, aminoalkyl, aminosulfonylalkyl, thioureidoalkyl, alkylsulfonyl, alkylsulfonylalkyl, cyanoalkyl, alkylcarbonyl, alkoxycarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonylalkyl, cycloalkyl, cycloalkylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, cycloalkoxyalkyl, bridged cycloalkyl, bridged cycloalkylalkyl, fused cycloalkyl, spirocycloalkyl, spirocycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heteroarylcarbonyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, heterocyclyloxyalkyl, fused heterocyclyl, fused heterocyclylalkyl, bridged heterocyclyl, bridged heterocyclylalkyl, spiroheterocyclyl, or spiroheterocyclylalkyl, wherein aryl, heteroaryl, or heterocyclyl, by itself or as part of another group, is unsubstituted or substituted with R^j, R^k, and/or R^l;

X^b is a bond or alkylene;

R^{11} is cycloalkyl, bridged cycloalkyl, fused cycloalkyl, spirocycloalkyl, monocyclic heteroaryl, oxetanyl, azetidinyl, 2-oxoazetidinyl, pyrrolidinyl, 2-oxopyrrolidinyl, piperidinyl, morpholinyl, bridged heterocyclyl, fused heterocyclyl, or spiroheterocyclyl, wherein heteroaryl or heterocyclyl is unsubstituted or substituted with R^m, R^n, and/or R^o;

R^d, R^e, R^g, R^h, R^j, R^k, R^m, and R^n are independently selected from alkyl, haloalkyl, haloalkoxy, alkoxy, hydroxy, alkylsulfonyl, halo, cyano, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aminosulfonyl, alkylaminosulfonyl,

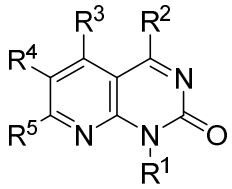
dialkylaminosulfonyl, sulfonylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, heterocyclylcarbonyl, and ureido;

R^f, R^i, R^l, and R^o are independently selected from alkyl, cycloalkyl, haloalkyl, haloalkoxy, alkoxy, hydroxy, halo, amino, alkylamino, cycloalkylsulfonylamino, cyano, cyanoalkyl, alkoxycarbonylalkyl, carboxyalkyl, or -X^c-R^{12} where X^c is bond, alkylene, or heteroalkylene; and

R^{12} is optionally substituted aryl, or optionally substituted heteroaryl,

provided that when R^1 is pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, or morpholinyl then R^f is not hydroxy

2. The MAT2A inhibitor for use of claim 1, wherein the MAT2A inhibitor is a compound of Formula (IIId):



(**IIId**)

or a pharmaceutically acceptable salt thereof.

3. The MAT2A inhibitor for use of claim 1 or 2, wherein

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;

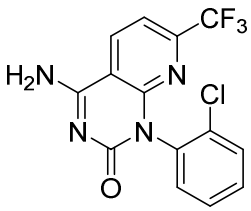
R^3 is hydrogen;

R^4 is hydrogen;

R^5 is haloalkyl; and

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

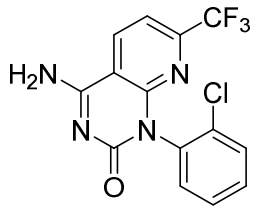
4. The MAT2A inhibitor for use of any one of claims 1 to 3, wherein the MAT2A inhibitor is Compound A:



Compound A

or a pharmaceutically acceptable salt thereof.

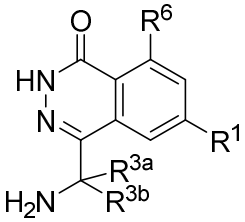
5. The MAT2A inhibitor for use of any one of claims 1 to 4, wherein the MAT2A inhibitor is Compound A:



Compound A.

6. The MAT2A inhibitor for use of claim 1, wherein the MAT2A inhibitor is selected from the group consisting of a compound from Table 1, or a pharmaceutically acceptable salt thereof.

7. The MAT2A inhibitor for use of any one of claims 1 to 6, 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;

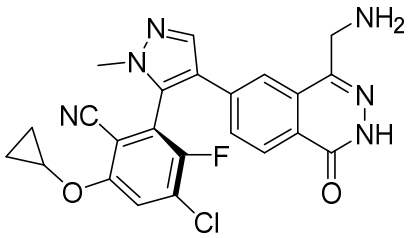
each R^4 is independently hydrogen or C_1- C_3 alkyl;

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.

