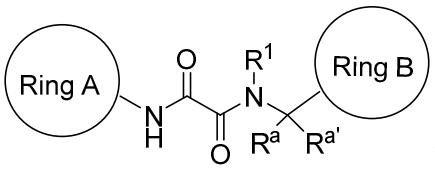
[0005] Accordingly, there is a need for PRMT5 inhibitors for treating diseases, such as cancers.

Summary

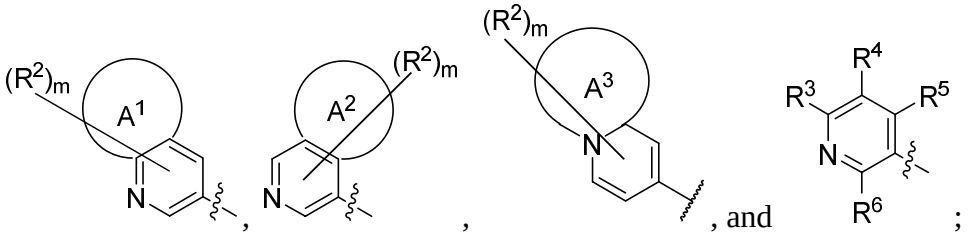
[0006] In one example, provided herein are compounds of Formula (A) or pharmaceutically acceptable salts thereof:

wherein:



Formula (A);

Ring A is selected from the group consisting of:



, , , and ;

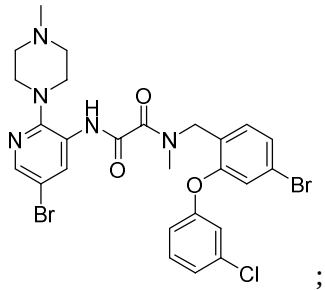
Ring B is selected from the group consisting of C_6–C_{10} aryl and 5-10 membered heteroaryl, each optionally substituted at any available position;

each of rings A^1 and A^2 is independently 5-6 membered carbocyclyl, 5-6 membered heterocyclyl, 5-6 membered heteroaryl or phenyl;

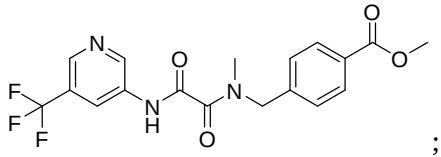
each ring A^3 is independently a 5-6 membered heterocyclyl or 5-6 membered heteroaryl, wherein the heterocyclyl and heteroaryl contain at least one nitrogen atom;

each R^1 is independently selected from the group consisting of –C_1–C_6 alkyl, –C_2–C_6 heteroalkyl, –C_2–C_6 haloalkyl, –C_3–C_{10} carbocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl and cycloalkylalkyl, each optionally substituted at any available position;

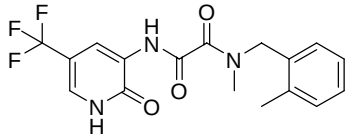
each R^2 is independently selected from the group consisting of –D, halo, =O, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a2}, –$N(R^{a2})_2$, –$C(=O)R^{a2}$, –$C(=O)OR^{a2}$, –$NR^{a2}C(=O)R^{a2}$, –$NR^{a2}C(=O)OR^{a2}$, –$C(=O)N(R^{a2})_2$, –


;

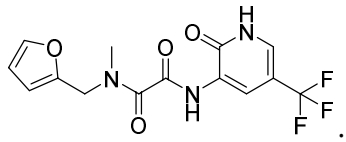
i) methyl 4-((N-methyl-2-oxo-2-((5-(trifluoromethyl)pyridin-3-yl)amino)acetamido)methyl)benzoate:


;

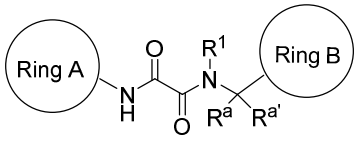
j) N1-methyl-N1-(2-methylbenzyl)-N2-(2-oxo-5-(trifluoromethyl)-1,2-dihydropyridin-3-yl)oxalamide:


;

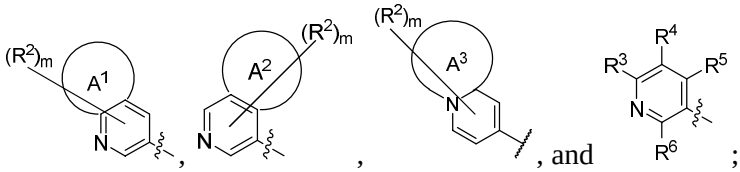
k) N1-(furan-2-ylmethyl)-N1-methyl-N2-(2-oxo-5-(trifluoromethyl)-1,2-dihydropyridin-3-yl)oxalamide:


.

