(CDK) in a cell with a compound or pharmaceutically acceptable salt or the pharmaceutical composition described herein.

**[0009a**] In one aspect, there is provided a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt as described herein and a pharmaceutically acceptable excipient

**[0009b]** In another aspect, there is provided a use of a compound, or a pharmaceutically acceptable salt thereof described herein, or the pharmaceutical composition described herein, in the manufacture of a medicament for treating cancer.

**[0009c]** In yet another aspect, there is provided a method of inhibiting a cyclin dependent kinase (CDK) in a cell with a compound, or pharmaceutically acceptable salt thereof as described herein, or the pharmaceutical composition as described herein.

## DETAILED DESCRIPTION OF THE INVENTION

**[0010]** While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

**[0011]** Basic functions for cell regulation, cell division, and cell proliferation are controlled by cyclin-dependent kinases (CDKs) activated by regulatory subunits such as cyclins. CDK inhibitors are useful in the treatment of cancer due to CDKs role in cell regulation. It has been shown that increased activity or transient abnormal activation of CDKs leads to the development of tumors; development of tumors are often associated with changes in the CDKs or regulators of CDKs.

**[0012]** CDKs bind to cyclin, which a regulatory protein., and without cyclin, it has little kinase activity. The cyclin-CDK complex is an active kinase typically modulated by phosphorylation and other binding proteins. There are currently 21 CDKs and 5 CDK-like genes that are known in the human genome. While many of the CDKs have been linked to transcription, CDK2, CDK4, and CDK6 are associated with the cell cycle. CDK2 is associated with DNA replication in higher eukaryotes whereas CDK4 and CDK6 are associated with various growth-regulatory signals.

**[0013]** CDK2 overexpression is associated with abnormal regulation of the cell cycle. Cyclin E, the cyclin partner of CDK2, binds to CDK2 to form an active kinase complex. The CDK2-cyclin E complex is important in the regulation of the G1/S transition, centrosome replication, and histone biosynthesis. Progressive phosphorylation can release the G1 transcription factor E2F and promote entry into the S phase. Another cyclin partner of CDK2, cyclin A, can bind and activate CDK2

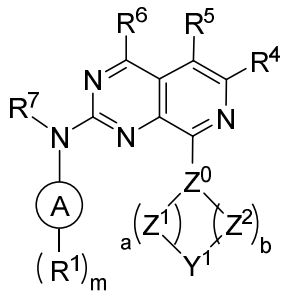
during the initial phase of the S phase, and promote endogenous substrate phosphorylation, which allows DNA replication and E2F inactivation to complete the S phase.

**[0014]** CDK4 and CDK6 are also associated with the cell cycle. CDK4 and CDK6 inhibitors can arrest the cell cycle form the G1 to S phase by blocking phosphorylation of Rb protein and inhibiting proliferation of Rb-positive tumor cells. Besides cell cycle activity, CDK4 and CDK6 inhibitors can also suppress tumor growth through other mechanisms including, but not limited to inducing senescence, promoting anti-tumor immune responses, regulation of cell metabolism, and enhancing cytostasis caused by signaling pathway inhibitors.

## CLAIMS

We Claim:

1. A compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (I0):



(I0)

wherein,

A is a ring selected from optionally substituted carbocycle, optionally substituted 4- to 8- membered heterocycle, optionally substituted tetrahydro-triazolopyrazine, and optionally substituted isoindoline;

$Z^0$ is –C(H)- or nitrogen;

each of $Z^1$, $Z^2$, and $Y^1$ are independently selected from -$C(R^2)_2$-, -C(O)-, -$NR^3$-, -$N(C(O)R^2)$-, -$NS(O_2)R^2$, -O-, -S-, -S(O)-, and -$S(O)_2$-;

each of a and b are independently selected from 1, 2, 3, and 4;

each $R^1$ is independently selected from halogen, -CN, -$NO_2$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocycle, and optionally substituted heterocycle;

m is selected from 0 to 5;

each $R^2$ is independently selected from hydrogen, halogen, -CN, -OH, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted -O-cycloalkyl, and optionally substituted heterocycloalkyl, or two $R^2$ substituents come together to form an optionally substituted heterocycle or an optionally substituted carbocycle, or $R^2$ and $R^3$ substituents come together to form an optionally substituted heterocycle;

each $R^3$ is independently selected from hydrogen, optionally substituted alkyl, optionally substituted $C_{3-4}$ carbocycle, and optionally substituted 3- to 4-membered heterocycloalkyl;

