

INHIBITORS OF CYCLIN-DEPENDENT KINASE 7 (CDK7)

BACKGROUND OF THE INVENTION

[1] The members of the cyclin-dependent kinase (CDK) family play critical regulatory roles in proliferation. Unique among the mammalian CDKs, CDK7 has consolidated kinase activities, regulating both the cell cycle and transcription. In the cytosol, CDK7 exists as a heterotrimeric complex and is believed to function as a CDK1/2-activating kinase (CAK), whereby phosphorylation of conserved residues in CDK1/2 by CDK7 is required for full catalytic CDK activity and cell cycle progression. In the nucleus, CDK7 forms the kinase core of the RNA polymerase (RNAP) II general transcription factor complex and is charged with phosphorylating the C-terminal domain (CTD) of RNAP II, a requisite step in gene transcriptional initiation. Together, the two functions of CDK7, *i.e.*, CAK and CTD phosphorylation, support critical facets of cellular proliferation, cell cycling, and transcription.

[2] Disruption of RNAP II CTD phosphorylation has been shown to preferentially affect proteins with short half-lives, including those of the anti-apoptotic BCL-2 family. Cancer cells have demonstrated ability to circumvent pro-cell death signaling through upregulation of BCL-2 family members. Therefore, inhibition of human CDK7 kinase activity is likely to result in anti-proliferative activity.

[3] The discovery of selective inhibitors of CDK7 has been hampered by the high sequence and structural similarities of the kinase domain of CDK family members. Therefore, there is a need for the discovery and development of selective CDK7 inhibitors. Such CDK7 inhibitors hold promise as a therapeutic agent for the treatment of CLL and other cancers.

BRIEF DESCRIPTION OF THE DRAWINGS

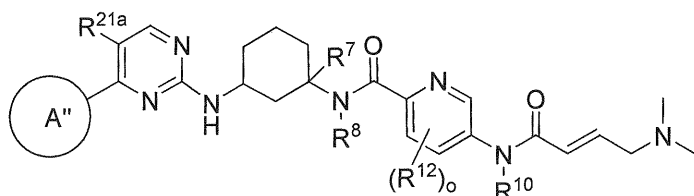
[4] Fig. 1 is a table of exemplary compounds of Formula I.

SUMMARY OF THE INVENTION

[5] The present ~~invention~~ disclosure provides inhibitors of one or more of the family of CDK proteins. The present ~~disclosure~~ invention further provides CDK7 inhibitors, in particular selective CDK7 inhibitors of Formula (I) or Formula (II), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof. The present

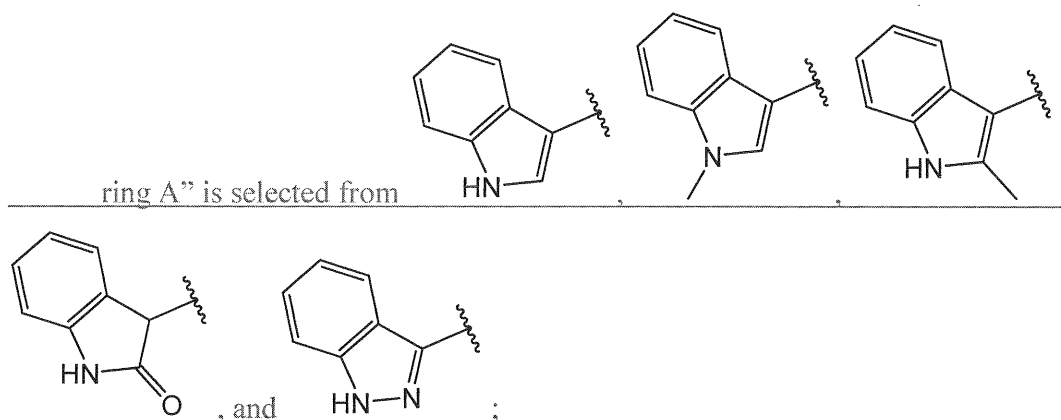
~~disclosure invention~~ additionally provides methods of using the compounds of the ~~invention~~present disclosure, and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, to study the inhibition of CDK7 and CDK12 and/or CDK13 and as therapeutics for the prevention and/or treatment of diseases associated with overexpression and/or aberrant activity of CDK7 and/or CDK12 and/or CDK13. In certain embodiments, the ~~inventive~~disclosed compounds are used for the prevention and/or treatment of proliferative diseases (e.g., cancers (e.g., leukemia, melanoma, multiple myeloma), benign neoplasms, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) in a subject.

In one aspect, there is provided a compound having structural Formula (Ic):



(Ic); or a pharmaceutically acceptable

salt thereof, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof,
wherein:



each of R⁷, R⁸ and R¹⁰ is independently selected from hydrogen and methyl;

R^{21a} is selected from -Cl, -CN, -CF₃, -CH₃, and -CH₂CH₃; and

each R¹² if present is halo; and

o is 0, 1, 2, or 3.

