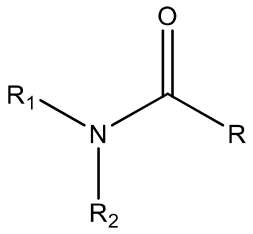
novel strategies are required to exploit this metabolic vulnerability and preferentially target PRMT5 in MTAP null tumors while sparing PRMT5 in normal tissues (MTAP WT). Targeting PRMT5 with an MTA-cooperative small molecule inhibitor could preferentially target the MTA bound state of PRMT5, enriched in MTAP null tumor cells, while providing an improved therapeutic index over normal cells where MTAP is intact and MTA levels are low.

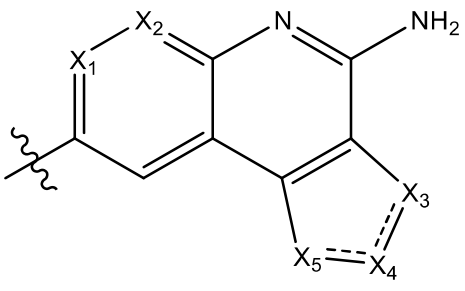
SUMMARY

[005] In one aspect, the disclosure provides a compound of Formula **I**



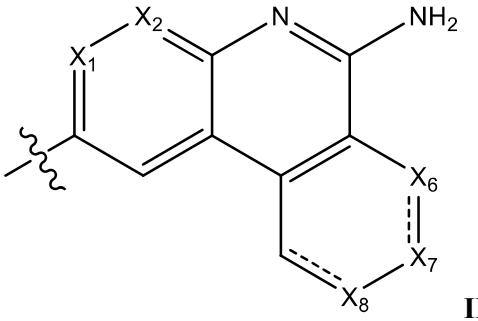
I

a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing:
wherein R^1, R^2 and the nitrogen atom to which they are attached form a five, six or seven membered ring that may be saturated or partially saturated, and comprises 0, 1 or 2 additional heteroatoms, same or different, selected from O, N or S, wherein the S atom is optionally substituted with one or two oxo groups;
wherein the ring formed by R^1, R^2 and the nitrogen atom to which they are attached can be substituted with 0, 1, 2 or 3 R^3;
wherein R^3 is in each instance selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, -OC_{1-6} alkyl, -OC_{1-6} haloalkyl, -$C(O)C_{1-6}$ alkyl, -$C(O)C_{1-6}$ haloalkyl, -$C(O)OC_{1-6}$ alkyl, -$C(O)OC_{1-6}$ haloalkyl, and five or six membered cycle that may be saturated, partially saturated, or aromatic, and comprises 0, 1 or 2 heteroatoms, same or different, selected from O, N and S, wherein the cycle may be optionally substituted with one or more R^a,
wherein R^a is in each instance selected from halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, pentafluorosulfanyl, -OC_{1-3} alkyl, and -OC_{1-3} haloalkyl;
wherein R is a tricycle selected from the formulae **IA** and **IB**:



IA

and



IB,

wherein  is a single or double bond,

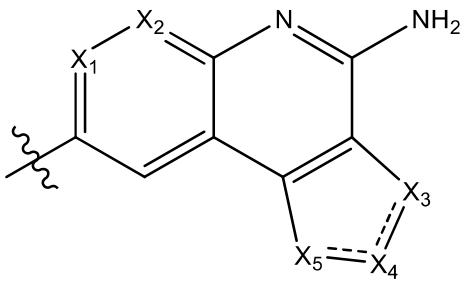
X^1, X^2, X^6, X^7 and X^8 are in each instance selected from optionally substituted N and C, wherein substituents are selected from $C_{1\text{-}3}$ alkyl;

wherein both X^1 and X^2 cannot be N at the same time, and X^6 and X^7, and X^7 and X^8 cannot be N at the same time;

further wherein if X^1 is C, it can be optionally substituted with halo;

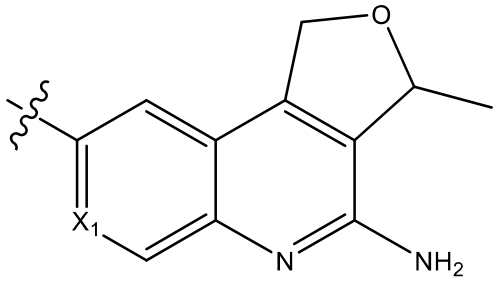
X^3, X^4 and X^5 are at each instance selected from optionally substituted C, O, N and S, wherein the substituents are selected from $C_{1\text{-}3}$ alkyl, and $C_{1\text{-}3}$ alkyl(OH), wherein alkyl can be optionally substituted with halo.

