

function by phosphorylating their substrates on certain specific Serine and Threonine residues, and the consensus sequence of [S/T]PX[K/R], where S/T is the target Ser or Thr for phosphorylation, P is proline, X is any amino acid, K is lysine, and R is arginine.

In animal cells, there are at least nine different CDKs, four of which (CDK1, 2, 3, and 4) are directly involved in cell cycle regulation. In mammalian cells, CDK1, with its binding partners cyclin A2 and B1, alone can drive the cell cycle. Cyclin-CDK complexes of earlier cell cycle phase can help to activate cyclin-CDK complexes in later phase.

The same CDK may form complexes with different cyclins to regulate different phases of the cell cycle. For example, CDK2 may form a complex with cyclin D or E to regulate G1 phase; form a complex with cyclin A or E to regulate S phase; and form a complex with cyclin A to regulate G2 phase. Meanwhile, CDK4 and CDK6 can form complexes with cyclins D1, D2, and D3.

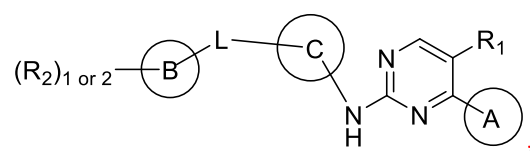
The highly homologous Cyclin-dependent kinases (CDKs) CDK4 and CDK6 in combination with Cyclin D are key regulators of the transition through the restriction point R between the G1 (growth) and S (DNA replication) phases of the cell cycle. CDK4/6 exert their effects via phosphorylation of the retinoblastoma protein (pRb). Once phosphorylated, pRb loses its inhibitory effect on the transcription of genes promoting entry into S phase.

By contrast, specific inhibition of CDK4/6 kinase activity by the endogenous protein modulator p16^{INK4} or by small molecule inhibitors results in hypophosphorylated pRb and arrest of the cells at the G1 restriction point. As the primary mechanism of regulating the G1 restriction point, the pathway regulated by these kinases is altered in a broad spectrum of human tumors, and thus inhibition of CDK4/CDK6 in these tumors has therapeutic benefit by preventing cell division.

There remains a need to provide CDK4/6 inhibitors which can be used in the treatment of cell proliferative disorders such as cancer.

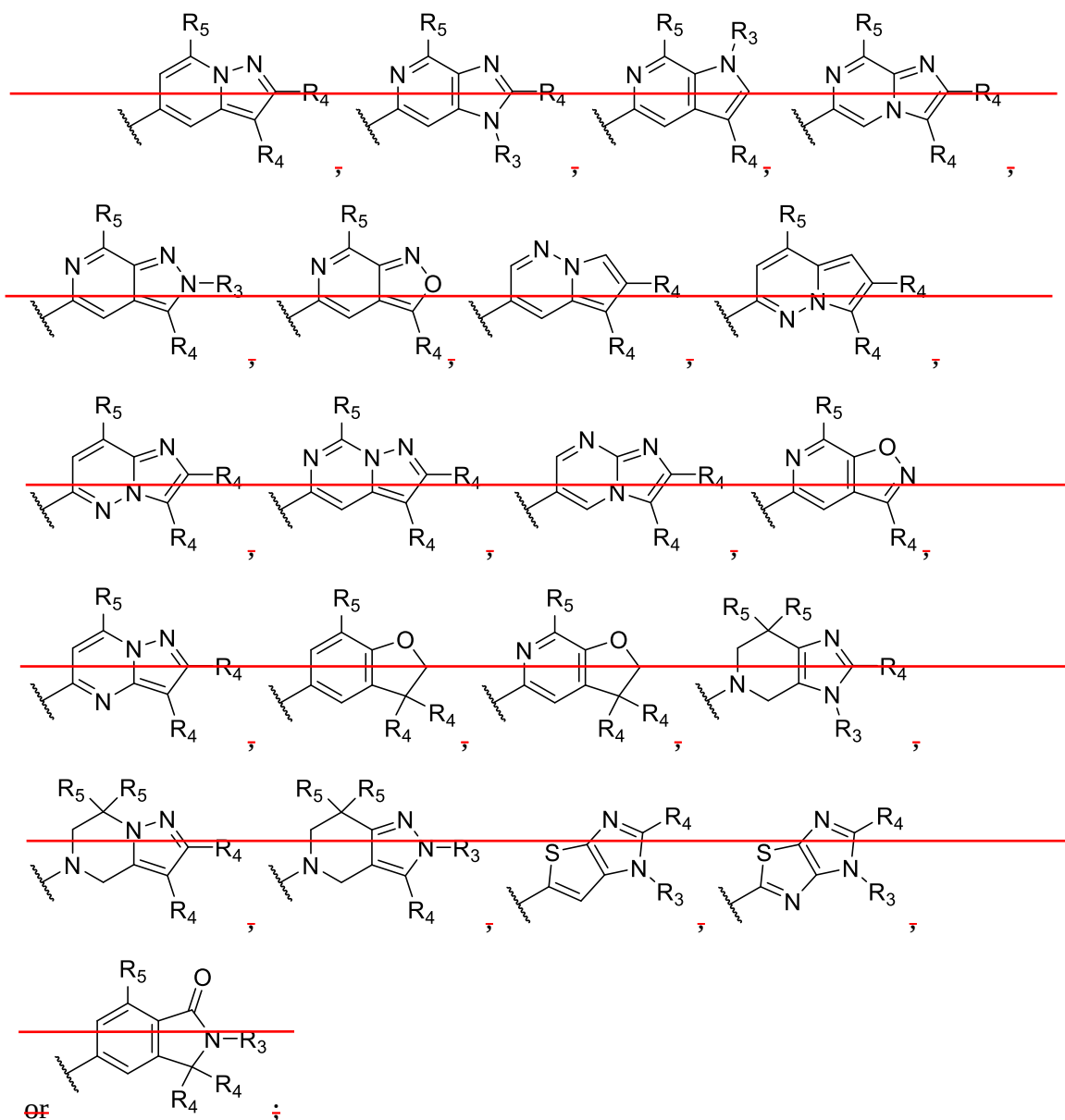
SUMMARY

In an aspect of the present disclosure, there is provided a compound represented by structural formula (I):



or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

ring A is



ring B is a bond, 3-10 membered heterocyclyl or 5-10 membered heteroaryl;

ring C is 5-6 membered heteroaryl, 5-10 membered heterocyclyl, phenyl,

5-10 membered bridged bicyclic group, each of which is optionally substituted with one or two R_{12} ;

Linker L is a bond, $-(CH_2)_q$, $-(CH_2)_qO$, $NR^a(CH_2)_q$, $C(O)$, $C(O)N(R^a)$, or $S(O)_2$;

each instance of R^a is H or CH_3 ;

R_1 is H, deuterium, halogen, $-OH$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, or C_{1-4} haloalkoxy;

each instance of R_2 is H, deuterium, halogen, $-OH$, CN , C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, $-(CH_2)_nOR_6$, $-(CH_2)_nSR_6$, $-(CH_2)_nC(O)R_6$, $-(CH_2)_nC(O)OR_6$,

~~-(CH₂)_nS(O)_mR₆, -(CH₂)_nNR₇R₈, -(CH₂)_nC(O)NR₇R₈, -(CH₂)_nNR₇C(O)R₆,
 -(CH₂)_nNR₇S(O)_mR₆, C₃₋₈ cycloalkyl, 3-10 membered heterocyclyl, 6-14 membered aryl, 5-14
 membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, heterocyclyl,
 aryl, or heteroaryl represented by R₂ is each optionally substituted with one or more groups
 selected from deuterium, halogen, CN, -OH,
 C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ alkoxy, and NR₇R₈; or~~

~~when ring B is 3-10 membered heterocyclyl, two R₂ attached to the same ring atom of
 ring B may form C₃₋₆ cycloalkyl or 3-6 membered heterocyclyl optionally substituted with
 one or more groups selected from deuterium, halogen, CN, -OH,
 C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ alkoxy, C₁₋₈ haloalkoxy, and NR₇R₈;~~

~~each instance of R₃ is independently selected from H, deuterium, C₁₋₈ alkyl,
 C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl; wherein the C₁₋₈
 alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl represented
 by R₃ is optionally substituted with one or more groups selected from deuterium, halogen,
 CN, -OH, C₁₋₈ alkyl, and C₁₋₈ haloalkyl;~~