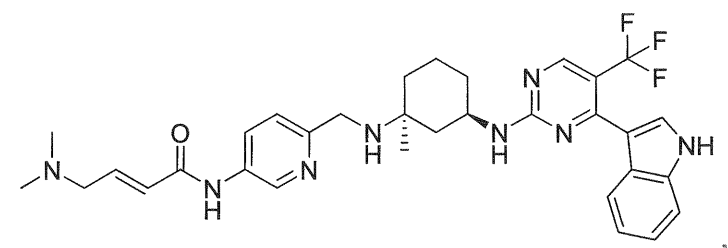
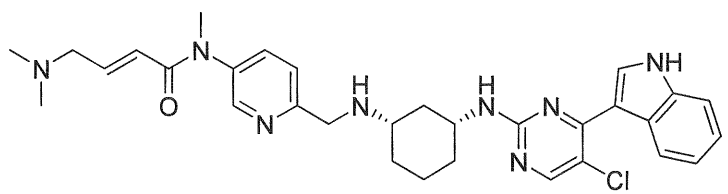
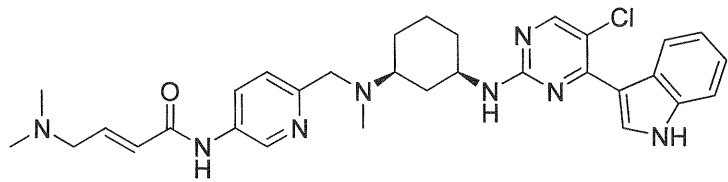
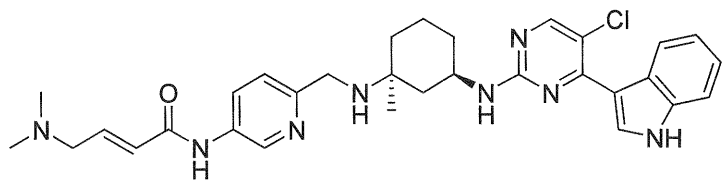
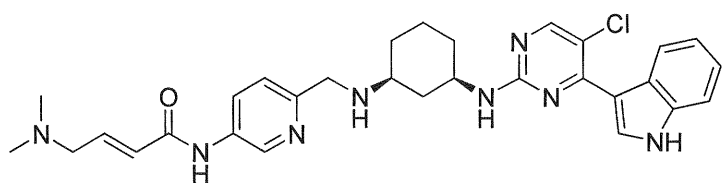
In another aspect, there is provided a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable excipient.

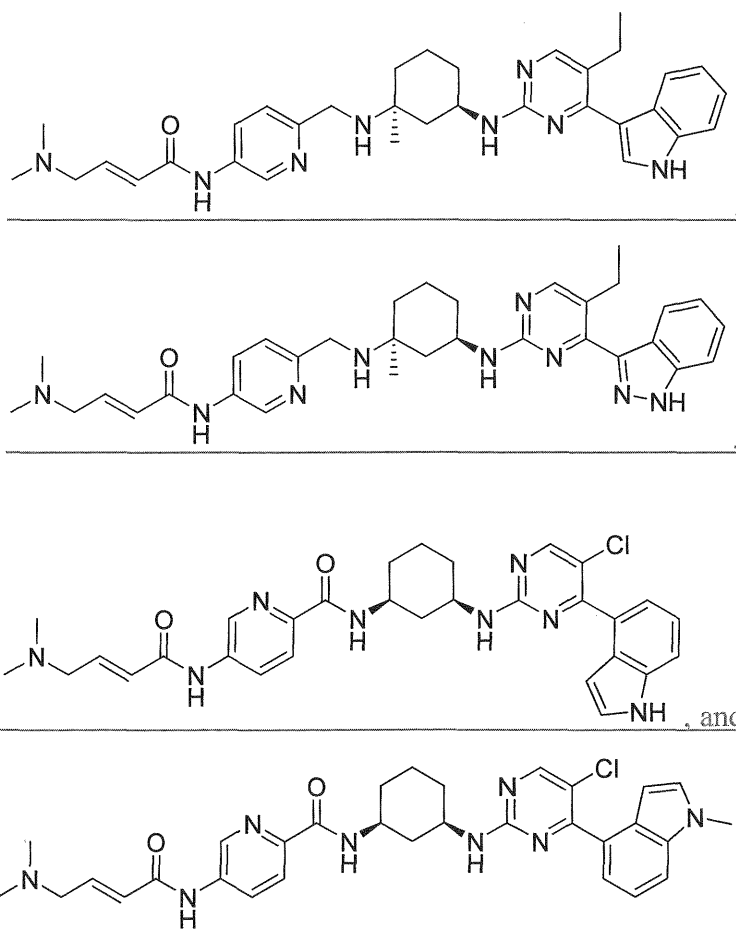
In another aspect, there is provided the use of the composition as disclosed herein in the

manufacture of a medicament, for treating a subject suffering from a disease or condition associated with aberrant activity of a CDK.

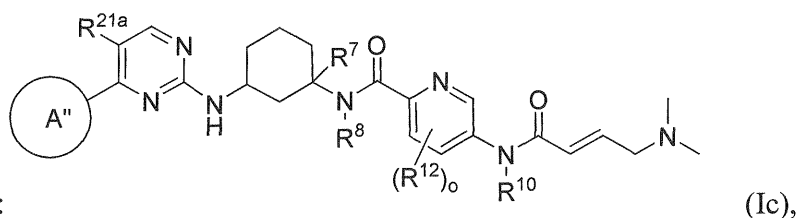
In yet another aspect, there is provided the use of the composition as disclosed herein in the manufacture of a medicament, for treating a disease or condition selected from cancer, benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, autoimmune disease, or an infectious disease.

