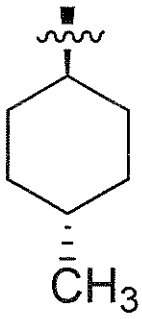
from –OH, halo, or –O-(C_1-C_6 alkyl); or R^{8e} and R^{8f}, when taken together, can represent =O; and

R' and R" are independently selected from –H, unsubstituted –(C_1-C_4 alkyl), or –(C_1-C_4 alkyl) substituted with 1 to 3 substituents independently selected from –OH or –F.

[013] In some embodiments of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^2 is a C_5-C_7 cycloalkyl group that is unsubstituted or is substituted with 1-3 substituents independently selected from unsubstituted –(C_1-C_6 alkyl), -OH, halo, -O-(C_1-C_6 alkyl), -CO_2H, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", -NR'R", or a substituted –(C_1-C_4 alkyl), wherein the substituted –(C_1-C_4 alkyl) is substituted with 1-3 substituents independently selected from halo, -OH, -OCH_3, -S(=O)$_2$-CH_3, or -C(=O)-CH_3.

[014] In some ~~embodiments~~examples of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^2 is an unsubstituted or substituted cyclohexyl ring. In some ~~such~~ embodiments, R^2 is a cyclohexyl group substituted with a –(C_1-C_2 alkyl) group. In still further ~~such embodiments~~examples, R^2 is a cyclohexyl group substituted with a methyl group. In some ~~such~~ embodiments, R^2 is a group of formula



where the ~~~ symbol indicates the point of attachment to the rest of the molecule. In some ~~embodiments~~examples, R^2 is an unsubstituted cyclohexyl group.

[015] In some ~~embodiments~~examples of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R' and R" are independently selected from –H or unsubstituted –(C_1-C_4 alkyl).

[016] In some ~~embodiments~~examples of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^2 is an unsubstituted or substituted cyclopentyl ring. In some such ~~embodiments~~examples, R^2 is a cyclopentyl group substituted with a –(C_1-C_2 alkyl) group. In still further such

~~embodiments~~examples, R^2 is a cyclopentyl group substituted with a methyl group. In some such ~~embodiments~~examples, R^2 is an unsubstituted cyclopentyl group.

[017] In some embodiments of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^1 is a group of Formula IA or IB. In some such embodiments, R^1 is a group of Formula IA. In other ~~such embodiments~~examples, R^1 is a group of Formula IB.

[018] In some ~~embodiments~~examples of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^1 is a group of Formula IC or ID. In some such ~~embodiments~~examples, R^1 is a group of Formula IC. In other such ~~embodiments~~examples, R^1 is a group of Formula ID.

[019] In some embodiments of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof,

R^2 is a C_5-C_7 cycloalkyl group that is unsubstituted or is substituted with 1-3 -(C_1-C_6 alkyl) groups;

R^{3a} is selected from –H, -(C_1-C_3 alkyl), or –O-(C_1-C_3 alkyl);

R^{3b} is -H;

R^{3c} is -H;

R^4 is -H;

R^5 is -H;

R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), or -C(=O)-C(=O)-OH, wherein the alkyl group of the –(C_1-C_6 alkyl) and -C(=O)-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -S(=O)$_2$-(C_1-C_6 alkyl), or –O-(C_1-C_6 alkyl);

R^{7a} is–H;

R^{7b} is –H; or is absent if R^1 is a group of Formula IB or Formula ID;

R^{7c} is –H; or is absent if R^1 is a group of Formula IA or Formula IC;

R^{8a} is -H;

R^{8b} is –H;

R^{8c} is selected from –H, -OH, or unsubstituted -(C_1-C_6 alkyl);

R^{8d} is –H;

R^{8e} is –H; and

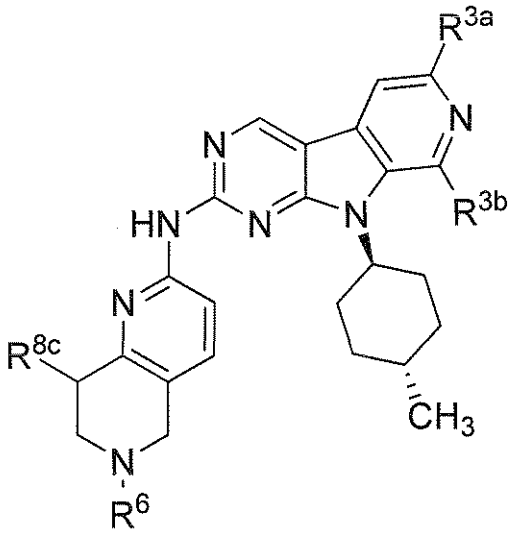
R^{8f} is –H.

[020] In some such ~~embodiments~~examples, R^1 is a group of Formula IA. In other ~~embodiments~~examples, R^1 is a group of Formula IB. In other ~~embodiments~~examples, R^1 is a group of Formula IC. In other ~~embodiments~~examples, R^1 is a group of Formula ID.

[021] In some ~~embodiments~~examples of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), -C(=O)-C(=O)-OH, -C(=O)-NR'R", or –S(=O)-NR'R", wherein the alkyl group of the –(C_1-C_6 alkyl) and -C(=O)-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -$S(=O)_2$-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -NR'R", or –CN.

[022] In some ~~embodiments~~examples of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, the compound is the glucuronide adduct.

[023] In some embodiments of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, the compound has the Formula IIA



IIA

R^{3a} is selected from –H, -F, or –Cl, -(C_1-C_3 alkyl), or -O-(C_1-C_3 alkyl);

R^{3b} is -H, halo, -OH, -O-(C_1-C_6 alkyl), unsubstituted –(C_1-C_6 alkyl), -NR'R", -C(=O)-(C_1-C_6 alkyl), -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from halo, -OH, -OCH_3, -CN, or -NO_2;

R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), -C(=O)-C(=O)-OH, -C(=O)-NR'R", or –S(=O)-NR'R", wherein the alkyl group of the –(C_1-C_6 alkyl) and -C(=O)-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -S(=O)$_2$-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -NR'R", or -CN; and

R^{8c} is selected from -H, -OH, unsubstituted –(C_1-C_6 alkyl), or a substituted -(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl).

[024] In some embodiments of the compound of Formula IIA or the pharmaceutically acceptable salt thereof, stereoisomer thereof, pharmaceutically acceptable salt of the stereoisomer, or the mixture thereof,

R^{3a} is selected from –H, -(C_1-C_3 alkyl), or –O-(C_1-C_3 alkyl);

R^{3b} is –H;

R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), or -C(=O)-C(=O)-OH, wherein the alkyl group of the –(C_1-C_6 alkyl) and -C(=O)-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -S(=O)$_2$-(C_1-C_6 alkyl), or –O-(C_1-C_6 alkyl); and

R^{8c} is selected from –H, unsubstituted –(C_1-C_6 alkyl), or –OH.

[025] In some embodiments of the compound of Formula IIA or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^{8c} is selected from –H, -CH_3, or –OH. In some such embodiments, R^{8c} is –H.

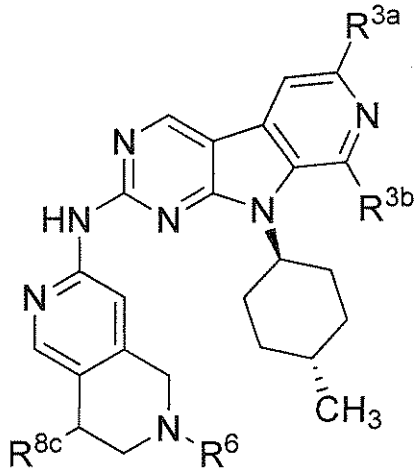
[026] In some ~~embodiments~~examples of the compound of Formula IIA or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^{3b} is –H.

[027] In some ~~embodiments~~examples of the compound of Formula IIA or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^{3a} is –H or –OCH_3. In some ~~such~~ embodiments, R^{3a} is –H.

[028] In some embodiments of the compound of Formula IIA or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^6 is selected from -H, -C(=O)-CH_3, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -C(=O)-CH_2OH, -C(=O)-C(=O)-OH, -$CH_2CH_2CF_3$, -CH_2CH_2F, -$CH_2CH_2S(=O)_2$-CH_3, or -$CH_2CH_2OCH_3$. In some ~~embodiments~~examples, R^6 is –H. In other embodiments, R^6 is selected from -C(=O)-CH_3 or -C(=O)-CH_2OH. In ~~still~~ other ~~embodiments~~examples, R^6 is selected from -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, or -$CH_2CH_2OCH_3$. In still other ~~embodiments~~examples, R^6 is

selected from $-CH_2CH_2CF_3$, $-CH_2CH_2F$, or $-CH_2CH_2S(=O)_2-CH_3$. In some ~~embodiments of any of these embodiments~~examples, R^{3a} is –H and R^{3b} is –H. In still other such ~~embodiments~~examples, R^{8c} is –H.

[029] In some ~~embodiments~~examples of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, the compound has the Formula IIIA



IIIA

R^{3a} is selected from –H, -F, or –Cl, $-(C_1-C_3$ alkyl), or $-O-(C_1-C_3$ alkyl);

R^{3b} is -H, halo, -OH, $-O-(C_1-C_6$ alkyl), unsubstituted $-(C_1-C_6$ alkyl), -NR'R", $-C(=O)-(C_1-C_6$ alkyl), $-C(=O)-O-(C_1-C_6$ alkyl), -C(=O)-NR'R", or a substituted $-(C_1-C_6$ alkyl), wherein the substituted $-(C_1-C_6$ alkyl) is substituted with 1-3 substituents independently selected from halo, -OH, $-OCH_3$, -CN, or $-NO_2$;

R^6 is selected from -H, $-(C_1-C_6$ alkyl), $-C(=O)-(C_1-C_6$ alkyl), -C(=O)-C(=O)-OH, -C(=O)-NR'R", or –S(=O)-NR'R", wherein the alkyl group of the $-(C_1-C_6$ alkyl) and $-C(=O)-(C_1-C_6$ alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, $-S(=O)_2-(C_1-C_6$ alkyl), $-O-(C_1-C_6$ alkyl), -NR'R", or -CN; and

R^{8c} is selected from -H, -OH, unsubstituted $-(C_1-C_6$ alkyl), or a substituted $-(C_1-C_6$ alkyl), wherein the substituted $-(C_1-C_6$ alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or $-O-(C_1-C_6$ alkyl).

[030] In some embodiments of the compound of Formula IIIA or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof,

R^{3a} is selected from –H, $-(C_1-C_3$ alkyl), or $-O-(C_1-C_3$ alkyl);

R^{3b} is –H;

R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), or -C(=O)-C(=O)-OH, wherein the alkyl group of the –(C_1-C_6 alkyl) and -C(=O)-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -S(=O)$_2$-(C_1-C_6 alkyl), or –O-(C_1-C_6 alkyl); and

R^{8c} is selected from –H, unsubstituted –(C_1-C_6 alkyl), or –OH.

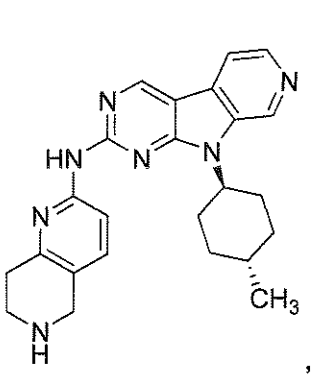
[031] In some ~~embodiments~~examples of the compound of Formula IIIA or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^{8c} is –H.

[032] In some ~~embodiments~~examples of the compound of Formula IIIA or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^{3b} is –H.