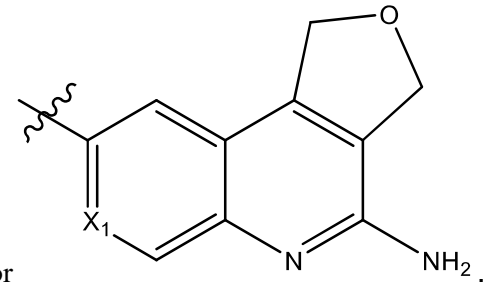
[006] In one example, the inventrion provides the compounds, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R is a tricycle of Formula **IA**



IA.

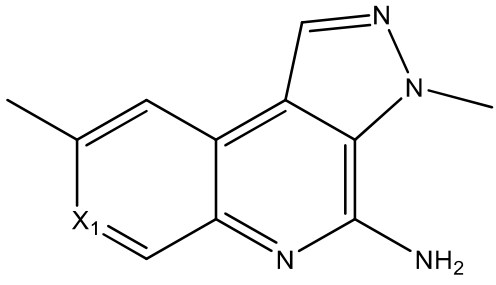
[007] In one example, R can be

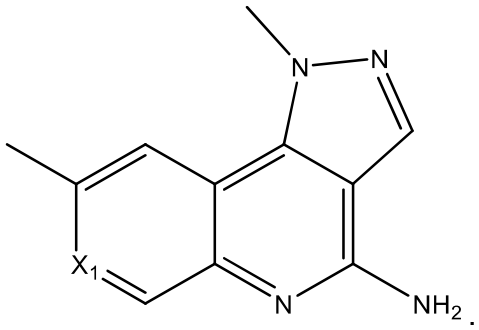


or


.

[008] In another example, R can be



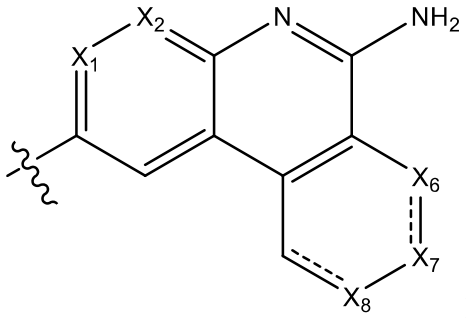
or


.

[009] The disclosure further provides the compounds, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein X^1 is C. In one example, X^1 can be substituted with halo.

[010] In one example, X^1 can be N.

[011] The disclosure discloses compounds, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R is a tricycle of Formula **IB**

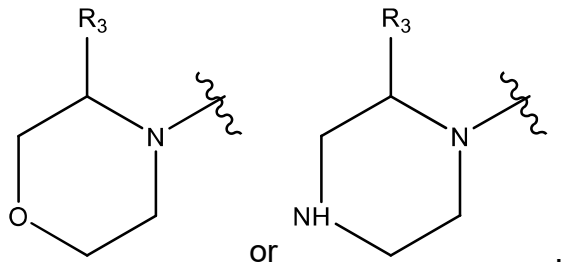


IB.

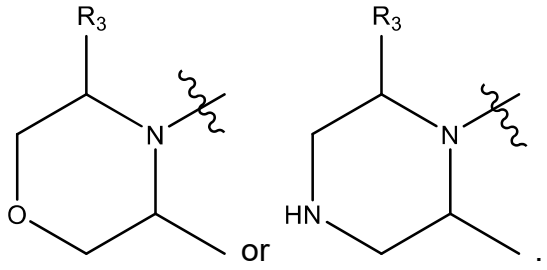
[012] In one example, X^1 can be N. In another example, X^7 can be N.