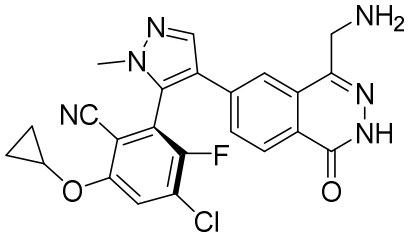
8. The MAT2A inhibitor for use of any one of claims 1 to 7, wherein the PRMT5 inhibitor is Compound C:



Compound C

or a pharmaceutically acceptable salt thereof.

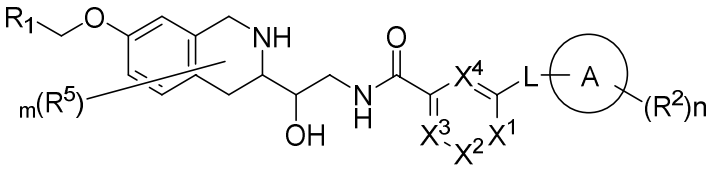
9. The MAT2A inhibitor for use of any one of claims 1 to 8, wherein the PRMT5 inhibitor is Compound C:



Compound C.

10. The MAT2A inhibitor for use of any one of claims 1 to 7, wherein the PRMT5 inhibitor is selected from the group consisting of a compound from Table 3 or a pharmaceutically acceptable salt thereof.

11. The MAT2A inhibitor for use of any one of claims 1 to 6, 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;

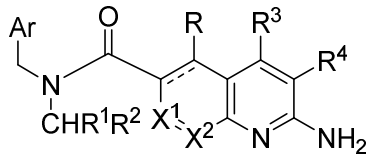
each R^5 is independently selected from =O, halo, -CN, -C_1-C_6 alkyl, -C_1-C_6 heteroalkyl, -C_1-C_6 haloalkyl, -C_3-C_9 carbocyclyl, 3-10 membered heterocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, -OR^3, -$N(R^3)_2$, -$C(=O)R^3$, -$C(=O)OR^3$, -$NR^3C(=O)R^3$, -$NR^3C(=O)0R^3$, -$C(=O)N(R^3)_2$, -$OC(=O)N(R^3)_2$,-$S(=O)R^3$, -$S(=O)_2R^3$, -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.

12. The MAT2A inhibitor for use of any one of claims 1 to 6, wherein the PRMT5 inhibitor is a compound a compound of Formula (IV):



(**IV**)

or a pharmaceutically acceptable salt thereof;

wherein

X^1 and X^2 are both in each instance independently N or C; wherein if X^1 is C it can be optionally substituted with halo or C_{1-6}alkyl;

Ar is a six membered aromatic ring having 0-2 N atoms, wherein each Ar could be independently substituted with 0-2 R^a groups;

wherein R^a is in each instance independently selected from cyano, halo, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, OR^b, NR^cR^d, -$C(O)NR^cR^d$, =S, -SO_2, -SO_2C_{1-6}alkyl, -C(O)H, -$C(O)C_{1-6}$ alkyl, $C(O)OC_{1-6}$ alkyl, difluoro-pyrrolidinyl, and 4 to 6-membered heterocyclic ring, with 0-2 heteroatoms independently selected from O and N, and which heterocyclic ring can be further independently substituted with 0-2 halogen, C_{1-6} alkyl, -C(O)H, -$C(O)C_{1-6}$ alkyl or optionally substituted cycloalcoxyl;

wherein each R^b is in each instance independently selected from H, optionally substituted C_{1-6} alkyl, wherein the substituents can be selected from halo; or oxetanyl;

wherein each R^c and R^d is independently selected from H, C_{1-3}alkyl, C_{1-3} haloalkyl or -CO;

wherein R^e in each instance is selected from H or C_{1-6} alkyl;

wherein R^f and R^g in each instance is independently selected from H and C_{1-6}alkyl;

wherein R is H or methyl;

wherein R^1 and R^2 are in each instance is independently selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkynyl, -$C(OR^e)$, optionally substituted single and double cyclyl having 0-3 N, S or O atoms; wherein the

substituents are selected from halo, optionally substituted C_{1-6}alkyl, -$C(O)NR^fR^g$, OH and an optionally substituted 5-membered ring having 0-3 N atoms;

or R^1 and R^2 and the carbon atom to which they are attached can form an optionally substituted single or double carbocyclic or heterocyclic ring, which may be saturated,