In a further aspect, there is provided a compound selected from any one of the compounds set forth below:





[6] In one aspect an embodiment, the present ~~disclosure invention~~ provides compounds of



structural formula (Ic):

and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, and isotopically labeled derivatives thereof, wherein Ring A^{''}, R⁷, R⁸, R¹⁰, R¹², R^{21a}, o and subvariables thereof are as defined herein.

[7] In another aspect an embodiment, the present ~~invention disclosure~~ provides pharmaceutical compositions comprising a compound of Formula (Ic) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the

pharmaceutical compositions described herein include a therapeutically effective amount of a compound of Formula (Ic) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof. The pharmaceutical composition may be useful for treating and/or preventing a proliferative or infectious disease.

[8] In another ~~aspect~~embodiment, the present ~~invention-disclosure~~ provides methods for treating and/or preventing proliferative diseases. Exemplary proliferative diseases include cancer (*e.g.*, leukemia, melanoma, multiple myeloma), benign neoplasm, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases. In other embodiments, the present ~~invention-disclosure~~ provides methods for treating and/or preventing an infectious disease (*e.g.*, a viral infection).

- [9] In still another ~~aspect~~embodiment, the present ~~invention~~disclosure provides methods of down-regulating the expression of CDK7 in a biological sample or subject.
- [10] Another ~~aspect~~embodiment of the ~~invention~~disclosure relates to methods of inhibiting the activity of CDK7 in a biological sample or subject.
- [11] The present ~~invention~~disclosure also provides methods of inhibiting cell growth in a biological sample or subject.
- [12] In still another ~~aspect~~embodiment, the present ~~invention~~disclosure provides methods of inducing apoptosis of a cell in a biological sample or a subject.
- [13] In yet another ~~aspect~~embodiment, the present ~~invention~~disclosure provides compounds of Formula (Ic), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, for use in the treatment of a proliferative disease in a subject.
- [14] In yet another ~~aspect~~embodiment, the present ~~invention~~disclosure provides compounds of Formula (Ic), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, for use in the treatment or prevention of an infectious disease in a subject. In certain embodiments, the infectious disease is a viral infection.
- [15] Another ~~aspect~~embodiment of the present ~~invention~~disclosure relates to kits comprising a container with a compound of Formula (Ic), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, or a pharmaceutical composition thereof. In certain embodiments, the kits described herein further include instructions for administering the compound of Formula (Ic), or the pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, or the pharmaceutical composition thereof.
- [16] In still another ~~aspect~~embodiment, the present ~~invention~~disclosure provides methods of inhibiting other CDKs, specifically CDK12 and/or CDK13, with a compound of Formula (Ic).
- [17] The details of one or more embodiments of the ~~invention~~present disclosure are set forth herein. Other features, objects, and advantages of the present disclosure ~~invention~~ will be apparent from the Detailed Description, the Figures, the Examples, and the Claims.

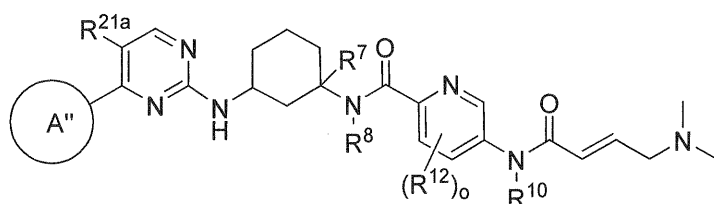
DEFINITIONS

- [18] Definitions of specific functional groups and chemical terms are described in more detail

CLAIMS

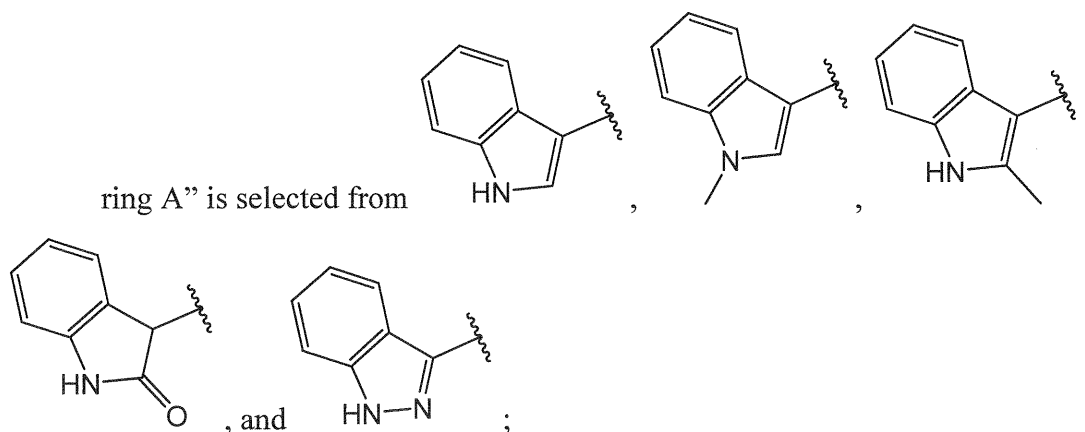
What is claimed is:

1. A compound having structural Formula (Ic):



(Ic); or a pharmaceutically

acceptable salt thereof, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein:



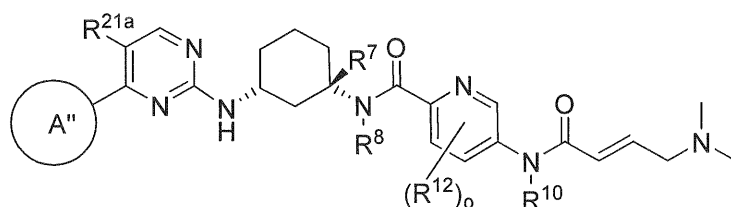
each of R^7 , R^8 and R^{10} is independently selected from hydrogen and methyl;

R^{21a} is selected from -Cl, -CN, -CF₃, -CH₃, and -CH₂CH₃; and

each R^{12} if present is halo; and

o is 0, 1, 2, or 3.