[013] The disclosure provides compounds, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R^1, R^2 and the nitrogen atom to which they are attached form a six membered ring that may be saturated or partially saturated, and comprises 0, 1 or 2 additional heteroatoms selected from O, N or S.

[014] In one example, the six membered ring can be



[015] In another example, the six membered ring is



[016] In one example, R^3 can be phenyl, pyridinyl, pyrazidinyl or pyrimidinyl, optionally substituted with one or more R^a.

[017] In one example, R^3 can be phenyl, optionally substituted with R^a. In a further example, R^a can be $C_{1\text{-}6}$ haloalkyl. In another example, R^a can be pentafluorosulfanyl.

[018] In another example, R3 can be pyridinyl, optionally substituted with one or more Ra. In a further example, R^a can be $C_{1\text{-}6}$ haloalkyl. In another example, R^a can be pentafluorosulfanyl.

[019] All possible combinations between examples and examples as disclosed above are comprised in the present disclosure.

[020] In one example, the disclosure provides the compound, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein the compound is selected from:

(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)((3R,5S)-3-(2-fluoro-4-(trifluoromethyl)phenyl)-5-methyl-4-morpholinyl)methanone,

((3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3R)-3-(4-fluoro-3-(trifluoromethoxy)phenyl)-4-morpholinyl)methanone,

((3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3R)-3-(4-fluoro-3-(trifluoromethyl)phenyl)-4-morpholinyl)methanone,

((3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3R)-3-(5-(trifluoromethyl)-2-pyridinyl)-4-morpholinyl)methanone,

4-((3S)-4-((4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)carbonyl)-3-morpholinyl)benzonitrile,
4-((3S,5R)-4-((4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)carbonyl)-5-methyl-3-morpholinyl)benzonitrile,
4-chloro-6-[rac-(3S)-4-(4-amino-1,3-dihydrofuro[3,4-c]quinoline-8-carbonyl)morpholin-3-yl]pyridine-3-carbonitrile,
6-[(3R)-4-(4-amino-1,3-dihydrofuro[3,4-c]quinoline-8-carbonyl)morpholin-3-yl]pyridine-3-carbonitrile,
6-[(3S)-4-(4-amino-1,3-dihydrofuro[3,4-c]quinoline-8-carbonyl)morpholin-3-yl]pyridine-3-carbonitrile,
methyl (3R,4S)-1-((4-amino-7-fluoro-1,3-dihydrofuro[3,4-c]quinolin-8-yl)carbonyl)-4-(4-(trifluoromethyl)phenyl)-3-pyrrolidinecarboxylate,
methyl (3S,4R)-1-((4-amino-7-fluoro-1,3-dihydrofuro[3,4-c]quinolin-8-yl)carbonyl)-4-(4-(trifluoromethyl)phenyl)-3-pyrrolidinecarboxylate,
tert-butyl (3R)-4-(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridine-8-carbonyl)-3-[4-(trifluoromethyl)phenyl]piperazine-1-carboxylate, and
tert-butyl (3S)-4-(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridine-8-carbonyl)-3-[4-(trifluoromethyl)phenyl]piperazine-1-carboxylate.

In one example, the disclosure provides the following compounds:
(4-amino-1-methyl-1H-pyrazolo[4,3-c][1,7]naphthyridin-8-yl)((3S)-3-(4-(trifluoromethyl)phenyl)-4-morpholinyl)methanone;
(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3S,5R)-3-(6-(cyclopropyloxy)-3-pyridazinyl)-5-methyl-4-morpholinyl)methanone;
(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3R,5S)-3-methyl-5-(6-(2,2,2-trifluoroethoxy)-3-pyridazinyl)-4-morpholinyl)methanone;
((3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c]quinolin-8-yl)((3S,5R)-3-(6-ethoxy-3-pyridazinyl)-5-methyl-4-morpholinyl)methanone ;
(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3S,5R)-3-(6-(difluoromethoxy)-3-pyridazinyl)-5-methyl-4-morpholinyl)methanone;
(4-amino-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(4-(pentafluoro-lambda~6~-sulfanyl)phenyl)-4-morpholinyl)methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S,5S)-3-methyl-5-[5-(trifluoromethyl)-2-pyridyl]morpholin-4-yl]methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[6-(trifluoromethyl)-3-pyridyl]morpholin-4-yl]methanone;