$R^4$ is selected from hydrogen, halogen, -CN, optionally substituted $C_{1-4}$ alkyl, optionally substituted $C_{3-4}$ carbocycle, and optionally substituted 3- to 4-membered heterocycloalkyl;

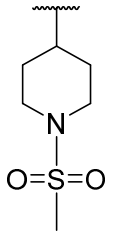
each of $R^5$, $R^6$, is independently selected from hydrogen, halogen, -CN, optionally substituted $C_{1-4}$ alkyl, optionally substituted $C_{3-4}$ carbocycle, and optionally substituted 3- to 4-membered heterocyclcoalkyl; and

$R^7$ is selected from hydrogen and optionally substituted $C_{1-4}$ alkyl, and

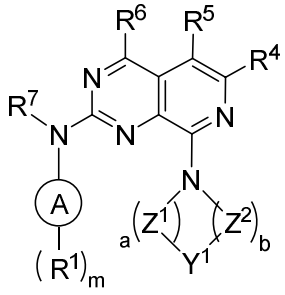
wherein if A is optionally substituted phenyl, m is from 1 to 5 and at least one $R^1$ is a heterocycloalkyl,

wherein if A is optionally substituted pyridine, optionally substituted pyridazine, or optionally substituted pyrimidine, $R^4$ is selected from hydrogen, halogen, and -CN,

wherein if A is an optionally substituted piperidine sulfonamide, then either (i) $Y^1$ is -$C(R^2)_2$- and the two $R^2$ substituents come together to form a ring selected from an optionally substituted heterocycle and an optionally substituted carbocycle, or (ii) $R^4$ is selected from hydrogen, halogen, methyl, and -CN, and

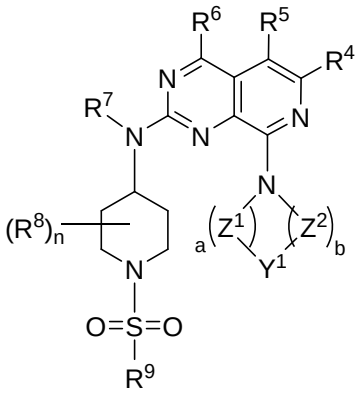
wherein if A-$R^1$ is  and $Z^0$ is CH, then $R^4$ is methyl or cyclopropyl.

2. The compound, or a pharmaceutically acceptable salt or solvate thereof, of claim 1 having the structure of Formula (I):

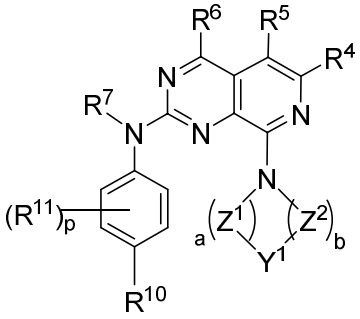
 (I),

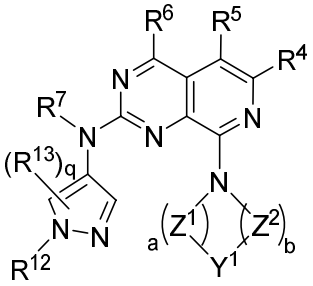
wherein, A is a ring selected from optionally substituted carbocycle, optionally substituted 4- to 6-membered heterocycle, and optionally substituted isoindoline;

3. The compound, or a pharmaceutically acceptable salt or solvate thereof, of claim 1 or 2 having the structure of one or more of Formulae (IA), (IB), (IC), (ID), or (IE):

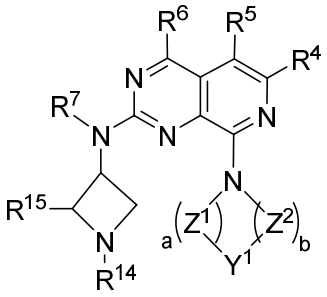


(IA),

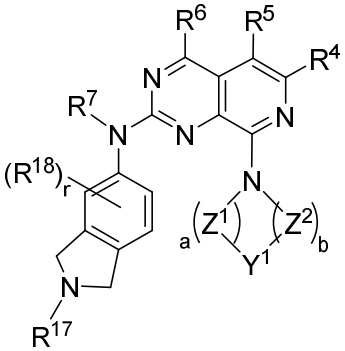




(IB),



(IC),



(ID), or



(IE),

wherein,

$R^8$ is selected from halogen, -CN, and optionally substituted $C_{1-4}$ alkyl;