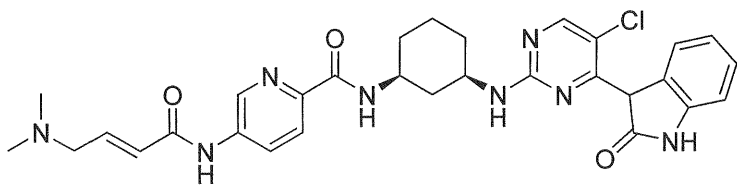
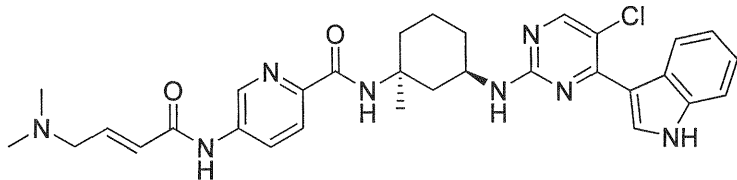
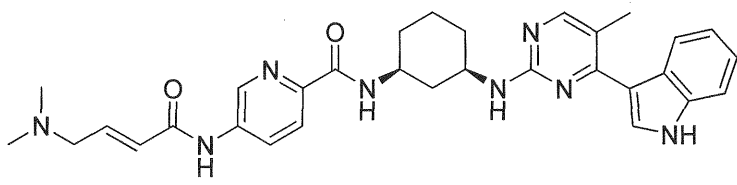
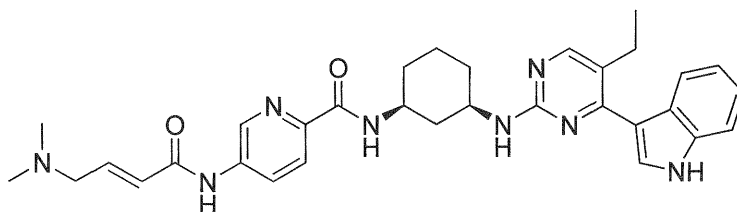
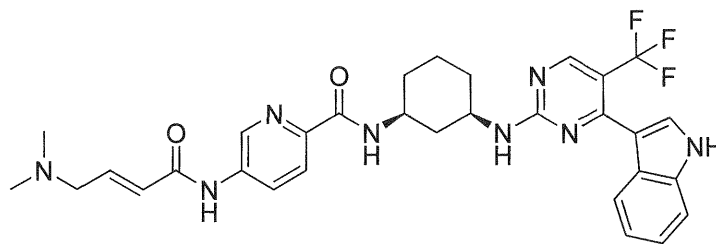
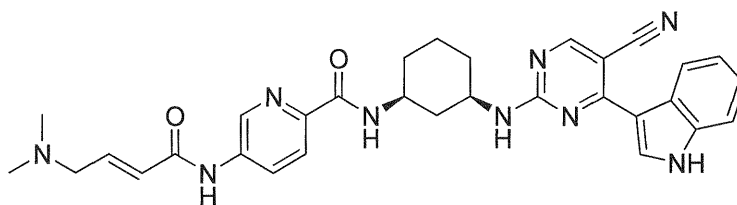
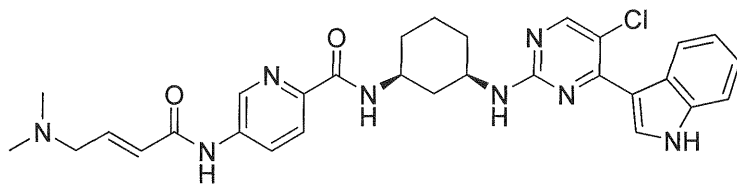
2. The compound of claim 1, having structural Formula (Ic'):