(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[5-(trifluoromethyl)-2-pyridyl]morpholin-4-yl]methanone;
((3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3S)-3-(4-(trifluoromethyl)phenyl)-4-morpholinyl)methanone;
[(3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c]quinolin-8-yl]-[(3S)-3-[4-(trifluoromethoxy)phenyl]morpholin-4-yl]methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[4-(trifluoromethoxy)phenyl]morpholin-4-yl]methanone;
(4-amino-3-methyl-3H-pyrazolo[3,4-c]quinolin-8-yl)((3R,5S)-3-methyl-5-(5-(trifluoromethyl)-2-pyridinyl)-4-morpholinyl)methanone;
(4-amino-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(4-(trifluoromethyl)phenyl)-4-morpholinyl)methanone;
(4-amino-7-fluoro-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(6-(difluoromethoxy)-3-pyridazinyl)-4-morpholinyl)methanone;
(4-amino-7-fluoro-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(6-(trifluoromethyl)-3-pyridazinyl)-4-morpholinyl)methanone;
(4-amino-7-fluoro-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3R)-3-(4-(trifluoromethyl)phenyl)-1-pyrrolidinyl)methanone; and
(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]methanone.

[021] In another aspect, the present disclosure provides a compound as disclosed herein for use as a medicament. In a further aspect, the present disclosure provides a use of a compound as disclosed herein, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing in the manufacuture of a medicament for treating a cancer, comprising that the compound as disclosed herein, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing is to be administered to a subject. The disclosure further provides methods of treating cancer comprising administering to a subject an effective amount of the compound of the disclosure, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing. In one example, the cancer is selected from lung, Head and Neck Squamous Cell Carcinoma (HNSCC), esophagus, lymphoid, glioblastoma, colon, melanoma, gastric, pancreatic, bile or bladder cancer. In one example, lung cancer could be Non-Small Cell Lung Carcinoma (NSCLC).

[022] In yet another aspect, the disclosure further provides pharmaceutical compositions, comprising the compounds of the disclosure, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

[023] The disclosure also provides methods of manufacturing a medication for treating a cancer, the method comprising administering to a subject an effective amount of the compound of the disclosure, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing. In one example, the cancer can be lung, Head and Neck Squamous Cell Carcinoma (HNSCC),

esophagus, lymphoid, glioblastoma, colon, bile, melanoma, gastric, pancreatic or bladder cancer. In one example, lung cancer could be Non-Small Cell Lung Carcinoma (NSCLC). The disclosure also provides the compound of the disclosure, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing for use in a method of treating a cancer, the method comprising administering to a subject an effective amount of such compound. In one example, the cancer can lung, Head and Neck Squamous Cell Carcinoma (HNSCC), esophagus, lymphoid, glioblastoma, colon, melanoma, gastric, pancreatic bile or bladder cancer. In one example, lung cancer could be Non-Small Cell Lung Carcinoma (NSCLC).

[024] The disclosure also provides the use of the compound of the present disclosure, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing in the manufacture of a medicament for treating a cancer. In one example, the cancer can be lung, Head and Neck Squamous Cell Carcinoma (HNSCC), esophagus, lymphoid, glioblastoma, colon, melanoma, gastric, pancreatic, bile or bladder cancer. In one example, lung cancer could be Non-Small Cell Lung Carcinoma (NSCLC).

[025] Other objects, features and advantages of the disclosure will become apparent to those skilled in the art from the following description and claims.