~~each instance of R₄ is independently selected from H, deuterium, halogen, CN,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, C(O)C₁₋₈ alkyl, C₃₋₈ cycloalkyl, or
 3-10 membered heterocyclyl; wherein the C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl,
 C₁₋₈ alkoxy, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl represented by R₄ or in the group
 represented by R₄ is each optionally substituted with one or more groups selected from
 deuterium, halogen, -OH, C₁₋₈ alkyl and C₁₋₈ haloalkyl; or~~

~~two R₄ groups attached to the same ring atom of ring A form C₃₋₆ cycloalkyl or 3-6
 membered heterocyclyl, each of which is optionally substituted with one or more groups
 selected from deuterium, halogen, CN, -OH, C₁₋₈ alkyl, C₁₋₈ haloalkyl,
 C₁₋₈ alkoxy, C₁₋₈ haloalkoxy, and NR₇R₈;~~

~~each instance of R₅ is H, deuterium, halogen, -OH, CN, C₁₋₄ alkyl,
 C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C(O)C₁₋₄ alkyl, or 3-6 membered heterocyclyl;~~

~~each instance of R₆ is independently H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl,
 C₃₋₈ cycloalkyl, 3-10 membered heterocyclyl, 6-14 membered aryl, 5-14 membered heteroaryl,
 wherein the C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl,
 3-10 membered heterocyclyl, 6-14 membered aryl, 5-14 membered heteroaryl represented by
 R₆ is each optionally substituted with one or more groups selected from halogen, CN, -OH,
 C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, and NR₇R₈;~~

~~each instance of R₇ and R₈ is independently H, C₁₋₄ alkyl or cyclopropyl;~~

~~each instance of R₁₂ is H, deuterium, halogen, -OH, CN, NH₂, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl; wherein the C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl represented by R₁₂ is optionally substituted with one or more groups selected from halogen, CN, -OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, and C₁₋₄ alkoxy;~~

~~q is 0, 1, or 2;~~

~~n is 0, 1, 2, 3, 4, or 5; and~~

~~m is 0, 1, or 2.~~

~~In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising an effective amount of the compound disclosed herein or a pharmaceutically acceptable salt, or a stereoisomer thereof, and a pharmaceutically acceptable carrier.~~

~~In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, or a stereoisomer thereof, in the manufacture of a medicament for treating cancer, wherein the cancer is selected from the group consisting of colorectal cancer, breast cancer, lung cancer, prostate cancer, glioblastoma, mantel cell lymphoma, chronic myeloid leukemia and acute myeloid leukemia.~~

~~In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for treating a cancer by inhibiting a cyclin-dependent kinase (CDK).~~

~~In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt, or a stereoisomer thereof, for use in treating cancer, wherein the cancer is selected from the group consisting of colorectal cancer, breast cancer, lung cancer, prostate cancer, glioblastoma, mantel cell lymphoma, chronic myeloid leukemia and acute myeloid leukemia, or for use in treating a cancer by inhibiting a cyclin-dependent kinase (CDK).~~

~~Described herein are compounds of Formulae (I), (II-A)-(II-J), and the compounds of the examples (collectively referred to herein as “the compounds of the invention” or “the compounds of the present disclosure”), that inhibit the activity of a cyclin-dependent kinase (CDK), e.g., CDK2, CDK4, and/or CDK6, and pharmaceutically acceptable salts, or stereoisomers thereof.~~

~~In one example, the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt, or a stereoisomer thereof:~~

function by phosphorylating their substrates on certain specific Serine and Threonine residues, and the consensus sequence of [S/T]PX[K/R], where S/T is the target Ser or Thr for phosphorylation, P is proline, X is any amino acid, K is lysine, and R is arginine.

In animal cells, there are at least nine different CDKs, four of which (CDK1, 2, 3, and 4) are directly involved in cell cycle regulation. In mammalian cells, CDK1, with its binding partners cyclin A2 and B1, alone can drive the cell cycle. Cyclin-CDK complexes of earlier cell-cycle phase can help to activate cyclin-CDK complexes in later phase.

The same CDK may form complexes with different cyclins to regulate different phases of the cell cycle. For example, CDK2 may form a complex with cyclin D or E to regulate G1 phase; form a complex with cyclin A or E to regulate S phase; and form a complex with cyclin A to regulate G2 phase. Meanwhile, CDK4 and CDK6 can form complexes with cyclins D1, D2, and D3.

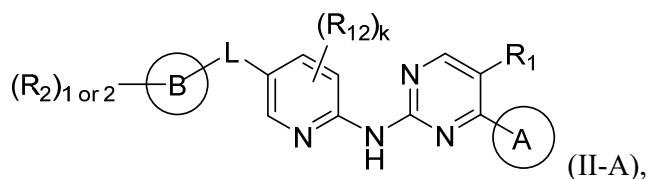
The highly homologous Cyclin-dependent kinases (CDKs) CDK4 and CDK6 in combination with Cyclin D are key regulators of the transition through the restriction point R between the G1 (growth) and S (DNA replication) phases of the cell cycle. CDK4/6 exert their effects via phosphorylation of the retinoblastoma protein (pRb). Once phosphorylated, pRb loses its inhibitory effect on the transcription of genes promoting entry into S phase.

By contrast, specific inhibition of CDK4/6 kinase activity by the endogenous protein modulator p16^{INK4} or by small molecule inhibitors results in hypophosphorylated pRb and arrest of the cells at the G1 restriction point. As the primary mechanism of regulating the G1 restriction point, the pathway regulated by these kinases is altered in a broad spectrum of human tumors, and thus inhibition of CDK4/CDK6 in these tumors has therapeutic benefit by preventing cell division.

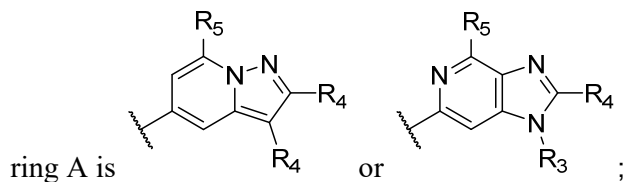
There remains a need to provide CDK4/6 inhibitors which can be used in the treatment of cell proliferative disorders such as cancer.

SUMMARY

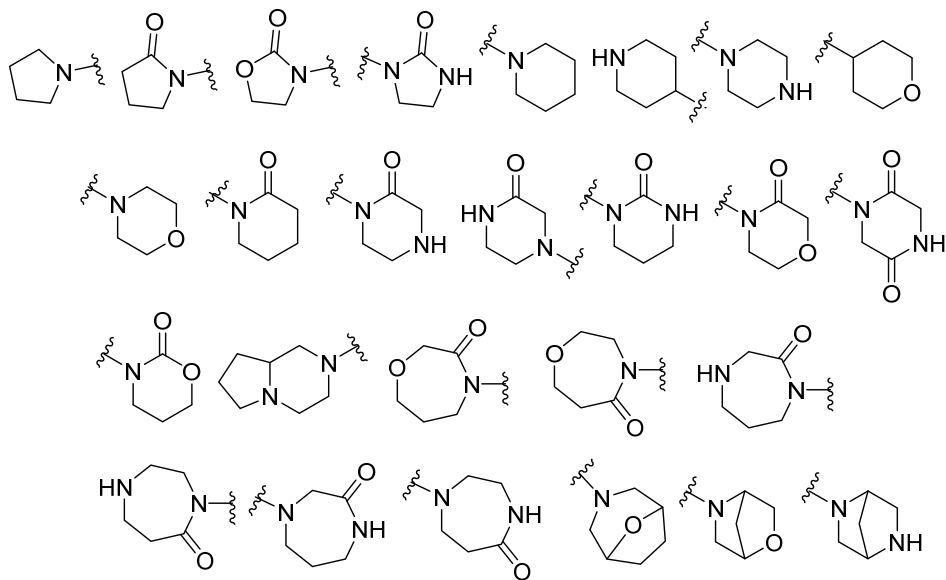
In one aspect of the present disclosure, there is provided a compound represented by structural formula (IIA):



or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein



ring B is



each of which is optionally substituted with one or two R₂ groups;