[033] In some ~~embodiments~~examples of the compound of Formula IIIA or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^{3a} is –H or –OCH_3. In some such embodiments, R^{3a} is –H

[034] In some ~~embodiments~~examples of the compound of Formula IIIA or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^6 is selected from -H, -C(=O)-CH_3, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -C(=O)-CH_2OH, -C(=O)-C(=O)-OH, -$CH_2CH_2CF_3$, -CH_2CH_2F, -$CH_2CH_2S(=O)_2$-CH_3, or -$CH_2CH_2OCH_3$. In other embodiments, R^6 is –H. In still other ~~embodiments~~examples, R^6 is selected from -C(=O)-CH_3 or -C(=O)-CH_2OH. In still other ~~embodiments~~examples, R^6 is selected from -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, or -$CH_2CH_2OCH_3$. In still further ~~embodiments~~examples, R^6 is selected from -$CH_2CH_2CF_3$, -CH_2CH_2F, or -$CH_2CH_2S(=O)_2$-CH_3. In some examples~~embodiments of any of these embodiments~~, R^{3a} is –H and R^{3b} is –H. In still other such ~~embodiments~~examples, R^{8c} is -H.

[035] In some embodiments of the compound of Formula, the compound is selected from



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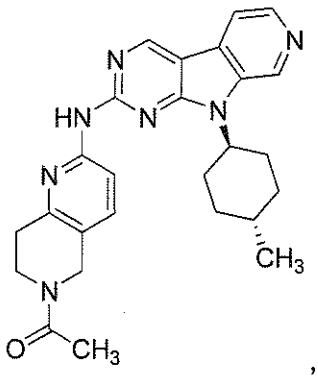

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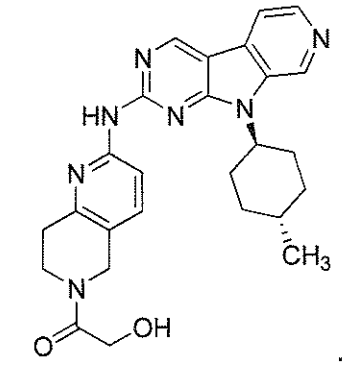
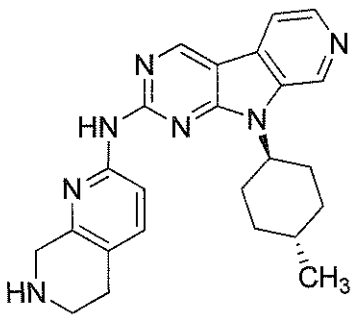
or is a pharmaceutical salt or hydrate thereof.

[035a] In another aspect, the present invention refers to a compound or a pharmaceutically acceptable salt or a hydrate thereof, wherein the compound has the formula



[035b] In another aspect, the present invention refers to a compound selected from



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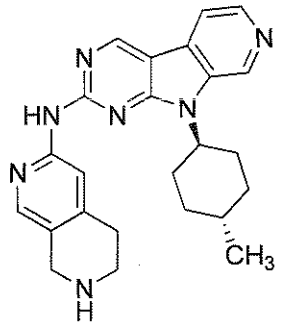

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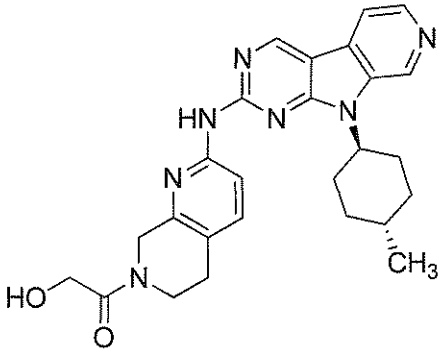

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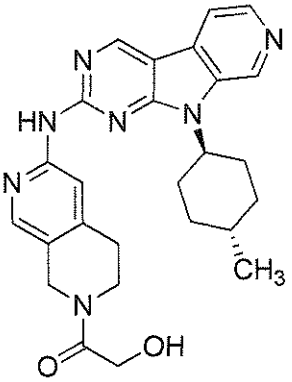

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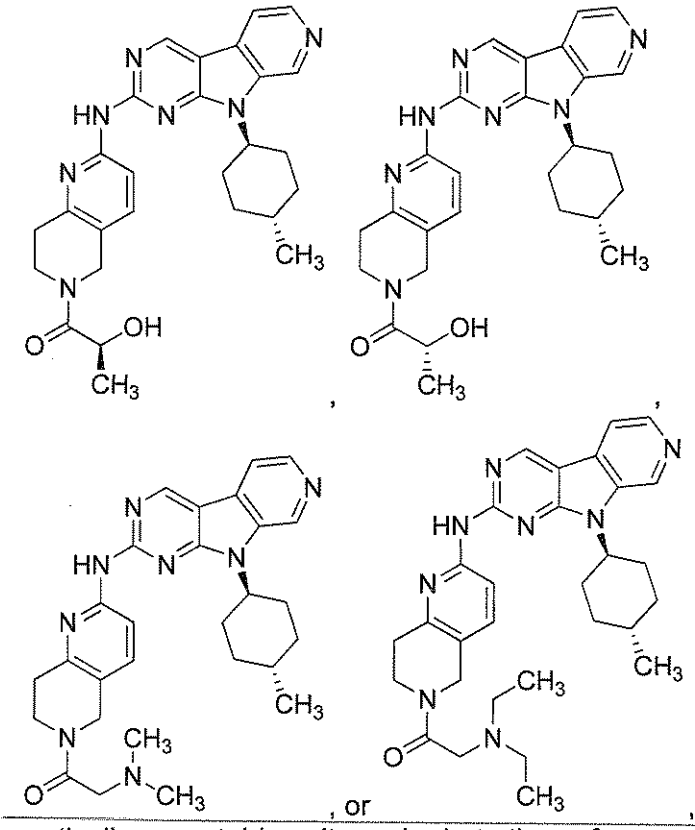


, or

or a pharmaceutically acceptable salt or a hydrate thereof.

[035c] In some embodiments, the compound is in a neutral form whereas in others it is a pharmaceutically acceptable salt. In some such embodiments, the salt is selected from a chloride salt, a methanesulfonate salt, or a benzenesulfonate salt. In some ~~such embodiments~~examples, the salt is a chloride salt. In other ~~embodiments~~examples, the salt is a methanesulfonate salt. In still other ~~embodiments~~examples, the compound is a benzenesulfonate salt. In other ~~embodiments~~examples, the compound is a hydrate of the neutral compound or of the salt. For example, in some ~~embodiments~~examples, the compound may be a chloride salt that is a monohydrate, a dihydrate, or a trihydrate.

[036] In some ~~embodiments~~examples of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, the compound is in a neutral form.

[037] In some embodiments of the compound of Formula I or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, the compound is a pharmaceutically acceptable salt. In some such embodiments, the salt is selected from a chloride salt, a methanesulfonate salt, or a benzenesulfonate salt. In some such ~~embodiments~~examples, the salt is a chloride salt. In other ~~embodiments~~examples, the salt is a methanesulfonate salt. In still other ~~embodiments~~examples, the compound is a benzenesulfonate salt.

[038] Also ~~provided~~described are pharmaceutical compositions that include at least one pharmaceutically acceptable carrier, excipient or diluent and a therapeutically effective amount of the compound, the pharmaceutically acceptable salt, the hydrate, or the mixture thereof according to any of the ~~embodiments~~examples described herein.

[038a] In one aspect, the present invention refers to the pharmaceutically acceptable salt or the hydrate thereof of claim 1, or 15, or 18, or 19.

[038b] In another aspect, the present invention refers to a pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of the compound, the pharmaceutically acceptable salt, the hydrate thereof, or the mixture thereof as defined in any one of claims 1, 15, 18 or 19 and at least one pharmaceutically acceptable excipient, carrier, or diluent.

[038c] In some such ~~embodiments~~examples, the compound is present in an amount effective for the treatment of cancer. In some ~~embodiments~~examples, the pharmaceutical composition includes at least one pharmaceutically acceptable carrier, excipient or diluent and a therapeutically effective amount of the compound in a neutral form. In other ~~embodiments~~examples, the pharmaceutical composition includes at least one pharmaceutically acceptable carrier, excipient or diluent and a therapeutically effective amount of the pharmaceutically acceptable salt. In some such ~~embodiments~~examples, the salt is a chloride salt. In other ~~embodiments~~examples the salt is a methanesulfonate salt. In still other ~~embodiments~~examples, the salt is a benzenesulfonate salt. In some of any of these ~~embodiments~~examples, the pharmaceutical composition further includes at least one second therapeutic agent. In some such ~~embodiments~~examples, the second therapeutic agent is one that is used in treating cancer. In some such ~~embodiments~~examples, the second therapeutic agent is used in treating acute myeloid leukemia or any of the other

cancers described below. In some ~~embodiments~~examples, the second therapeutic agent is selected from cytosine arabinoside, daunorubicin, idarubicin, doxorubicin, cyclophosphamide, etoposide, carboplatin, fludarabine, mitoxantrone, dexamethasone, rituximab, midostaurin, a granulocyte colony-stimulating factor, filgrastim, PEG-filgrastim, lenograstim, decitabine, azacitidine, paclitaxel, gemcitibine, motesanib disphosphate, panitumumab, an antibody directed against CD33, or a CD33 bispecific T-cell engager antibody. In other ~~embodiments~~examples, the second therapeutic agent is selected from cytosine arabinoside, daunorubicin, idarubicin, doxorubicin, cyclophosphamide, etoposide, carboplatin, fludarabine, mitoxantrone, dexamethasone, rituximab, midostaurin, a granulocyte colony-stimulating factor, filgrastim, PEG-filgrastim, lenograstim, decitabine, azacitidine, paclitaxel, gemcitibine, motesanib disphosphate, panitumumab. In still other such ~~embodiments~~examples, the second therapeutic agent is selected from cytosine arabinoside, daunorubicin, idarubicin, doxorubicin, cyclophosphamide, etoposide, carboplatin, fludarabine, mitoxantrone, dexamethasone, rituximab, midostaurin, decitabine, azacitidine, paclitaxel, gemcitibine, or motesanib disphosphate. In some such ~~embodiments~~examples, the second therapeutic agent is cytosine arabinoside. In other ~~embodiments~~examples, the second therapeutic agent is daunorubicin, idarubicin, or doxorubicin. In still other ~~embodiments~~examples, the second therapeutic agent is azacitidine or decitabine. In some ~~embodiments~~examples, the second therapeutic agent is an anthracycline. In some ~~embodiments~~examples, the second therapeutic agent is an aurora kinase inhibitor such as *N*-(4-((3-(2-amino-4-pyrimidinyl)-2-pyridinyl)oxy)phenyl)-4-(4-methyl-2-thienyl)-1-phthalazinamine or another compound disclosed in WO 2007/087276.

[039] Further ~~provided~~described are pharmaceutical compositions that include at least one pharmaceutically acceptable carrier, and a therapeutically effective amount of the composition of matter of any of the ~~embodiments~~examples described herein in combination with at least one additional compound such as a cytotoxic agent or a compound that inhibits another kinase.