$R^9$ is selected from optionally substituted $C_{3-6}$ carbocycle, optionally substituted $C_{5-6}$ heteroaryl, and 3- to 6- membered heterocycloalkyl;

$R^{10}$ is optionally substituted alkyl or optionally substituted heterocycloalkyl;

$R^{11}$ is selected from halogen, -CN, and optionally substituted $C_{1-4}$ alkyl;

$R^{12}$ is selected from an optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted cycloalkyl, and optionally substituted cycloalkylalkyl; or $R^{12}$ and $R^{13}$ come together to form an optionally substituted heterocycle;

$R^{13}$ is selected from halogen, -CN, and optionally substituted $C_{1-4}$ alkyl;

n is selected from 0 to 9;

$R^{14}$ is selected from -$SOR^{16}$-, and optionally substituted heterocycloalkyl;

$R^{15}$ is selected from hydrogen, halogen, -CN, and optionally substituted $C_{1-4}$ alkyl;

$R^{16}$ is selected from optionally substituted $C_{1-4}$ alkyl, optionally substituted $C_{3-6}$ carbocycle, and optionally substituted 3- to 6- membered heterocycloalkyl;

$R^{17}$ is selected from -$SOR^{19}$-, optionally substituted alkyl, optionally substituted carbocycle, and optionally substituted heterocycloalkyl;

$R^{18}$ is selected from halogen, -CN, and optionally substituted $C_{1-4}$ alkyl;

$R^{19}$ is selected from optionally substituted $C_{1-4}$ alkyl, optionally substituted $C_{3-6}$ carbocycle, and optionally substituted 3- to 6- membered heterocycloalkyl;

r is selected from 0 to 5.

p is selected from 0 to 4;

q is selected from 0 to 2; and

wherein when the compound is of formula (IA), either (i) $Y^1$ is -$C(R^2)_2$- and the two $R^2$ substituents come together to form a ring selected from an optionally substituted heterocycle and an optionally substituted carbocycle, or (ii) $R^4$ is selected from hydrogen, halogen, and -CN.

4. The compound, or a pharmaceutically acceptable salt or solvate thereof, of claim 3 having the structure of Formula (IA).
5. The compound, or a pharmaceutically acceptable salt or solvate thereof, of claim 3 having the structure of Formula (IB).
6. The compound, or a pharmaceutically acceptable salt or solvate thereof, of claim 3 having the structure of Formula (IC).
7. The compound, or a pharmaceutically acceptable salt or solvate thereof, of claim 3 having the structure of Formula (IE).
8. The compound or pharmaceutically acceptable salt of any one of claims 1-7, wherein $Z^1$ and $Z^2$ are independently selected from -$C(R^2)_2$-, -$NR^3$-, -O-, and -S-.
9. The compound or pharmaceutically acceptable salt of claim 8, wherein $Z^1$ and $Z^2$ are independently -$C(R^2)_2$-.
10. The compound or pharmaceutically acceptable salt of claim 9 , wherein each of a and b are independently selected from 1 and 2.
11. The compound or pharmaceutically acceptable salt of any one of claims 1-10, wherein $Y^1$ is selected from -$C(R^2)_2$-, -$NR^3$-, -$NS(O_2)R^2$, -O-, -$S(O)_2$-, and -S-.
12. The compound or pharmaceutically acceptable salt of claim 11, wherein $Y^1$ is selected from -$C(R^2)_2$- and -$NR^3$.

13. The compound or pharmaceutically acceptable salt of any one of claims 1-12, wherein each $R^2$ is independently selected from hydrogen, OH, halogen, -CN, optionally substituted alkyl, optionally substituted -O-alkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl.

14. The compound or pharmaceutically acceptable salt of claim 13 , wherein each $R^2$ is independently selected from hydrogen, halogen, -CN, cyclopropyl, cyclobutyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl.