Linker L is a bond;

R₁ is H;

each instance of R₂ is H, deuterium, halogen, -OH, CN, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, -(CH₂)_nOR₆, -(CH₂)_nSR₆, -(CH₂)_nC(O)R₆, -(CH₂)_nC(O)OR₆, -(CH₂)_nS(O)_mR₆, -(CH₂)_nNR₇R₈, -(CH₂)_nC(O)NR₇R₈, -(CH₂)_nNR₇C(O)R₆, -(CH₂)_nNR₇S(O)_mR₆, C₃₋₈ cycloalkyl, 3-10 membered heterocyclyl, 6-14 membered aryl, 5-14 membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl represented by R₂ is each optionally substituted with one or more groups selected from deuterium, halogen, CN, -OH, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ alkoxy, and NR₇R₈;

each instance of R₃ is H, deuterium, C₁₋₄ alkyl optionally substituted with -OH, or C₃₋₆ cycloalkyl optionally substituted with -OH;

each instance of R₄ is H, deuterium, halogen, C₁₋₄ alkyl optionally substituted with fluoro, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl optionally substituted with methyl, or 3-6 membered heterocyclyl; or two R₄ groups attached to the same ring atom of ring A form C₃₋₆ cycloalkyl or 3-6 membered heterocyclyl, each of which is optionally

substituted with one or more groups selected from halogen, CN, -OH, C₁₋₂ alkyl, C₁₋₂ alkoxy, and NR₇R₈;

each instance of R₅ is H, deuterium, halogen, CN, -OH, C₁₋₄ alkyl, C₁₋₄ alkoxy, or C₁₋₄ haloalkoxy;

each instance of R₆ is independently H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, 3-10 membered heterocyclyl, 6-14 membered aryl, 5-14 membered heteroaryl, wherein the C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, 3-10 membered heterocyclyl, 6-14 membered aryl, 5-14 membered heteroaryl represented by R₆ is each optionally substituted with one or more groups selected from halogen, CN, -OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, and NR₇R₈;

each instance of R₇ and R₈ is independently H, C₁₋₄ alkyl or cyclopropyl;

each instance of R₁₂ is H, F, Cl, CH₃, or CF₃;

k is 0, 1, or 2;

n is 0, 1, 2, 3, 4, or 5; and

m is 0, 1, or 2.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising an effective amount of the compound disclosed herein or a pharmaceutically acceptable salt, or a stereoisomer thereof, and a pharmaceutically acceptable carrier.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, or a stereoisomer thereof, in the manufacture of a medicament for treating cancer, wherein the cancer is selected from the group consisting of colorectal cancer, breast cancer, lung cancer, prostate cancer, glioblastoma,

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for treating a cancer by inhibiting a cyclin-dependent kinase (CDK).

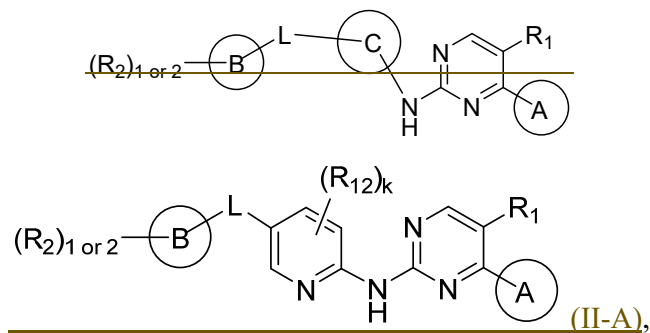
In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt, or a stereoisomer thereof, for use in treating cancer, wherein the cancer is selected from the group consisting of colorectal cancer, breast cancer, lung cancer, prostate cancer, glioblastoma, mantle cell lymphoma, chronic myeloid leukemia and acute myeloid leukemia, or for use in treating a cancer by inhibiting a cyclin-dependent kinase (CDK).

Described herein are compounds of Formulae (I), (II-A)-(II-J), and the compounds of the examples (collectively referred to herein as “the compounds of the invention” or “the compounds of the present disclosure”), that inhibit the activity of a cyclin-dependent kinase (CDK), *e.g.*, CDK2, CDK4, and/or CDK6, and pharmaceutically acceptable salts, or stereoisomers thereof.

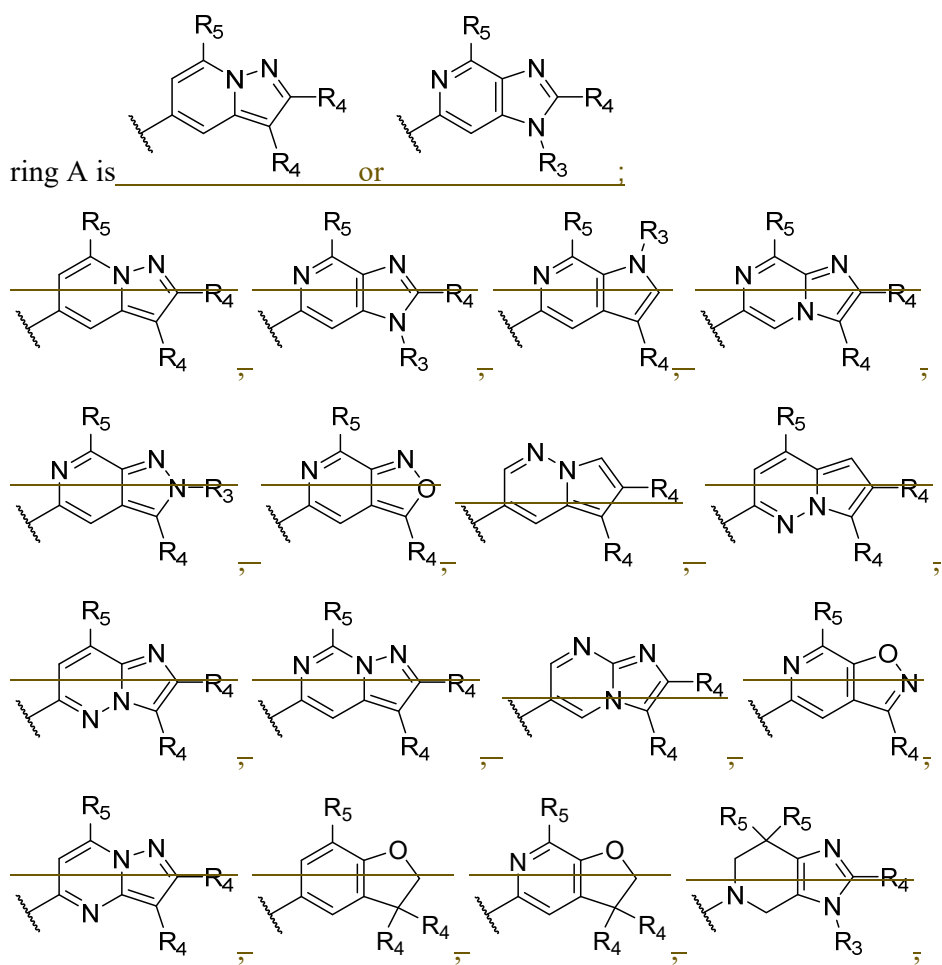
In one example, the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt, or a stereoisomer thereof:

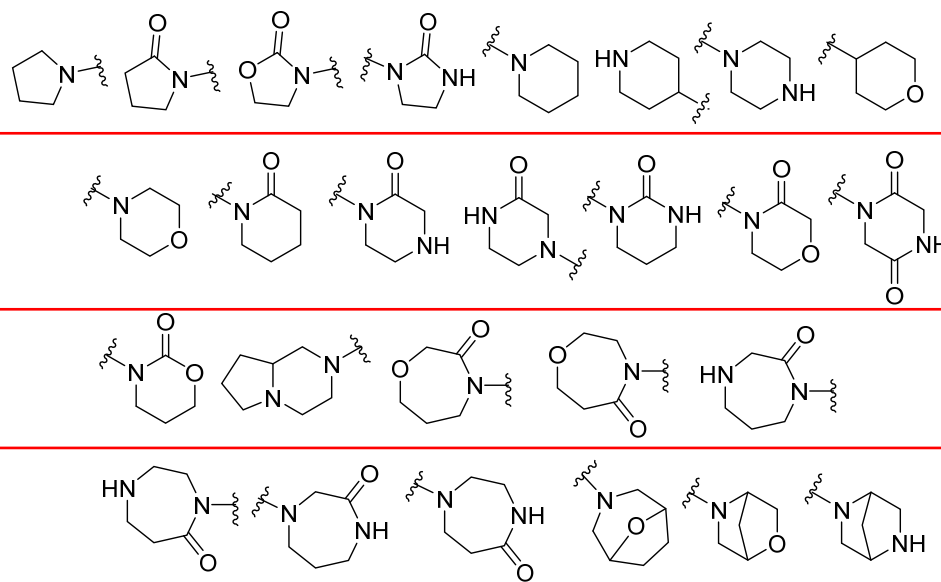
CLAIMS

1. A compound represented by structural formula (IIA):



or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein





each instance of R₂ is H, deuterium, halogen, -OH, CN, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, -(CH₂)_nOR₆, -(CH₂)_nSR₆, -(CH₂)_nC(O)R₆, -(CH₂)_nC(O)OR₆, -(CH₂)_nS(O)_mR₆, -(CH₂)_nNR₇R₈, -(CH₂)_nC(O)NR₇R₈, -(CH₂)_nNR₇C(O)R₆, -(CH₂)_nNR₇S(O)_mR₆, C₃₋₈ cycloalkyl, 3-10 membered heterocyclyl, 6-14 membered

aryl, 5-14 membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl represented by R₂ is each optionally substituted with one or more groups selected from deuterium, halogen, CN, -OH, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ alkoxy, and NR₇R₈; ~~or~~

~~when ring B is 3-10 membered heterocyclyl, two R₂ attached to the same ring atom of ring B may form C₃₋₆ cycloalkyl or 3-6 membered heterocyclyl optionally substituted with one or more groups selected from deuterium, halogen, CN, -OH, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ alkoxy, C₁₋₈ haloalkoxy, and NR₇R₈;~~

each instance of R₃ is ~~independently selected from~~ H, deuterium, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl; wherein the C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl represented by R₃ is optionally substituted with ~~one or more groups selected from deuterium, halogen, CN, -OH, C₁₋₈ alkyl, and C₁₋₈ haloalkyl~~ or C₃₋₆ cycloalkyl optionally substituted with -OH;

each instance of R₄ is ~~independently selected from~~ H, deuterium, halogen, CN, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, C(O)C₁₋₈ alkyl, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl; wherein the C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl represented by R₄ or in the group represented by R₄ is each optionally substituted with fluoro, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl optionally substituted with methyl, or 3-6 membered heterocyclyl ~~one or more groups selected from deuterium, halogen, -OH, C₁₋₈ alkyl and C₁₋₈ haloalkyl;~~ or two R₄ groups attached to the same ring atom of ring A form C₃₋₆ cycloalkyl or 3-6 membered heterocyclyl, each of which is optionally substituted with one or more groups selected from ~~deuterium,~~ halogen, CN, -OH, C₁₋₈ alkyl, ~~C₁₋₈ haloalkyl,~~ C₁₋₈ alkoxy, ~~C₁₋₈ haloalkoxy,~~ and NR₇R₈;

each instance of R₅ is H, deuterium, halogen, CN, -OH, ~~CN~~, C₁₋₄ alkyl, ~~C₁₋₄ haloalkyl,~~ C₁₋₄ alkoxy, or C₁₋₄ haloalkoxy, ~~C(O)C₁₋₄ alkyl, or 3-6 membered heterocyclyl;~~

each instance of R₆ is independently H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, 3-10 membered heterocyclyl, 6-14 membered aryl, 5-14 membered heteroaryl, wherein the C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, 3-10 membered heterocyclyl, 6-14 membered aryl, 5-14 membered heteroaryl represented by R₆ is each optionally substituted with one or more groups selected from halogen, CN, -OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, and NR₇R₈;

each instance of R₇ and R₈ is independently H, C₁₋₄ alkyl or cyclopropyl;

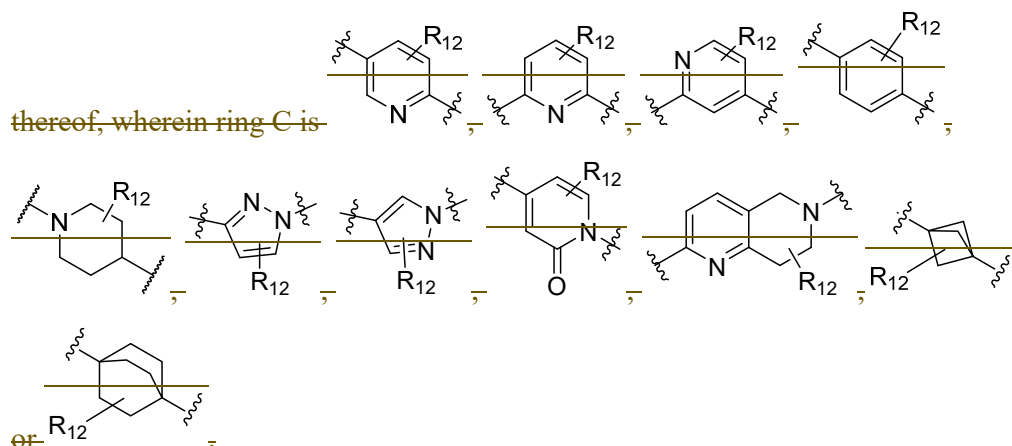
each instance of R₁₂ is H, ~~deuterium, halogen, OH, CN, NH₂, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl;~~
~~wherein the C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl represented by R₁₂ is optionally substituted with one or more groups selected from halogen, CN, OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, and C₁₋₄ alkoxyF, Cl, CH₃, or CF₃;~~

~~qk~~ is 0, 1, or 2;

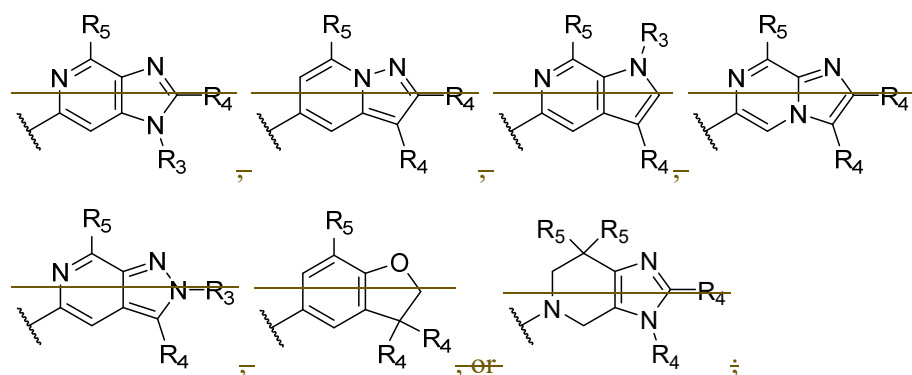
n is 0, 1, 2, 3, 4, or 5; and

m is 0, 1, or 2.

~~2. The compound of claim 1 or a pharmaceutically acceptable salt, or a stereoisomer~~



~~3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring A is~~



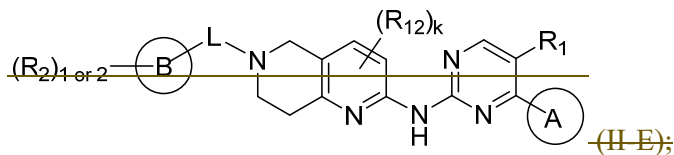
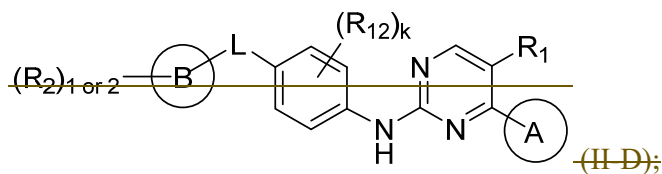
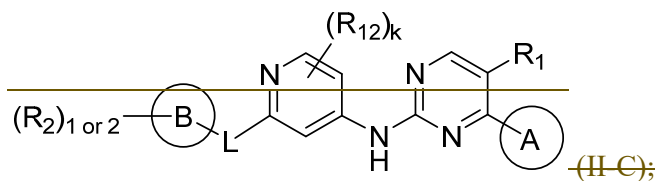
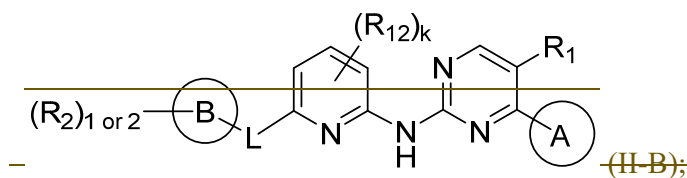
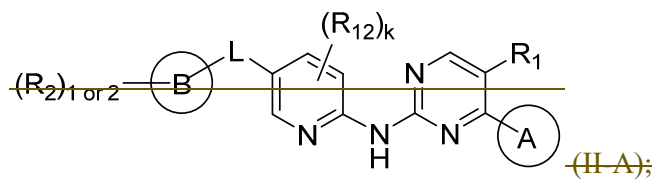
~~wherein~~