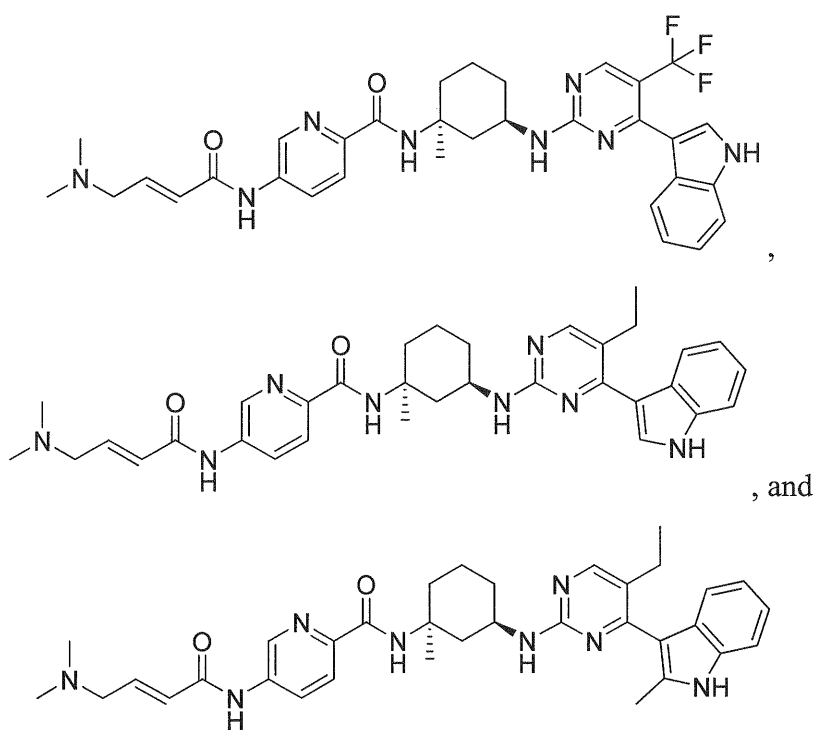


(Ic'), wherein ring A'', R^7 , R^8 ,

R^{10} , R^{21a} , R^{12} and o are as defined in claim 1.

3. The compound of claim 1 or 2, wherein each R¹², if present, is fluoro.
4. The compound of any one of claims 1-3, wherein o is 0.
5. The compound of claim 1, selected from any one of the compounds set forth below:





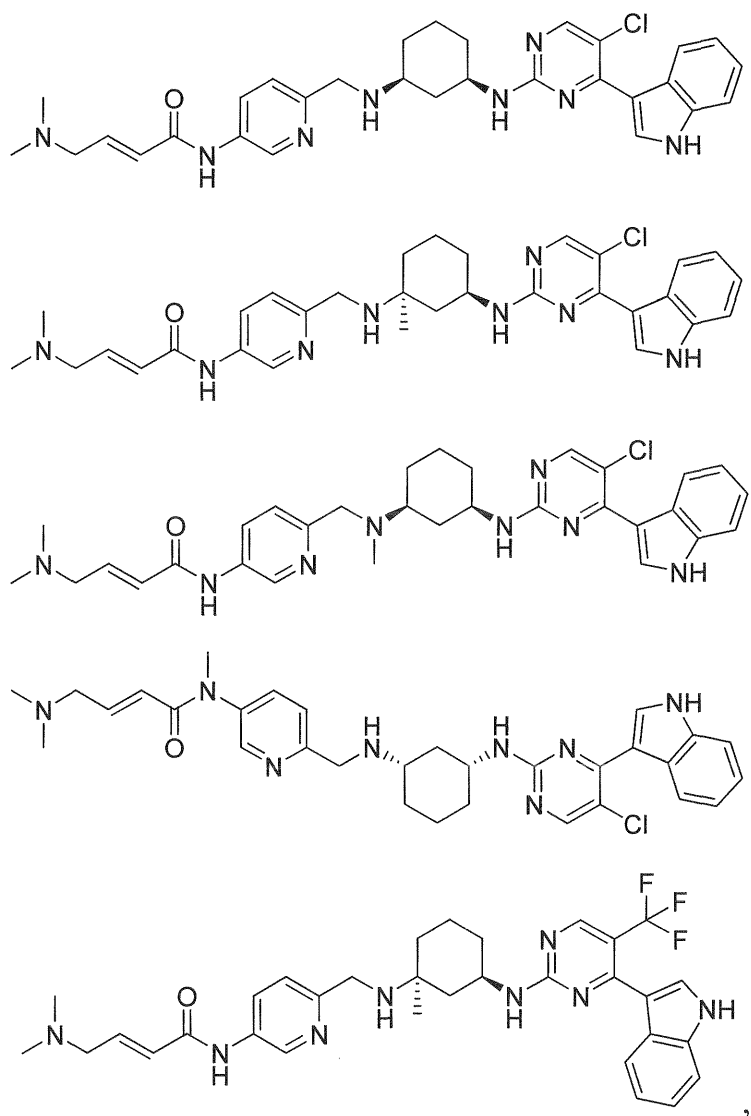
6. A pharmaceutical composition comprising a compound of any one of claims 1-5 or 16 and a pharmaceutically acceptable excipient.
7. Use of the composition of claim 6 in the manufacture of a medicament, for treating a subject suffering from a disease or condition associated with aberrant activity of a CDK.
8. Use of the composition of claim 6 in the manufacture of a medicament, for treating a disease or condition selected from cancer, benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, autoimmune disease, or an infectious disease.
9. The use of claim 8, wherein the subject is a human.
10. The use of any one of claims 8-9, wherein the disease is cancer.
11. The use of claim 10, wherein the cancer is selected from a blood cancer, melanoma, a bone cancer, a breast cancer, a brain cancer, or a lung cancer.
12. The use of claim 11, wherein the cancer is a blood cancer selected from chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), T-cell acute lymphoblastic leukemia (T-ALL), chronic myelogenous leukemia (CML), acute