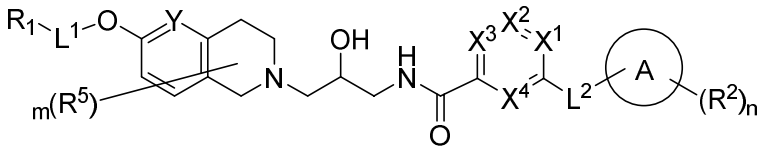
partially saturated or aromatic and further wherein the heterocyclic ring includes 1, 2 or 3 heteroatoms independently selected from N, O, and S;

wherein the substituents are selected from the group of optionally substituted C_{1-6} alkyl, halo, CN, OR^e and -C(OR^e),

provided that R^1 and R^2 are not both H at the same time;

and wherein R^3 and R^4 are in each instance independently selected from H, halogen, alkynyl, cyano and C_{1-6} alkyl, optionally substituted with halo or deuterium.

13. The MAT2A inhibitor for use of any one of claims 1 to 6, wherein the PRMT5 inhibitor is a compound a compound of Formula (V):



(**V**)

or a pharmaceutically acceptable salt thereof;

wherein

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

Y is N, CH or CR^5;

L^1 is a bond or C_1-C_4-alkylene substituted with 0-2 instances of R^6;

L^2 is a bond, --NH-- or --O--;

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

R^1 is a 3-7 membered carbocycle, a 4-7 membered heterocycle or 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, -- C_3-C_9 heterocyclyl, heterocyclylalkyl, cycloalkylalkyl, --OR^3, --$N(R^3)_2$, --C(=O)R^3, --C(=O)R^3, --CH_2C(=O)R^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^3 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_7 carbocyclyl, C_3-C_7 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, --C_3-C_9 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, --C_3-C_9 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, --$S(=O)(=NR^3)R^3$, --$NR^3S(=O)R^3$ and --$S(=O)_2N(R^3)_2$ wherein each alkyl, carbocyclyl, heterocyclyl, heterocyclylalkyl, cycloalkylalkyl is optionally substituted;

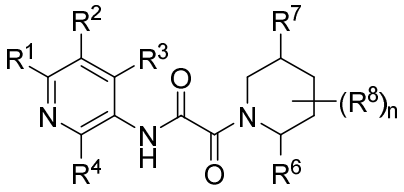
each R^5 is independently selected from =O, halo, --CN, --C_1-C_6 alkyl, --C_1-C_6 heteroalkyl, --C_1-C_6 haloalkyl, --C_3-C_9 carbocyclyl, --C_3-C_9 heterocyclyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, --OR^3, --$N(R^3)_2$, --$C(=O)R^3$, --$C(=O)OR^3$, --$NR^3C(=O)R^3$, --$NR^3C(=O)OR^3$, --$C(=O)N(R^3)_2$, --$OC(=O)N(R^3)_2$, --$S(=O)R^3$, --$S(=O)_2R^3$, --SR^3, --$S(=O)(=NR^3)R^3$, --$NR^3S(=O)_2R^3$, --$S(=O)_2N(R^3)_2$, or two R^5 can be taken together with the atoms to which they are attached to form a C_3-C_9 carbocycle or a C_3-C_9 heterocycle;

each R^6 is independently selected from halo, --C_1-C_4 alkyl, --C_1-C_4 haloalkyl, --OC_1-C_4 alkyl, --OC_1-C_4 haloalkyl, or two R^6 can be taken together with the atoms to which they are attached to form a C_3-C_7 carbocycle or a C_3-C_7 heterocycle;

m is 0, 1, 2 or 3; and

n is 0, 1, 2 or 3.

14. The MAT2A inhibitor for use of any one of claims 1 to 6, wherein the PRMT5 inhibitor is a compound a compound of Formula (VI):