[040] In other ~~embodiments~~examples, ~~the invention provides~~it is described a method of treating cancer. In some such ~~embodiments~~examples, the cancer is resistant to other agents such as to an anthracycline therapeutic agent. Such methods typically include administering to a subject an effective amount of the compound, the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof of any of the ~~embodiments~~examples or a pharmaceutical composition of any of the ~~embodiments~~examples. In some such ~~embodiments~~examples,

the cancer is selected from acute myeloid leukemia, acute lymphoblastic leukemia myelodysplastic syndrome, multiple myeloma, chronic myeloid leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, another lymphoma, another myeloma, or another leukemia. Examples of other cancers that may be treated with the compounds ~~of the present invention~~described herein include Burkitt's lymphoma and mantle cell lymphoma. In some such ~~embodiments~~examples, the cancer is acute myeloid leukemia. In some such ~~embodiments~~examples, the subject is a human patient with mutant FLT3 such as a patient with FLT3-ITD positive acute myeloid leukemia. In some such ~~embodiments~~examples, the method may also include determining whether the patient has FLT3-ITD positive acute myeloid leukemia. For example, such a method might include obtaining a sample from a patient and analyzing whether the sample is FLT3-ITD positive. In other such ~~embodiments~~examples, the subject is a human patient with wild type FLT3 acute myeloid leukemia. In another ~~embodiment~~example, the cancer is acute lymphoblastic leukemia. In other ~~embodiments~~examples, the cancer is selected from breast cancer, colorectal cancer, small cell lung carcinoma, head and neck, glioblastoma, pancreatic, gastrointestinal, liver, prostate, ovarian, testicular, endometrial, bladder, melanoma, osteosarcoma, or another sarcoma. In some ~~embodiments~~examples, the cancer is Rb-positive whereas in other embodiments, the cancer is not Rb-positive. In some ~~embodiments~~examples, the subject is a mammal, and in some ~~embodiments~~examples, is a human cancer patient. In some such ~~embodiments~~examples, the cancer is a hematological cancer. In other ~~embodiments~~examples, the cancer is a solid tumor. In some ~~embodiments~~examples, the method includes administering to a subject an effective amount of the compound, the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof of any of the embodiments or a pharmaceutical composition of any of the ~~embodiments~~examples where the patient is a human cancer patient with mutant FLT3 and in some such ~~embodiments~~examples is a human cancer patient with FLT3-ITD.

[041] As noted above, the compounds of the invention have been found to be active in cancer cells, for example acute myeloid leukemia cells, that are both wild type and mutant with respect to FLT3. Therefore, in some ~~embodiments~~examples, ~~the invention provides~~described herein are methods for treating cancer in patients with wild type FLT3 whereas in other ~~embodiments~~examples, ~~the invention provides~~ methods are described for treating cancer in patients with mutant FLT3. Such methods typically include administering to a subject such as a human cancer patient an effective amount of the compound, the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof of any of the

~~embodiments~~examples or a pharmaceutical composition of any of the ~~embodiments~~examples. In some such ~~embodiments~~examples, the cancer is acute myeloid leukemia. In some such ~~embodiments~~examples, the subject is a human patient with mutant FLT3 such as a patient that tests positive for a mutant FLT3 acute myeloid leukemia. Examples of FLT3 mutants include, but are not limited to, FLT3-ITD, FLT3 with activation loop point mutations such as FLT3-D835Y, FLT3-D835H, and FLT3-D835V, FLT3-K663Q, and FLT3-N841I. Therefore, in some ~~embodiments~~examples, the FLT3 mutant is FLT3-ITD. In other ~~embodiments~~examples, the FLT3 mutant is FLT3-D835Y. In still other ~~embodiments~~examples, the FLT3 mutant is FLT3-D835H. In other ~~embodiments~~examples, the FLT3 mutant is FLT3-D835V. In still other ~~embodiments~~examples, the FLT3 mutant is FLT3-K663Q. In still further such ~~embodiments~~examples, the FLT3 mutant is FLT3-N841I. In some such ~~embodiments~~examples, the method may include determining whether the patient has mutant FLT3 acute myeloid leukemia. For example, such a method might include obtaining a sample from a patient and analyzing whether the sample tests positive for one or more FLT3 mutant. In some ~~embodiments~~examples, the method includes administering to a subject an effective amount of the compound, the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof of any of the ~~embodiments~~examples or a pharmaceutical composition of any of the ~~embodiments~~examples where the patient is a human cancer patient with mutant FLT3 and in some such ~~embodiments~~examples is a human cancer patient with acute myeloid leukemia.

[042] In some methods of treating cancer, the patient is a human cancer patient with a solid or hematological tumor in which the tumor exhibits low $p15^{INK4B}$ and/or low $p16^{INK4A}$ expression and in some such ~~embodiments~~examples is a human patient with acute myeloid leukemia where the tumor exhibits low $p15^{INK4B}$ and/or low $p16^{INK4A}$ expression. In some ~~embodiments~~examples, a tumor that exhibits low $p15^{INK4B}$ and/or low $p16^{INK4A}$ expression is determined using an assay that measures the levels of these proteins or mRNA or both and compares them to the levels in a normal myeloid tumor. This method could also be used for other tumor types. A tumor that contains less of the $p15^{INK4B}$ and/or $p16^{INK4A}$ proteins or mRNA or both than is found in a normal cell would be one that exhibits low $p15^{INK4B}$ and/or $p16^{INK4A}$ expression. In some ~~embodiments~~examples, the tumor includes less than 90%, less than 80%, less than 70%, less than 60%, or less than 50% of $p15^{INK4B}$ and/or $p16^{INK4A}$ than occurs in a normal cell.

[043] Any of the methods described herein may include the use of a second therapeutic agent such as those described above. For example, in one ~~embodiment~~example, the invention provides a method of treating cancer which includes administering to a

subject (a) an effective amount of the compound, the pharmaceutically acceptable salt thereof, the hydrate thereof or the mixture thereof of any of the ~~embodiments~~examples or the pharmaceutical composition of any of the ~~embodiments~~examples; and (b) at least one second therapeutic agent used in the treatment of cancer. In some such ~~embodiments~~examples, the second therapeutic agent is used in treating acute myeloid leukemia or any of the other cancers described herein. In some ~~embodiments~~examples, the second therapeutic agent is selected from cytosine arabinoside, daunorubicin, idarubicin, doxorubicin, cyclophosphamide, etoposide, carboplatin, fludarabine, mitoxantrone, dexamethasone, rituximab, midostaurin, a granulocyte colony-stimulating factor, filgrastim, PEG-filgrastim, lenograstim, decitabine, azacitidine, paclitaxel, gemcitibine, motesanib disphosphate, panitumumab, an antibody directed against CD33, or a CD33 bispecific T-cell engager antibody. In other ~~embodiments~~examples, the second therapeutic agent is selected from cytosine arabinoside, daunorubicin, idarubicin, doxorubicin, cyclophosphamide, etoposide, carboplatin, fludarabine, mitoxantrone, dexamethasone, rituximab, midostaurin, a granulocyte colony-stimulating factor, filgrastim, PEG-filgrastim, lenograstim, decitabine, azacitidine, paclitaxel, gemcitibine, motesanib disphosphate, panitumumab. In still other such ~~embodiments~~examples, the second therapeutic agent is selected from cytosine arabinoside, daunorubicin, idarubicin, doxorubicin, cyclophosphamide, etoposide, carboplatin, fludarabine, mitoxantrone, dexamethasone, rituximab, midostaurin, decitabine, azacitidine, paclitaxel, gemcitibine, or motesanib disphosphate. In some such ~~embodiments~~examples, the second therapeutic agent is cytosine arabinoside. In other ~~embodiments~~examples, the second therapeutic agent is daunorubicin, idarubicin, or doxorubicin. In still other ~~embodiments~~examples, the second therapeutic agent is azacitidine or decitabine. In some ~~embodiments~~examples, the second therapeutic agent is an anthracycline. In some ~~embodiments~~examples, the second therapeutic agent is an aurora kinase inhibitor such as *N*-(4-((3-(2-amino-4-pyrimidinyl)-2-pyridinyl)oxy)phenyl)-4-(4-methyl-2-thienyl)-1-phthalazinamine or another compound disclosed in WO 2007/087276. In some ~~embodiments~~examples, the compound, the pharmaceutically acceptable salt thereof, or the mixture thereof of any of the ~~embodiments~~examples or the pharmaceutical composition of any of the ~~embodiments~~examples is administered to the subject after the at least one second therapeutic agent is administered to the subject. In other ~~embodiments~~examples, the compound, the pharmaceutically acceptable salt thereof, or the hydrate thereof, or the mixture thereof of any of the ~~embodiments~~examples or the pharmaceutical composition of any of the ~~embodiments~~examples is administered to the subject before the at least one second

therapeutic agent is administered to the subject. In still other ~~embodiments~~examples, the compound, the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof of any of the ~~embodiments~~examples or the pharmaceutical composition of any of the ~~embodiments~~examples is administered to the subject at the same time that the at least one second therapeutic agent is administered to the subject.

[044] Also described herein is~~The invention further provides~~ a compound for use in the preparation of a medicament. Any of the compounds, salts, hydrates or mixtures of any of the ~~embodiments~~examples described herein can be used to prepare the medicament. In some ~~embodiments~~examples, the cancer is selected from acute myeloid leukemia, myelodysplastic syndrome, multiple myeloma, chronic myeloid leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, another lymphoma, another myeloma, or another leukemia. In some such ~~embodiments~~examples, the cancer is acute myeloid leukemia. In other ~~embodiments~~examples, the cancer is selected from breast cancer, colorectal cancer, small cell lung carcinoma, head and neck, glioblastoma, pancreatic, gastrointestinal, liver, prostate, ovarian, testicular, endometrial, bladder, melanoma, osteosarcoma, or another sarcoma. In some ~~embodiments~~examples, the cancer is Rb-positive whereas in other embodiments, the cancer is not Rb-positive. In some ~~embodiments~~examples, the subject is a human cancer patient and, in some such ~~embodiments~~examples, the cancer is a hematological cancer.

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

BRIEF DESCRIPTION OF THE DRAWINGS

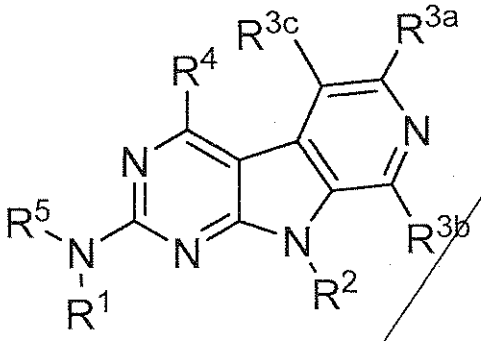
[046] Figure 1 is a graph showing the dose dependent anti-tumor activity observed after twice daily dosing (BID) with Example 5 in CrTac:NCR-*Foxn1*^{nu} nude mice with MOLM13 subcutaneous xenograft tumors.

[047] Figure 2 is a graph showing the dose dependent anti-tumor activity observed after twice daily dosing (BID) with Example 5 in CrTac:NCR-*Foxn1*^{nu} nude mice with Colo 205 subcutaneous xenograft tumors.

[048] Figure 3 is an X-ray Powder Diffraction (XRPD) Spectrum of the hydrochloride salt of Example 5 showing 2Theta (°) on the x-axis and Intensity (counts) on the y axis.