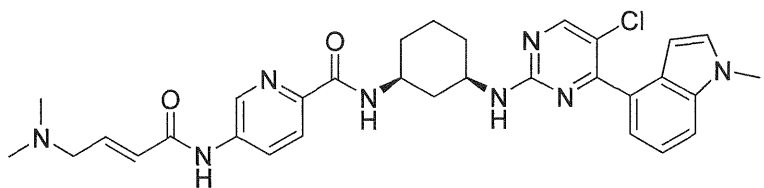
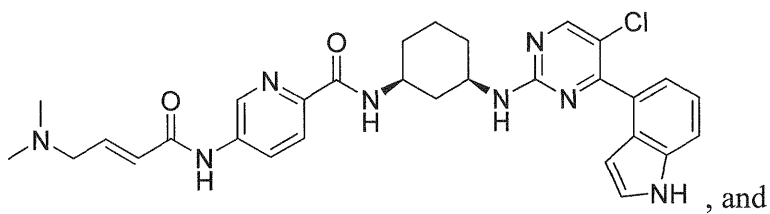
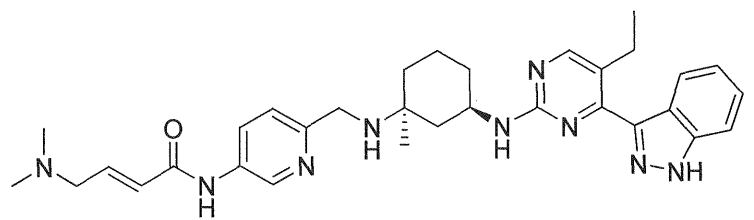
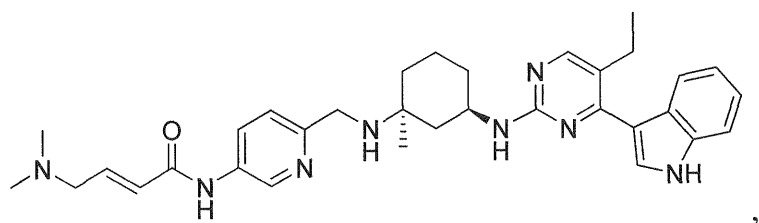
myelogenous leukemia (AML), lymphoma, and multiple myeloma.

13. The use of claim 11, wherein the cancer is selected from osteosarcoma, Ewing's sarcoma, triple-negative breast cancer (TNBC), neuroblastoma, and small cell lung cancer (SCLC).

14. The use of any one of claims 8-13, wherein the composition is used in conjunction with one or more additional agents independently selected from anti-proliferative agents, anti-cancer agents, immunosuppressant agents, and pain-relieving agents.

15. A compound selected from any one of the compounds set forth below:

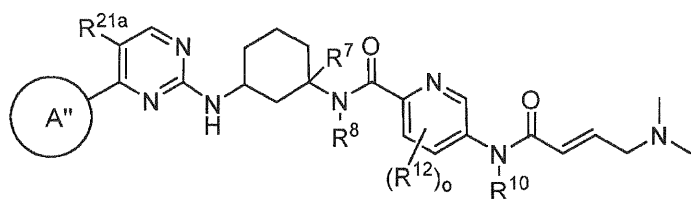




CLAIMS

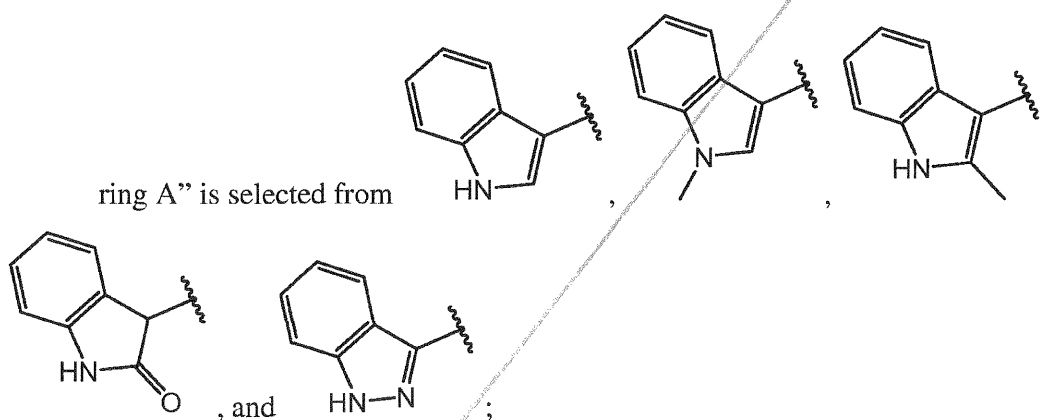
What is claimed is:

1. A compound having structural Formula (Ic):



(Ic); or a pharmaceutically acceptable

salt thereof, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein:



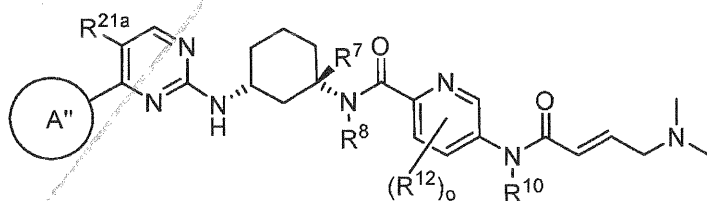
each of R^7 , R^8 and R^{10} is independently selected from hydrogen and methyl;

R^{21a} is selected from -Cl, -CN, -CF₃, -CH₃, and -CH₂CH₃; and

each R^{12} if present is halo; and

o is 0, 1, 2, or 3.

2. The compound of claim 1, having structural Formula (Ic'):



(Ic'), wherein R^7 , R^8 , R^{10} , R^{21a} , R^{12}

and o are as defined in claim 1.