(**VI**)

or a pharmaceutically acceptable salt thereof;

wherein

each R^1 is independently selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a1}, –$N(R^{a1})_2$, –$C(=O)R^{a1}$, –$C(=O)OR^{a1}$, –$NR^{a1}C(=O)R^{a1}$, –$NR^{a1}C(=O)OR^{a1}$, –$C(=O)N(R^{a1})_2$, –$OC(=O)N(R^{a1})_2$,-$S(=O)R^{a1}$, – $S(=O)_2R^{a1}$, –SR^{a1}, –$S(=O)(=NR^{a1})R^{a1}$, –$NR^{a1}S(=O)_2R^{a1}$ and –$S(=O)_2N(R^{a1})_2$;

each R^2 is independently selected from halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_1–C_6 haloalkoxy, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a2}, –$N(R^{a2})_2$, –$C(=O)R^{a2}$, –$C(=O)OR^{a2}$, –$NR^{a2}C(=O)R^{a2}$, –$NR^{a2}C(=O)OR^{a2}$, –$C(=O)N(R^{a2})_2$, –$C(=O)N(OR^{a2})(R^{a2})$, –$OC(=O)N(R^{a2})_2$,-$S(=O)R^{a2}$, –$S(=O)_2R^{a2}$, –SR^{a2}, –$S(=O)(=NR^{a2})R^{a2}$, –$NR^{a2}S(=O)_2R^{a2}$ and –$S(=O)_2N(R^{a2})2$;

each R^3 is independently selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a3}, –$N(R^{a3})_2$, –$C(=O)R^{a3}$, –$C(=O)OR^{a3}$, –$NR^{a3}C(=O)R^{a3}$, –$NR^{a3}C(=O)OR^{a3}$, –$C(=O)N(R^{a3})_2$, –$OC(=O)N(R^{a3})_2$,-$S(=O)R^{a3}$, – $S(=O)_2R^{a3}$, –SR^{a3}, –$S(=O)(=NR^{a3})R^{a3}$, –$NR^{a3}S(=O)_2R^{a3}$ and –$S(=O)_2N(R^{a3})_2$;

each R^4 is independently selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a4}, –$N(R^{a4})_2$, –$C(=O)R^{a4}$, –$C(=O)OR^{a4}$, –$NR^{a4}C(=O)R^{a4}$, –$NR^{a4}C(=O)OR^{a4}$, –$C(=O)N(R^{a4})_2$, –$OC(=O)N(R^{a4})_2$, –$S(=O)R^{a4}$, –$S(=O)_2R^{a4}$, –SR^{a4}, –$S(=O)(=NR^{a4})R^{a4}$, –$NR^{a4}S(=O)2R^{a4}$ and –$S(=O)_2N(R^{a4})_2$;

each R^6 is independently absent or selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C6–C10 aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a6}, –$N(R^{a6})_2$, –$C(=O)R^{a6}$, –$C(=O)OR^{a6}$, –$NR^{a6}C(=O)R^{a6}$, –$NR^{a6}C(=O)OR^{a6}$, –$C(=O)N(R^{a6})_2$, –$OC(=O)N(R^{a6})_2$,-$S(=O)R^{a6}$, –$S(=O)_2R^{a6}$, –SR^{a6}, –$S(=O)(=NR^{a6})R^{a6}$, – $NR^{a6}S(=O)_2R^{a6}$ and –$S(=O)_2N(R^{a6})_2$, wherein each alkyl, carbocyclyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position;

each R^7 is independently absent or selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C1– C6 hydroxyalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, 5-6-membered monocyclic heteroaryl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a7}, –$N(R^{a7})_2$, –$C(=O)R^{a7}$, –$C(=O)OR^{a7}$, –$NR^{a7}C(=O)R^{a7}$, –$NR^{a7}C(=O)OR^{a7}$, –$C(=O)N(R^{a7})_2$, –$OC(=O)N(R^{a7})_2$,-$S(=O)R^{a7}$, –$S(=O)_2R^{a7}$, –SR^{a7}, –$S(=O)(=NR^{a7})R^{a7}$, –$NR^{a7}S(=O)_2R^{a7}$ and – $S(=O)_2N(R^{a7})_2$;

each R^8 is independently selected from H, –D, =O, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a8}, –$N(R^{a8})_2$, –$C(=O)R^{a8}$, –$C(=O)OR^{a8}$, –$NR^{a8}C(=O)R^{a8}$, –$NR^{a8}C(=O)OR^{a8}$, –$CH_2C(=O)N(R^{a8})_2$ –$C(=O)N(R^{a8})_2$, –$OC(=O)N(R^{a8})_2$, –CH2C(=O)$N(R^{a8})_2$,-$S(=O)R^{a8}$, –$S(=O)_2R^{a8}$, –SR^{a8}, –$S(=O)(=NR^{a8})R^{a8}$, –$NR^{a8}S(=O)_2R^{a8}$ and –$S(=O)_2N(R^{a8})_2$ wherein two instances of R^8 together with the atom or atoms to which they are attached can be taken together to form a 3-10 member cycloalkyl or