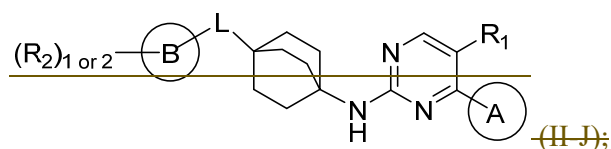
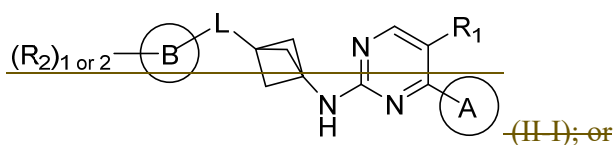
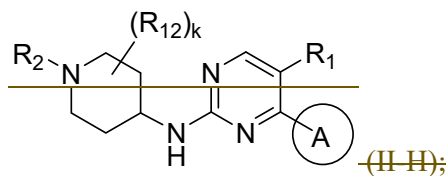
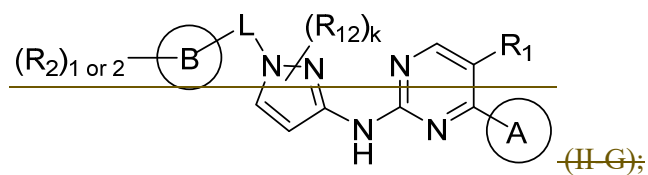
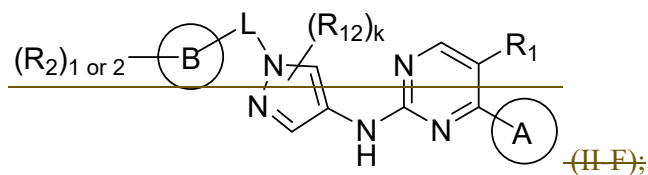
~~each instance of R₃ is H, deuterium, C₁₋₄ alkyl optionally substituted with OH, or C₃₋₆ cycloalkyl optionally substituted with OH;~~

each instance of R_4 is H, deuterium, halogen, C_{1-4} alkyl optionally substituted with fluoro, C_{2-4} alkenyl, C_{3-6} cycloalkyl optionally substituted with methyl, or 3-6 membered heterocyclyl; or two R_4 -groups attached to the same ring atom of ring A form C_{3-6} cycloalkyl or 3-6 membered heterocyclyl, each of which is optionally substituted with one or more groups selected from halogen, CN, OH, C_{1-2} alkyl, C_{1-2} alkoxy, and NR_7R_8 ;

R_5 is H, deuterium, halogen, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, or C_{1-4} haloalkoxy.

4. The compound of any one of claims 1-3, wherein the compound is represented by structural formulae (II A) - (II J):





or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein R_{12} is H, F, Cl, CH_3 , or CF_3 ; and k is 0, 1, or 2.

5. ~~The compound of any one of claims 1-4 or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein L is a bond, (CH_2) , $O(CH_2)$, $C(=O)$, or $S(O)_2$.~~
6. ~~The compound of any one of claims 1-5 or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring B is 4-10 membered heterocyclyl or 5-6 membered monocyclic heteroaryl optionally substituted with one or two R_2 groups.~~
72. The compound of ~~any one of claims 1-6~~ claim 1 or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

each instance of R_2 is H, halogen, CN, -OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, $-(CH_2)_nOR_6$, $-(CH_2)_nC(O)R_6$, $-(CH_2)_nC(O)OR_6$, $-(CH_2)_nS(O)_2R_6$, $-(CH_2)_nNR_7R_8$, $-(CH_2)_nC(O)NR_7R_8$, $-(CH_2)_nC(O)NHR_7$, $-(CH_2)_nNR_7C(O)R_6$,

$-(CH_2)_nNR_7S(O)_2R_6$, C_{3-8} cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl; ~~or~~

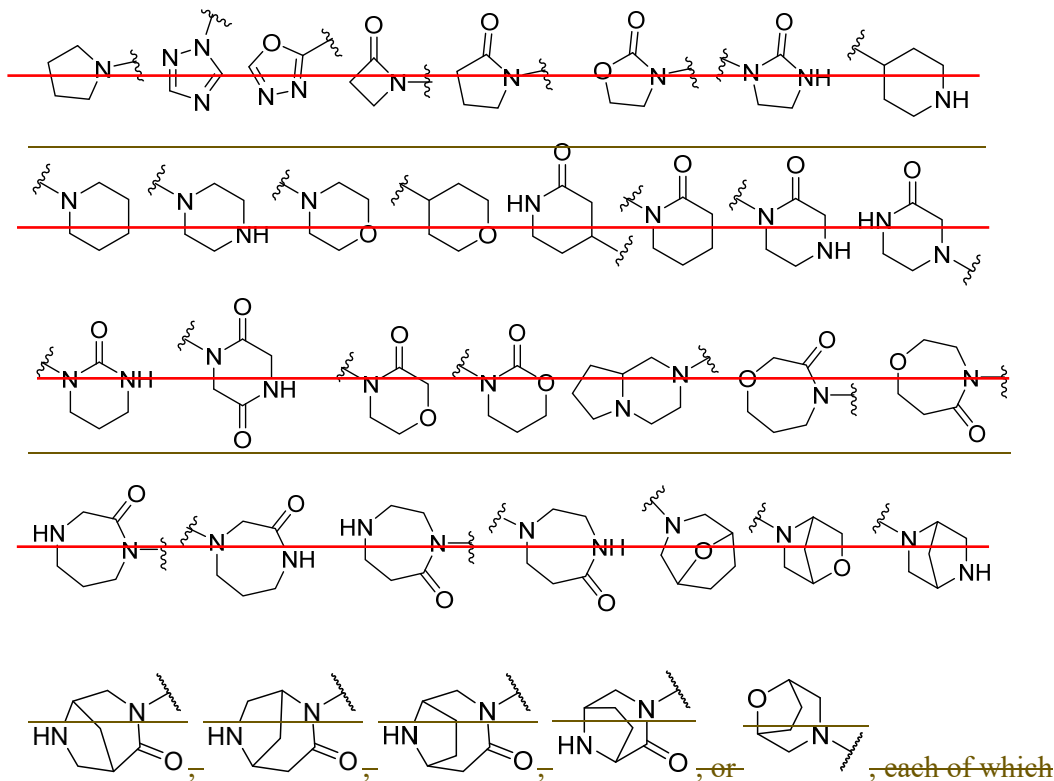
~~two R_2 attached to the same ring atom of ring B form 3-6 heterocyclyl (when ring B is 3-10 membered heterocyclyl) optionally substituted with one or more groups selected from halogen, $-OH$, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, C_{1-2} haloalkoxy, and NR_7R_8 ;~~

each instance of R_6 is independently H, C_{1-4} alkyl, C_{3-6} cycloalkyl, 3-7 membered heterocyclyl, phenyl, 5-6 membered heteroaryl, wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, 3-7 membered heterocyclyl, phenyl, 5-6 membered heteroaryl represented by R_6 is each optionally substituted with halogen, CN, $-OH$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, or NR_7R_8 ; and

n is 0, 1, or 2.