WHAT IS CLAIMED:

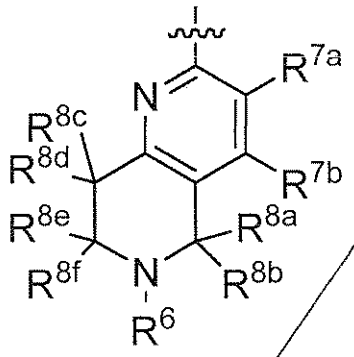
1. A compound of Formula I:



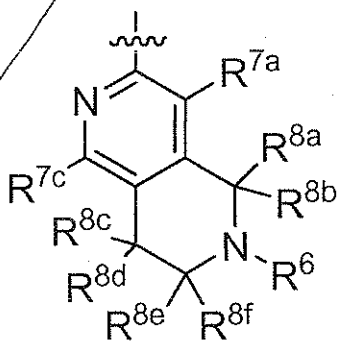
I

or a pharmaceutically acceptable salt thereof, a hydrate thereof, or a mixture thereof, wherein:

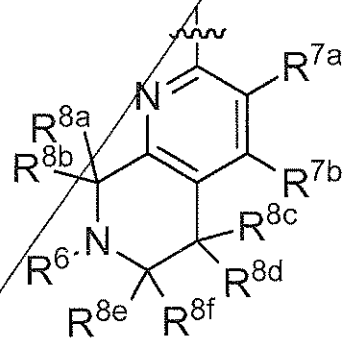
R^1 is a group of Formula IA, Formula IB, Formula IC, or Formula ID



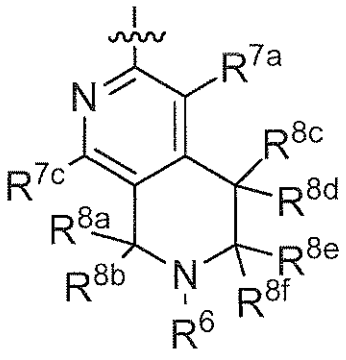
IA



IB



IC



ID

wherein the ~~~ symbol indicates the point of attachment of the group of Formula IA, IB, IC, or ID to the rest of the molecule;

R^2 is a C_5-C_7 cycloalkyl group, is a 5 to 7-membered heterocyclyl group that includes 1, 2, or 3 heteroatoms selected from N, O, and S, or is a C_7-C_{10} bicyclic group; wherein the C_5-C_7 cycloalkyl group, the 5 to 7 membered heterocyclyl group, or the C_7-C_{10} bicyclic group is unsubstituted or is substituted with 1-3 substituents independently selected from unsubstituted –(C_1-C_6 alkyl), -OH, halo, -O-(C_1-C_6 alkyl), -CO_2H, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", -NR'R", or a substituted –(C_1-C_4 alkyl), wherein the substituted –(C_1-C_4 alkyl) is substituted with 1-3 substituents independently selected from halo, -OH, -OCH_3, -S(=O)$_2$-CH_3, or -C(=O)-CH_3;

R^{3a} is selected from –H, -F, or –Cl, -(C_1-C_3 alkyl), or -O-(C_1-C_3 alkyl);

R^{3b} is -H, halo, -OH, -O-(C_1-C_6 alkyl), unsubstituted –(C_1-C_6 alkyl), -NR'R", -C(=O)-(C_1-C_6 alkyl), -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from halo, -OH, -OCH_3, -CN, or -NO_2;

R^{3c} is -H, -(C_1-C_3 alkyl), or halo;

R^4 is -H;

R^5 is -H;

R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-C(=O)-OH, -C(=O)-NR'R", or –S(=O)-NR'R", wherein the alkyl group of the –(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), and -C(=O)-O-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -S(=O)$_2$-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -NR'R", or -CN;

R^{7a} is–H, -CH_3, or halo;

R^{7b} is –H, -(C_1-C_6 alkyl), or halo; or R^{7b} is absent if R^1 is a group of Formula IB or Formula ID;

R^{7c} is –H, unsubstituted –(C_1-C_6 alkyl), halo, -O-(C_1-C_6 alkyl), -NO_2, -CN, -NR'R", -CO_2H, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, -O-(C_1-C_6 alkyl), -CN, -NR'R", or –S(=O)$_2$-CH_3; or R^{7c} is absent if R^1 is a group of Formula IA or Formula IC;

R^{8a} is -H, unsubstituted –(C_1-C_6 alkyl), or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl);

R^{8b} is -H, unsubstituted –(C_1-C_6 alkyl), or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl); or R^{8a} and R^{8b}, when taken together, can represent =O;

R^{8c} is selected from -H, -OH, unsubstituted –(C_1-C_6 alkyl), or a substituted -(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl);

R^{8d} is -H, unsubstituted –(C_1-C_6 alkyl), or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl);

R^{8e} is -H, unsubstituted –(C_1-C_6 alkyl), or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl);

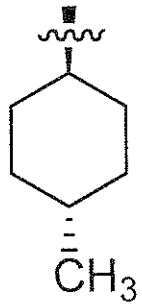
R^{8f} is -H, unsubstituted –(C_1-C_6 alkyl), or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl); or R^{8e} and R^{8f}, when taken together, can represent =O; and

R' and R" are independently selected from –H, unsubstituted –(C_1-C_4 alkyl), or –(C_1-C_4 alkyl) substituted with 1 to 3 substituents independently selected from –OH or -F.

2. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^2 is a C_5-C_7 cycloalkyl group that is unsubstituted or is substituted with 1-3 substituents independently selected from unsubstituted –(C_1-C_6 alkyl), -OH, halo, -O-(C_1-C_6 alkyl), -CO_2H, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", -NR'R", or a substituted –(C_1-C_4 alkyl), wherein the substituted –(C_1-C_4 alkyl) is substituted with 1-3 substituents independently selected from halo, -OH, -OCH_3, -S(=O)$_2$-CH_3, or -C(=O)-CH_3.

3. The compound of claim 2 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^2 is a cyclohexyl group substituted with a –(C_1-C_2 alkyl) group.

4. The compound of claim 3 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^2 is a group of formula



wherein the ~~~ symbol indicates the point of attachment to the rest of the molecule.

5. The compound of any one of claims 1-4 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^1 is a group of Formula IA or IB.

6. The compound of claim 5 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^1 is a group of Formula IA.

7. The compound of claim 1, wherein:

R^2 is a C_5-C_7 cycloalkyl group that is unsubstituted or is substituted with 1-3 -(C_1-C_6 alkyl) groups;

R^{3a} is selected from –H, -(C_1-C_3 alkyl), or –O-(C_1-C_3 alkyl);

R^{3b} is -H;

R^{3c} is -H;

R^4 is -H;

R^5 is -H;

R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), or -C(=O)-C(=O)-OH, wherein the alkyl group of the –(C_1-C_6 alkyl) and -C(=O)-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -$S(=O)_2$-(C_1-C_6 alkyl), or –O-(C_1-C_6 alkyl);

R^{7a} is–H;

R^{7b} is –H; or is absent if R^1 is a group of Formula IB or Formula ID;

R^{7c} is –H; or is absent if R^1 is a group of Formula IA or Formula IC;

R^{8a} is -H;

R^{8b} is –H;

R^{8c} is selected from –H, -OH, or unsubstituted -(C_1-C_6 alkyl);

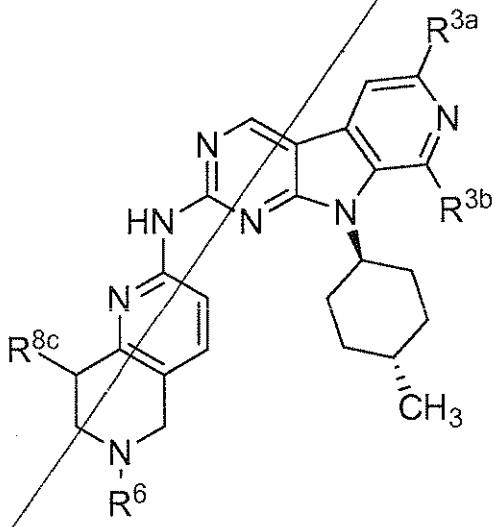
R^{8d} is –H;

R^{8e} is –H; and

R^{8f} is –H,

or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof.

8. The compound of claim 1, wherein the compound has the Formula IIA



IIA

or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof,

wherein:

R^{3a} is selected from –H, -F, or –Cl, -(C_1-C_3 alkyl), or -O-(C_1-C_3 alkyl);

R^{3b} is -H, halo, -OH, -O-(C_1-C_6 alkyl), unsubstituted –(C_1-C_6 alkyl), -NR'R", -C(=O)-(C_1-C_6 alkyl), -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from halo, -OH, $-OCH_3$, -CN, or $-NO_2$;

R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), -C(=O)-C(=O)-OH, -C(=O)-NR'R", or –S(=O)-NR'R", wherein the alkyl group of the –(C_1-C_6 alkyl) and -C(=O)-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents

independently selected from –OH, F, -S(=O)$_2$-(C$_1$-C$_6$ alkyl), -O-(C$_1$-C$_6$ alkyl), -NR'R", or -CN; and

R^{8c} is selected from -H, -OH, unsubstituted –(C$_1$-C$_6$ alkyl), or a substituted -(C$_1$-C$_6$ alkyl), wherein the substituted –(C$_1$-C$_6$ alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C$_1$-C$_6$ alkyl).

9. The compound of claim 8, wherein:

R^{3a} is selected from –H, -(C$_1$-C$_3$ alkyl), or –O-(C$_1$-C$_3$ alkyl);

R^{3b} is –H;

R^6 is selected from -H, -(C$_1$-C$_6$ alkyl), -C(=O)-(C$_1$-C$_6$ alkyl), or -C(=O)-C(=O)-OH, wherein the alkyl group of the –(C$_1$-C$_6$ alkyl) and -C(=O)-(C$_1$-C$_6$ alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -S(=O)$_2$-(C$_1$-C$_6$ alkyl), or –O-(C$_1$-C$_6$ alkyl); and

R^{8c} is selected from –H, unsubstituted –(C$_1$-C$_6$ alkyl), or –OH,

or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof.

10. The compound of claim 8 or claim 9 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^{8c} is selected from -H, -CH$_3$, or -OH.

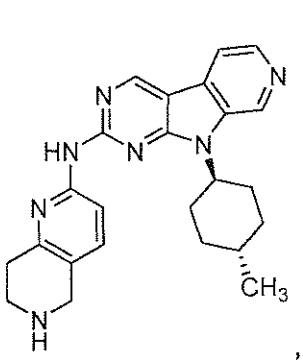
11. The compound of claim 10 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^{8c} is –H.

12. The compound of claim 11 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^{3a} is –H.

13. The compound of any one of claims 7-12 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^6 is selected from -H, -C(=O)-CH$_3$, -CH$_2$CH$_2$OH, -CH$_2$CH$_2$CH$_2$OH, -C(=O)-CH$_2$OH, -C(=O)-C(=O)-OH, -CH$_2$CH$_2$CF$_3$, -CH$_2$CH$_2$F, -CH$_2$CH$_2$S(=O)$_2$-CH$_3$, or -CH$_2$CH$_2$OCH$_3$.

14. The compound of claim 13 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^6 is selected from -C(=O)-CH_3 or -C(=O)-CH_2OH.