heterocyclyl ring (e.g., a ring that together with the piperidine ring of Structure I can form a bridged, fused or spiro bicyclic heterocyclic ring);

each R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a6}, R^{a7} and R^{a8} is independently selected from H, C_1–C_6 alkyl, – C_1–C_6 heteroalkyl, C_3–C_9 cycloalkyl, 3-7 membered heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, 5-6 membered heteroaryl, arylalkyl and heteroarylalkyl wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position (e.g., substituted with 0, 1, 2 or 3 instances of R^9, wherein each R^9 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 cycloalkyl, 3-10 membered heterocyclyl, C6–C10 aryl, 5-10 membered heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, – OR^b, –$N(R^b)_2$, –$C(=O)R^b$, –$C(=O)OR^b$, –$NR^bC(=O)R^b$, –$NR^bC(=O)OR^b$, –$C(=O)N(R^b)_2$, – $OC(=O)N(R^b)_2$,-$S(=O)R^b$, –$S(=O)_2R^b$, –SR^b, –$S(=O)(=NR^b)R^b$, –$NR^bS(=O)_2R^b$ and – $S(=O)_2N(R^b)_2$, wherein each R^b is independently selected from H, –C_1–C_6 alkyl (e.g., –Me, –Et, –Pr, –^{i}Pr,–^{n}Bu, –^{t}Bu, –sec-Bu, –iso-Bu)), and C_3–C_9 cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl); and

n is 0, 1, 2 or 3;

provided that:

(i) when R^1 is H, R^2 is not halo, –OPr, –$N(CH_3)_2$ or –CF_3;

(ii) when R^1 is OR^{a1}, R^2 is not –OR^{a2};

(iii) when R^1 is H and R^2 is –CH3, R^8 groups cannot be taken together to form a ring and R^6 is not absent or H, and is not thiazolyl, furanyl or pyrrolyl;

(iv) when R^2 is Me, R^1 is not optionally substituted piperidine

(v) the compound is not:

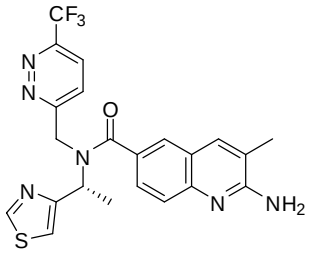
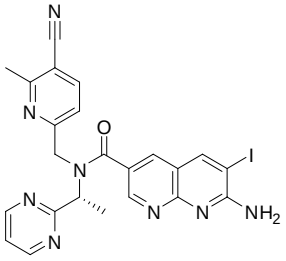
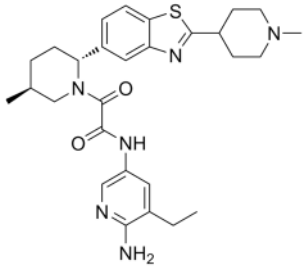
A. 5-(2-(5-methyl-2-(p-tolyl)piperidin-1-yl)-2-oxoacetamido)nicotinamide or any of its enantiomers or diastereomers;

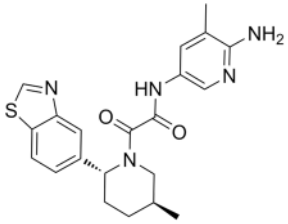
B. 2-(2-(4-(2H-tetrazol-5-yl)phenyl)-5-methylpiperidin-1-yl)-N-(5,6-dimethylpyridin- 3-yl)-2-oxoacetamide or any of its enantiomers or diastereomers;

C. 2-cyano-5-(2-(5-methyl-2-phenylpiperidin-1-yl)-2-oxoacetamido)nicotinamide or any of its enantiomers or diastereomers.

15. The MAT2A inhibitor for use of any one of claims 1 to 6, wherein the PRMT5 inhibitor is selected from the group consisting of a compound from Table 2, Table 4, Table 5, Table 6, and Table 11, or a pharmaceutically acceptable salt thereof.

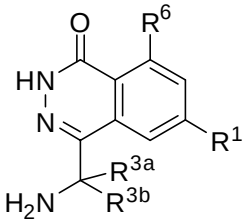
16. The MAT2A inhibitor for use of any one of claims 1 to 6, wherein the PRMT5 inhibitor is a compound selected from the group consisting of




, and


,

or a pharmaceutically acceptable salt thereof.