[0006a] In one aspect, the present disclosure refers to a compound of Formula (A) or a pharmaceutically acceptable salt thereof; wherein:


Formula (A);

Ring A is selected from the group consisting of:


, and ;

Ring B is selected from the group consisting of C_6–C_{10} aryl and 5-10 membered heteroaryl, each optionally substituted at any available position;

each of rings A^1 and A^2 is independently 5-6 membered carbocyclyl, 5-6 membered heterocyclyl, 5-6 membered heteroaryl or phenyl;

each ring A^3 is independently a 5-6 membered heterocyclyl or 5-6 membered heteroaryl, wherein the heterocyclyl and heteroaryl contain at least one nitrogen atom;

each R^1 is independently selected from the group consisting of –C_1–C_6 alkyl, –C_2–C_6 heteroalkyl, –C_2–C_6 haloalkyl, –C_3–C_{10} carbocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl and cycloalkylalkyl, each optionally substituted at any available position;

each R^2 is independently selected from the group consisting of –D, halo, =O, –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^{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 the group consisting of 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 the group consisting of 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^5 is independently selected from the group consisting of 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, $–OR^{a5}$, $–N(R^{a5})_2$, $–C(=O)R^{a5}$, $–C(=O)OR^{a5}$, $–NR^{a5}C(=O)R^{a5}$, $–NR^{a5}C(=O)OR^{a5}$, $–C(=O)N(R^{a5})_2$, $–OC(=O)N(R^{a5})_2$,$-S(=O)R^{a5}$, $–S(=O)_2R^{a5}$, $–SR^{a5}$, $–S(=O)(=NR^{a5})R^{a5}$, $–NR^{a5}S(=O)_2R^{a5}$ and $–S(=O)_2N(R^{a5})_2$;

each R^6 is independently selected from the group consisting of 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, $–OR^{a6}$, $–N(R^{a6})_2$, $–C(=O)R^{a6}$, $–C(=O)OR^{a6}$, $–NR^{a6}C(=O)R^{a6}$, $–NR^{a6}C(=O)OR^{a6}$, $–C(=O)N(R^{a6})_2$, $–OC(=O)N(R^{a6})_2$, $–S(=O)R^{a6}$, $–S(=O)_2R^{a6}$, $–SR^{a6}$, $–S(=O)(=NR^{a6})R^{a6}$, $–NR^{a6}S(=O)_2R^{a6}$ and $–S(=O)_2N(R^{a6})_2$;

each R^a and R^a’ are independently selected from H and C_1-C_6 alkyl;

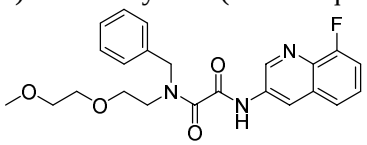
each R^{a2}, R^{a3}, R^{a4}, R^{a5} and R^{a6} is independently selected from the group consisting of H, $–C_1–C_6$ alkyl, $–C_1–C_6$ heteroalkyl, $C_3–C_9$ cycloalkyl, 3-7 membered heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, 5-6 membered heteroaryl, arylalkyl and heteroarylalkyl wherein 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 the group consisting of =O, halo, –CN, $–C_1–C_6$ alkyl, $–C_1–C_6$ heteroalkyl, $–C_1–C_6$ hydroxyalkyl,$–C_1–C_6$ haloalkyl, $–C_3–C_9$ cycloalkyl, 3-10 membered heterocyclyl, $C_6–C_{10}$ 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 the group consisting of H, $–C_1–C_6$ alkyl (*e.g.*, –Me, –Et, –Pr, $–^iPr$,$–^nBu$, $–^tBu$, *–sec*-Bu, *–iso*-Bu) and C_3-C_9 cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl); and

m is 0, 1, 2 or 3; wherein

(i) when R^4 is $–CH_3$ then R^3 is not H and;