15. The compound of claim 1, wherein the compound is selected from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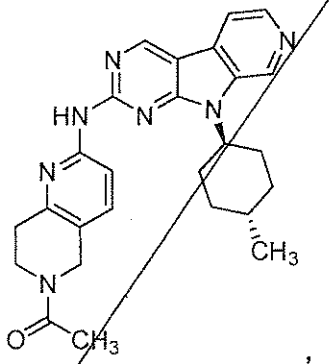
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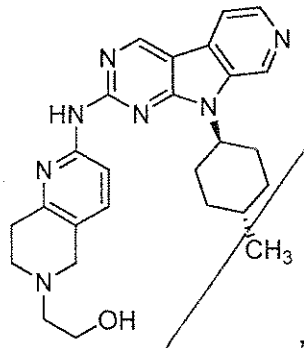
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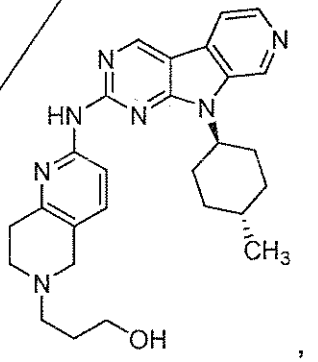
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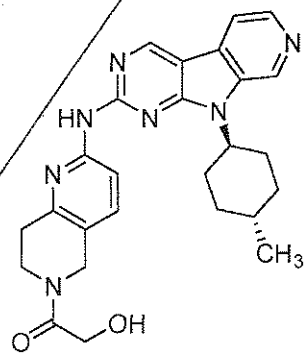
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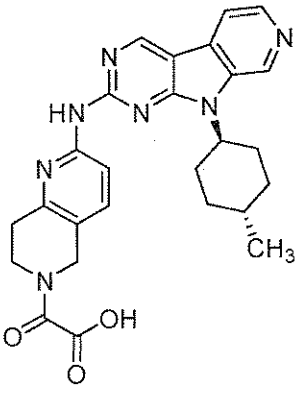
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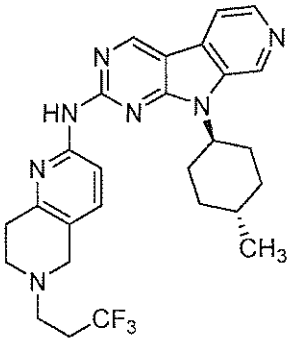
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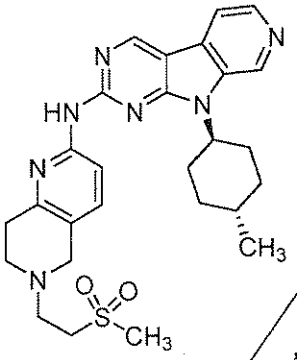
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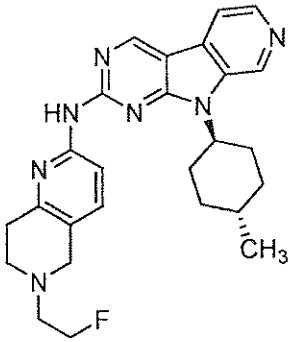
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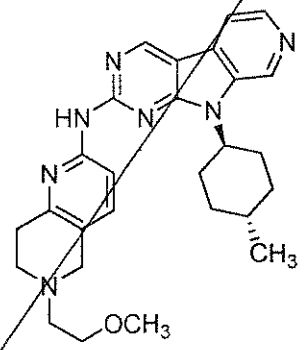
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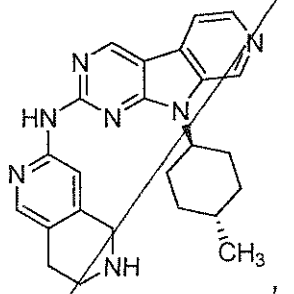
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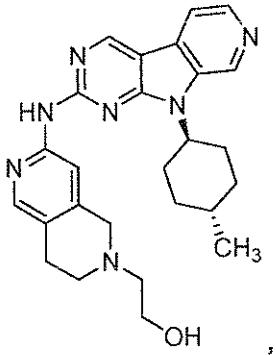
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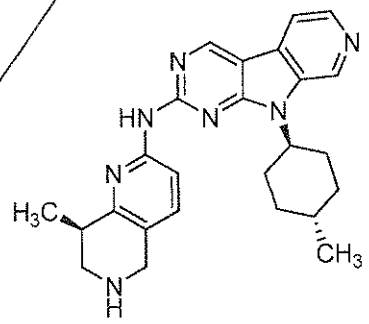
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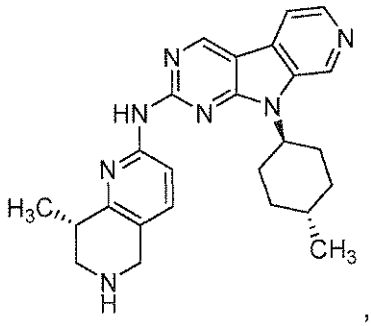
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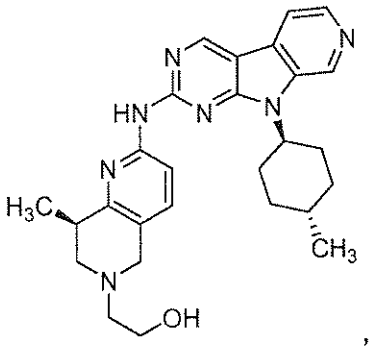
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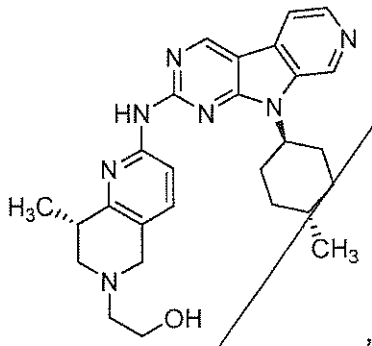
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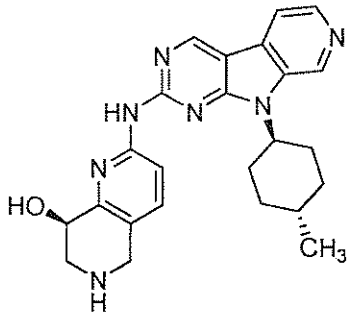
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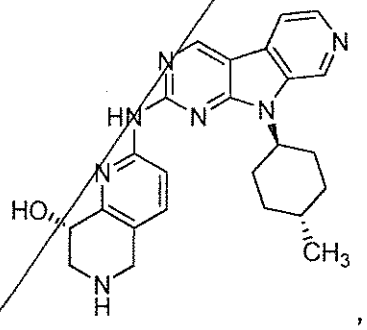
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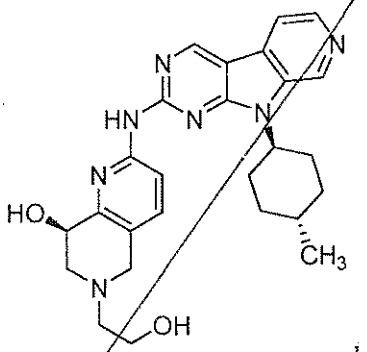
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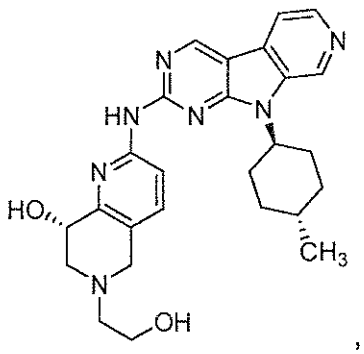
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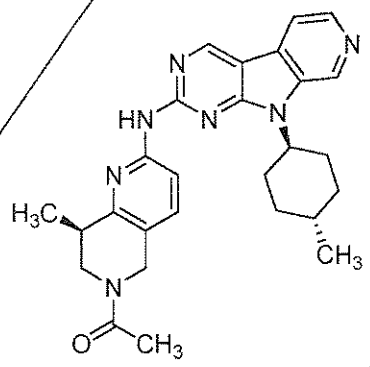
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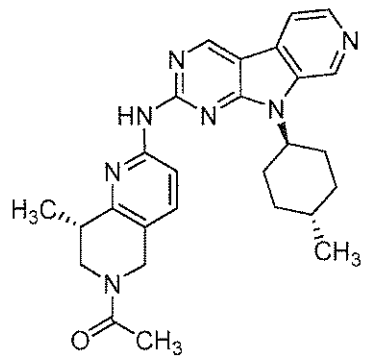
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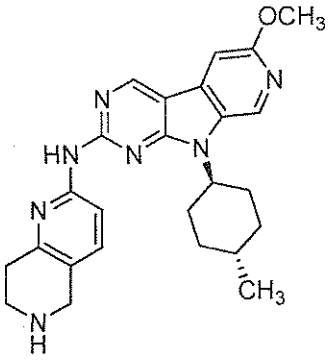
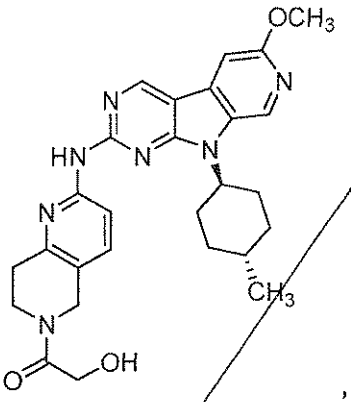
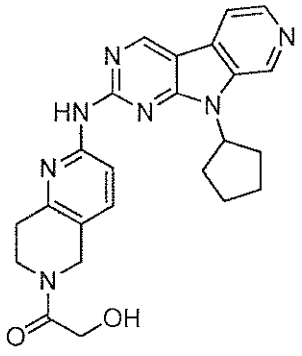
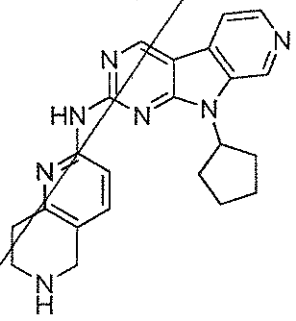
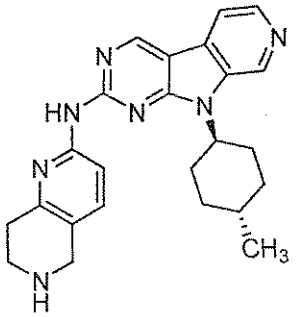





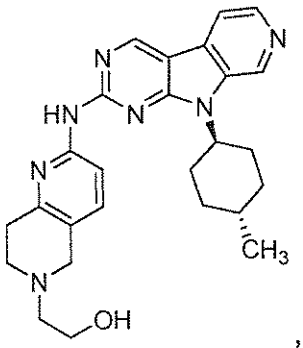
or the pharmaceutically acceptable salt or the hydrate thereof.

16. The compound of claim 1, wherein the compound is



or the pharmaceutically acceptable salt or the hydrate thereof.

17. The compound of claim 1, wherein the compound is



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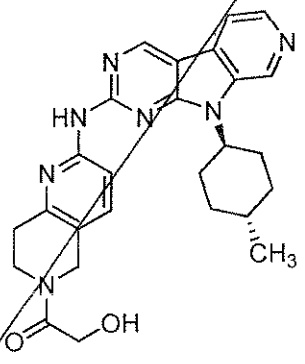
or the pharmaceutically acceptable salt or the hydrate thereof.