15. The compound, or a pharmaceutically acceptable salt or solvate thereof, of claim 14, wherein each $R^2$ is independently selected from hydrogen, -CN and cyclopropyl.

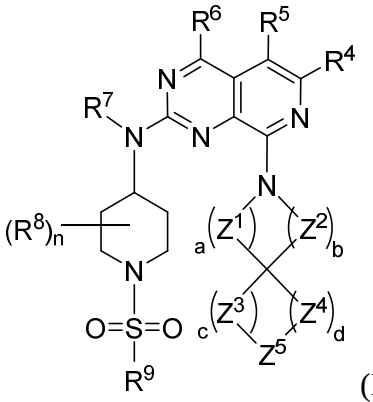
16. The compound or pharmaceutically acceptable salt of any one of claims 1-15, wherein two $R^2$ substituents come together to form an optionally substituted heterocycle or an optionally substituted carbocycle.

17. The compound or pharmaceutically acceptable salt of any one of claims 1-15, wherein each $R^3$ is selected from hydrogen, optionally substituted alkyl, cyclopropyl, cyclobutyl, optionally substituted oxetane, and optionally substituted azetidine.

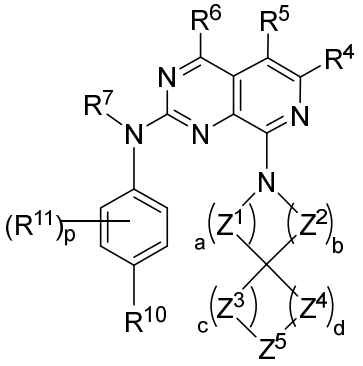
18. The compound or pharmaceutically acceptable salt of claim 17, wherein each $R^3$ is selected from methyl, methoxyethlene, $CD_3$, cyclopropyl and cyclobutyl.

19. The compound or pharmaceutically acceptable salt of claim 18, wherein $R^3$ is cyclopropyl.

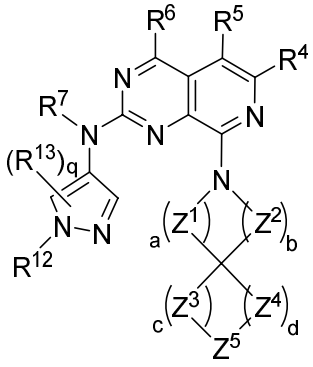
20. The compound, or a pharmaceutically acceptable salt or solvate thereof of any one of claims 1-3 having the structure of one or more of Formulae (IAA), (IBB), (ICC), (IDD), or (IEE):



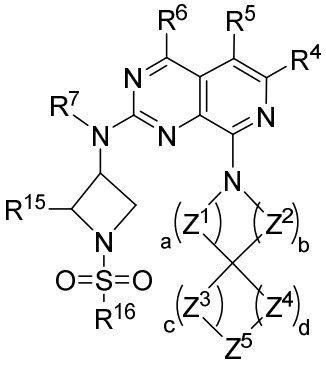
(IAA),



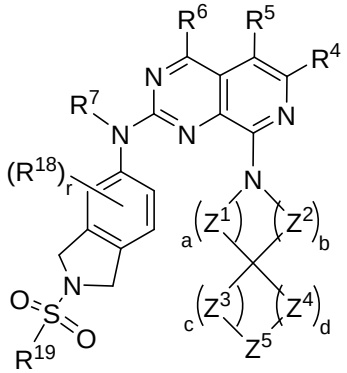
(IBB),



(ICC),



(IDD),



or (IEE)

wherein,

$R^8$ is selected from halogen, -CN, and optionally substituted $C_{1-4}$ alkyl;

$R^9$ is selected from optionally substituted $C_{3-6}$ carbocycle, optionally substituted $C_{5-6}$ heteroaryl, and 3- to 6- membered heterocycloalkyl;

$R^{10}$ is optionally substituted heterocycloalkyl;

$R^{11}$ is selected from halogen, -CN, and optionally substituted $C_{1-4}$ alkyl;

$R^{12}$ is optionally substituted heterocycloalkyl; or $R^{12}$ and $R^{13}$ come together to form an optionally substituted heterocycle;

$R^{13}$ is selected from halogen, -CN, and optionally substituted $C_{1-4}$ alkyl;

$R^{15}$ is selected from hydrogen, halogen, -CN, and optionally substituted $C_{1-4}$ alkyl;