~~8. The compound of any one of claims 1-7 or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein R_4 is H, F, Cl, or CH_3 .~~

~~9. The compound of any one of claims 1-8 or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring B is~~

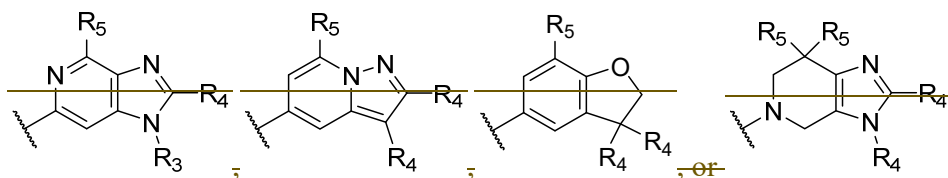


~~103.~~ The compound of ~~any one of claims 1-9~~claim 1 or 2 or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

each instance of R₂ is H, halogen, CN, -OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, -(CH₂)_nS(O)₂C₁₋₄ alkyl, -(CH₂)_nNR₇R₈, C₃₋₄ cycloalkyl, or 3-6 membered heterocyclyl; and n is 0, 1, or 2;~~or~~

~~two R₂ attached to the same ring atom of ring B form 3-6 heterocyclyl when ring B is 4-7 membered heterocyclyl.~~

~~11. The compound of any one of claims 1-10 or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring A is~~



~~12. The compound of any one of claims 1-11 or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein R₁ is H or F.~~

~~134.~~ The compound of any one of claims 1-~~123~~ or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

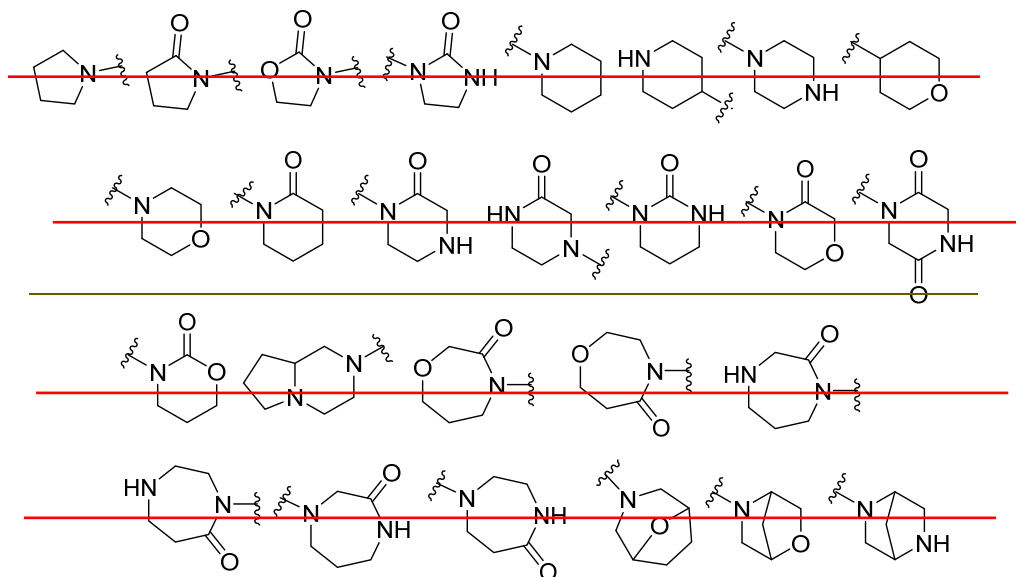
each instance of R₃ is H, C₁₋₃ alkyl optionally substituted with -OH, or C₃₋₆ cycloalkyl optionally substituted with -OH;

each instance of R₄ is H, halogen, C₁₋₃ alkyl, C₂₋₄ alkenyl, cyclopentyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl; and

each instance of R₅ is H, F, CN, methoxy, OCHF₂.

~~14. The compound of any one of claims 1-13 or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein L is a bond.~~

~~15. The compound of any one of claims 1-14 or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring B is~~



~~each of which is optionally substituted with one or two R₂ groups.~~

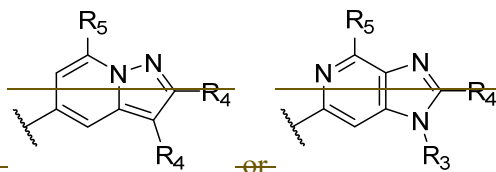
~~165.~~ The compound of any one of claims 1-~~154~~ or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

each instance of R₂ is H, halogen, CN, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, NH₂, N(CH₃)₂, NHCyclopropyl, -(CH₂)_nS(O)₂C₁₋₃ alkyl, cyclopropyl, azetidiny optionally substituted with F, oxetanyl, morpholinyl, piperidinyl, tetrahydro-2H-pyranyl, ~~or~~

~~two R₂ attached to the same ring atom of ring B form 2,5-pyrrolidinedionyl or 2-pyrrolidonyl when ring B is piperidinyl; and~~

n is 0, 1, or 2.

~~17.~~ The compound of any one of claims 1-16 or a pharmaceutically acceptable salt, or a



~~stereoisomer thereof, wherein ring A is~~

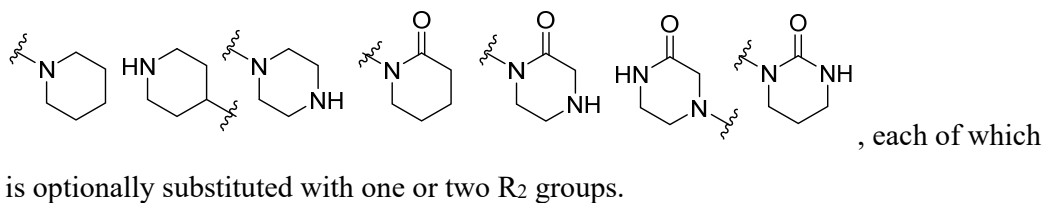
~~186.~~ The compound of any one of claims 1-~~175~~ or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

each instance of R₃ is H or C₁₋₃ alkyl;
each instance of R₄ is H or C₁₋₃ alkyl; and
each instance of R₅ is H, F, or OMe.

~~19.~~ The compound of any one of claims ~~1-18~~ or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ~~R₄~~ is H.

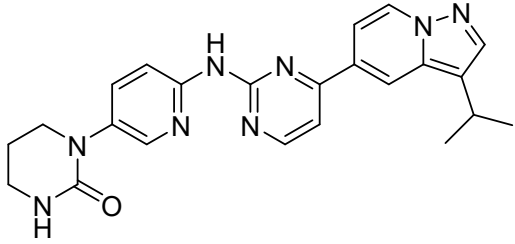
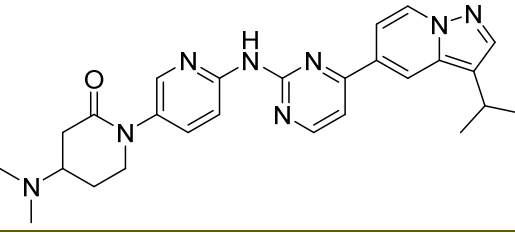
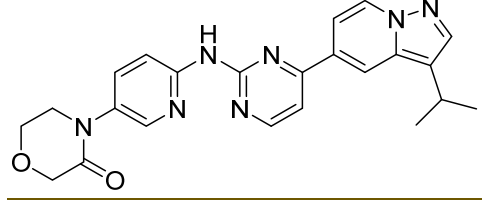
~~207.~~ The compound of any one of claims ~~1-196~~ or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ~~ring C is unsubstituted~~ k is 0.