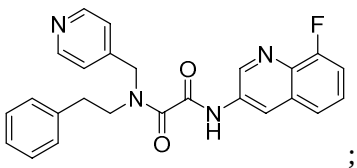
(ii) the compound is not one of compounds a) to k) or a pharmaceutically acceptable salt thereof:

a) N1-benzyl-N2-(8-fluoroquinolin-3-yl)-N1-(2-(2-methoxyethoxy)ethyl)oxalamide:



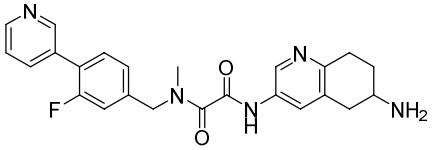
;

b) N1-(8-fluoroquinolin-3-yl)-N2-phenethyl-N2-(pyridin-4-ylmethyl)oxalamide:



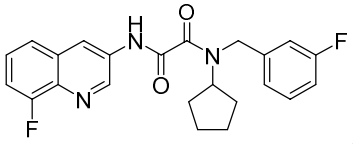
;

c) N1-(6-amino-5,6,7,8-tetrahydroquinolin-3-yl)-N2-(3-fluoro-4-(pyridin-3-yl)benzyl)-N2-methyloxalamide:



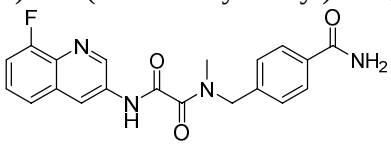
;

d) N1-cyclopentyl-N1-(3-fluorobenzyl)-N2-(8-fluoroquinolin-3-yl)oxalamide:



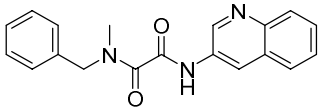
;

e) N1-(4-carbamoylbenzyl)-N2-(8-fluoroquinolin-3-yl)-N1-methyloxalamide:



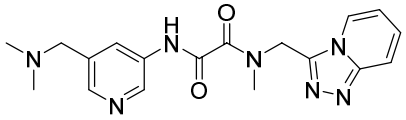
;

f) N1-benzyl-N1-methyl-N2-(quinolin-3-yl)oxalamide:



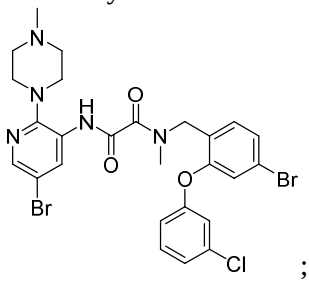
;

g) N1-([1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl)-N2-(5-((dimethylamino)methyl)pyridin-3-yl)-N1-methyloxalamide:



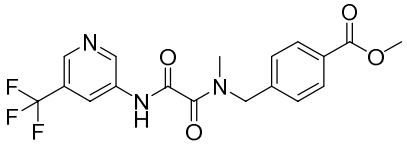
;

h) N1-(4-bromo-2-(3-chlorophenoxy)benzyl)-N2-(5-bromo-2-(4-methylpiperazin-1-yl)pyridin-3-yl)-N1-methyloxalamide:



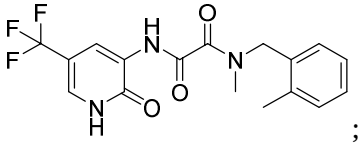
;

i) methyl 4-((N-methyl-2-oxo-2-((5-(trifluoromethyl)pyridin-3-yl)amino)acetamido)methyl)benzoate:



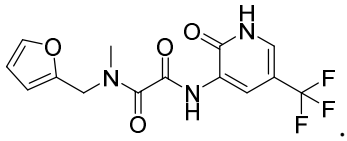
;

j) N1-methyl-N1-(2-methylbenzyl)-N2-(2-oxo-5-(trifluoromethyl)-1,2-dihydropyridin-3-yl)oxalamide:

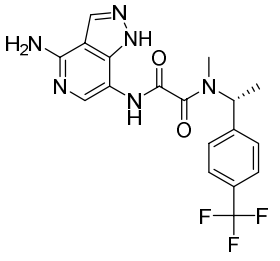


;

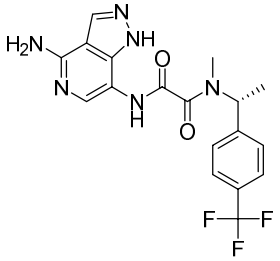
k) N1-(furan-2-ylmethyl)-N1-methyl-N2-(2-oxo-5-(trifluoromethyl)-1,2-dihydropyridin-3-yl)oxalamide:


.