DETAILED DESCRIPTION OF THE INVENTION

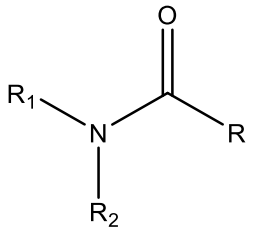
Definitions

[026] As used herein, if any variable occurs more than one time in a chemical formula, its definition on each occurrence is independent of its definition at every other occurrence. If the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound. The compounds of the present disclosure may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), enantiomers, or diastereomers. Accordingly, any chemical structures within the scope of the specification depicted, in whole or in part, with a relative configuration encompass all possible enantiomers and stereoisomers of the illustrated compounds including the stereoisomerically pure form (*e.g.*, geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into the component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan.

[027] Certain compounds of the invention may possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, enantiomers, diastereomers, geometric isomers and individual isomers are

CLAIMS

1. A compound of Formula **I**



I

a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing:

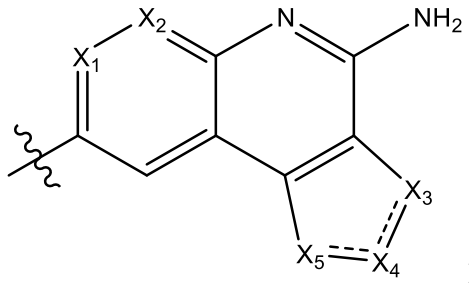
wherein R^1, R^2 and the nitrogen atom to which they are attached form a five, six or seven membered ring that may be saturated or partially saturated, and comprises 0, 1 or 2 additional heteroatoms, same or different, selected from O, N or S, wherein the S atom is optionally substituted with one or two oxo groups;

wherein the ring formed by R^1, R^2 and the nitrogen atom to which they are attached can be substituted with 0, 1, 2 or 3 R^3;

wherein R^3 is in each instance selected from $C_{1\text{-}6}$ alkyl, halo, $C_{1\text{-}6}$ haloalkyl, -$OC_{1\text{-}6}$ alkyl, -$OC_{1\text{-}6}$ haloalkyl, -$C(O)C_{1\text{-}6}$ alkyl, -$C(O)C_{1\text{-}6}$ haloalkyl, -$C(O)OC_{1\text{-}6}$ alkyl, -$C(O)OC_{1\text{-}6}$ haloalkyl, and five or six membered cycle that may be saturated, partially saturated, or aromatic, and comprises 0, 1 or 2 heteroatoms, same or different, selected from O, N and S, wherein the cycle may be optionally substituted with one or more R^a,

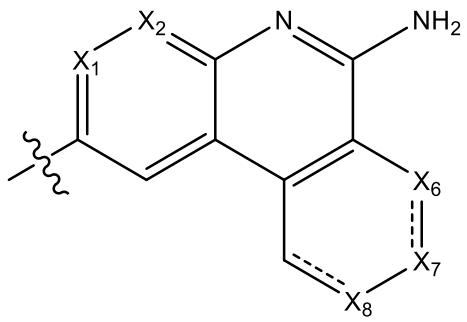
wherein R^a is in each instance selected from halo, CN, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ haloalkyl, pentafluorosulfanyl, -$OC_{1\text{-}3}$ alkyl, and -$OC_{1\text{-}3}$ haloalkyl;

wherein R is a tricycle selected from the formulae **IA** and **IB**:



IA

and



IB,

wherein  is a single or double bond,

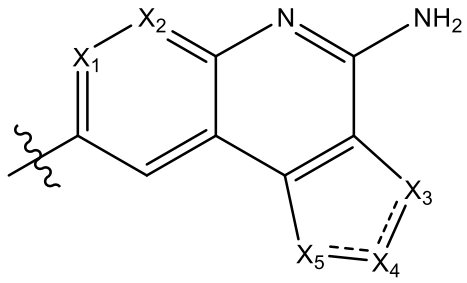
X^1, X^2, X^6, X^7 and X^8 are in each instance selected from optionally substituted N and C, wherein substituents are selected from C_{1-3} alkyl;

wherein both X^1 and X^2 cannot be N at the same time, and X^6 and X^7, and X^7 and X^8 cannot be N at the same time;

further wherein if X^1 is C, it can be optionally substituted with halo;

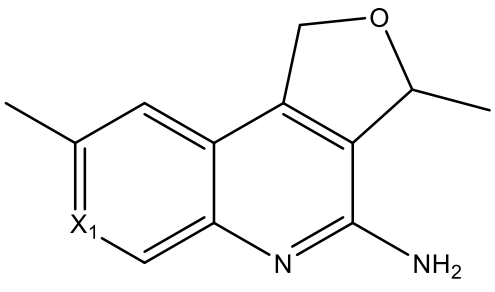
X^3, X^4 and X^5 are at each instance selected from optionally substituted C, O, N and S, wherein the substituents are selected from C_{1-3} alkyl, and C_{1-3} alkyl(OH), wherein alkyl can be optionally substituted with halo.