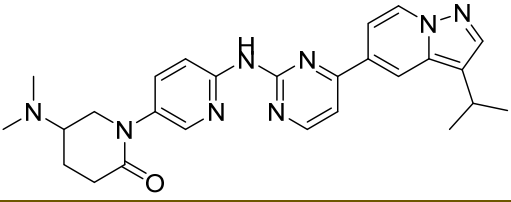
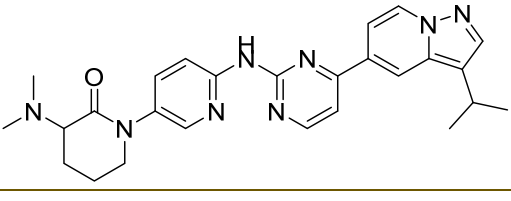
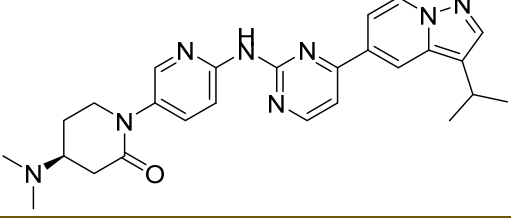
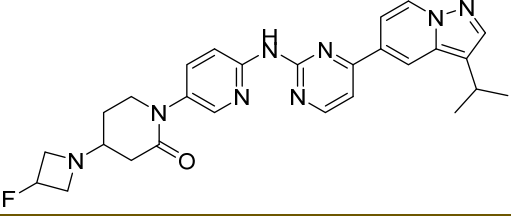
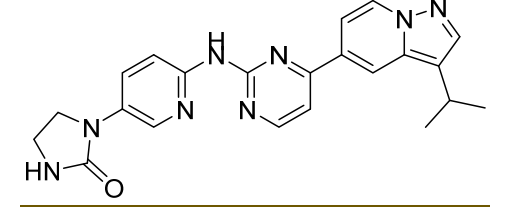
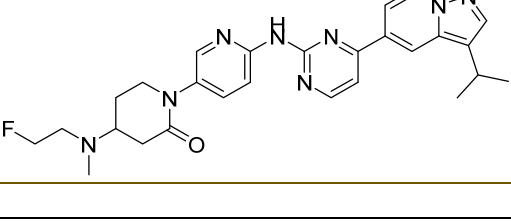
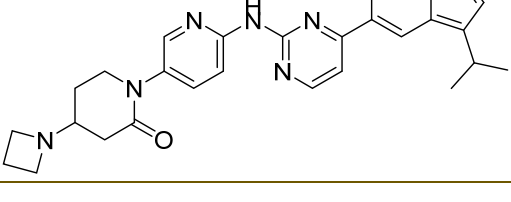
~~218.~~ The compound of any one of claims ~~1-207~~ or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring B is

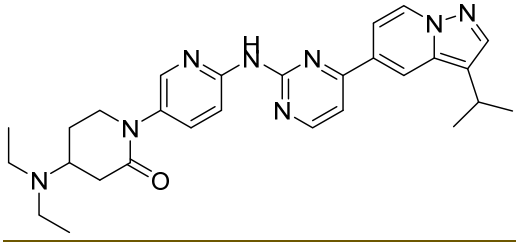
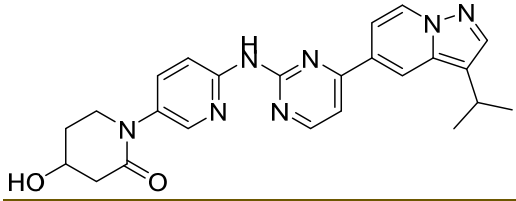
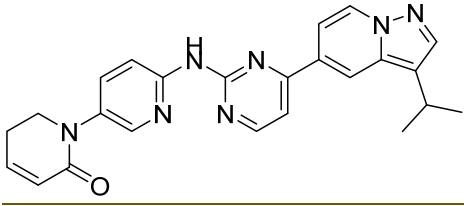
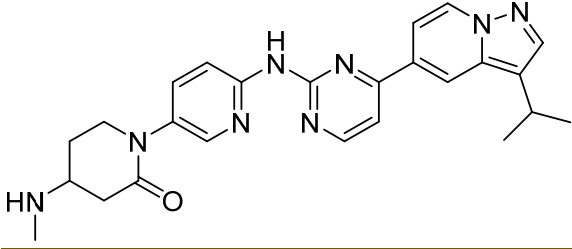
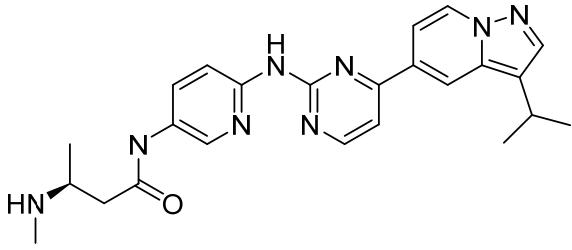
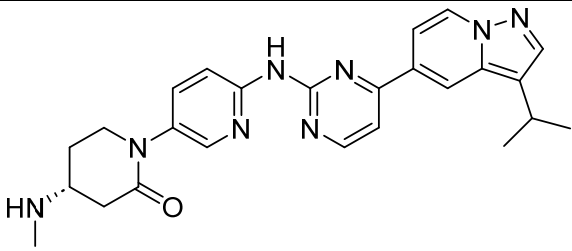


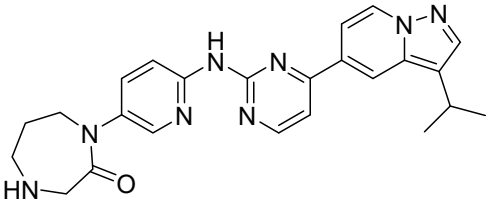
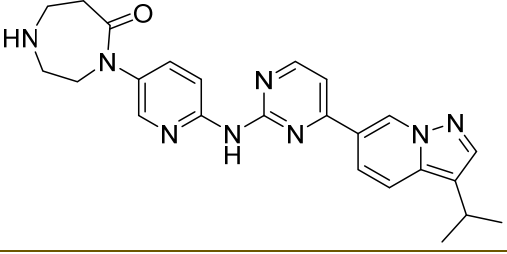
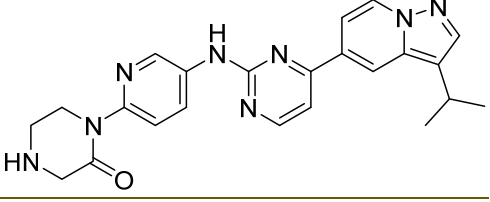
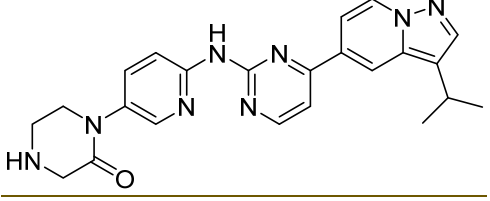
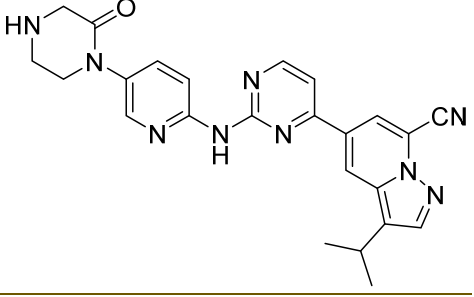
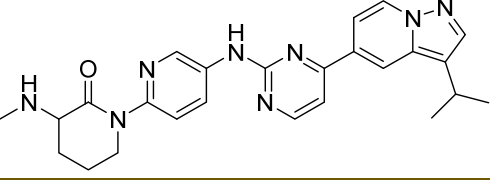
~~229.~~ The compound of any one of claims ~~1-218~~ or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein each instance of R₂ is H, halogen, CN, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, NH₂, N(CH₃)₂, NHcyclopropyl.