3. The compound of claim 1 or 2, wherein each R¹², if present, is fluoro.
4. The compound of any one of claims 1-3, wherein o is 0.
5. The compound of claim 1, selected from any one of Compounds 106, 110, 248, 261, 262, 264, 265, 267, 269, 282, 294, 377, 390, 399, 403, 407, 411, 412, 413.
6. A pharmaceutical composition comprising a compound of any one of claims 1-5 and a pharmaceutically acceptable excipient.
7. The composition of claim 6 for use in treating a subject suffering from a disease or condition associated with aberrant activity of a CDK.
8. The composition of claim 7, wherein the subject is suffering from a disease or condition associated with aberrant activity of CDK7.
9. The composition of claim 7 or 8, wherein the disease or condition is selected from cancer, benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, autoimmune disease, or an infectious disease.
10. The composition of any one of claims 7-9, wherein the subject is a human.
11. The composition of any one of claims 7-10, wherein the disease is cancer.
12. The composition of claim 11, wherein the cancer is selected from a blood cancer, melanoma, a bone cancer, a breast cancer, a brain cancer, or a lung cancer.
13. The composition of claim 12, wherein the cancer is a blood cancer selected from chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), T-cell acute lymphoblastic leukemia (T-ALL), chronic myelogenous leukemia (CML), acute myelogenous leukemia

(AML), lymphoma, and multiple myeloma.

14. The composition of claim 12, wherein the disease is selected from osteosarcoma, Ewing's sarcoma, triple-negative breast cancer (TNBC), neuroblastoma, and small cell lung cancer (SCLC).

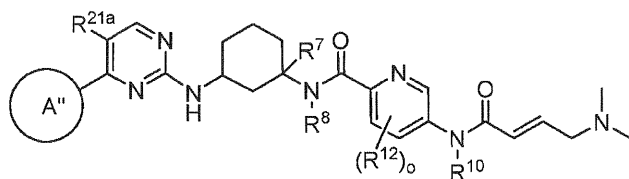
15. The composition of any one of claims 7-14, wherein the composition is used in conjunction with one or more additional agents independently selected from anti-proliferative agents, anti-cancer agents, immunosuppressant agents, and pain-relieving agents.

AMENDED CLAIMS

received by the International Bureau on 29 July 2015 (29.07.2015)

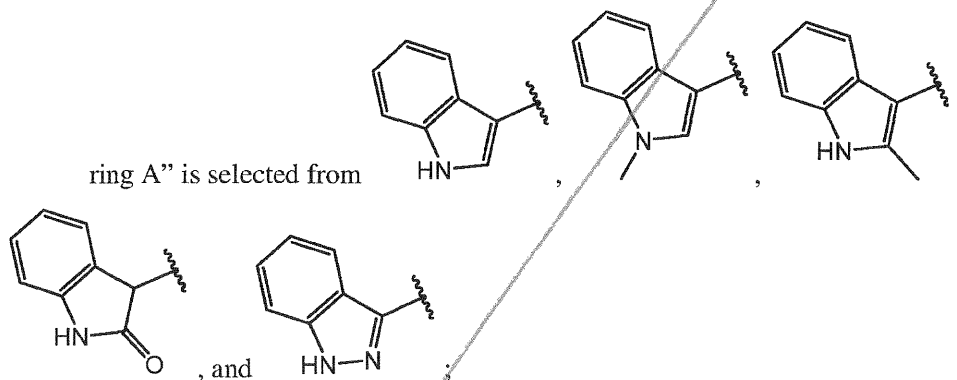
What is claimed is:

1. A compound having structural Formula (Ic):



(Ic); or a pharmaceutically acceptable

salt thereof, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein:



ring A'' is selected from

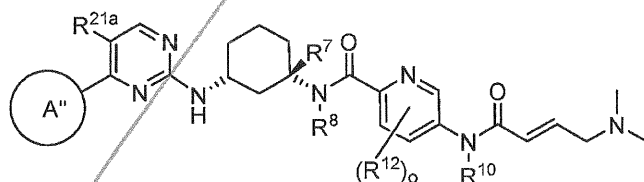
each of R^7 , R^8 and R^{10} is independently selected from hydrogen and methyl;