$R^{16}$ is selected from optionally substituted $C_{1-4}$ alkyl, optionally substituted $C_{3-6}$ carbocycle, and optionally substituted 3- to 6- membered heterocycloalkyl;

$R^{19}$ is selected from optionally substituted $C_{1-4}$ alkyl, optionally substituted $C_{3-6}$ carbocycle, and optionally substituted 3- to 6- membered heterocycloalkyl;

n is selected from 0 to 9;

p is selected from 0 to 4;

q is selected from 0 to 2;

each of $Z^1$, $Z^2$, $Z^3$, $Z^4$ and $Z^5$ are independently selected from $-C(R^2)_2-$, -C(O)-, $-NR^3-$, $-N(C(O)R^2)-$, $-NS(O_2)R^3$, -O-, -S-, -S(O)-, and $-S(O)_2-$, wherein $Z^5$ is additionally selected from a bond; and

each of a, b, c, and d are independently selected from 1, 2, 3, and 4.

21. The compound, or a pharmaceutically acceptable salt or solvate thereof, of claim 20 having the structure of Formula (IAA).

22. The compound, or a pharmaceutically acceptable salt or solvate thereof, of claim 20 having the structure of Formula (IBB).

23. The compound, or a pharmaceutically acceptable salt or solvate thereof, of claim 20 having the structure of Formula (ICC).

24. The compound, or a pharmaceutically acceptable salt or solvate thereof, of claim 20 having the structure of Formula (IEE).

25. The compound or pharmaceutically acceptable salt of any one of claims 20- 24, wherein each of $Z^1$, $Z^2$, $Z^3$, $Z^4$ and $Z^5$ are independently selected from $-C(R^2)_2-$, $-NR^3-$, $-N(C(O)R^2)-$, $-NS(O_2)R^3$, -O-, and $-S(O)_2-$, wherein $Z^5$ is additionally selected from a bond.

26. The compound or pharmaceutically acceptable salt of claim 25, wherein each of $Z^1$, $Z^2$, $Z^3$, $Z^4$ and $Z^5$ are independently selected from $-C(R^2)_2-$, $-NR^3-$, -O-, and $-S(O)_2-$, wherein $Z^5$ is additionally selected from a bond.

27. The compound or pharmaceutically acceptable salt of claims 20 -26, wherein each $R^2$ is independently selected from hydrogen, halogen, -CN, OH, optionally substituted alkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl, or two $R^2$ substituents come together to form an optionally substituted heterocycle or an optionally substituted carbocycle.

28. The compound or pharmaceutically acceptable salt of claim 27, wherein each $R^2$ is selected from hydrogen, fluoro,CN, cyclopropyl, cyclobutyl, -$C_{1-4}$ alkyl, -$C_{1-4}$ haloalkyl, -O-$C_{1-4}$ alkyl, -$C_{1-4}$ alkylene-O-$C_{1-3}$ alkyl, -$C_{1-4}$ alkylene-OH, optionally substituted oxetane, and optionally substituted azetidine .

29. The compound or pharmaceutically acceptable salt of any one of claims 20-28, wherein $R^3$ is selected from hydrogen, -$(CH_2)_2OMe$, -$S(O)_2CH_3$, -$C_{1-4}$ alkylene-O-$C_{1-3}$ alkyl, $C_{1-4}$ alkyl, cyclopropyl, cyclobutyl, optionally substituted oxetane, and optionally substituted azetidine.

30. The compound or pharmaceutically acceptable salt of claim 29, wherein $R^3$ is selected from hydrogen, -$(CH_2)_2OMe$, $C_{1-4}$ alkyl, cyclopropyl, cyclobutyl, optionally substituted oxetane, and optionally substituted azetidine.

31. The compound or pharmaceutically acceptable salt of claim 30, wherein $R^3$ is selected from hydrogen, methyl, ethyl, propyl, $CD_3$, and cyclopropyl.

32. The compound or pharmaceutically acceptable salt of any one of claims 20-31, wherein each a, b, c, and d are each independently selected from 1 and 2.

33. The compound or pharmaceutically acceptable salt of claim 1 or 2, wherein A is selected from optionally substituted cyclohexane, optionally substituted pyridine, optionally substituted piperidine, optionally substituted tetrahydropyran, optionally substituted azabicyclo[3.1.0]hexane, optionally substituted azetidine, and optionally substituted tetrahydroisoquinoline.

34. The compound, or pharmaceutically acceptable salt thereof, of claim 1 or 2, wherein A is optionally substituted piperidine.

35. The compound or pharmaceutically acceptable salt of claim 34, wherein A is substituted with $SO_2R^9$. wherein $R^9$ is selected from optionally substituted $C_{3-6}$ carbocycle, optionally substituted $C_{5-6}$ heteroaryl, and 3- to 6- membered heterocycloalkyl.

36. The compound or pharmaceutically acceptable salt of claim 34 or 35, wherein m is selected from 0 to 1.

37. The compound or pharmaceutically acceptable salt of any one of claims 34-36, wherein each $R^1$ is independently selected from optionally substituted alkyl, optionally substituted carbocycle, and optionally substituted heterocycle.

38. The compound or pharmaceutically acceptable salt of claim 37, wherein each $R^1$ is independently selected from optionally substituted alkyl and optionally substituted heterocycle.

39. The compound or pharmaceutically acceptable salt of claim 37, wherein each $R^1$ is independently selected from methyl, ethyl, and optionally substituted diazaspiro[3.3]heptane.

40. The compound or pharmaceutically acceptable salt of any one of claims 1-13, and 34-39 wherein $Z^1$ and $Z^2$ are independently selected from $-C(R^2)_2-$, $-NR^3-$, -O-, and -S-.

41. The compound or pharmaceutically acceptable salt of claim 40, wherein $Z^1$ and $Z^2$ are each $-C(R^2)_2-$.

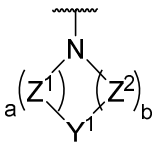
42. The compound or pharmaceutically acceptable salt of claims 40 or 41, wherein each of a and b are independently selected from 1 and 2.