17. A protein arginine methyltransferase 5 (PRMT5) inhibitor for use in treating cancer in a subject in need thereof, wherein the PRMT5 inhibitor is administer in combination with a methionine adenosyltransferase II alpha (MAT2A) inhibitor; and the PRMT5 inhibitor is 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;

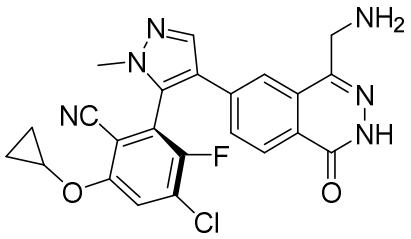
R^{3a} and R^{3b} are each independently hydrogen or deuterium, or R^{3a} and R^{3b} together are oxo;

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.

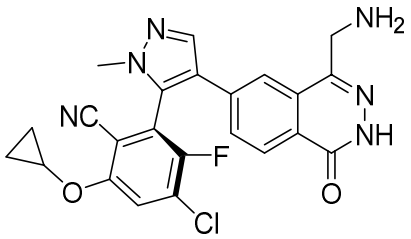
18. The PRMT5 inhibitor for use of claim 17, wherein the PRMT5 inhibitor is Compound C:



Compound C

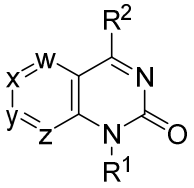
or a pharmaceutically acceptable salt thereof.

19. The PRMT5 inhibitor for use of claim 17, wherein the PRMT5 inhibitor is Compound C:



Compound C.

20. The PRMT5 inhibitor for use of any one of claims 17 to 19, wherein the methionine adenosyltransferase II alpha (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, alkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, halo, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyloxy, cyano, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, hydroxyalkyl, hydroxyalkoxy, hydroxyalkylamino, alkoxyalkyl, alkoxyalkoxy, alkoxyalkylamino, aminoalkyl, aminoalkoxy, aminoalkylamino, heteroaryl, heteroaryloxy, heteroaralkyloxy, heteroarylamino, heterocyclyl, heterocyclyloxy, heterocyclylamino, heterocyclylalkyloxy, heterocyclyloxyalkoxy, or heterocyclyloxyalkylamino, wherein heterocyclyl or heteroaryl, by itself or as part of another group, is unsubstituted or substituted with R^a, R^b, and/or R^c independently selected from alkyl, cycloalkyl, haloalkyl, haloalkoxy, alkoxy, hydroxy, halo, cyano, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, or aminoalkyl;

R^5 is alkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, halo, haloalkyl, haloalkoxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, hydroxyalkyl, hydroxyalkoxy, hydroxyalkylamino, alkoxyalkyl, alkoxyalkoxy, alkoxyalkylamino, aminoalkyl, aminoalkoxy, aminoalkylamino, heteroaryl, heteroaryloxy, heteroarylamino, heterocyclyl, heterocyclyloxy, heterocyclylamino, heterocyclyloxyalkoxy, or heterocyclyloxyalkylamino, wherein heterocyclyl or heteroaryl, by itself or as part of another group, is unsubstituted or substituted with R^a, R^b, and/or R^c independently selected from alkyl, cycloalkyl, haloalkyl, haloalkoxy, alkoxy, hydroxy, halo, cyano, hydroxyalkyl, alkoxyalkyl, or aminoalkyl;

R^4 and R^6 are independently 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 cycloalkyl, bridged cycloalkyl, fused cycloalkyl, spirocycloalkyl, aryl, heteroaryl, hetercyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, and morpholinyl, bridged heterocyclyl, fused heterocyclyl, or spiroheterocyclyl, wherein aryl, heteroaryl, or heterocyclyl is unsubstituted or substituted with R^d, R^e, and/or R^f;

R^2 is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl, aminosulfonylalkyl, -O-R^8, -NR^9R^{10}, or -X^b-R^{11};

R^8 is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, cycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, bridged cycloalkyl, bridged cycloalkylalkyl, fused cycloalkyl, spirocycloalkyl, spirocycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, heterocyclyloxyalkyl, fused heterocyclyl, fused heterocyclylalkyl, bridged heterocyclyl, bridged heterocyclylalkyl, spiroheterocyclyl, or spiroheterocyclylalkyl, wherein aryl, heteroaryl, or heterocyclyl, by itself or as part of another group, is unsubstituted or substituted with R^g, R^h, and/or R^i;

R^9 is hydrogen, alkyl, deuteroalkyl, or cycloalkyl;

R^{10} is hydrogen, alkyl, deuteroalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, haloalkoxyalkyl, aminoalkyl, aminosulfonylalkyl, thioureidoalkyl, alkylsulfonyl, alkylsulfonylalkyl, cyanoalkyl, alkylcarbonyl, alkoxycarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonylalkyl, cycloalkyl, cycloalkylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, cycloalkoxyalkyl, bridged cycloalkyl, bridged cycloalkylalkyl, fused cycloalkyl, spirocycloalkyl, spirocycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heteroarylcarbonyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, heterocyclyloxyalkyl, fused heterocyclyl, fused heterocyclylalkyl, bridged heterocyclyl, bridged heterocyclylalkyl, spiroheterocyclyl, or spiroheterocyclylalkyl, wherein aryl, heteroaryl, or heterocyclyl, by itself or as part of another group, is unsubstituted or substituted with R^j, R^k, and/or R^l;

X^b is a bond or alkylene;

R^{11} is cycloalkyl, bridged cycloalkyl, fused cycloalkyl, spirocycloalkyl, monocyclic heteroaryl, oxetanyl, azetidinyl, 2-oxoazetidinyl, pyrrolidinyl, 2-oxopyrrolidinyl, piperidinyl, morpholinyl, bridged heterocyclyl, fused heterocyclyl, or spiroheterocyclyl, wherein heteroaryl or heterocyclyl is unsubstituted or substituted with R^m, R^n, and/or R^o;

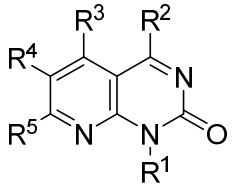
R^d, R^e, R^g, R^h, R^j, R^k, R^m, and R^n are independently selected from alkyl, haloalkyl, haloalkoxy, alkoxy, hydroxy, alkylsulfonyl, halo, cyano, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, sulfonylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, heterocyclylcarbonyl, and ureido;

R^f, R^i, R^l, and R^o are independently selected from alkyl, cycloalkyl, haloalkyl, haloalkoxy, alkoxy, hydroxy, halo, amino, alkylamino, cycloalkylsulfonylamino, cyano, cyanoalkyl, alkoxycarbonylalkyl, carboxyalkyl, or -X^c-R^{12} where X^c is bond, alkylene, or heteroalkylene; and

R^{12} is optionally substituted aryl, or optionally substituted heteroaryl,

provided that when R^1 is pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, or morpholinyl then R^f is not hydroxy.

21. The PRMT5 inhibitor for use of any one of claims 17-20, wherein the MAT2A inhibitor is a compound of Formula (IIId):



(**IIId**)

or a pharmaceutically acceptable salt thereof.

22. The PRMT5 inhibitor for use of any one of claims 17 to 21, wherein

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;

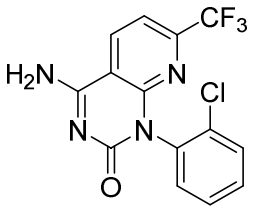
R^3 is hydrogen;

R^4 is hydrogen;

R^5 is haloalkyl; and

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

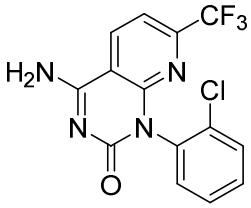
23. The PRMT5 inhibitor for use of any one of claims 17 to 22, wherein the MAT2A inhibitor is Compound A:



Compound A

or a pharmaceutically acceptable salt thereof.

24. The PRMT5 inhibitor for use of any one of claims 17 to 23, wherein the MAT2A inhibitor is Compound A:



Compound A.

25. The MAT2A or PRMT5 inhibitor for use of any one of claims 1 to 24, 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.

26. The MAT2A or PRMT5 inhibitor for use of any one of claims 1 to 25, 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.

27. The MAT2A or PRMT5 inhibitor for use of any one of claims 1 to 26, wherein the cancer is a solid tumor.

28. The MAT2A or PRMT5 inhibitor for use of any one of claims 1 to 27, wherein MAT2A inhibitor and PRMT5 inhibitor are administered concurrently or sequentially.