R^{21a} is selected from -Cl, -CN, -CF₃, -CH₃, and -CH₂CH₃; and

each R^{12} if present is halo; and

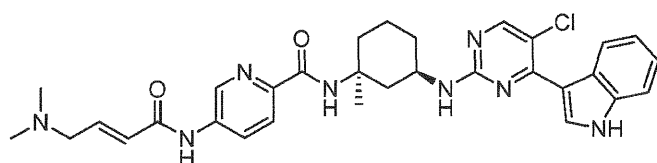
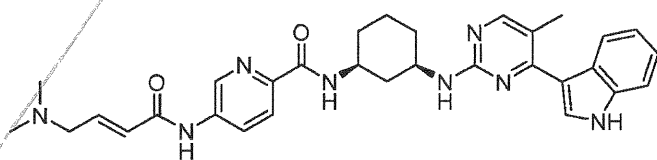
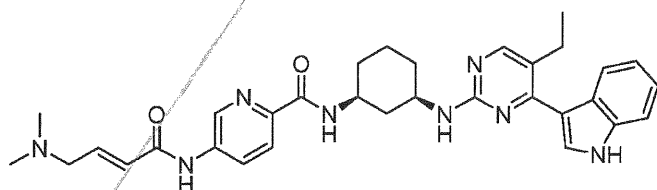
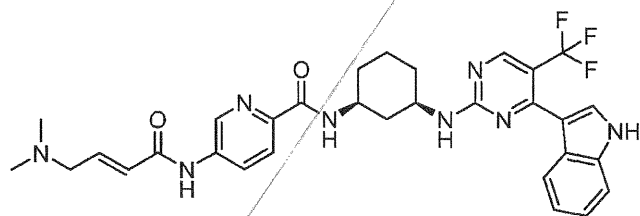
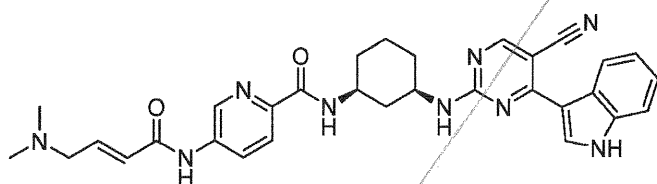
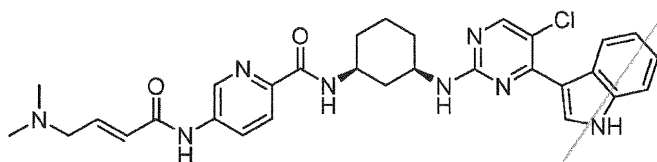
o is 0, 1, 2, or 3.

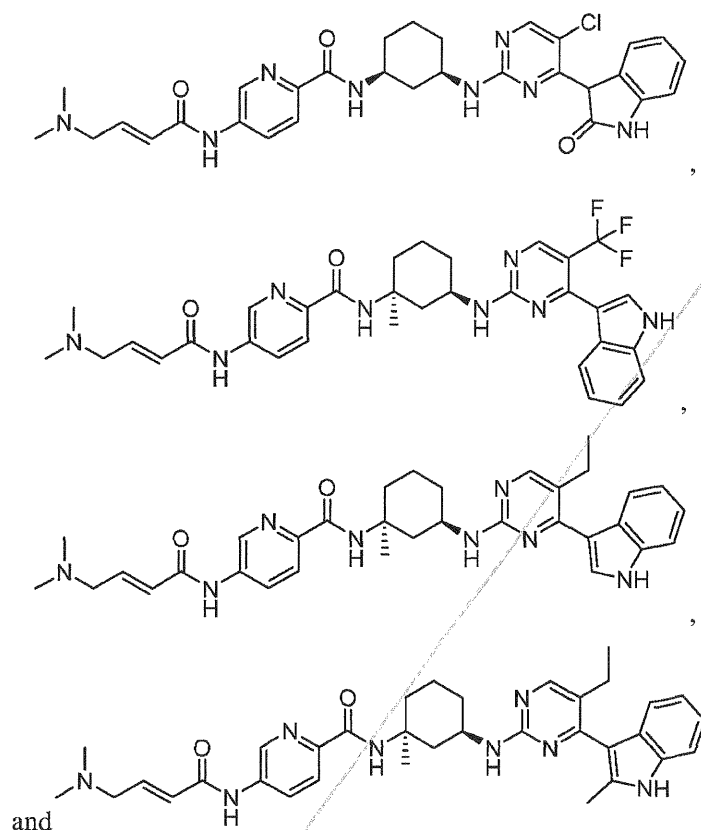
2. The compound of claim 1, having structural Formula (Ic'):

(Ic'), wherein ring A'', R^7 , R^8 , R^{10} ,

R^{21a} , R^{12} , and o are as defined in claim 1.

3. The compound of claim 1 or 2, wherein each R¹², if present, is fluoro.
4. The compound of any one of claims 1-3, wherein o is 0.
5. The compound of claim 1, selected from any one of the compounds set forth below:





6. A pharmaceutical composition comprising a compound of any one of claims 1-5 or 16 and a pharmaceutically acceptable excipient.
7. The composition of claim 6 for use in treating a subject suffering from a disease or condition associated with aberrant activity of a CDK.
8. The composition for use of claim 7, wherein the subject is suffering from a disease or condition associated with aberrant activity of CDK7.
9. The composition of claim 6, for use in treating a disease or condition selected from cancer, benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, autoimmune disease, or an infectious disease.

10. The composition for use of claim 9, wherein the subject is a human.
11. The composition for use of any one of claims 9-10, wherein the disease is cancer.
12. The composition for use of claim 11, wherein the cancer is selected from a blood cancer, melanoma, a bone cancer, a breast cancer, a brain cancer, or a lung cancer.
13. The composition for use of claim 12, wherein the cancer is a blood cancer selected from chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), T-cell acute lymphoblastic leukemia (T-ALL), chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML), lymphoma, and multiple myeloma.
14. The composition for use of claim 12, wherein the cancer is selected from osteosarcoma, Ewing's sarcoma, triple-negative breast cancer (TNBC), neuroblastoma, and small cell lung cancer (SCLC).
15. The composition for use of any one of claims 9-14, wherein the composition is used in conjunction with one or more additional agents independently selected from anti-proliferative agents, anti-cancer agents, immunosuppressant agents, and pain-relieving agents.
16. A compound selected from any one of the compounds set forth below:

