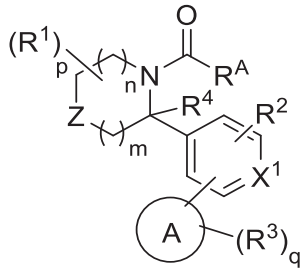
CLAIMS

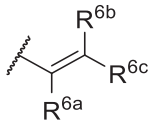
WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein;

R^A is , wherein

R^{6a} is H, D, halogen, or C_1-C_6 haloalkyl, and

R^{6b} and R^{6c} are each independently H or D;

ring A is aryl, heteroaryl, or heterocyclyl;

Z is O, $S(=O)_2$, $C(R^1)_2$, or NR^7;

R^7 is $-C(=O)R^{7a}$, $S(=O)R^{7a}$, or $S(=O)_2R^{7a}$, wherein R^{7a} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_7 cycloalkyl;

each R^1 is independently H, halogen, -OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, or $-C(=O)N(R^b)_2$,

or two R^1 are taken together with the atom(s) to which they are attached form an optionally substituted C_3-C_8 cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl;

X^1 is N or CR^2;

each R^2 is independently H, halogen, CN, OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted C_1-C_6 hydroxyalkyl;

R^4 is H or optionally substituted C_1-C_6 alkyl;

or one of R^2 and R^4 together with the atoms to which they are attached form an optionally substituted 5 to 7-membered heterocycloalkyl;

each R^3 is independently H, D, halogen, oxo (=O), thio (=S), -CN, -OH, $-OR^a$, -SH, $-SR^a$, $-S(=O)R^a$, $-NO_2$, $-N(R^b)_2$, $-S(=O)_2R^a$, $-NHS(=O)_2R^a$, $-S(=O)_2N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NH_2$, $-OC(=O)N(R^b)_2$, $-NR^bC(=O)N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6

hydroxyalkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted 4 to 8-membered heterocycloalkyl;

or two R^3 on adjacent atoms combine together with the atom(s) to which they are attached to form an optionally substituted aryl, optionally substituted heteroaryl ring, or optionally substituted heterocycloalkyl;

each R^a is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_6 alkyl(aryl), -C_1-C_6 alkyl(heteroaryl), -C_1-C_6 alkyl(cycloalkyl), or -C_1-C_6 alkyl(heterocycloalkyl); wherein each alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three -OH, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

each R^b is independently H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three -OH, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

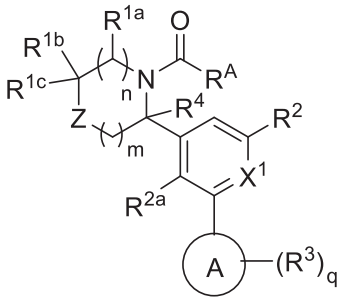
m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

p is an integer from 1-12; and

q is an integer from 1-10.

2. The compound of claim 1, wherein the compound has the structure of Formula (II), or a pharmaceutically acceptable salt thereof:



Formula (II)

wherein,

Z is O, $S(=O)_2$, $CR^{1d}R^{1e}$, or NR^7;

R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently H, halogen, -OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, or -$C(=O)N(R^b)_2$;

or R^{1a} and R^{1b} together with atoms to which they are attached form an optionally substituted C_3-C_8 cycloalkyl;

or R^{1b} and R^{1c} together with the carbon atom to which they are attached form an optionally substituted C_3-C_8 cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl;

or R^{1d} and R^{1e} together with the carbon atom to which they are attached form an optionally substituted C_3-C_8 cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl;

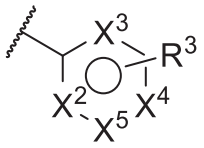
R^{2a} is H, halogen, CN, OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, or optionally substituted C_1-C_6 hydroxyalkyl; and

R^4 is H or optionally substituted C_1-C_6 alkyl;

or R^{2a} and R^4 together with the atoms to which they are attached form an optionally substituted 5 to 7-membered heterocycloalkyl.

3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is H; and R^{1b} and R^{1c} are each independently H, halogen, -OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, or $-C(=O)N(R^b)_2$.

4. The compound of any one of claim 1-3, or a pharmaceutically acceptable salt thereof, wherein ring A is:



wherein,

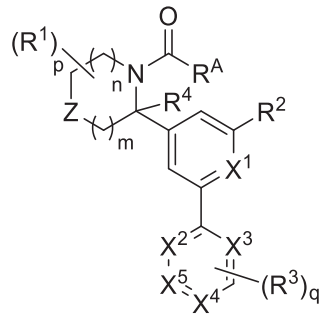
X^2, X^3, X^4, and X^5 are each independently N, NR^{3a}, or CR^3;

each R^{3a} is independently H or an optionally substituted C_1-C_6 alkyl;

each R^3 is independently H, D, halogen, oxo (=O), -CN, -OH, $-OR^a$, -SH, $-SR^a$, $-S(=O)R^a$, $-NO_2$, $-N(R^b)_2$, $-S(=O)_2R^a$, $-NHS(=O)_2R^a$, $-S(=O)_2N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NH_2$, $-OC(=O)N(R^b)_2$, $-NR^bC(=O)N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted 4 to 8-membered heterocycloalkyl;

or two R^3 or two R^{3a} or R^3 and R^{3a} on adjacent atoms combine together with the atom(s) to which they are attached to form an optionally substituted aryl, optionally substituted heteroaryl ring, or optionally substituted heterocycloalkyl.

5. The compound of claim 1, wherein the compound is of Formula (III), or a pharmaceutically acceptable salt thereof:



Formula (III)

wherein,

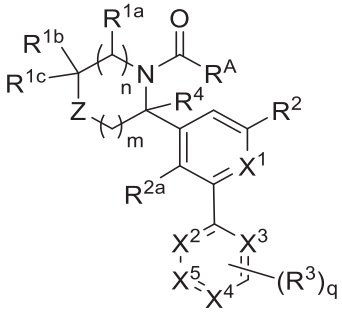
X^2, X^3, X^4, and X^5 are each independently N, NR^{3a}, or CR^3;

each R^{3a} is independently H or an optionally substituted C_1-C_6 alkyl;

each R^3 is independently H, D, halogen, oxo (=O), -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -NO_2, -$N(R^b)_2$, -$S(=O)_2R^a$, -$NHS(=O)_2R^a$, -$S(=O)_2N(R^b)_2$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NH_2$, -$OC(=O)N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted 4 to 8-membered heterocycloalkyl;

or two R^3 on adjacent atoms combine together with the atom(s) to which they are attached to form an optionally substituted aryl, optionally substituted heteroaryl ring, or optionally substituted heterocycloalkyl.

6. The compound of claim 1, wherein the compound is of Formula (IIIa), or a pharmaceutically acceptable salt thereof:



Formula (IIIa)

wherein,

Z is O, $S(=O)_2$, $CR^{1d}R^{1e}$, or NR^7;

R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are ach independently H, halogen, -OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, or -$C(=O)N(R^b)_2$;

or R^{1a} and R^{1b} together with atoms to which they are attached form an optionally substituted C_3-C_8 cycloalkyl;

or R^{1b} and R^{1c} together with the carbon atom to which they are attached form an optionally substituted C_3-C_8 cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl;

or R^{1d} and R^{1e} together with the carbon atom to which they are attached form an optionally substituted C_3-C_8 cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl;

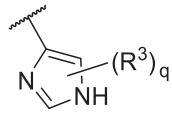
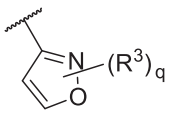
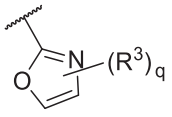
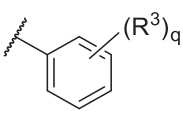
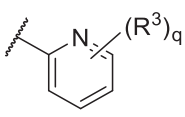
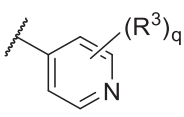
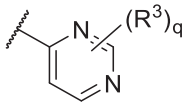
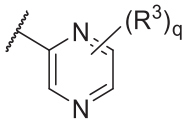
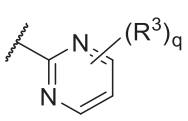
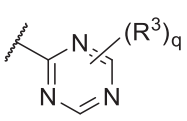
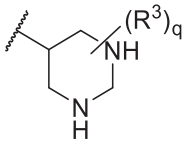
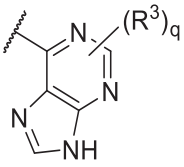
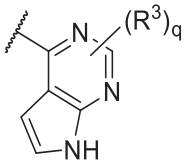
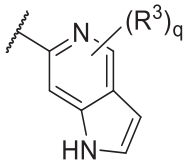
R^2 is halogen or CN;

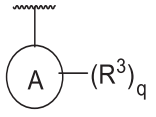
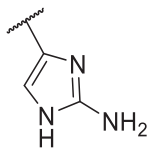
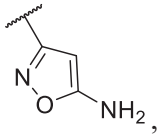
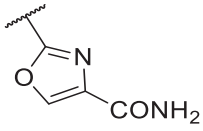
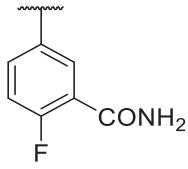
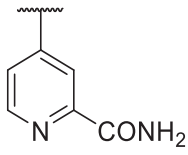
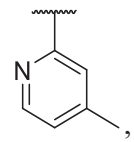
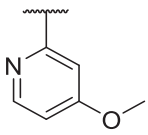
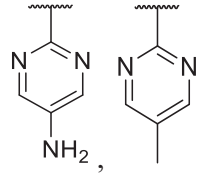
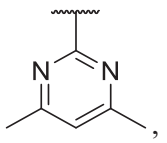
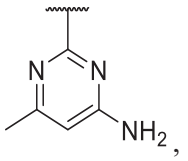
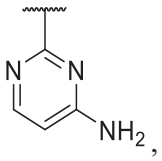
X^2, X^3, X^4, and X^5 are each independently N, NR^{3a}, or CR^3;

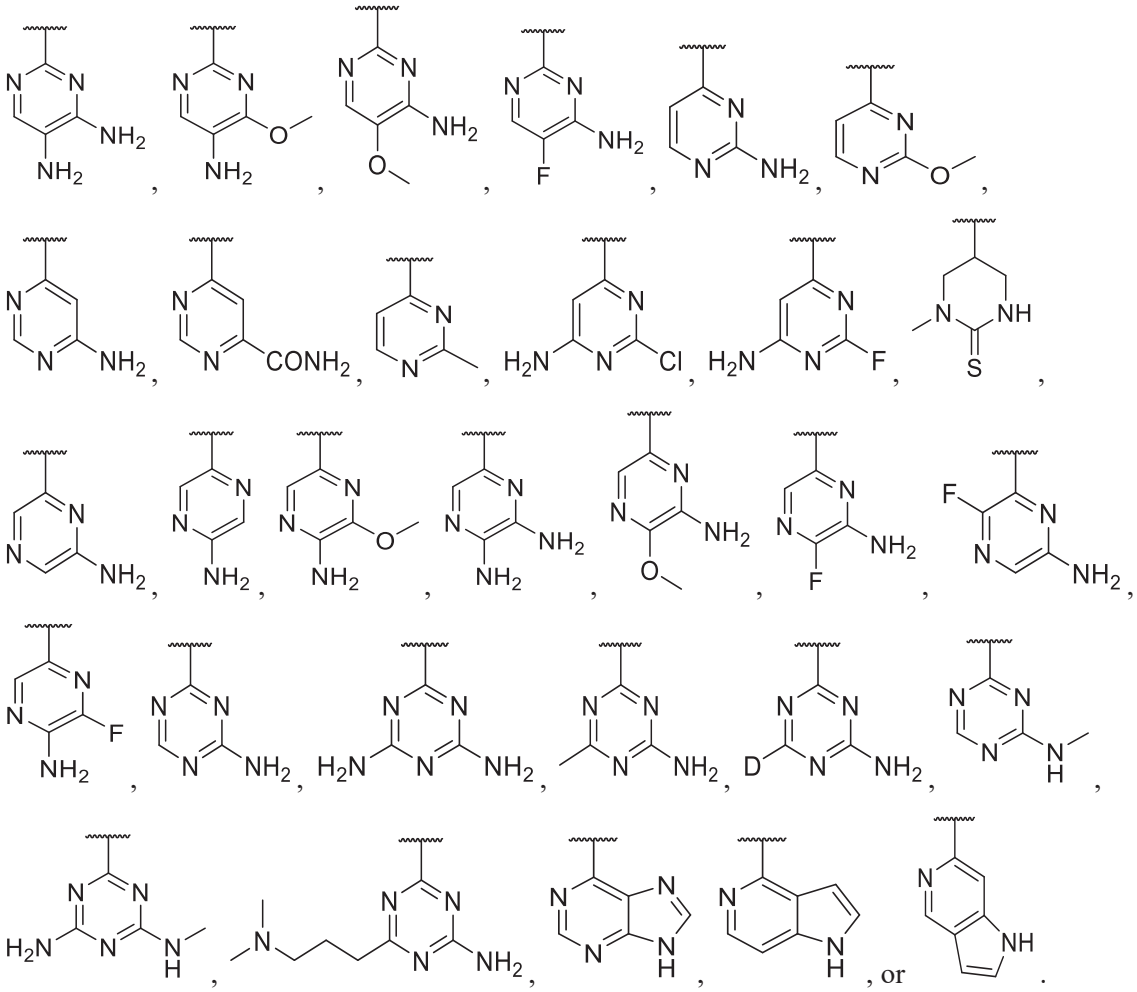
each R^{3a} is independently H or an optionally substituted C_1-C_6 alkyl; and

