

INHIBITORS OF CYCLIN-DEPENDENT KINASES

CROSS REFERENCE TO RELATED APPLICATIONS

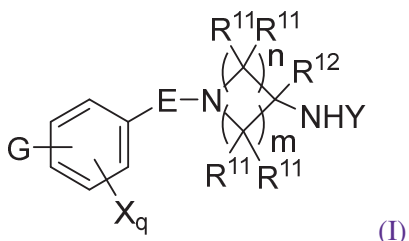
[0001] This application claims the benefit of U.S. Provisional Application No. 62/691,879, filed June 29, 2018, which is incorporated by reference in the disclosure of this application.

BACKGROUND

[0002] Cyclin-dependent kinases (CDKs) are a family of multifunctional enzymes that modify various protein substrates involved in cell cycle progression. Specifically, CDKs phosphorylate their substrates by transferring phosphate groups from ATP to specific stretches of amino acids in the substrates. The deregulation of CDKs is involved in the etiology of many human diseases, including cancers.

BRIEF SUMMARY OF THE INVENTION

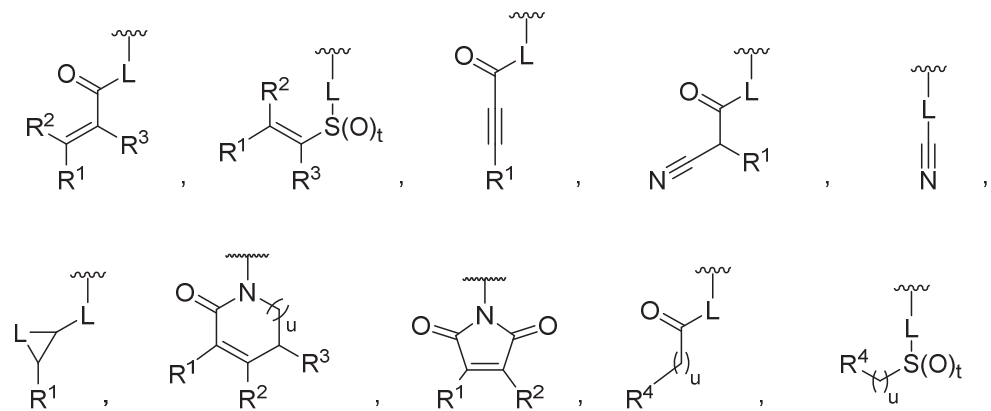
[0002a] In one aspect, provided herein is a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (I):

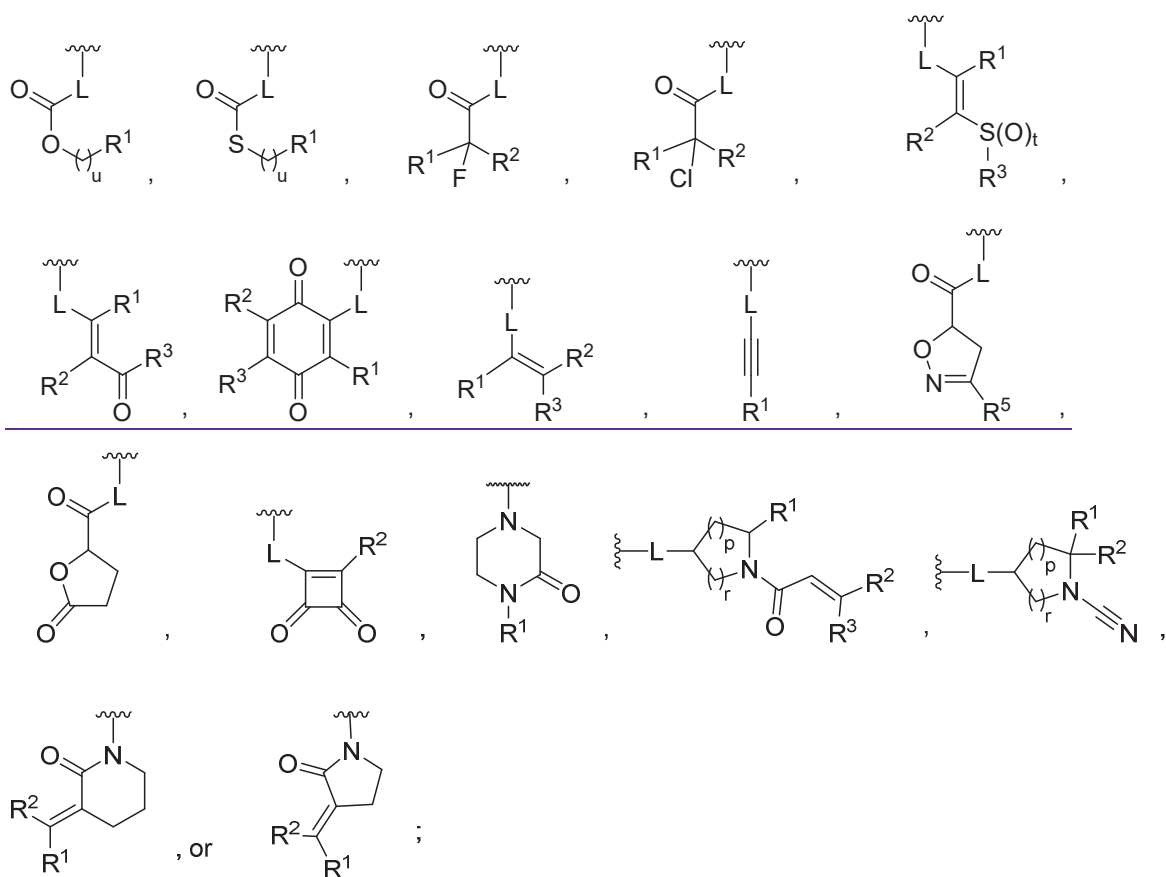


wherein,

E is -C(O)-;

G is selected from a group having the structure:





wherein,

L is O, NH, N(optionally substituted C1-C4 alkyl), or -NH-CH₂-* wherein the * denotes the point of attachment to the phenyl ring;

t is 0, 1, or 2;

u is 1, or 2;

p is 0, 1, or 2;

r is 0, 1, or 2;

R¹ is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

R² is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R³ is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R⁴ is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

R⁵ is optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

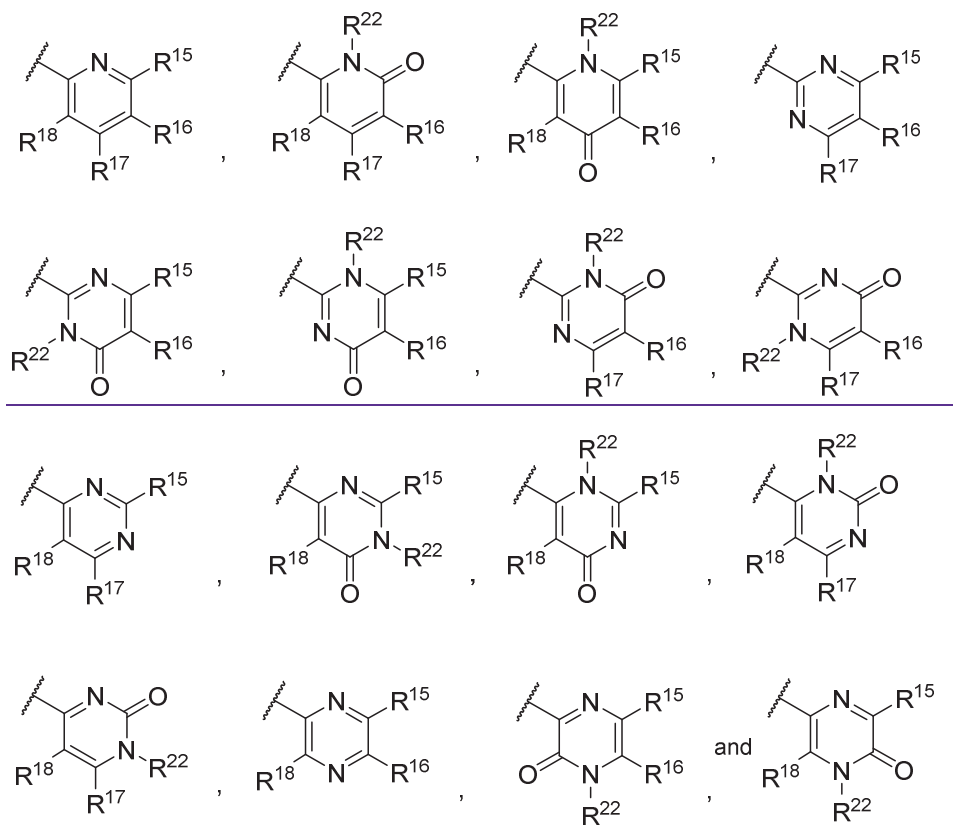
each R¹¹ is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, -OH, optionally substituted C1-C4 alkoxy, or two R¹¹ groups on the same carbon atom form an oxo;

R¹² is hydrogen or optionally substituted C1-C4 alkyl;

q is 0, 1, 2, or 3; n is 1; m is 2 or 3;

each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -OR²², -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally

substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -OR²², -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹.

R¹⁷ is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -OR²², -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹.

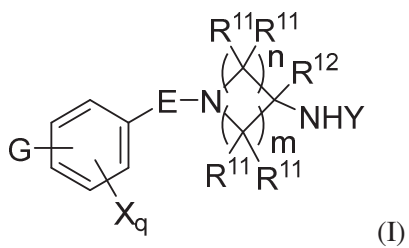
R¹⁸ is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -OR²², -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹.

each R²¹ is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and
each R²² is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[0002b] In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula (I) as described herein, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0003] Provided herein are inhibitors of cyclin-dependent kinases (CDKs), pharmaceutical compositions comprising said compounds, and methods for using said compounds for the treatment of diseases.

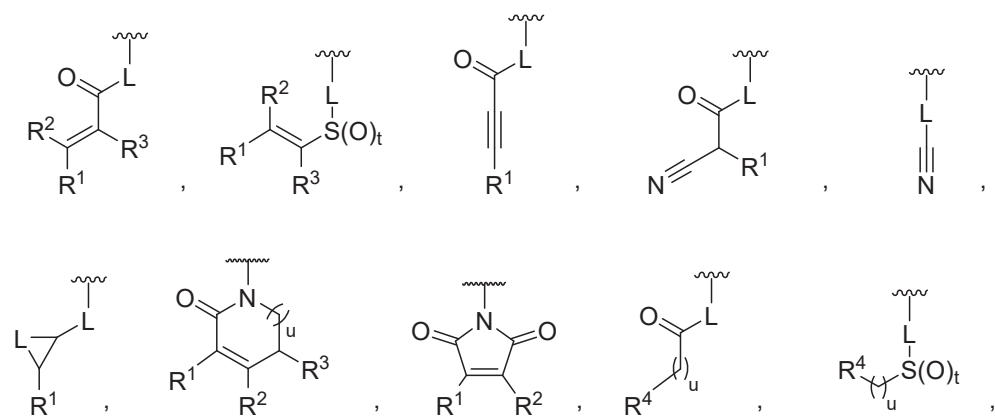
[0004] One ~~embodiment~~example provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (I):

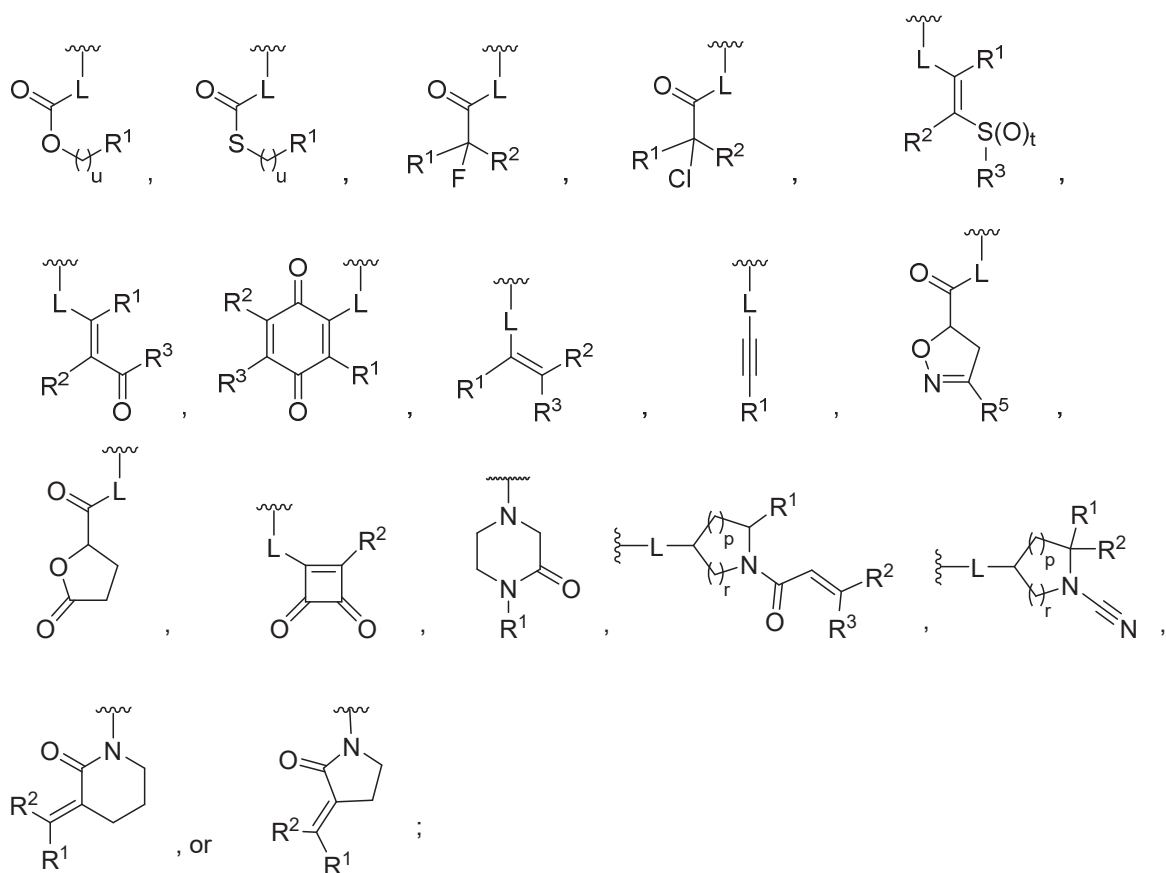


wherein,

E is selected from a bond, $-\text{SO}_2-$, $-\text{C}(\text{O})-$, $-\text{CH}_2-$, $-\text{CH}(\text{R}^4)-$, or $-\text{C}(\text{R}^4)_2-$;

G is selected from a group having the structure:





wherein,

L is O, NH, N(optionally substituted C1-C4 alkyl), or -NH-CH₂-* wherein the * denotes the point of attachment to the phenyl ring;

t is 0, 1, or 2;

u is 1, or 2;

p is 0, 1, or 2;

r is 0, 1, or 2;

R¹ is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

R² is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R³ is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R⁴ is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

R⁵ is optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

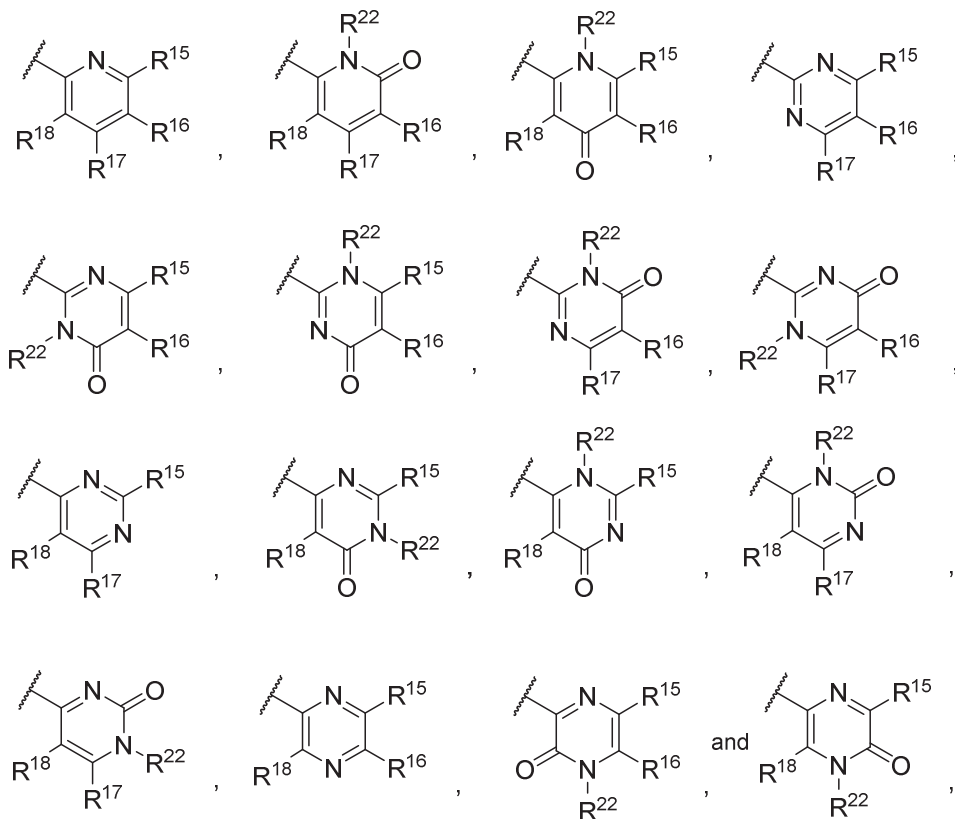
each R¹¹ is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, -OH, optionally substituted C1-C4 alkoxy, or two R¹¹ groups on the same carbon atom form an oxo;

R¹² is hydrogen or optionally substituted C1-C4 alkyl;

q is 0, 1, 2, or 3; n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -OR²², -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl,

optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-\text{OR}^{22}$, $-\text{N}(\text{R}^{22})_2$, $-\text{SO}_2\text{R}^{21}$, $-\text{N}(\text{R}^{22})\text{SO}_2\text{R}^{21}$, $-\text{SO}_2\text{N}(\text{R}^{22})_2$, $-\text{N}(\text{R}^{22})\text{SO}_2\text{N}(\text{R}^{22})_2$, $-\text{CON}(\text{R}^{22})_2$, $-\text{N}(\text{R}^{22})\text{CO}_2\text{R}^{21}$, $-\text{N}(\text{R}^{22})\text{CON}(\text{R}^{22})_2$, $-\text{N}(\text{R}^{22})\text{COR}^{21}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{22})_2$, $-\text{OSO}_2\text{N}(\text{R}^{22})_2$, or $-\text{N}(\text{R}^{22})\text{SO}_3\text{R}^{21}$;

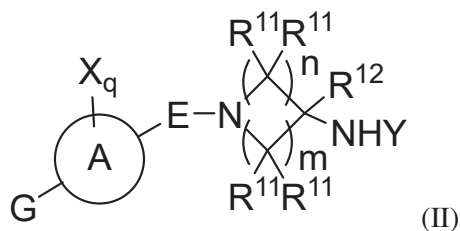
R^{17} is selected from hydrogen, halogen, $-\text{CN}$, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-\text{OR}^{22}$, $-\text{N}(\text{R}^{22})_2$, $-\text{SO}_2\text{R}^{21}$, $-\text{N}(\text{R}^{22})\text{SO}_2\text{R}^{21}$, $-\text{SO}_2\text{N}(\text{R}^{22})_2$, $-\text{N}(\text{R}^{22})\text{SO}_2\text{N}(\text{R}^{22})_2$, $-\text{CON}(\text{R}^{22})_2$, $-\text{N}(\text{R}^{22})\text{CO}_2\text{R}^{21}$, $-\text{N}(\text{R}^{22})\text{CON}(\text{R}^{22})_2$, $-\text{N}(\text{R}^{22})\text{COR}^{21}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{22})_2$, $-\text{OSO}_2\text{N}(\text{R}^{22})_2$, or $-\text{N}(\text{R}^{22})\text{SO}_3\text{R}^{21}$;

R^{18} is selected from hydrogen, halogen, $-\text{CN}$, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-\text{OR}^{22}$, $-\text{N}(\text{R}^{22})_2$, $-\text{SO}_2\text{R}^{21}$, $-\text{N}(\text{R}^{22})\text{SO}_2\text{R}^{21}$, $-\text{SO}_2\text{N}(\text{R}^{22})_2$, $-\text{N}(\text{R}^{22})\text{SO}_2\text{N}(\text{R}^{22})_2$, $-\text{CON}(\text{R}^{22})_2$, $-\text{N}(\text{R}^{22})\text{CO}_2\text{R}^{21}$, $-\text{N}(\text{R}^{22})\text{CON}(\text{R}^{22})_2$, $-\text{N}(\text{R}^{22})\text{COR}^{21}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{22})_2$, $-\text{OSO}_2\text{N}(\text{R}^{22})_2$, or $-\text{N}(\text{R}^{22})\text{SO}_3\text{R}^{21}$;

each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[0005] One [embodiment example](#) provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (II):

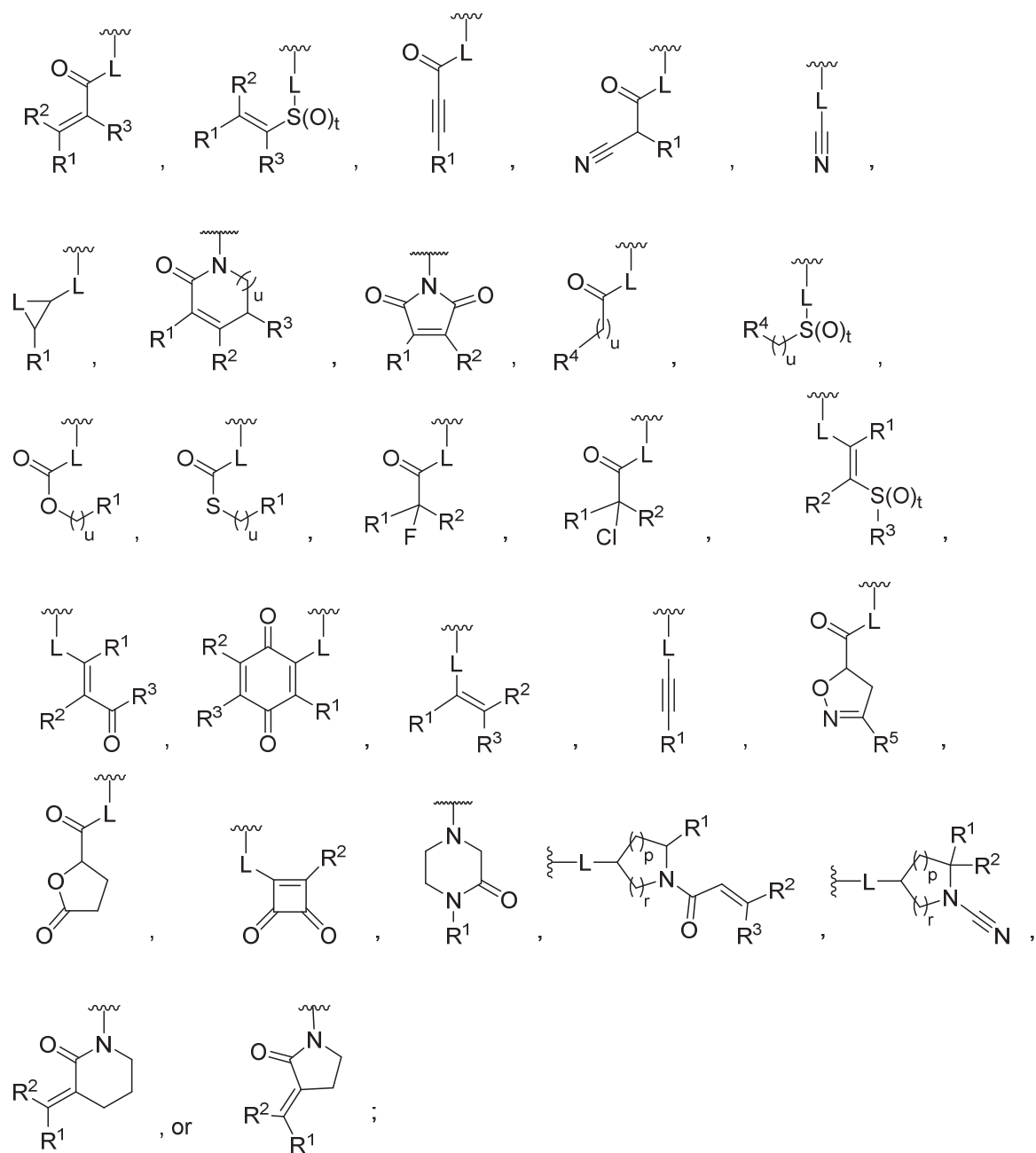


wherein,

ring A is a monocyclic heteroaryl;

E is selected from a bond, $-\text{SO}_2-$, $-\text{C}(\text{O})-$, $-\text{CH}_2-$, $-\text{CH}(\text{R}^4)-$, or $-\text{C}(\text{R}^4)_2-$;

G is selected from a group having the structure:



wherein,

L is O, NH, or N(optionally substituted C1-C4 alkyl);

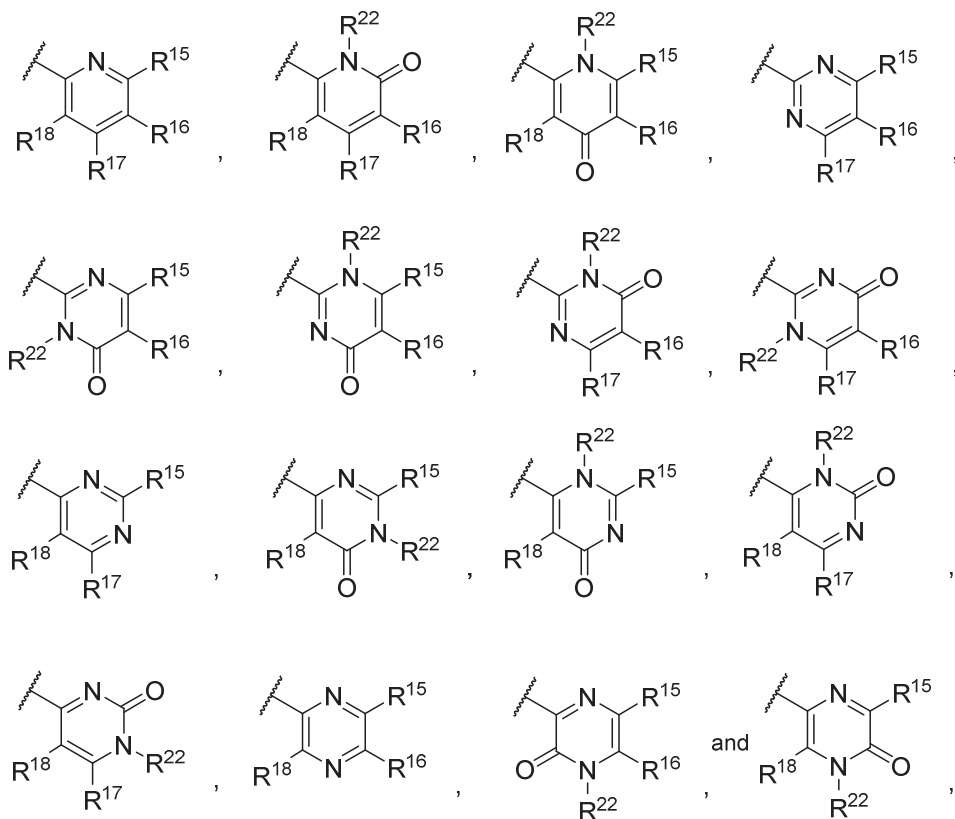
t is 0, 1, or 2;

u is 1, or 2;

p is 0, 1, or 2;

r is 0, 1, or 2;

R^1 is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;
 R^2 is selected from hydrogen, or optionally substituted C1-C4 alkyl;
 R^3 is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;
each R^4 is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;
 R^5 is optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;
each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, -OH, optionally substituted C1-C4 alkoxy, or two R^{11} groups on the same carbon atom form an oxo;
 R^{12} is hydrogen or optionally substituted C1-C4 alkyl;
q is 0, 1, 2, or 3;
n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;
each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycl, optionally substituted aryl, or optionally substituted heteroaryl;
Y is a group selected from:



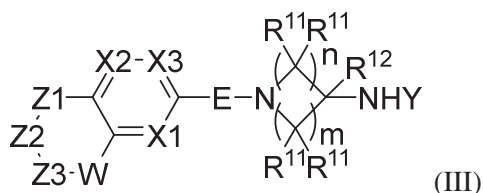
wherein,

-CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹;

each R²¹ is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R²² is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[0006] One ~~embodiment~~example provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (III):



wherein,

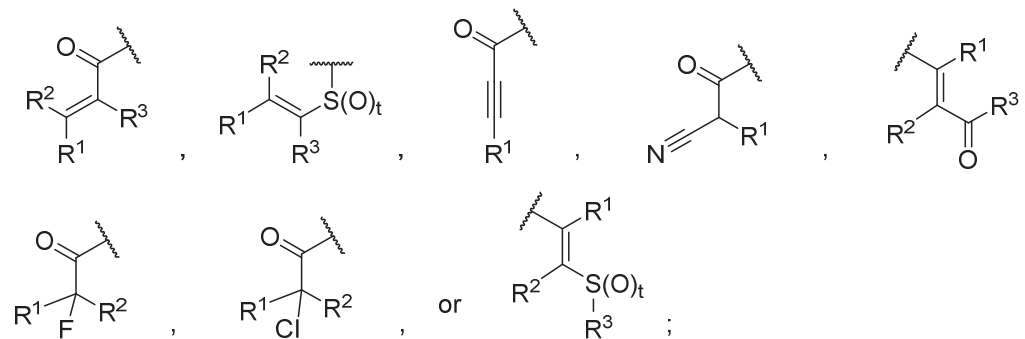
Z1, Z2, and Z3 are selected from CH₂ or N-G, with the provision that only one of Z1, Z2, or Z3 is N-G;

X1, X2 and X3 are each independently N or C-R⁷;

W is absent, O, S, SO₂, NH, NR¹², C(R¹¹)₂;

E is selected from a bond, -SO₂-, -C(O)-, -CH₂-, -CH(R⁴)-, or -C(R⁴)₂-;

G is selected from a group having the structure:



wherein,

t is 0, 1, or 2;

R¹ is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R² is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R³ is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R⁴ is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

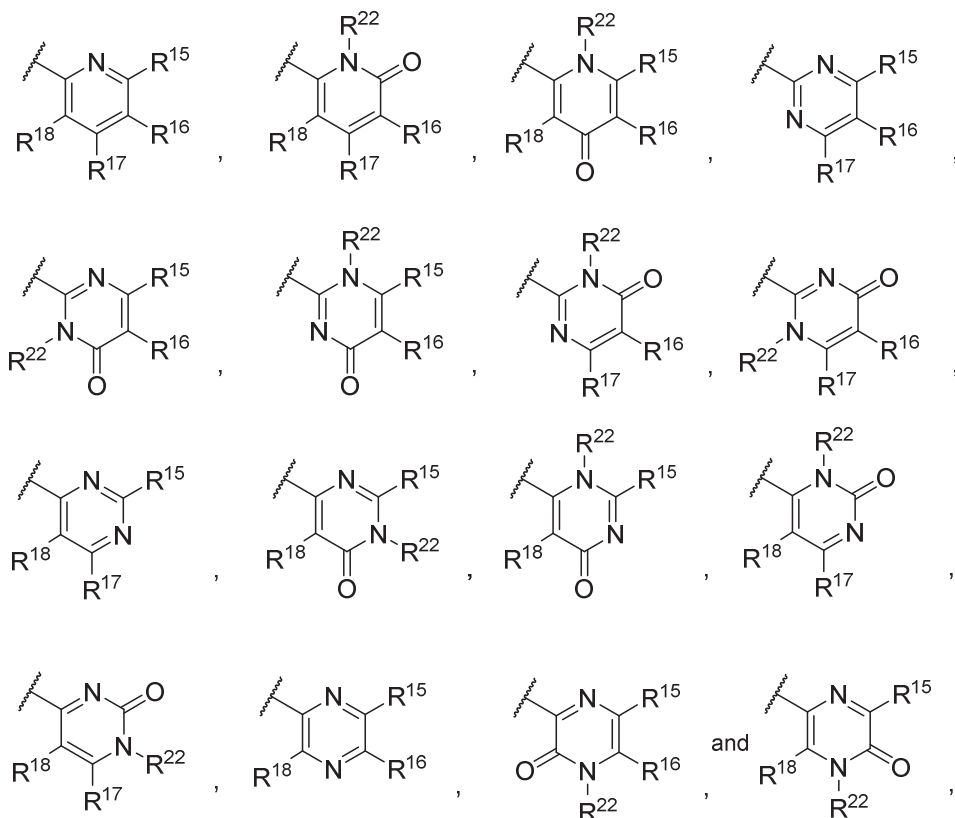
each R^7 is independently hydrogen, halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl

each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, or two R^{11} groups on the same carbon atom form an oxo;

each R^{12} is independently hydrogen or optionally substituted C1-C4 alkyl;

n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R¹⁶ is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹;

R¹⁷ is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹;

R¹⁸ is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹;

each R²¹ is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R²² is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[0007] One [embodiment example](#) provides a pharmaceutical composition comprising a compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0008] One [embodiment example](#) provides a method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (I), or pharmaceutically acceptable

salt or solvate thereof. Another [embodimentexample](#) provides the method wherein the disease or disorder is cancer.

[0009] One [embodimentexample](#) provides a method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof. Another [embodimentexample](#) provides the method wherein the disease or disorder is cancer.

[0010] One [embodimentexample](#) provides a pharmaceutical composition comprising a compound of Formula (II), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0011] One [embodimentexample](#) provides a method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (II), or pharmaceutically acceptable salt or solvate thereof. Another [embodimentexample](#) provides the method wherein the disease or disorder is cancer.

[0012] One [embodimentexample](#) provides a method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (II), or pharmaceutically acceptable salt or solvate thereof. Another [embodimentexample](#) provides the method wherein the disease or disorder is cancer.

[0013] One [embodimentexample](#) provides a pharmaceutical composition comprising a compound of Formula (III), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0014] One [embodimentexample](#) provides a method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (III), or pharmaceutically acceptable salt or solvate thereof. Another [embodimentexample](#) provides the method wherein the disease or disorder is cancer.

[0015] One [embodimentexample](#) provides a method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (III), or pharmaceutically acceptable salt or solvate thereof. Another [embodimentexample](#) provides the method wherein the disease or disorder is cancer.

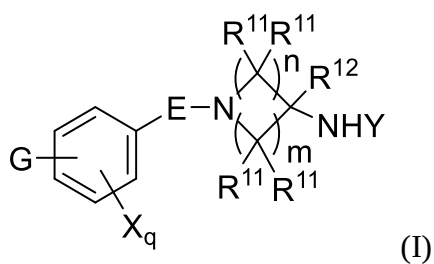
INCORPORATION BY REFERENCE

[0016] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference for the specific purposes identified herein.

CLAIMS

We claim:

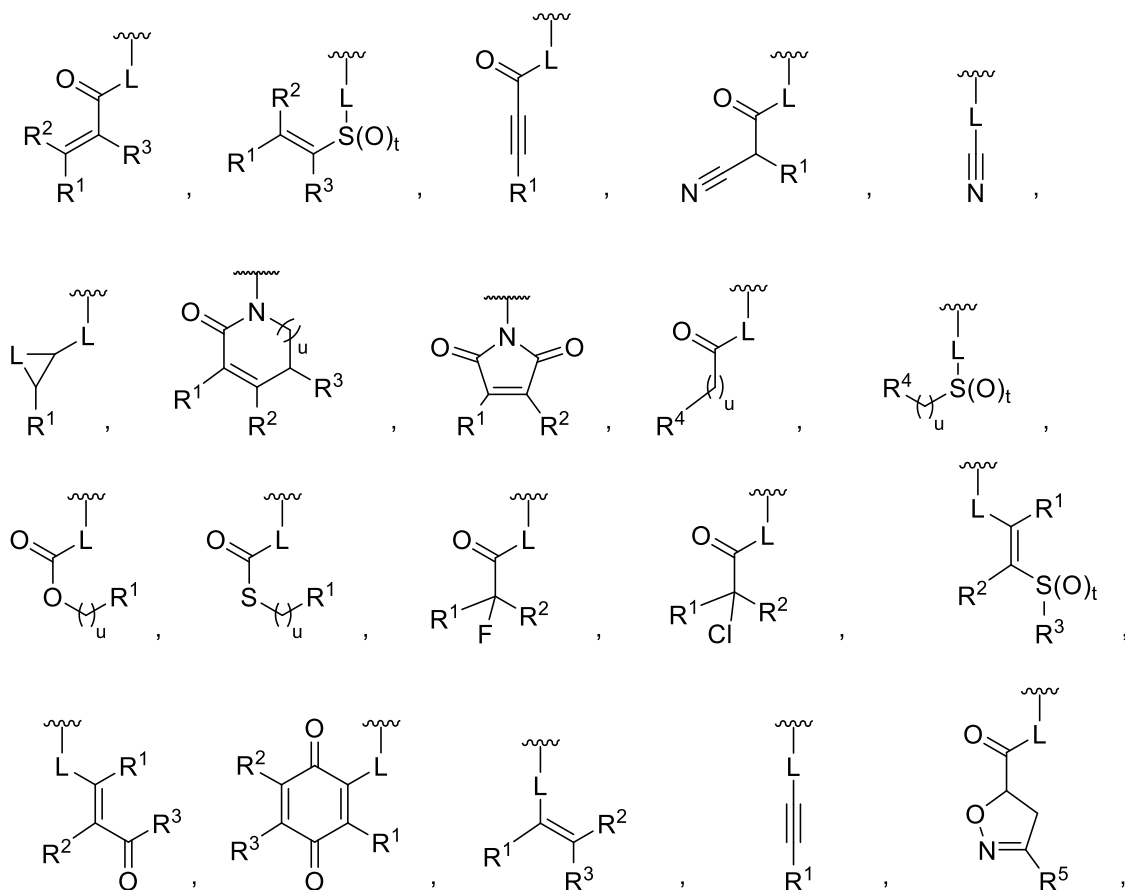
1. A compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (I):

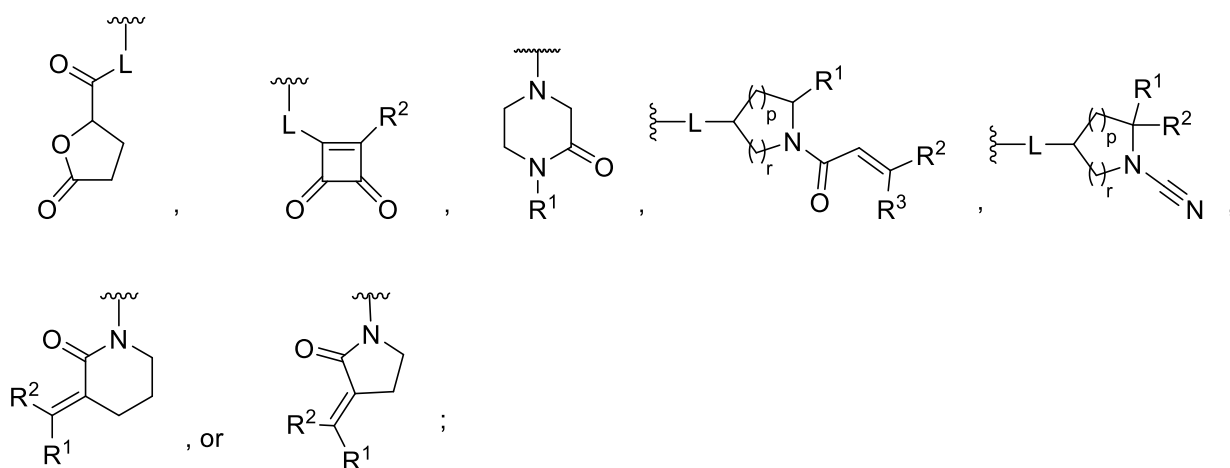


wherein,

E is ~~-C(O)-selected from a bond, -SO₂-, -C(O)-, -CH₂-, -CH(R⁴)-, or -C(R⁴)₂-;~~

G is selected from a group having the structure:





wherein,

L is O, NH, N(optionally substituted C1-C4 alkyl), or -NH-CH₂-* wherein the * denotes the point of attachment to the phenyl ring;

t is 0, 1, or 2;

u is 1, or 2;

p is 0, 1, or 2;

r is 0, 1, or 2;

R¹ is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

R² is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R³ is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R⁴ is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

R⁵ is optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

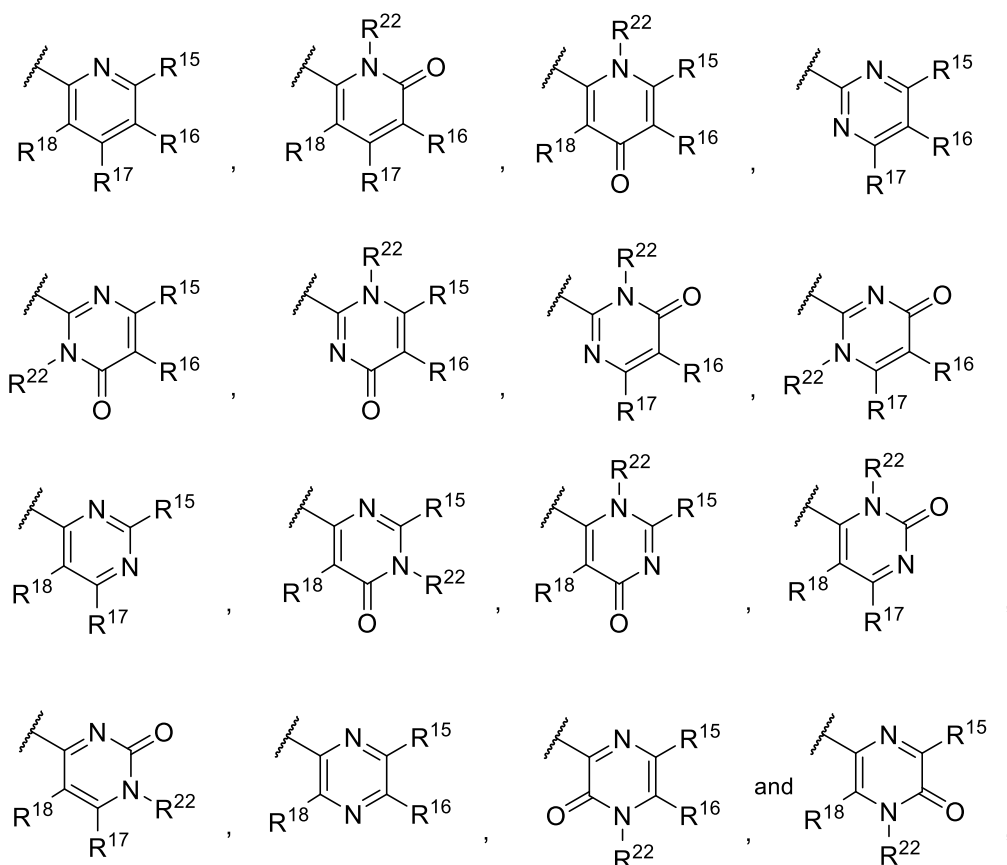
each R¹¹ is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, -OH, optionally substituted C1-C4 alkoxy, or two R¹¹ groups on the same carbon atom form an oxo;

R¹² is hydrogen or optionally substituted C1-C4 alkyl;

q is 0, 1, 2, or 3; n is ~~0, 1, 2, or 3~~; m is ~~0, 1, 2~~, or 3;

each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -OR²², -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, ~~optionally substituted heteroaryl~~, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -OR²², -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹;

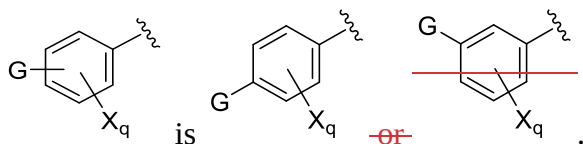
R¹⁷ is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -OR²², -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹;

R¹⁸ is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -OR²², -N(R²²)₂, -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹;

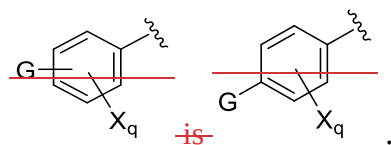
each R²¹ is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R²² is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

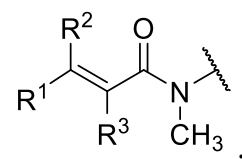
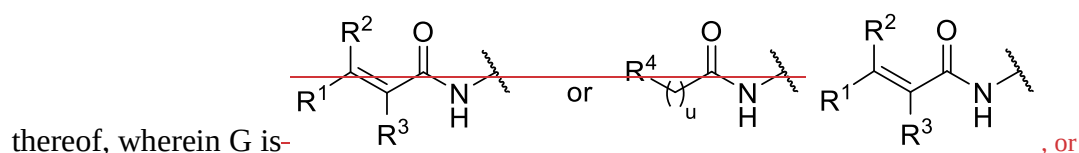
2. The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein



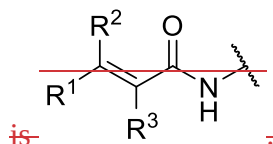
3. The compound of claim ~~1~~ 2, or pharmaceutically acceptable salt or solvate thereof, wherein q is 0 or 1



4. The compound of ~~any one of~~ claims 1-3, or pharmaceutically acceptable salt or solvate



5. ~~The compound of claim 4, or pharmaceutically acceptable salt or solvate thereof, wherein G~~



6.5. The compound of claim 45 or pharmaceutically acceptable salt or solvate thereof, wherein R³ is hydrogen or -CN.

7. ~~The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein L is NH.~~

8. ~~The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein t is 2.~~

9. ~~The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein q is 0, 1, or 2.~~

10. ~~The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein q is 0, or 1.~~

11. ~~The compound of any one of claims 1-10, or pharmaceutically acceptable salt or solvate thereof, wherein X is a halogen.~~

12.6. The compound of ~~any one of~~ claims 41-41, or pharmaceutically acceptable salt or solvate thereof, wherein R² is hydrogen.

13.7. The compound of ~~any one of~~ claims 41-42, or pharmaceutically acceptable salt or solvate thereof, wherein R³ is hydrogen.

14. ~~The compound of any one of claims 1-13, or pharmaceutically acceptable salt or solvate thereof, wherein R² and R³ is hydrogen.~~

15.8. The compound of ~~any one of~~ claims 41-44, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is hydrogen.

16.9. The compound of ~~any one of~~ claims 41-44, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is optionally substituted C1-C4 alkyl.

~~17. The compound of any one of claims 1-14, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is optionally substituted C1-C2 alkyl.~~

~~18.10.~~ The compound of ~~any one of~~ claims ~~91-14~~, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is optionally substituted C1 alkyl.

~~19.11.~~ The compound of claim ~~108~~, or pharmaceutically acceptable salt or solvate thereof, wherein the C1 alkyl is substituted with an optionally substituted amino group.

~~20. The compound of claim 19, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted amino group is a dimethylamino.~~

~~21. The compound of any one of claims 1-14, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is —CH₂—N(Me)₂.~~

~~22.12.~~ The compound of ~~any one of~~ claims ~~41-14~~, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is optionally substituted heterocyclalkyl.

~~23.13.~~ The compound of claim ~~122~~, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclalkyl comprises an optionally substituted C1 alkyl.

~~24. The compound of claim 22 or 23, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclalkyl comprises and an optionally substituted N-linked heterocycl.~~

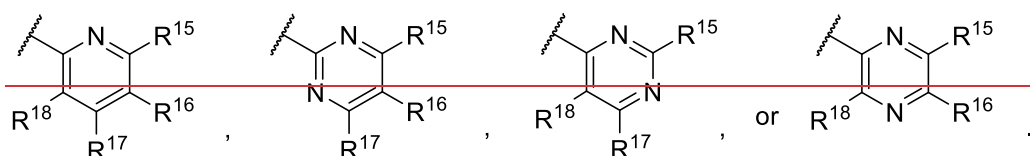
~~25.14.~~ The compound of claim ~~1324~~, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted N-linked heterocycl is an N-linked pyrrolidine or piperidine.

~~26. The compound of any one of claims 1-25, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 1.~~

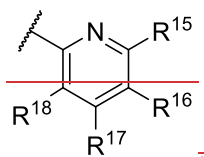
~~27.15.~~ The compound of ~~any one of~~ claims 1-25, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 2.

~~28. The compound of any one of claims 1-25, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 3.~~

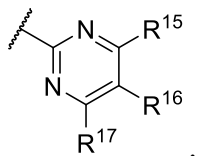
~~29. The compound of any one of claims 1-28, or pharmaceutically acceptable salt or solvate thereof, wherein Y is selected from:~~



~~30. The compound of any one of claims 1-28, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:~~



~~31.16.~~ The compound of ~~any one of~~ claims ~~1-28~~, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:



~~32.17.~~ The compound of ~~any one of~~ claims ~~1629-31~~, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁵ is hydrogen.

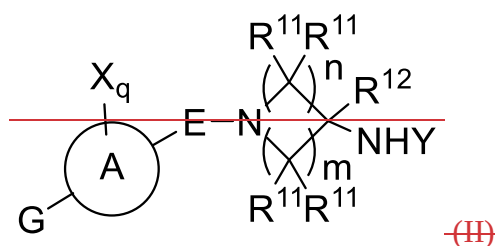
~~33.— The compound of any one of claims 29-31, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁶ is hydrogen.~~

~~34.18.~~ The compound of ~~any one of~~ claims ~~1629-31~~, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁷ is hydrogen.

~~35.— The compound of any one of claims 29-31, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁸ is hydrogen.~~

~~36.19.~~ The compound of ~~any one of~~ claims ~~1629-31~~, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁵ and R¹⁶ are hydrogen.

~~37.— A compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (II):~~

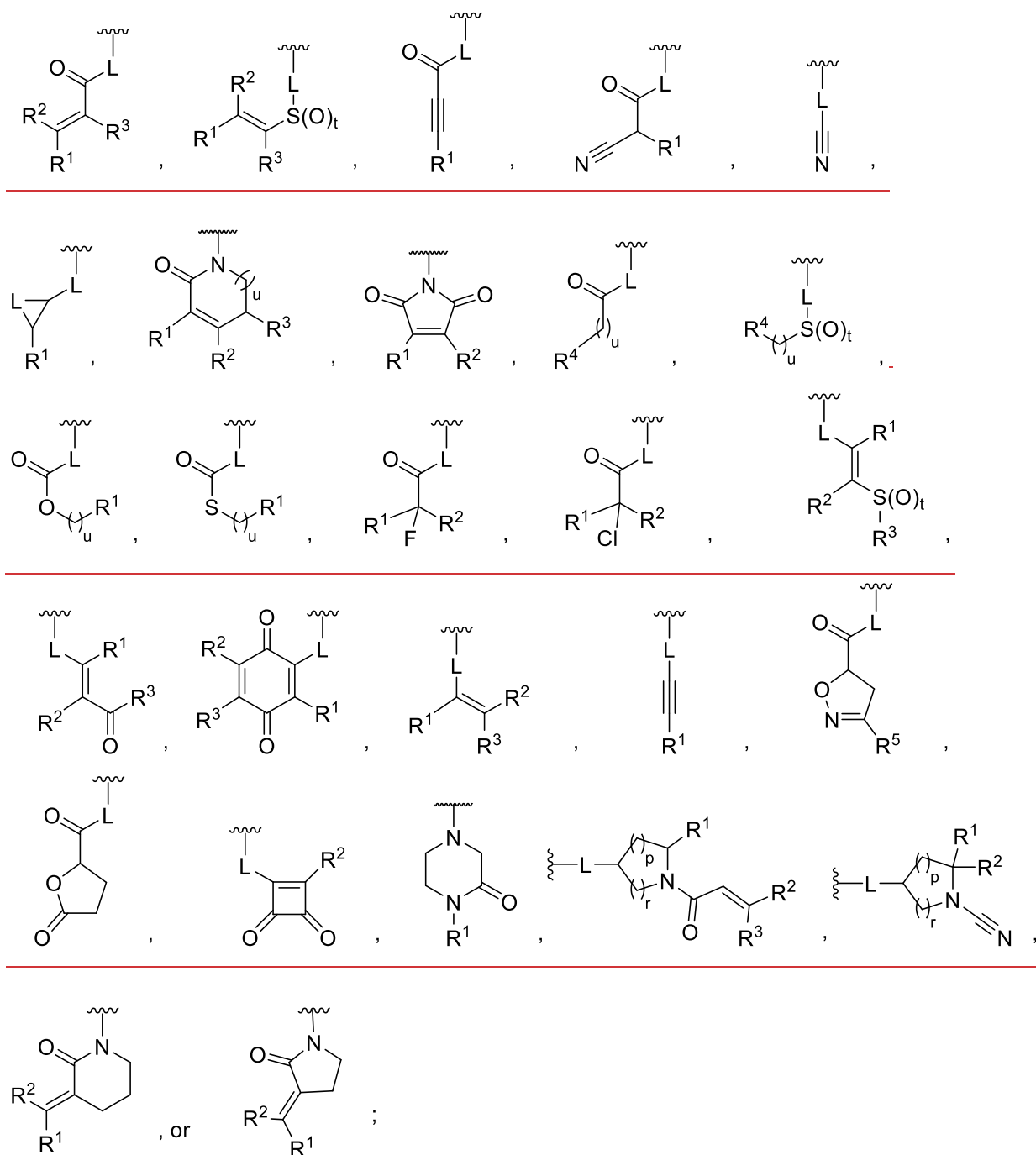


~~wherein,~~

~~ring A is a monocyclic heteroaryl;~~

~~E is selected from a bond, SO₂, C(O), CH₂, CH(R⁴), or C(R⁴)₂;~~

~~G is selected from a group having the structure:~~



wherein,

L is O, NH, or N(optionally substituted C1-C4 alkyl);

t is 0, 1, or 2;

u is 1, or 2;

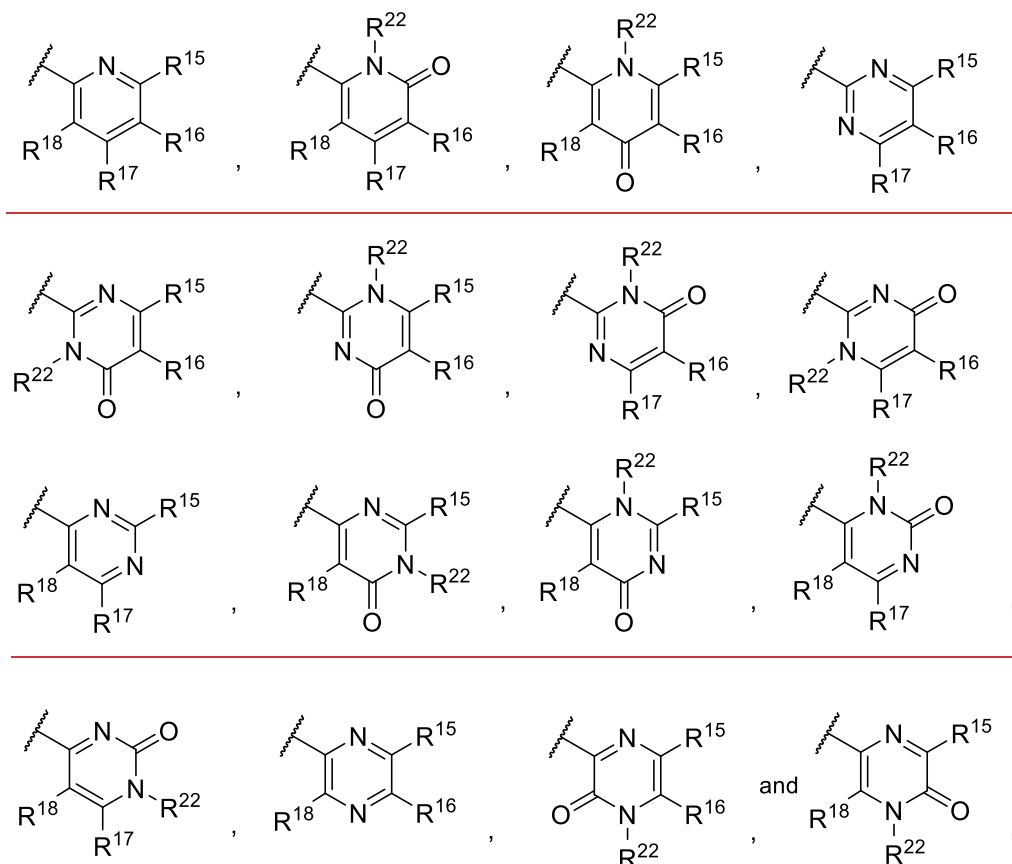
p is 0, 1, or 2;

r is 0, 1, or 2;

R¹ is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

R² is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R^3 is selected from hydrogen, ~~CN~~, or optionally substituted C1-C4 alkyl;
each R^4 is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;
 R^5 is optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;
each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, ~~OH~~, optionally substituted C1-C4 alkoxy, or two R^{11} groups on the same carbon atom form an oxo;
 R^{12} is hydrogen or optionally substituted C1-C4 alkyl;
 q is 0, 1, 2, or 3;
 n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;
each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycl, optionally substituted aryl, or optionally substituted heteroaryl;
 Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, ~~CN~~, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted

heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, OR^{22} , $\text{N(R}^{22})_2$, SO_2R^{21} , $\text{N(R}^{22})\text{SO}_2\text{R}^{21}$, $\text{SO}_2\text{N(R}^{22})_2$, $\text{N(R}^{22})\text{SO}_2\text{N(R}^{22})_2$, $\text{CON(R}^{22})_2$, $\text{N(R}^{22})\text{CO}_2\text{R}^{21}$, $\text{N(R}^{22})\text{CON(R}^{22})_2$, $\text{N(R}^{22})\text{COR}^{21}$, $\text{OC(O)N(R}^{22})_2$, $\text{OSO}_2\text{N(R}^{22})_2$, or $\text{N(R}^{22})\text{SO}_3\text{R}^{21}$;

R^{16} is selected from hydrogen, halogen, CN , optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, OR^{22} , $N(R^{22})_2$, SO_2R^{21} , $N(R^{22})SO_2R^{21}$, $SO_2N(R^{22})_2$, $N(R^{22})SO_2N(R^{22})_2$, $CON(R^{22})_2$, $N(R^{22})CO_2R^{21}$, $N(R^{22})CON(R^{22})_2$, $N(R^{22})COR^{21}$, $OC(O)N(R^{22})_2$, $OSO_2N(R^{22})_2$, or $N(R^{22})SO_3R^{21}$;

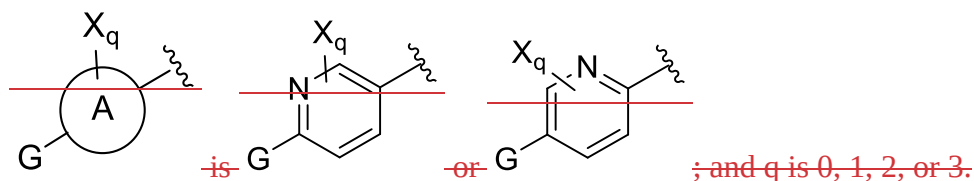
R^{17} is selected from hydrogen, halogen, CN , optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl O , optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, OR^{22} , $N(R^{22})_2$, SO_2R^{21} , $N(R^{22})SO_2R^{21}$, $SO_2N(R^{22})_2$, $N(R^{22})SO_2N(R^{22})_2$, $CON(R^{22})_2$, $N(R^{22})CO_2R^{21}$, $N(R^{22})CON(R^{22})_2$, $N(R^{22})COR^{21}$, $OC(O)N(R^{22})_2$, $OSO_2N(R^{22})_2$, or $N(R^{22})SO_3R^{21}$;

R^{18} is selected from hydrogen, halogen, CN , optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, OR^{22} , $N(R^{22})_2$, SO_2R^{21} , $N(R^{22})SO_2R^{21}$, $SO_2N(R^{22})_2$, $N(R^{22})SO_2N(R^{22})_2$, $CON(R^{22})_2$, $N(R^{22})CO_2R^{21}$, $N(R^{22})CON(R^{22})_2$, $N(R^{22})COR^{21}$, $OC(O)N(R^{22})_2$, $OSO_2N(R^{22})_2$, or $N(R^{22})SO_3R^{21}$;

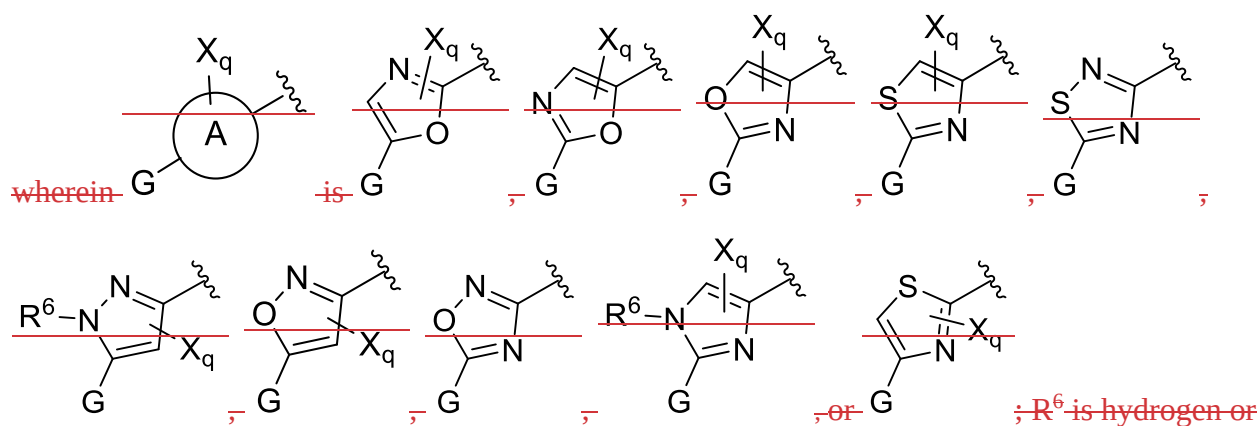
each R²¹ is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

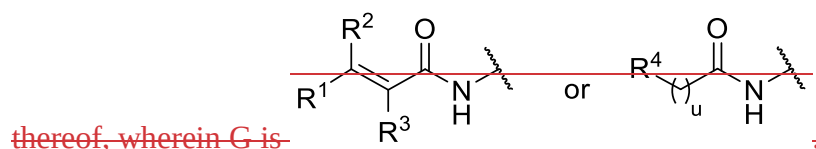
38. ~~The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof, wherein~~



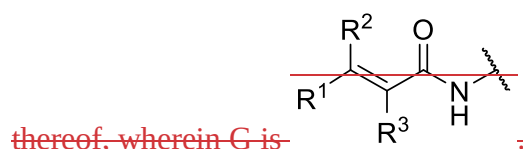
39. ~~The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof,~~



40. ~~The compound of any one of claims 37-39, or pharmaceutically acceptable salt or solvate~~



41. ~~The compound of any one of claims 37-40, or pharmaceutically acceptable salt or solvate~~



42. ~~The compound of claim 41 or pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen or CN.~~

43. ~~The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof, wherein L is NH.~~

44. ~~The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof, wherein t is 2.~~

45. ~~The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof, wherein q is 0 or 1.~~

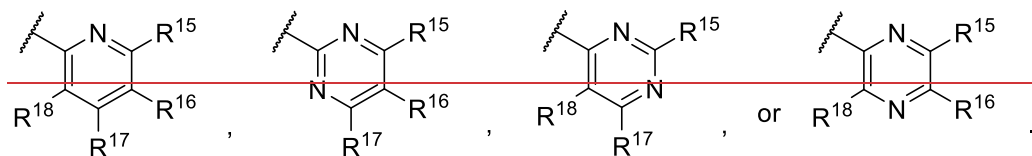
46. — ~~The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof, wherein q is 0.~~
47. — ~~The compound of any one of claims 37-46, or pharmaceutically acceptable salt or solvate thereof, wherein X is a halogen.~~
48. — ~~The compound of any one of claims 37-47, or pharmaceutically acceptable salt or solvate thereof, wherein R² is hydrogen.~~
49. — ~~The compound of any one of claims 37-47, or pharmaceutically acceptable salt or solvate thereof, wherein R³ is hydrogen.~~
50. — ~~The compound of any one of claims 37-47, or pharmaceutically acceptable salt or solvate thereof, wherein R² and R³ is hydrogen.~~
51. — ~~The compound of any one of claims 37-50, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is hydrogen.~~
52. — ~~The compound of any one of claims 37-50, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is optionally substituted C1-C4 alkyl.~~
53. — ~~The compound of any one of claims 37-50, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is optionally substituted C1-C2 alkyl.~~
54. — ~~The compound of any one of claims 37-50, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is optionally substituted C1 alkyl.~~
55. — ~~The compound of claim 54, or pharmaceutically acceptable salt or solvate thereof, wherein the C1 alkyl is substituted with an optionally substituted amino group.~~
56. — ~~The compound of claim 55, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted amino group is a dimethylamino.~~
57. — ~~The compound of any one of claims 37-56, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is —CH₂—N(Me)₂.~~
58. — ~~The compound of any one of claims 37-54, or pharmaceutically acceptable salt or solvate thereof, wherein R¹ is optionally substituted heterocyclalkyl.~~
59. — ~~The compound of claim 58, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclalkyl comprises an optionally substituted C1 alkyl.~~
60. — ~~The compound of claim 58 or 59, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclalkyl comprises an optionally substituted N-linked heterocycl.~~
61. — ~~The compound of claim 60, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted N-linked heterocycl is an N-linked pyrrolidine or piperidine.~~

62. — ~~The compound of any one of claims 37-61, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 1.~~

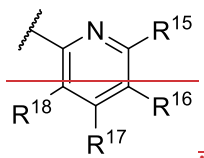
63. — ~~The compound of any one of claims 37-61, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 2.~~

64. — ~~The compound of any one of claims 37-61, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 3.~~

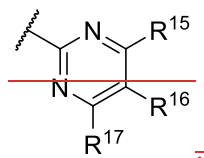
65. — ~~The compound of any one of claims 37-64, or pharmaceutically acceptable salt or solvate thereof, wherein Y is selected from:~~



66. — ~~The compound of any one of claims 37-64, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:~~



67. — ~~The compound of any one of claims 37-64, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:~~



68. — ~~The compound of any one of claims 65-67, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁵ is hydrogen.~~

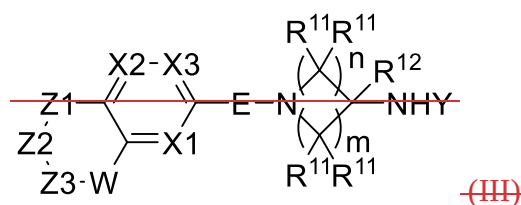
69. — ~~The compound of any one of claims 65-67, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁶ is hydrogen.~~

70. — ~~The compound of any one of claims 65-67, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁷ is hydrogen.~~

71. — ~~The compound of any one of claims 65-67, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁸ is hydrogen.~~

72. — ~~The compound of any one of claims 65-67, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁵ and R¹⁶ are hydrogen.~~

73. — ~~A compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (III):~~



wherein,

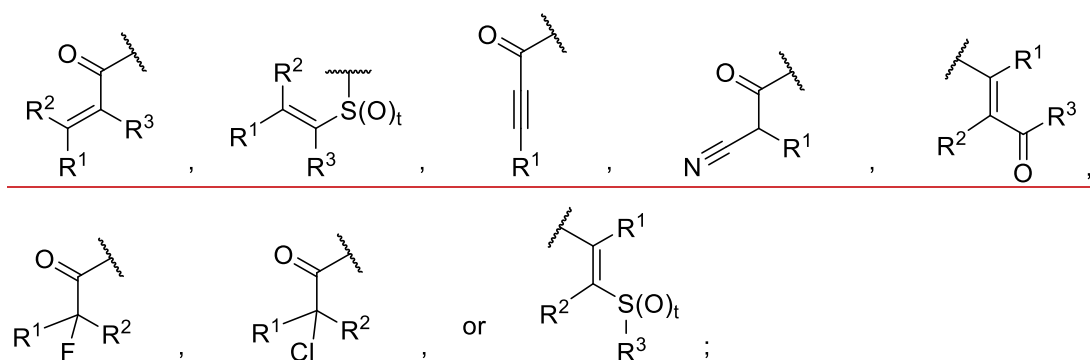
Z1, Z2, and Z3 are selected from CH₂ or N-G, with the provision that only one of Z1, Z2, or Z3 is N-G;

X1, X2 and X3 are each independently N or C-R⁷;

W is absent, O, S, SO₂, NH, NR¹², C(R¹¹)₂;

E is selected from a bond, SO₂, C(O), CH₂, CH(R⁴), or C(R⁴)₂;

G is selected from a group having the structure:



wherein,

t is 0, 1, or 2;

R¹ is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

R² is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R³ is selected from hydrogen, CN, or optionally substituted C1-C4 alkyl;

each R⁴ is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclalkyl;

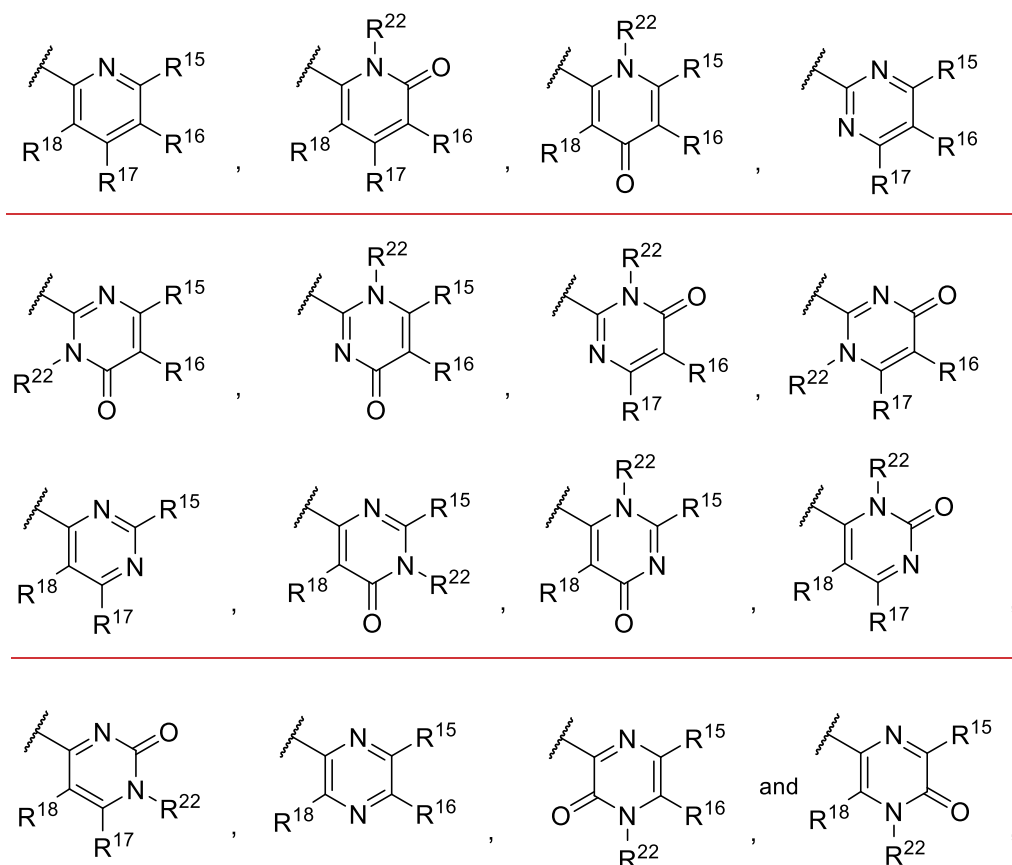
each R⁷ is independently hydrogen, halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycl, optionally substituted aryl, or optionally substituted heteroaryl

each R¹¹ is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, or two R¹¹ groups on the same carbon atom form an oxo;

each R¹² is independently hydrogen or optionally substituted C1-C4 alkyl;

n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

Y is a group selected from:



wherein,

R¹⁵ is selected from hydrogen, halogen, ~~CN~~, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, ~~N(R²²)₂, SO₂R²¹, N(R²²)SO₂R²¹, SO₂N(R²²)₂, N(R²²)SO₂N(R²²)₂, CON(R²²)₂, N(R²²)CO₂R²¹, N(R²²)CON(R²²)₂, N(R²²)COR²¹, OC(O)N(R²²)₂, OSO₂N(R²²)₂, or N(R²²)SO₃R²¹;~~

R¹⁶ is selected from hydrogen, halogen, ~~CN~~, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, ~~N(R²²)₂, SO₂R²¹, N(R²²)SO₂R²¹, SO₂N(R²²)₂, N(R²²)SO₂N(R²²)₂, CON(R²²)₂, N(R²²)CO₂R²¹, N(R²²)CON(R²²)₂, N(R²²)COR²¹, OC(O)N(R²²)₂, OSO₂N(R²²)₂, or N(R²²)SO₃R²¹;~~

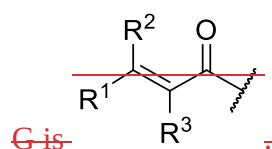
R^{17} is selected from hydrogen, halogen, $-CN$, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{18} is selected from hydrogen, halogen, $-CN$, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

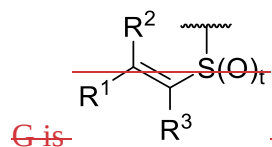
each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

74. The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein



75. The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein



76. The compound of claim 74 or 75 or pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen or $-CN$.

77. The compound of claim 73 or 75, or pharmaceutically acceptable salt or solvate thereof, wherein t is 2.

~~78. — The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein W is O.~~

~~79. — The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein W is CH_2 .~~

~~80. — The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein W is NH or NR^{12} .~~

~~81. — The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein W is SO_2 .~~

~~82. — The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein W is absent.~~

~~83. — The compound of any one of claims 73–82, or pharmaceutically acceptable salt or solvate thereof, wherein R^2 is hydrogen.~~

~~84. — The compound of any one of claims 73–83, or pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen.~~

~~85. — The compound of any one of claims 73–83, or pharmaceutically acceptable salt or solvate thereof, wherein R^2 and R^3 is hydrogen.~~

~~86. — The compound of any one of claims 73–85, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is hydrogen.~~

~~87. — The compound of any one of claims 73–85, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1–C4 alkyl.~~

~~88. — The compound of any one of claims 73–85, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1–C2 alkyl.~~

~~89. — The compound of any one of claims 73–85, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1 alkyl.~~

~~90. — The compound of claim 89, or pharmaceutically acceptable salt or solvate thereof, wherein the C1 alkyl is substituted with an optionally substituted amino group.~~

~~91. — The compound of claim 90, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted amino group is a dimethylamino.~~

~~92. — The compound of any one of claims 73–85, or 87–91, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $\text{CH}_2\text{N}(\text{Me})_2$.~~

~~93. — The compound of any one of claims 73–85, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted heterocyclalkyl.~~

~~94. — The compound of claim 93, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclalkyl comprises an optionally substituted C1 alkyl.~~

95. — ~~The compound of claim 93 or 94, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclalkyl comprises an optionally substituted N-linked heterocycl.~~

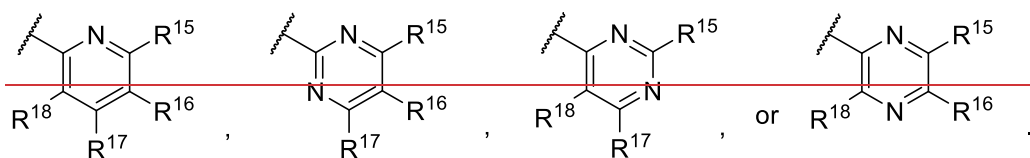
96. — ~~The compound of claim 95, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted N-linked heterocycl is an N-linked pyrrolidine or piperidine.~~

97. — ~~The compound of any one of claims 73-96, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 1.~~

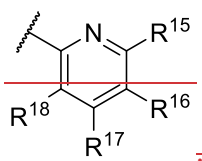
98. — ~~The compound of any one of claims 73-96, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 2.~~

99. — ~~The compound of any one of claims 73-96, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 3.~~

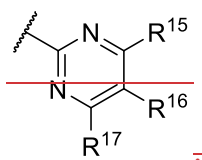
100. — ~~The compound of any one of claims 73-99, or pharmaceutically acceptable salt or solvate thereof, wherein Y is selected from:~~



101. — ~~The compound of any one of claims 73-100, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:~~



102. — ~~The compound of any one of claims 73-100, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:~~



103. — ~~The compound of any one of claims 100-102, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁵ is hydrogen.~~

104. — ~~The compound of any one of claims 100-102, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁶ is hydrogen.~~

105. — ~~The compound of any one of claims 100-102, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁷ is hydrogen.~~

~~106.—The compound of any one of claims 100–102, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁸ is hydrogen.~~

~~107.—The compound of any one of claims 100–102, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁵ and R¹⁶ are hydrogen.~~

~~108.—The compound of any one of claims 1–107, or pharmaceutically acceptable salt or solvate thereof, wherein E is a bond.~~

~~109.—The compound of any one of claims 1–107, or pharmaceutically acceptable salt or solvate thereof, wherein E is —SO₂—.~~

~~110.—The compound of any one of claims 1–107, or pharmaceutically acceptable salt or solvate thereof, wherein E is —C(O)—.~~

~~111.—The compound of any one of claims 1–107, or pharmaceutically acceptable salt or solvate thereof, wherein E is —CH₂—.~~

~~112.—The compound of any one of claims 1–107, or pharmaceutically acceptable salt or solvate thereof, wherein E is —CH(R⁴)—.~~

~~113.—The compound of any one of claims 1–107, or pharmaceutically acceptable salt or solvate thereof, wherein E is —C(R⁴)₂—.~~

~~114.—A compound, or pharmaceutically acceptable salt or solvate thereof, selected from a compound presented in Table 1.~~

~~115.—A compound, or pharmaceutically acceptable salt or solvate thereof, selected from a compound presented in Table 2.~~

~~116.—A compound, or pharmaceutically acceptable salt or solvate thereof, selected from a compound presented in Table 3.~~

20. The compound of claim 16, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁶ is not hydrogen.

21. The compound of claim 16, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁶ is halogen.

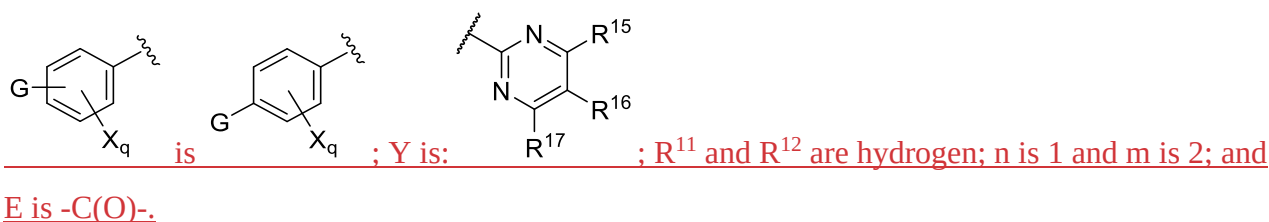
22. The compound of claim 16, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁶ is optionally substituted alkyl, optionally substituted fluoroalkyl, or optionally substituted alkynyl.

23. The compound of claim 16, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁶ is selected from halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkynyl.

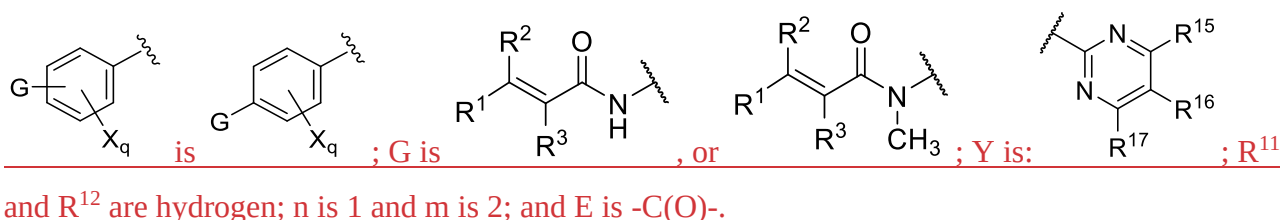
24. The compound of claim 16, or pharmaceutically acceptable salt or solvate thereof, wherein R¹⁵ is hydrogen, R¹⁶ is selected from halogen, -CN, optionally substituted alkyl, optionally

substituted fluoroalkyl, optionally substituted alkynyl, and R¹⁷ is hydrogen or optionally substituted alkoxy.

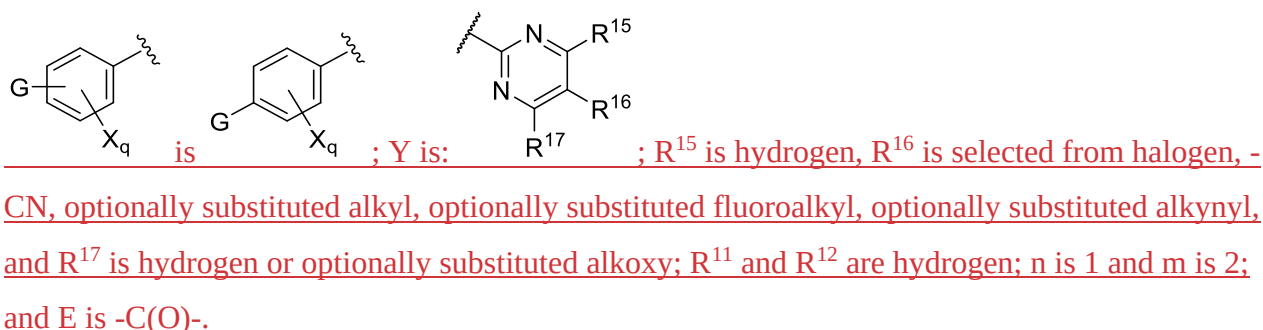
25. The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein



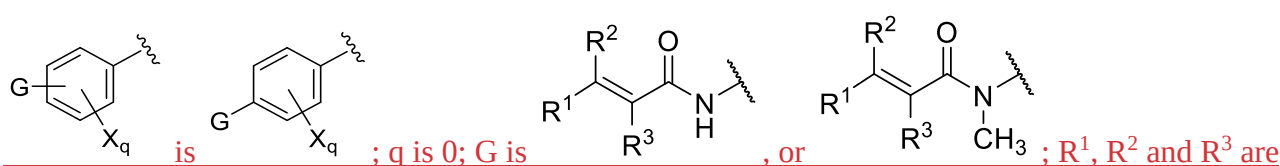
26. The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein

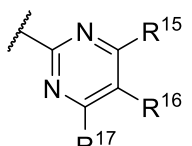
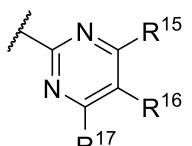


27. The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein



28. The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein




 each hydrogen; Y is: 
 ; R¹⁵ is hydrogen, R¹⁶ is selected from halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkynyl, and R¹⁷ is hydrogen or optionally substituted alkoxy; R¹¹ and R¹² are hydrogen; n is 1 and m is 2; and E is -C(O)-.

117:29. A pharmaceutical composition comprising a compound of Formula (I) as described in ~~any one of~~ claims 1-36 or 108-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

~~118.— A pharmaceutical composition comprising a compound of Formula (II) as described in any one of claims 37-72 or 108-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.~~

~~119.— A pharmaceutical composition comprising a compound of Formula (III) as described in any one of claims 73-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.~~

~~120.— A pharmaceutical composition comprising a compound as described in any one of claims 114-116, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.~~

~~121.— A method of preparing a pharmaceutical composition comprising mixing a compound of any one of claims 1-113, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.~~

~~122.— A compound of any one of claims 1-113, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body.~~

~~123.— A compound of any one of claims 1-113, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of cancer, neoplastic disease, or hyperproliferative disorder.~~

~~124.— Use of a compound of any one of claims 1-113, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer or neoplastic disease.~~

~~125.— A method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (I) as described in any one of claims 1-36 or 108-113, or pharmaceutically acceptable salt or solvate thereof.~~

~~126.— A method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (II) as described in any one of claims 37-72 or 108-113, or pharmaceutically acceptable salt or solvate thereof.~~

~~127.— A method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (III) as described in any one of claims 73-113, or pharmaceutically acceptable salt or solvate thereof.~~

~~128.— A method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of any one of claims 114-116, or pharmaceutically acceptable salt or solvate thereof.~~

~~129.— A method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (I) as described in any one of claims 1-36 or 108-113, or pharmaceutically acceptable salt or solvate thereof.~~

~~130.— A method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (II) as described in any one of claims 37-72 or 108-113, or pharmaceutically acceptable salt or solvate thereof.~~

~~131.— A method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (III) as described in any one of claims 73-113, or pharmaceutically acceptable salt or solvate thereof.~~

~~132.— A method of treating cancer in a patient in need thereof comprising administering to the patient a compound of any one of claims 114-116, or pharmaceutically acceptable salt or solvate thereof.~~

~~133.— A method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound of Formula (I) as described in any one of claims 1-36 or 108-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.~~

~~134.— A method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound of Formula (II) as described in any one of claims 37-72 or 108-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.~~

~~135.— A method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound of Formula (II) as described in any one of claims 73-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.~~

~~136.— A method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound of any one of claims 114-116, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.~~

~~137. A method of inhibiting CDK12 enzyme comprising contacting the enzyme with a compound of any one of claims 1-116.~~