18. The compound of claim 1, wherein the compound is



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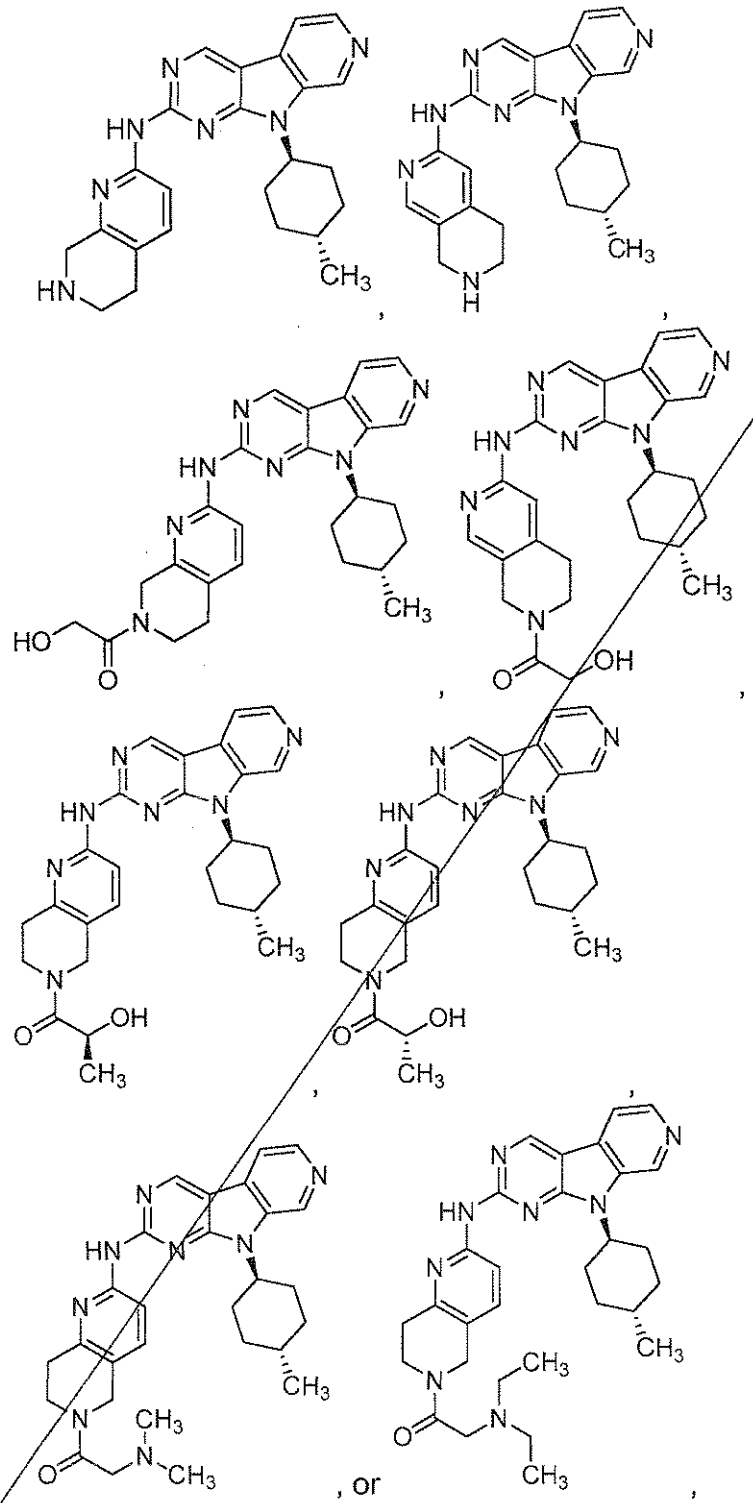
or the pharmaceutically acceptable salt or the hydrate thereof.

19. The compound of claim 1, wherein the compound is selected from



, or

or the pharmaceutically acceptable salt or the hydrate thereof.

20. The compound of any one of claims 1-19 in a neutral form.

21. The pharmaceutically acceptable salt or a hydrate thereof of any one of claims 1-19.

22. The pharmaceutically acceptable salt or a hydrate thereof of claim 21, wherein the pharmaceutically acceptable salt or hydrate thereof is selected from a chloride salt, a methanesulfonate salt, or a benzenesulfonate salt.

23. A pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of the compound, the pharmaceutically acceptable salt, the hydrate thereof, or the mixture thereof according to any one of claims 1-22 and at least one pharmaceutically acceptable excipient, carrier, or diluent.

24. A method of treating cancer, the method comprising: administering to a subject an effective amount of the compound, the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof of any one of claims 1-22 or the pharmaceutical composition of claim 23.

25. The method of claim 24, wherein the cancer is selected from acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, multiple myeloma, chronic myeloid leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, another lymphoma, another myeloma, or another leukemia.

26. The method of claim 25, wherein the cancer is acute myeloid leukemia.

27. The method of claim 24, wherein the cancer is selected from breast cancer, colorectal cancer, small cell lung carcinoma, head and neck, glioblastoma, pancreatic, gastrointestinal, liver, prostate, ovarian, testicular, endometrial, bladder, melanoma, osteosarcoma, or another sarcoma.

28. The method of any one of claims 24-27, wherein the cancer is Rb-positive.

29. A method of treating cancer, the method comprising: administering to a subject

(a) an effective amount of the compound, the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof of any one of claims 1-22 or the pharmaceutical composition of claim 23; and

(b) at least one second therapeutic agent used in the treatment of cancer.

30. The method of claim 29, wherein the second therapeutic agent is cytosine arabinoside, daunorubicin, idarubicin, doxorubicin, cyclophosphamide, etoposide, carboplatin, fludarabine, mitoxantrone, dexamethasone, rituximab, midostaurin, a granulocyte colony-stimulating factor, filgrastim, PEG-filgrastim, lenograstim, decitabine, azacitidine, paclitaxel, gemcitibine, motesanib disphosphate, panitumumab, an antibody directed against CD33, or a CD33 bispecific T-cell engager antibody.

31. The compound of any one of claims 1-22 in the preparation of a medicament.

32. The compound of any one of claims 1-22 or the pharmaceutically acceptable salt, or the hydrate thereof, or the mixture thereof or the pharmaceutical composition of claim 23 for treating cancer.

33. The compound of claim 32 or the pharmaceutically acceptable salt, or the hydrate thereof, or the mixture thereof, wherein the cancer is selected from acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, multiple myeloma, chronic myeloid leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, another lymphoma, another myeloma, or another leukemia.

34. The compound of claim 32 or the pharmaceutically acceptable salt, or the hydrate thereof, or the mixture thereof, wherein the cancer is acute myeloid leukemia.

35. The compound of claim 32 or the pharmaceutically acceptable salt, or the hydrate thereof, or the mixture thereof, for use in treating a human cancer patient, wherein the cancer is a hematological cancer.

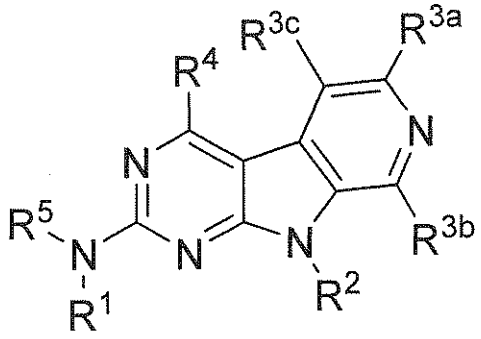
36. The use of the compound of any one of claims 1-22 or the pharmaceutically acceptable salt, or the hydrate thereof, or the mixture thereof in the preparation of a medicament for treating cancer.

37. The use of claim 36, wherein the cancer is selected from acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, multiple myeloma, chronic myeloid leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, another lymphoma, another myeloma, or another leukemia.

38. The use of claim 36, wherein the cancer is acute myeloid leukemia.

WHAT IS CLAIMED:

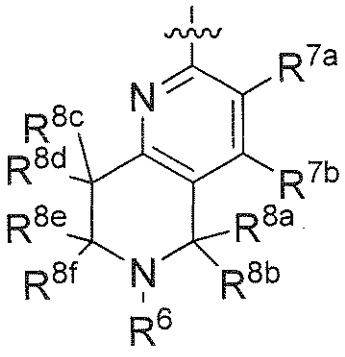
1. A compound of Formula I:



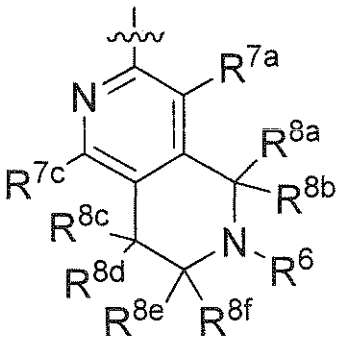
I

or a pharmaceutically acceptable salt thereof, a hydrate thereof, or a mixture thereof, wherein:

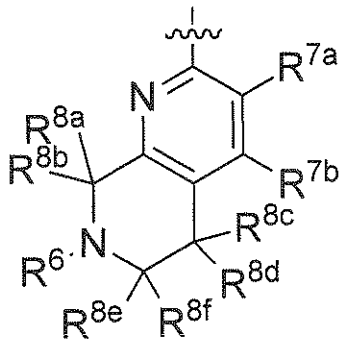
R^1 is a group of Formula IA, Formula IB, Formula IC, or Formula ID



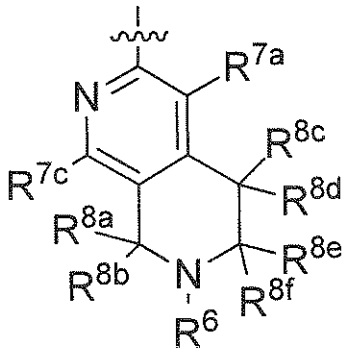
IA



IB



IC



ID

wherein the ~~~ symbol indicates the point of attachment of the group of Formula IA, IB, IC, or ID to the rest of the molecule;

R^2 is a C_5-C_7 cycloalkyl group, is a 5 to 7-membered heterocyclyl group that includes 1, 2, or 3 heteroatoms selected from N, O, and S, or is a C_7-C_{10} bicyclic group; wherein the C_5-C_7 cycloalkyl group, the 5 to 7 membered heterocyclyl group, or the C_7-C_{10} bicyclic group is unsubstituted or is substituted with 1-3 substituents independently selected from unsubstituted –(C_1-C_6 alkyl), -OH, halo, -O-(C_1-C_6 alkyl), -CO_2H, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", -NR'R", or a substituted –(C_1-C_4 alkyl), wherein the substituted –(C_1-C_4 alkyl) is substituted with 1-3 substituents independently selected from halo, -OH, -OCH_3, -S(=O)$_2$-CH_3, or -C(=O)-CH_3;

R^{3a} is selected from –H, -F, or –Cl, -(C_1-C_3 alkyl), or -O-(C_1-C_3 alkyl);

R^{3b} is -H, halo, -OH, -O-(C_1-C_6 alkyl), unsubstituted –(C_1-C_6 alkyl), -NR'R", -C(=O)-(C_1-C_6 alkyl), -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from halo, -OH, -OCH_3, -CN, or -NO_2;

R^{3c} is -H, -(C_1-C_3 alkyl), or halo;

R^4 is -H;

R^5 is -H;

R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-C(=O)-OH, -C(=O)-NR'R", or –S(=O)-NR'R", wherein the alkyl group of the –(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), and -C(=O)-O-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -S(=O)$_2$-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -NR'R", or -CN;

R^{7a} is–H, -CH_3, or halo;

R^{7b} is –H, -(C_1-C_6 alkyl), or halo; or R^{7b} is absent if R^1 is a group of Formula IB or Formula ID;

R^{7c} is –H, unsubstituted –(C_1-C_6 alkyl), halo, -O-(C_1-C_6 alkyl), -NO_2, -CN, -NR'R", -CO_2H, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, -O-(C_1-C_6 alkyl), -CN, -NR'R", or –S(=O)$_2$-CH_3; or R^{7c} is absent if R^1 is a group of Formula IA or Formula IC;

R^{8a} is -H, unsubstituted –(C_1-C_6 alkyl), or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl);

R^{8b} is -H, unsubstituted –(C_1-C_6 alkyl), or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl); or R^{8a} and R^{8b}, when taken together, can represent =O;

R^{8c} is selected from -H, -OH, unsubstituted –(C_1-C_6 alkyl), or a substituted -(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl);

R^{8d} is -H, unsubstituted –(C_1-C_6 alkyl), or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl);

R^{8e} is -H, unsubstituted –(C_1-C_6 alkyl), or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl);

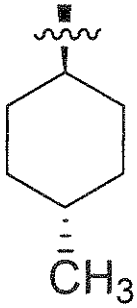
R^{8f} is -H, unsubstituted –(C_1-C_6 alkyl), or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl); or R^{8e} and R^{8f}, when taken together, can represent =O; and

R' and R" are independently selected from –H, unsubstituted –(C_1-C_4 alkyl), or –(C_1-C_4 alkyl) substituted with 1 to 3 substituents independently selected from –OH or -F.

2. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^2 is a C_5-C_7 cycloalkyl group that is unsubstituted or is substituted with 1-3 substituents independently selected from unsubstituted –(C_1-C_6 alkyl), -OH, halo, -O-(C_1-C_6 alkyl), -CO_2H, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", -NR'R", or a substituted –(C_1-C_4 alkyl), wherein the substituted –(C_1-C_4 alkyl) is substituted with 1-3 substituents independently selected from halo, -OH, -OCH_3, -S(=O)$_2$-CH_3, or -C(=O)-CH_3.

3. The compound of claim 2 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^2 is a cyclohexyl group substituted with a –(C_1-C_2 alkyl) group.

4. The compound of claim 3 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^2 is a group of formula



wherein the ~~~ symbol indicates the point of attachment to the rest of the molecule.

5. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^1 is a group of Formula IA or IB.

6. The compound of claim 5 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^1 is a group of Formula IA.

7. The compound of claim 1, wherein:

R^2 is a C_5-C_7 cycloalkyl group that is unsubstituted or is substituted with 1-3 -(C_1-C_6 alkyl) groups;

R^{3a} is selected from –H, -(C_1-C_3 alkyl), or –O-(C_1-C_3 alkyl);

R^{3b} is -H;

R^{3c} is -H;

R^4 is -H;

R^5 is -H;

R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), or -C(=O)-C(=O)-OH, wherein the alkyl group of the –(C_1-C_6 alkyl) and -C(=O)-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -$S(=O)_2$-(C_1-C_6 alkyl), or –O-(C_1-C_6 alkyl);

R^{7a} is–H;

R^{7b} is –H; or is absent if R^1 is a group of Formula IB or Formula ID;

R^{7c} is –H; or is absent if R^1 is a group of Formula IA or Formula IC;

R^{8a} is -H;

R^{8b} is –H;

R^{8c} is selected from –H, -OH, or unsubstituted -(C_1-C_6 alkyl);

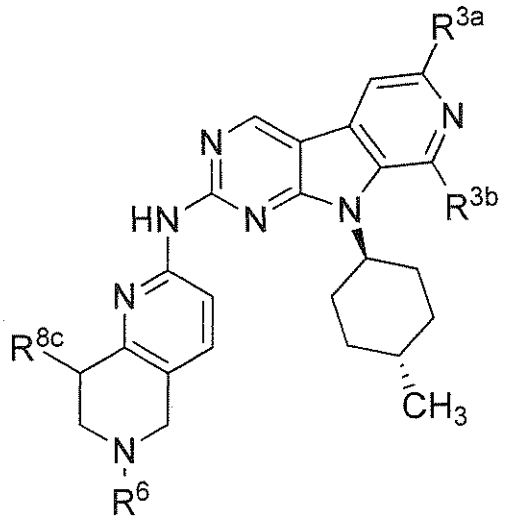
R^{8d} is –H;

R^{8e} is –H; and

R^{8f} is –H,

or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof.

8. The compound of claim 1, wherein the compound has the Formula IIA



IIA

or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein:

R^{3a} is selected from –H, -F, or –Cl, -(C_1-C_3 alkyl), or -O-(C_1-C_3 alkyl);

R^{3b} is -H, halo, -OH, -O-(C_1-C_6 alkyl), unsubstituted –(C_1-C_6 alkyl), -NR'R", -C(=O)-(C_1-C_6 alkyl), -C(=O)-O-(C_1-C_6 alkyl), -C(=O)-NR'R", or a substituted –(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from halo, -OH, -OCH_3, -CN, or -NO_2;

R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), -C(=O)-C(=O)-OH, -C(=O)-NR'R", or –S(=O)-NR'R", wherein the alkyl group of the –(C_1-C_6 alkyl) and -C(=O)-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -$S(=O)_2$-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -NR'R", or -CN; and

R^{8c} is selected from -H, -OH, unsubstituted –(C_1-C_6 alkyl), or a substituted -(C_1-C_6 alkyl), wherein the substituted –(C_1-C_6 alkyl) is substituted with 1-3 substituents independently selected from –OH, halo, or –O-(C_1-C_6 alkyl).

9. The compound of claim 8, wherein:

R^{3a} is selected from –H, -(C_1-C_3 alkyl), or –O-(C_1-C_3 alkyl);

R^{3b} is –H;

R^6 is selected from -H, -(C_1-C_6 alkyl), -C(=O)-(C_1-C_6 alkyl), or -C(=O)-C(=O)-OH, wherein the alkyl group of the –(C_1-C_6 alkyl) and -C(=O)-(C_1-C_6 alkyl) groups is unsubstituted or is substituted with 1-3 substituents independently selected from –OH, F, -$S(=O)_2$-(C_1-C_6 alkyl), or –O-(C_1-C_6 alkyl); and

R^{8c} is selected from –H, unsubstituted –(C_1-C_6 alkyl), or –OH,

or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof.

10. The compound of claim 9 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^{8c} is selected from -H, $-CH_3$, or -OH.

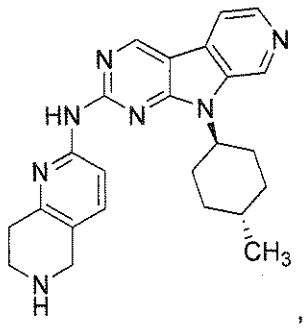
11. The compound of claim 10 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^{8c} is –H.

12. The compound of claim 11 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^{3a} is –H.

13. The compound of claim 12 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^6 is selected from -H, $-C(=O)-CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-C(=O)-CH_2OH$, $-C(=O)-C(=O)-OH$, $-CH_2CH_2CF_3$, $-CH_2CH_2F$, $-CH_2CH_2S(=O)_2-CH_3$, or $-CH_2CH_2OCH_3$.

14. The compound of claim 13 or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, wherein R^6 is selected from $-C(=O)-CH_3$ or $-C(=O)-CH_2OH$.

15. A compound selected from



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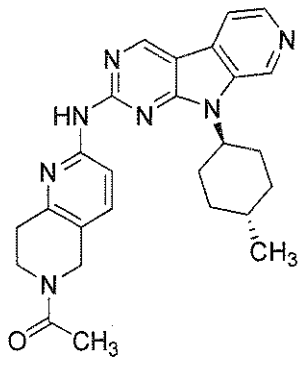

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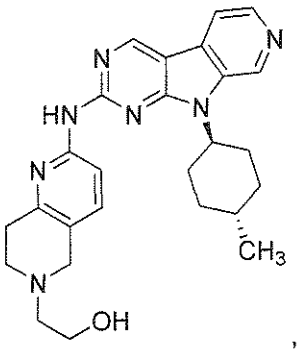

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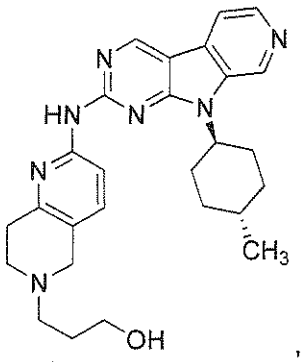

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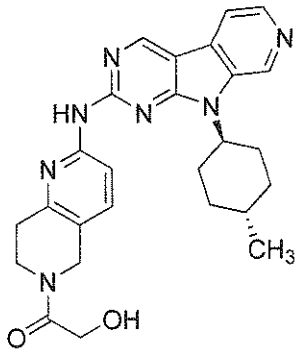

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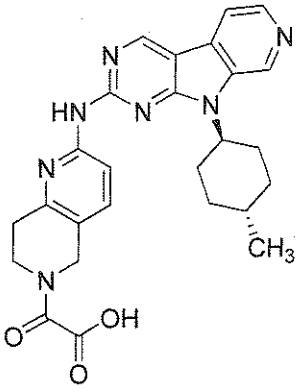

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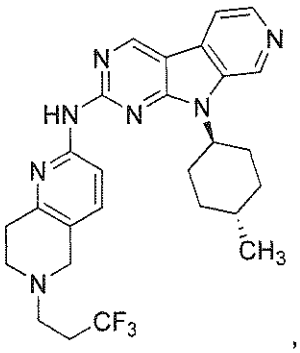

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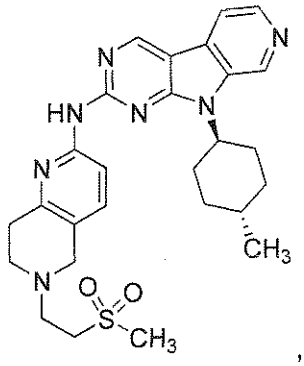

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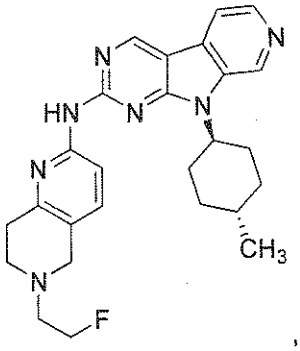

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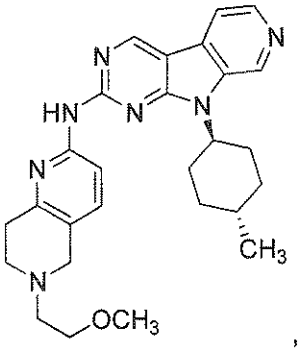

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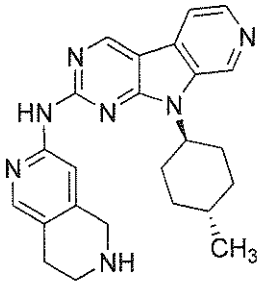
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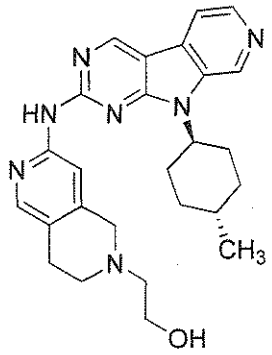
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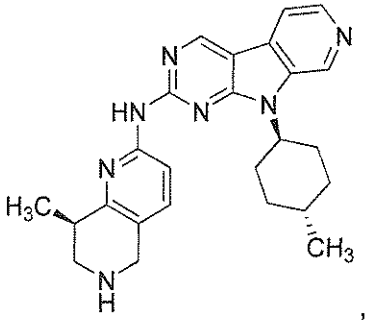
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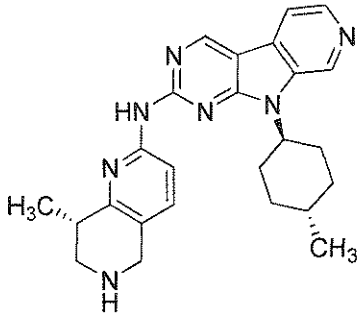
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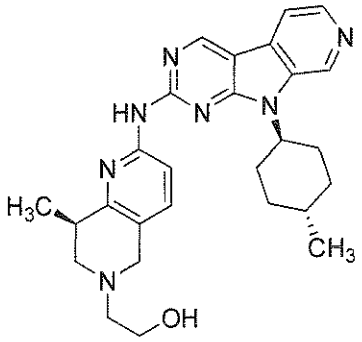
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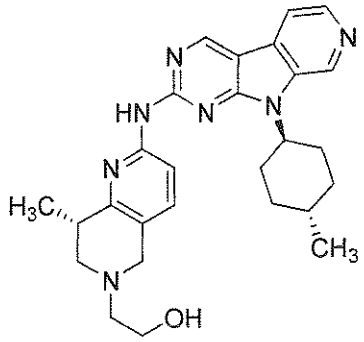
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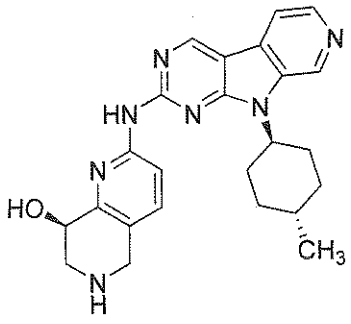
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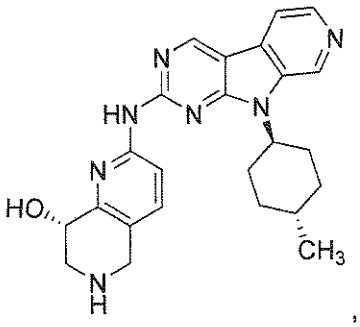
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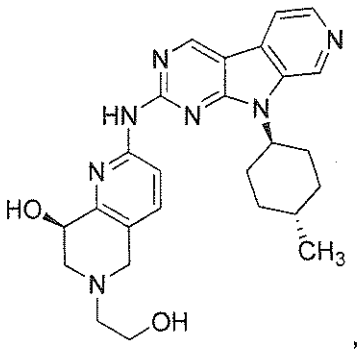