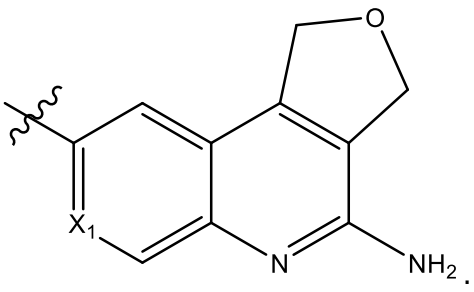
2. The compound of claim 1, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R is a tricycle of Formula **IA**



IA.

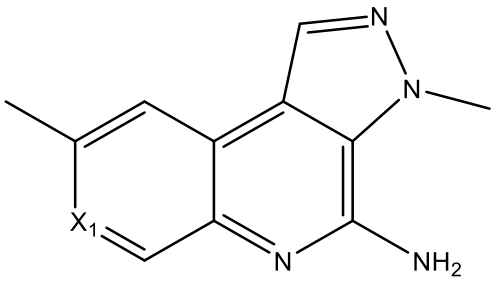
3. The compound of claim 2, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R is

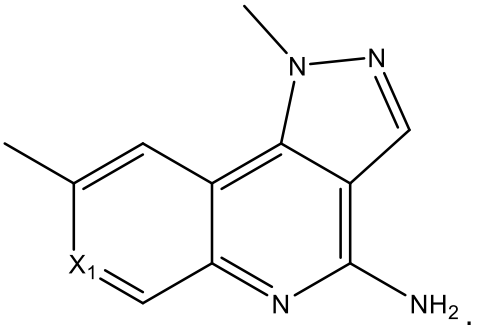


or


.

4. The compound of claim 2, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R is



or


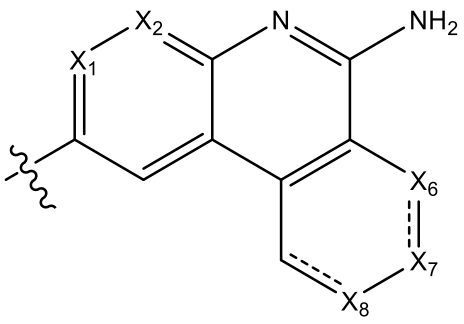
.

5. The compound of any of claims 3 or 4, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein X^1 is C.

6. The compound of claim 5, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein X^1 is substituted with halo.

7. The compound of any of claims 3 or 4, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein X^1 is N.

8. The compound of claim 1, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R is a tricycle of Formula **IB**



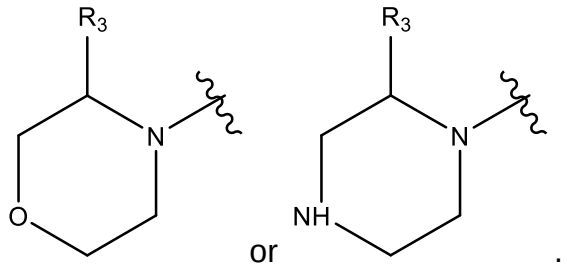
IB

9. The compound of claim 8, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein X^1 is N.

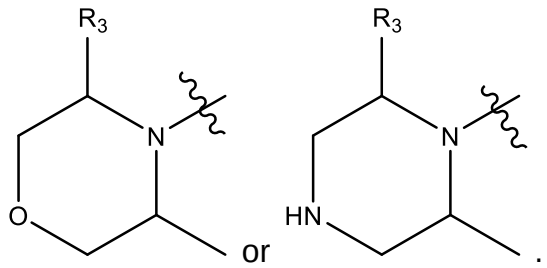
10. The compound of claim 9, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein X^7 is N.