each R^3 is independently H, D, halogen, oxo (=O), -CN, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -NO_2, -$N(R^b)_2$, -$S(=O)_2R^a$, -$NHS(=O)_2R^a$, -$S(=O)_2N(R^b)_2$, -C(=O)R^a, -C(=O)OR^b, -$C(=O)NH_2$, -$OC(=O)N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted 4 to 8-membered heterocycloalkyl;

or two R^3 on adjacent atoms combine together with the atom(s) to which they are attached to form an optionally substituted aryl, optionally substituted heteroaryl ring, or optionally substituted heterocycloalkyl.

7. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein ring A is , , , , , , , , , , , , , or .

8. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein  is: , , , , , , , , , , 



9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein, R^A is .

10. A compound selected from:

(R)-1-(3-(3-(4-amino-1,3,5-triazin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one;

(R)-1-(5-(3-(4-amino-1,3,5-triazin-2-yl)-5-chlorophenyl)-2,2-dimethylmorpholino)prop-2-en-1-one;

(R)-1-(3-(3-(6-aminopyrimidin-4-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one;

(R)-1-(3-(3-chloro-5-(5-methylpyrimidin-2-yl)phenyl)morpholino)prop-2-en-1-one;

(R)-1-(3-(3-chloro-5-(4,6-dimethylpyrimidin-2-yl)phenyl)morpholino)prop-2-en-1-one;

(R)-1-(3-(3-(4-amino-6-methylpyrimidin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one;

(R)-1-(3-(3-(4-aminopyrimidin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one;

1-((3R,5R)-3-(3-(4-amino-1,3,5-triazin-2-yl)-5-chlorophenyl)-5-methylmorpholino)prop-2-en-1-one;

(R)-1-(3-(3-chloro-5-(4-methylpyridin-2-yl)phenyl)morpholino)prop-2-en-1-one;

(R)-1-(3-(3-chloro-5-(4-methoxypyridin-2-yl)phenyl)morpholino)prop-2-en-1-one;

1-((3R,5R)-3-(3-chloro-5-(2-methylpyrimidin-4-yl)phenyl)-5-methylmorpholino)prop-2-en-1-one;

1-((3R,5R)-3-(3-(2-aminopyrimidin-4-yl)-5-chlorophenyl)-5-methylmorpholino)prop-2-en-1-one;

1-((3R,5R)-3-(3-(6-aminopyrimidin-4-yl)-5-chlorophenyl)-5-methylmorpholino)prop-2-en-1-one;

(R)-1-(5-(3-(2-aminopyrimidin-4-yl)-5-chlorophenyl)-2,2-dimethylmorpholino)prop-2-en-1-one;
(R)-1-(5-(3-(6-aminopyrimidin-4-yl)-5-chlorophenyl)-2,2-dimethylmorpholino)prop-2-en-1-one;
(R)-1-(5-(3-(4-aminopyrimidin-2-yl)-5-chlorophenyl)-2,2-dimethylmorpholino)prop-2-en-1-one;
(R)-1-(5-(3-(5-aminopyrimidin-2-yl)-5-chlorophenyl)-2,2-dimethylmorpholino)prop-2-en-1-one;
(R)-1-(3-(3-chloro-5-(4,6-diamino-1,3,5-triazin-2-yl)phenyl)morpholino)prop-2-en-1-one;
(R)-1-(3-(3-(4-amino-1,3,5-triazin-2-yl-6-d)-5-chlorophenyl)morpholino)prop-2-en-1-one;
(R)-1-(3-(3-chloro-5-(4-(methylamino)-1,3,5-triazin-2-yl)phenyl)morpholino)prop-2-en-1-one;
(R)-1-(3-(3-(4-amino-6-(methylamino)-1,3,5-triazin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one;
(R)-1-(3-(3-(6-aminopyrazin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one;
(R)-1-(3-(3-(5-aminopyrazin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one;
(R)-1-(3-(3-chloro-5-(4,5-diaminopyrimidin-2-yl)phenyl)morpholino)prop-2-en-1-one;
(R)-1-(3-(3-(5-amino-4-methoxypyrimidin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one;
(R)-1-(3-(3-(5-amino-6-methoxypyrazin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one;
(R)-1-(3-(3-chloro-5-(5,6-diaminopyrazin-2-yl)phenyl)morpholino)prop-2-en-1-one;
(R)-1-(3-(3-(6-amino-5-methoxypyrazin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one;
(R)-1-(3-(3-(4-amino-5-methoxypyrimidin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one;
(R)-1-(5-(3-chloro-5-(5,6-diaminopyrazin-2-yl)phenyl)-2,2-dimethylmorpholino)prop-2-en-1-one;
(R)-1-(5-(3-chloro-5-(4,5-diaminopyrimidin-2-yl)phenyl)-2,2-dimethylmorpholino)prop-2-en-1-one;
(R)-2-(3-(4-acryloylmorpholin-3-yl)-5-chlorophenyl)isonicotinamide;
or a pharmaceutically acceptable salt thereof.

11. (R)-1-(3-(3-(4-aminopyrimidin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.
12. (R)-1-(3-(3-(4-aminopyrimidin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one.
13. A pharmaceutical composition comprising (R)-1-(3-(3-(4-aminopyrimidin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient or carrier.
14. A pharmaceutical composition comprising (R)-1-(3-(3-(4-aminopyrimidin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one and a pharmaceutically acceptable excipient or carrier.
15. Use of a therapeutically effective amount of of R)-1-(3-(3-(4-aminopyrimidin-2-yl)-5-chlorophenyl)morpholino)prop-2-en-1-one, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating cancer.
16. The use of claim 15, wherein the cancer is selected from the group consisting of lung cancer, bladder cancer, uterine cancer, head and neck cancer, esophageal cancer, ovarian cancer, liver cancer, cervical cancer, cholangiocarcinoma, gastric cancer, kidney cancer, and pancreatic cancer.

17. The use of claim 15, wherein the cancer is selected from the group consisting of non-small cell lung cancer, squamous non-small cell lung cancer, lung adenocarcinoma, esophageal cancer, squamous cell esophageal carcinoma, esophageal adenocarcinoma, head and neck cancer, squamous cell head and neck carcinoma, bladder cancer, squamous cell bladder carcinoma, uterine corpus endometrial carcinoma, cervical cancer, and cervical squamous cell carcinoma.