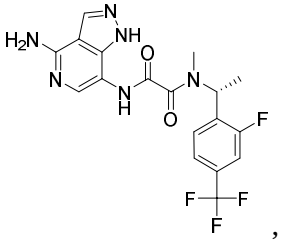
[0006b] In one aspect, the present disclosure refers to a compound of Formula


, or a pharmaceutically acceptable salt thereof.

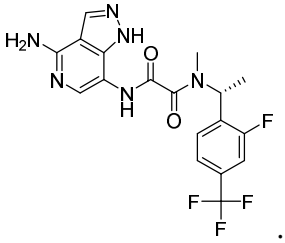
[0006c] In one aspect, the present disclosure refers to a compound of Formula


.

[0006d] In one aspect, the present disclosure refers to a compound of Formula


, or a pharmaceutically acceptable salt thereof.

[0006e] In one aspect, the present disclosure refers to a compound of Formula


.

[0007] In one example, provided is a pharmaceutical composition comprising a compound of Formula (A), or a pharmaceutically acceptable salt thereof, as defined in any of the examples described herein and a pharmaceutically acceptable carrier. In some examples, the pharmaceutical composition further comprises a second therapeutic agent.

[0007a] In one aspect,the present disclosure refers to a composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0008] In one example, provided is a method of treating an MTAP-deficient and/or an MTA-accumulating disease in a subject in need thereof by administering to the subject an

effective amount (*e.g.*, a therapeutically effective amount) of compound of Formula (A), or a pharmaceutically acceptable salt thereof, as defined in any of the examples described herein or a pharmaceutically acceptable composition thereof. In some examples, the compound or composition is administered in combination with a second therapeutic agent.

[0008a] In one aspect, the present disclosure refers to use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or of a composition disclosed herein, in the manufacture of a medicament for treating an MTAP-deficient and/or an MTA-accumulating disease in a subject in need thereof.

[0009] In one example, provided is a method of treating a cancer in a subject in need thereof comprising the steps of:

a) assessing the level of MTAP and/or MTA in a test sample obtained from said subject, wherein the MTA level can be assessed directly (*e.g.*, by ELISA or LC-MS/MS) or indirectly (*e.g.*, by SDMA-modified protein ELISA or IHC, or by RNA splicing);

b) comparing the test sample with a reference, wherein MTAP deficiency and/or MTA accumulation in said test sample compared to the reference indicates the cancer in said subject will respond to therapeutic treatment with a PRMT5 inhibitor; and

c) administering an effective amount (*e.g.*, a therapeutically effective amount) of a compound of Formula (A) as defined in any of the examples described herein or a pharmaceutical composition thereof to the subject identified in step b).

[0010] In an example, provided is a use of a compound of Formula (A), or a pharmaceutically acceptable salt thereof, as defined in any of the examples described herein, or of a pharmaceutically acceptable composition as described herein for treating an MTAP-deficient and/or an MTA-accumulating disease in a subject in need thereof. In an example, the compound or composition is configured to be administered in combination with a second therapeutic agent.

[0011] In an example, provided is a compound of Formula (A), or a pharmaceutically acceptable salt thereof, as defined in any of the examples described herein, or a pharmaceutically acceptable composition as described herein for treating an MTAP-deficient and/or an MTA-accumulating disease in a subject in need thereof. In an example, the compound or composition is configured to be administered in combination with a second therapeutic agent.

[0012] In an example, provided is a use of a compound of compound of Formula (A), or a pharmaceutically acceptable salt thereof, as defined in any of the examples described herein, or of a pharmaceutically acceptable composition as described herein in the manufacturing of a medicament for treating an MTAP-deficient and/or an MTA-accumulating disease in a subject in need thereof. In an example, the medicament is configured to be administered in combination with a second therapeutic agent.