11. The compound of claim 5 or claim 7, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R^1, R^2 and the nitrogen atom to which they are attached form a six membered ring that may be saturated or partially saturated, and comprises 0, 1 or 2 additional heteroatoms selected from O, N or S.

12. The compound of claim 11, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein the six membered ring is

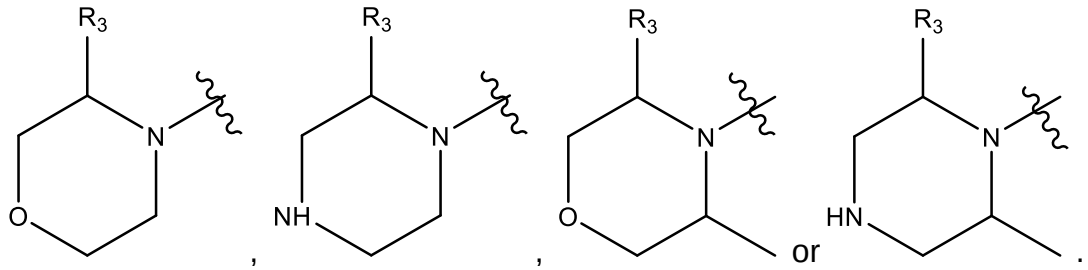


13. The compound of claim 11, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein the six membered ring is



14. The compound of claim 8, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R^1, R^2 and the nitrogen atom to which they are attached form a six membered ring that may be saturated or partially saturated, and comprises 0, 1 or 2 additional heteroatoms selected from O, N or S.

15. The compound of claim 14, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein the six membered ring is



, , or .

16. The compound of claim 12, 13, 14 or 15, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is in each instance independently selected from C_{1-6} alkyl, halo, and five or six membered cycle that may be saturated, partially saturated, or aromatic, and comprises 0, 1 or 2 heteroatoms selected from O, N and S.

17. The compound of claim 16, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is phenyl, pyridinyl, pyrazidinyl or pyrimidinyl, optionally substituted with one or more R^a.

18. The compound of claim 17, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein R^a is in each instance selected from halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -OC_{1-3} alkyl, and -OC_{1-3} haloalkyl.

19. A compound of any of claims 1-18, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing, wherein the compound is selected from:

(4-amino-1-methyl-1H-pyrazolo[4,3-c][1,7]naphthyridin-8-yl)((3S)-3-(4-(trifluoromethyl)phenyl)-4-morpholinyl)methanone;
(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3S,5R)-3-(6-(cyclopropyloxy)-3-pyridazinyl)-5-methyl-4-morpholinyl)methanone;
(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3R,5S)-3-methyl-5-(6-(2,2,2-trifluoroethoxy)-3-pyridazinyl)-4-morpholinyl)methanone;
((3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c]quinolin-8-yl)((3S,5R)-3-(6-ethoxy-3-pyridazinyl)-5-methyl-4-morpholinyl)methanone;

(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3S,5R)-3-(6-(difluoromethoxy)-3-pyridazinyl)-5-methyl-4-morpholinyl)methanone;
(4-amino-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(4-(pentafluoro-lambda~6~-sulfanyl)phenyl)-4-morpholinyl)methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S,5S)-3-methyl-5-[5-(trifluoromethyl)-2-pyridyl]morpholin-4-yl]methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[6-(trifluoromethyl)-3-pyridyl]morpholin-4-yl]methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[5-(trifluoromethyl)-2-pyridyl]morpholin-4-yl]methanone;
((3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3S)-3-(4-(trifluoromethyl)phenyl)-4-morpholinyl)methanone;
[(3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c]quinolin-8-yl]-[(3S)-3-[4-(trifluoromethoxy)phenyl]morpholin-4-yl]methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[4-(trifluoromethoxy)phenyl]morpholin-4-yl]methanone;
(4-amino-3-methyl-3H-pyrazolo[3,4-c]quinolin-8-yl)((3R,5S)-3-methyl-5-(5-(trifluoromethyl)-2-pyridinyl)-4-morpholinyl)methanone;
(4-amino-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(4-(trifluoromethyl)phenyl)-4-morpholinyl)methanone;
(4-amino-7-fluoro-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(6-(difluoromethoxy)-3-pyridazinyl)-4-morpholinyl)methanone;
(4-amino-7-fluoro-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(6-(trifluoromethyl)-3-pyridazinyl)-4-morpholinyl)methanone;
(4-amino-7-fluoro-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3R)-3-(4-(trifluoromethyl)phenyl)-1-pyrrolidinyl)methanone; and
(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]methanone.