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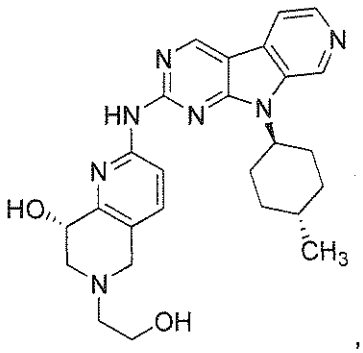

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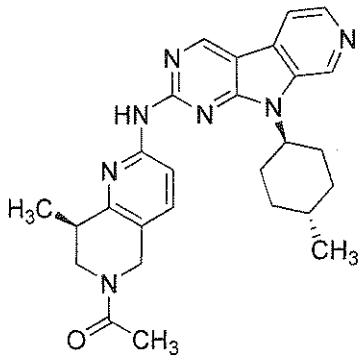

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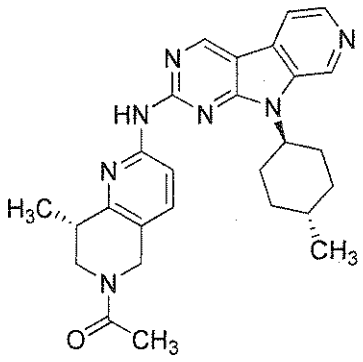

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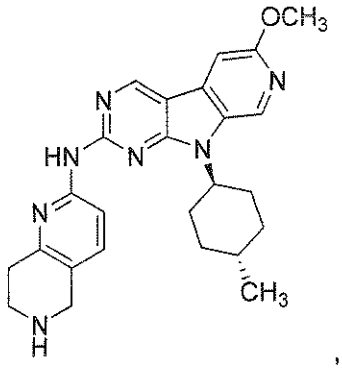

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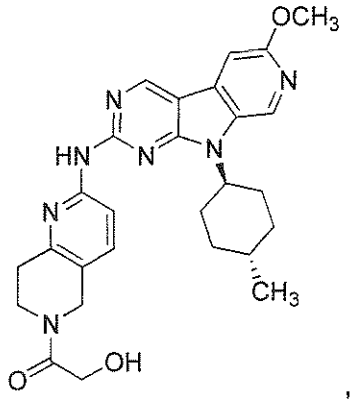

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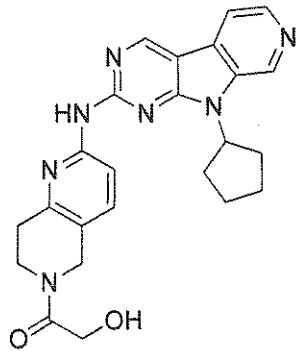

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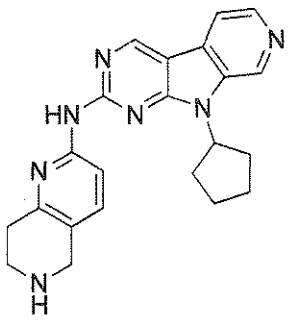

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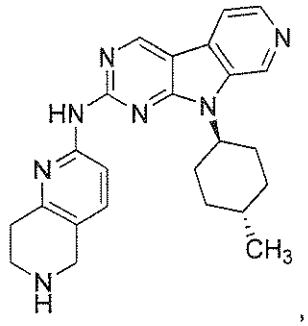
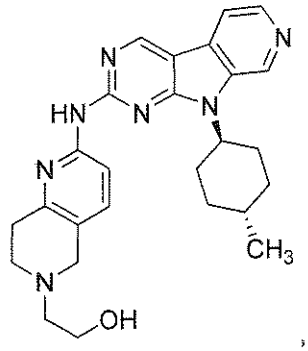
or a pharmaceutically acceptable salt or a hydrate thereof.

16. The compound of claim 15, wherein the compound is



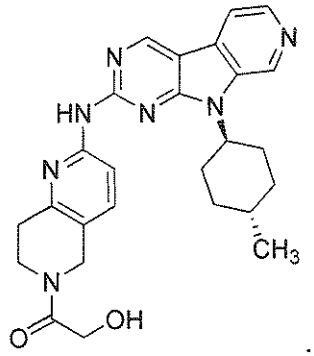
or the pharmaceutically acceptable salt or the hydrate thereof.

17. The compound of claim 15, wherein the compound is

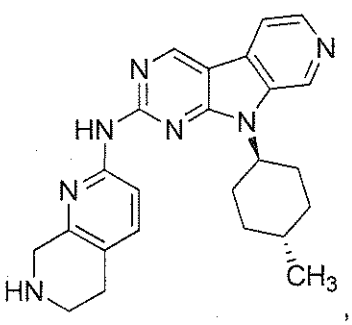


or the pharmaceutically acceptable salt or the hydrate thereof.

18. A compound or a pharmaceutically acceptable salt or a hydrate thereof, wherein the compound has the formula



19. A compound selected from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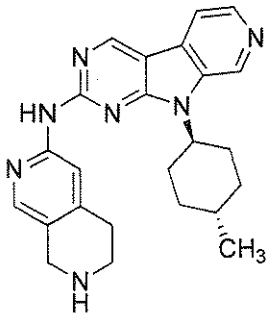
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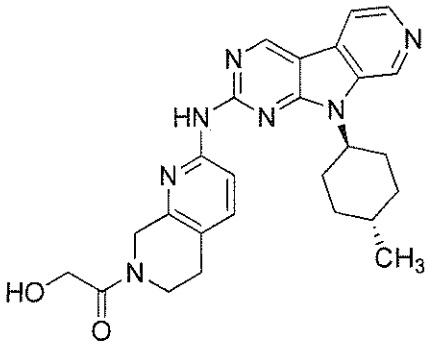
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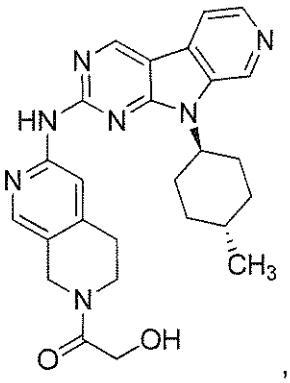
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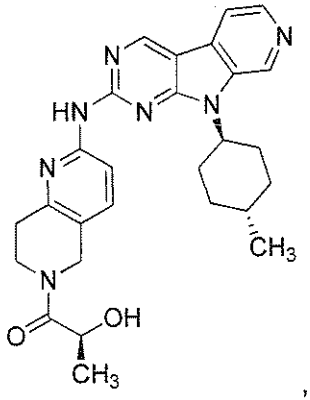
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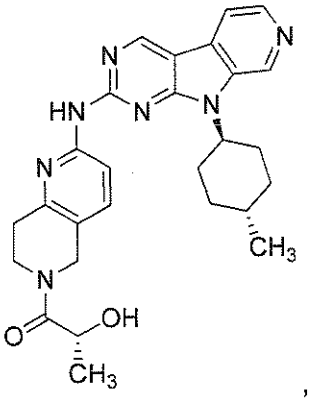
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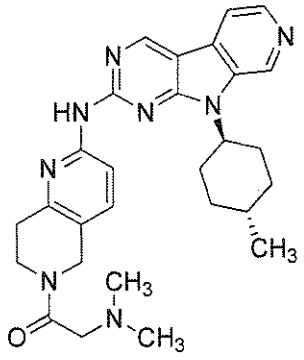
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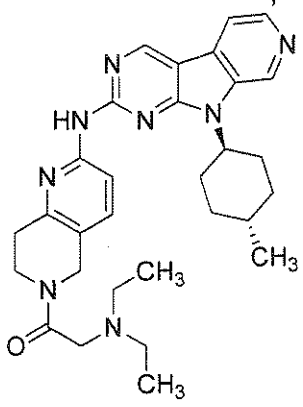
, or
or a pharmaceutically acceptable salt or a hydrate thereof.

20. The compound of claim 1 in a neutral form.

21. The pharmaceutically acceptable salt or the hydrate thereof of claim 1.

22. The pharmaceutically acceptable salt or the hydrate thereof of claim 21, wherein the pharmaceutically acceptable salt or the hydrate thereof is selected from a chloride salt, a methanesulfonate salt, or a benzenesulfonate salt.

23. A pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of the compound, the pharmaceutically acceptable salt, the hydrate thereof, or the mixture thereof according to claim 1 and at least one pharmaceutically acceptable excipient, carrier, or diluent.

24. The compound of claim 15 in a neutral form.

25. The pharmaceutically acceptable salt or the hydrate thereof of claim 15.

26. The pharmaceutically acceptable salt or the hydrate thereof of claim 25, wherein the pharmaceutically acceptable salt or the hydrate thereof is selected from a chloride salt, a methanesulfonate salt, or a benzenesulfonate salt.

27. A pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of the compound, the pharmaceutically acceptable salt, or the hydrate thereof according to claim 15 and at least one pharmaceutically acceptable excipient, carrier, or diluent.

28. The compound of claim 19 in a neutral form.

29. The pharmaceutically acceptable salt or the hydrate thereof of claim 19.

30. The pharmaceutically acceptable salt or the hydrate thereof of claim 29, wherein the pharmaceutically acceptable salt or the hydrate thereof is selected from a chloride salt, a methanesulfonate salt, or a benzenesulfonate salt.

31. A pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of the compound, the pharmaceutically acceptable salt, or the hydrate thereof according to claim 19 and at least one pharmaceutically acceptable excipient, carrier, or diluent.

32. The compound of claim 18 in a neutral form.

33. The pharmaceutically acceptable salt or the hydrate thereof of claim 18.

34. The pharmaceutically acceptable salt or the hydrate thereof of claim 33, wherein the pharmaceutically acceptable salt or the hydrate thereof is selected from a chloride salt, a methanesulfonate salt, or a benzenesulfonate salt.

35. A pharmaceutical composition, the pharmaceutical composition comprising a therapeutically effective amount of the compound, the pharmaceutically acceptable salt, or the hydrate thereof according to claim 18 and at least one pharmaceutically acceptable excipient, carrier, or diluent.