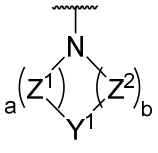
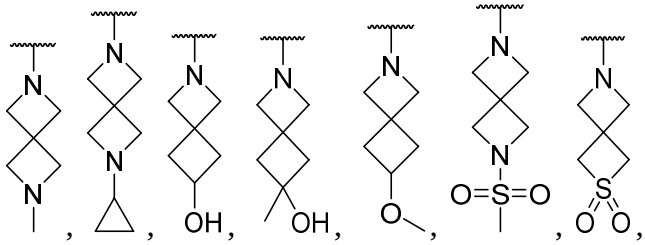
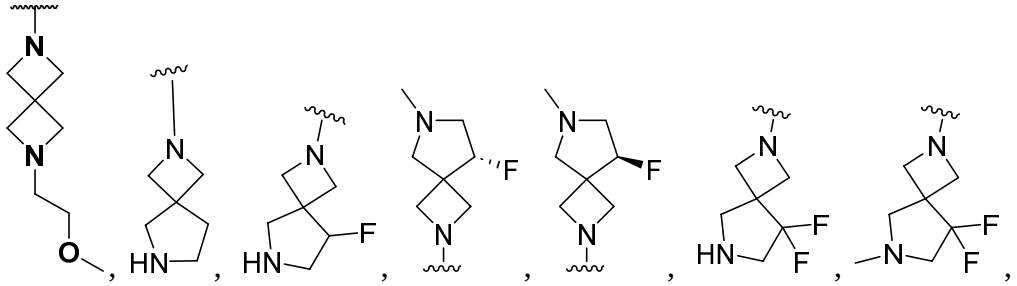
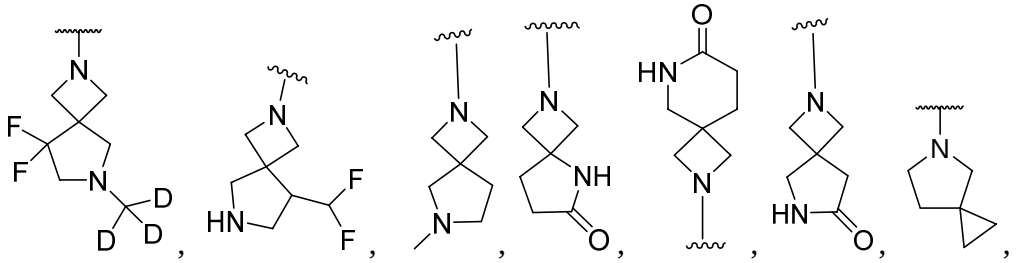
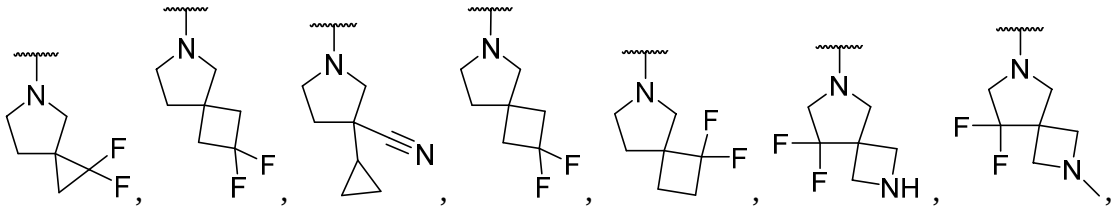
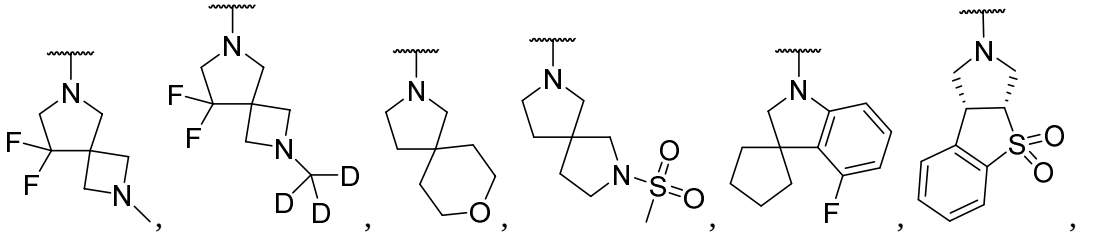
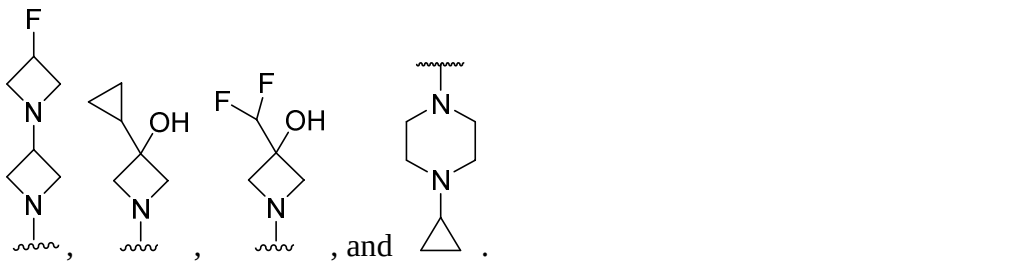
43. The compound or pharmaceutically acceptable salt of any one of claims 1-13, and 34-42, wherein $Y^1$ is selected from $-C(R^2)_2-$, $-NR^3-$, -O-, and -S-.

44. The compound or pharmaceutically acceptable salt of claim 43, wherein $Y^1$ is selected from $-C(R^2)_2-$ and $-NR^3$.

45. The compound or pharmaceutically acceptable salt of claim 44, wherein $Y^1$ is $-C(R^2)_2-$ and two $R^2$ substituents come together to form a ring selected from an optionally substituted heterocycle and an optionally substituted carbocycle.

46. The compound or pharmaceutically acceptable salt of claim 45, wherein $Y^1$ is $-C(R^2)_2-$ and the two $R^2$ substituents come together to form a ring selected from an optionally substituted heterocycle.

47. The compound or pharmaceutically acceptable salt of any one of claims 1-19, and 34-46, wherein the N containing heterocyclic ring depicted as  in Formula (IA), (IB), (IC), (ID), and (IE) is selected from optionally substituted azetidine, optionally substituted pyrrolidine, optionally substituted piperidine, optionally substituted piperazine, optionally substituted morpholine, optionally substituted tetrahydrothienopyrroledioxide, and optionally substituted dihydroindole.

48. The compound or pharmaceutically acceptable salt of any one of claims 1-19, and 34-46, wherein the N containing heterocyclic ring depicted as  in Formula (IA), (IB), (IC), (ID), and (IE) is selected from , , , , , , and .

49. The compound or pharmaceutically acceptable salt of any one of claims, 1-32 or 34-48, wherein $R^4$ is selected from hydrogen, halogen, optionally substituted $C_{1-2}$ alkyl, optionally substituted $C_{3-4}$ carbocycle, and optionally substituted 3- to 4 membered heterocycloalkyl.

50. The compound or pharmaceutically acceptable salt of claim 49, wherein $R^4$ is selected from hydrogen and optionally substituted $C_1$ alkyl.

51. The compound or pharmaceutically acceptable salt of claim 50, wherein $R^4$ is selected from hydrogen, methyl, and -$CHF_2$.

52. The compound or pharmaceutically acceptable salt of any one of claims 1-32 or 34-48, wherein $R^4$ is selected from hydrogen, halogen, and -CN.

53. The compound or pharmaceutically acceptable salt of any one of claims 1-32 or 34-48, wherein $R^4$ is selected from hydrogen.

54. The compound or pharmaceutically acceptable salt of any one of claims 1-32 or 34-48, wherein $R^4$ is not optionally substituted phenyl.

55. The compound or pharmaceutically acceptable salt of any one of claims 1-32 or 34-48, wherein $R^4$ is not optionally substituted alkyl.

56. The compound or pharmaceutically acceptable salt of any one of claims 1-32, 34-39, or p50-55, wherein $R^5$ is selected from hydrogen, halogen, optionally substituted $C_{1-2}$ alkyl, optionally substituted $C_{3-4}$ carbocycle, and optionally substituted 3- to 4 membered heterocycloalkyl.

57. The compound or pharmaceutically acceptable salt of claim 56, wherein $R^5$ is selected from hydrogen, halogen, and optionally substituted $C_{1-2}$ alkyl.

58. The compound or pharmaceutically acceptable salt of claim 57, wherein $R^5$ is selected from hydrogen and fluoro.

59. The compound or pharmaceutically acceptable salt of any one of claims 1-32, 34-39, or 50-58, wherein $R^6$ is selected from hydrogen, halogen, optionally substituted $C_{1-2}$ alkyl, optionally substituted $C_{3-4}$ carbocycle, and optionally substituted 3- to 4 membered heterocycloalkyl.

60. The compound or pharmaceutically acceptable salt of claim 59, wherein $R^6$ is selected from hydrogen, halogen, and optionally substituted $C_{1-2}$ alkyl.

61. The compound or pharmaceutically acceptable salt of claim 60, wherein $R^6$ is hydrogen.

62. The compound or pharmaceutically acceptable salt of any one of claims 1-32, 34-39, or 50-61, wherein $R^7$ is hydrogen.

63. The compound or pharmaceutically acceptable salt of any one of claims 3-4, 8-21, or 25-32, wherein $R^9$ is selected from cyclopentyl, methylcyclopentyl, cyclobutylmethylene, cyclopentylmethylene, and n-methyl pyrazolyl.

64. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound is selected from Table 1.

65. The compound, or pharmaceutically acceptable salt thereof, of claim 2, wherein the compound is selected from Table 1.

66. The compound, or pharmaceutically acceptable salt thereof, of claim 3, wherein the compound is selected from Table 1.

67. The compound, or pharmaceutically acceptable salt thereof, of claim 20, wherein the compound is selected from Table 1.

68. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt of any one of claims 1 to 67 and a pharmaceutically acceptable excipient.

69. Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-67 or the pharmaceutical composition of claim 68, in the manufacture of a medicament for treating cancer.

70. The use of claim 66, wherein the cancer is a solid tumor.

71. The use of claim 69 or 70, wherein the cancer is selected from ovarian cancer, breast cancer, colon cancer, and brain cancer.

72. The use of claim 71, wherein the cancer is ovarian cancer or breast cancer.

73. A method of inhibiting a cyclin dependent kinase (CDK) in a cell with a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 67 or the pharmaceutical composition of claim 68.

74. The method of claim 73, wherein the CDK is selected from CDK 2, CDK 4, CD6, or any combination thereof.

75. The method of claim 74, wherein the CDK is selected from CDK 2/4, CDK 2/6, CDK 4/6, and CDK 2/4/6.

**76.** The method of claim 75, wherein the CDK is CDK 2/4/6.