20. A compound of any of claims 1-19, or the pharmaceutically acceptable salt of any of the foregoing, wherein the compound is selected from:

(4-amino-1-methyl-1H-pyrazolo[4,3-c][1,7]naphthyridin-8-yl)((3S)-3-(4-(trifluoromethyl)phenyl)-4-morpholinyl)methanone;
(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3S,5R)-3-(6-(cyclopropyloxy)-3-pyridazinyl)-5-methyl-4-morpholinyl)methanone;
(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3R,5S)-3-methyl-5-(6-(2,2,2-trifluoroethoxy)-3-pyridazinyl)-4-morpholinyl)methanone;
((3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c]quinolin-8-yl)((3S,5R)-3-(6-ethoxy-3-pyridazinyl)-5-methyl-4-morpholinyl)methanone;
(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3S,5R)-3-(6-(difluoromethoxy)-3-pyridazinyl)-5-methyl-4-morpholinyl)methanone;
(4-amino-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(4-(pentafluoro-lambda~6~-sulfanyl)phenyl)-4-morpholinyl)methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S,5S)-3-methyl-5-[5-(trifluoromethyl)-2-pyridyl]morpholin-4-yl]methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[6-(trifluoromethyl)-3-pyridyl]morpholin-4-yl]methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[5-(trifluoromethyl)-2-pyridyl]morpholin-4-yl]methanone;
((3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)((3S)-3-(4-(trifluoromethyl)phenyl)-4-morpholinyl)methanone;
[(3R)-4-amino-3-methyl-1,3-dihydrofuro[3,4-c]quinolin-8-yl]-[(3S)-3-[4-(trifluoromethoxy)phenyl]morpholin-4-yl]methanone;
(4-amino-1,3-dihydrofuro[3,4-c]quinolin-8-yl)-[(3S)-3-[4-(trifluoromethoxy)phenyl]morpholin-4-yl]methanone;
(4-amino-3-methyl-3H-pyrazolo[3,4-c]quinolin-8-yl)((3R,5S)-3-methyl-5-(5-(trifluoromethyl)-2-pyridinyl)-4-morpholinyl)methanone;
(4-amino-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(4-(trifluoromethyl)phenyl)-4-morpholinyl)methanone;
(4-amino-7-fluoro-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(6-(difluoromethoxy)-3-pyridazinyl)-4-morpholinyl)methanone;
(4-amino-7-fluoro-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3S)-3-(6-(trifluoromethyl)-3-pyridazinyl)-4-morpholinyl)methanone;

(4-amino-7-fluoro-1-methyl-1H-pyrazolo[4,3-c]quinolin-8-yl)((3R)-3-(4-(trifluoromethyl)phenyl)-1-pyrrolidinyl)methanone; and
(4-amino-1,3-dihydrofuro[3,4-c][1,7]naphthyridin-8-yl)-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]methanone.

21. A compound of any of claims 1-20 for use as a medicament.

22. Use of a compound of any of claims from 1 to 20, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing in the manufacuture of a medicament for treating a cancer, comprising that the compound of any of claims 1-20, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing is to be administered to a subject.

23. The use of claim 22, wherein the cancer is selected from ovarian, lung, HNSCC, lymphoid, glioblastoma, colon, melanoma, gastric, bile duct, pancreatic or bladder cancer.

24. A pharmaceutical composition, comprising any of the compound of claims 1-20, the tautomer thereof, the stereoisomer thereof, or the pharmaceutically acceptable salt of any of the foregoing or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.