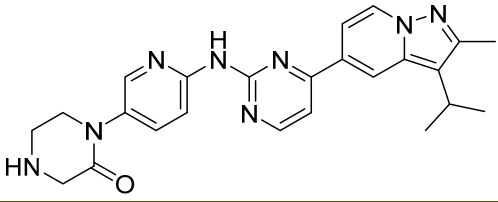
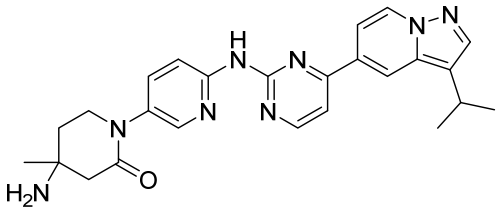
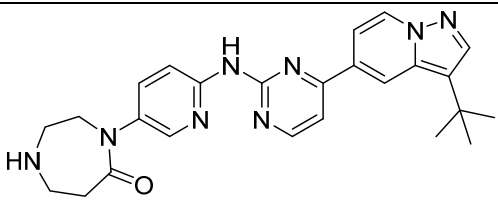
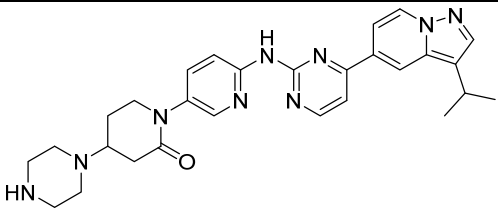
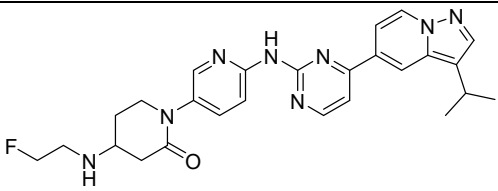
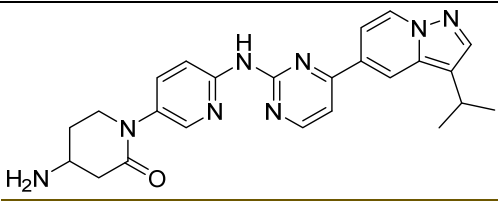
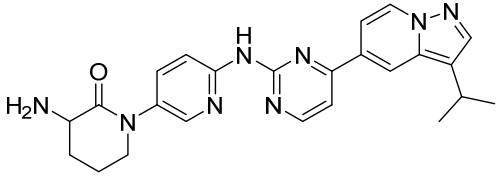
~~2310.~~ The compound of claim 1, or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein the compound is:

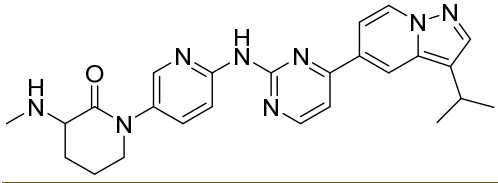
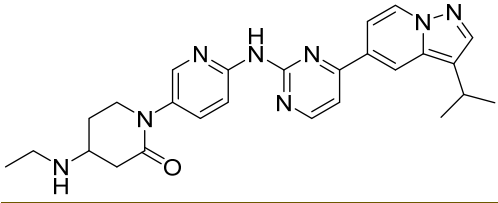
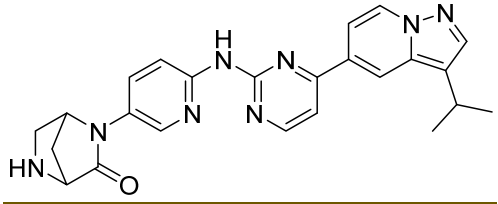
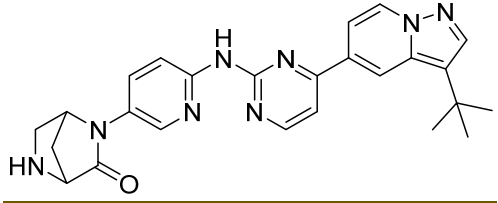
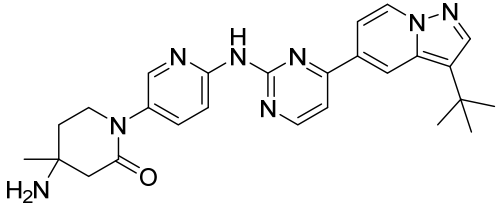
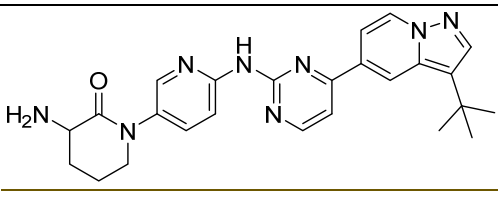
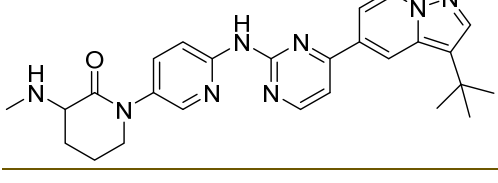
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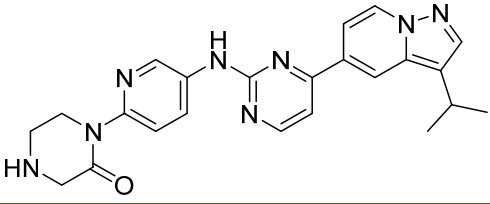
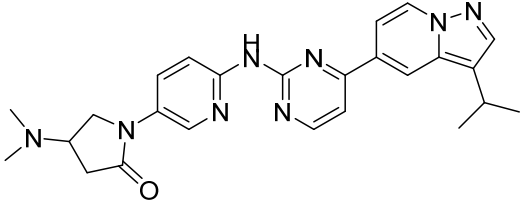
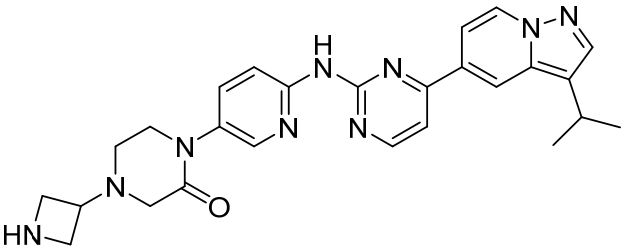
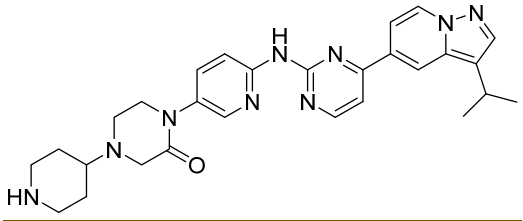
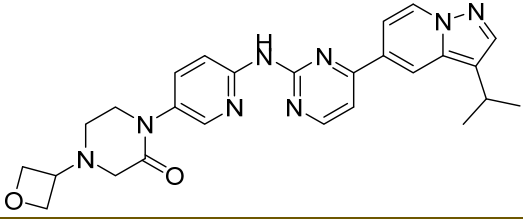
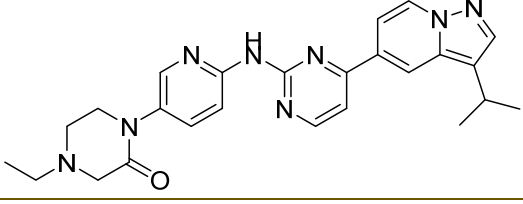
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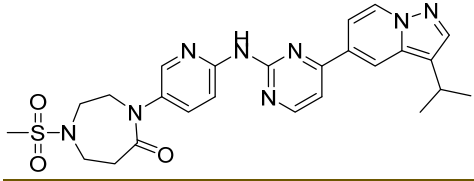
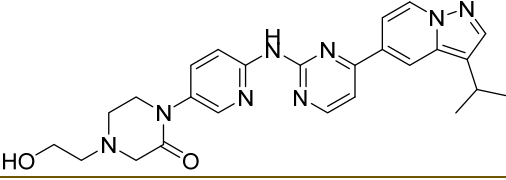
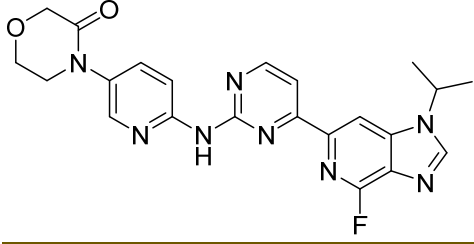
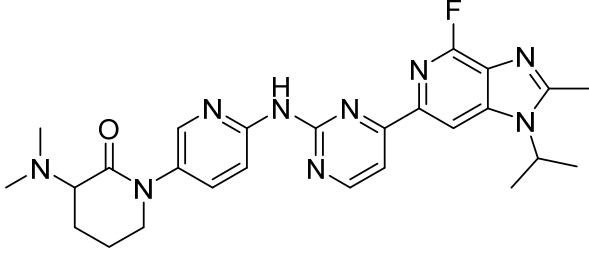
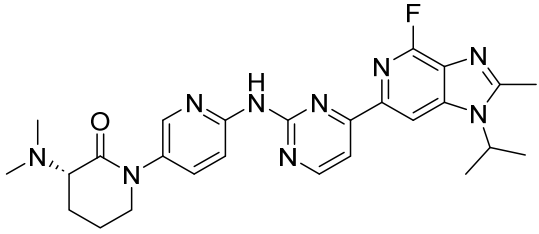
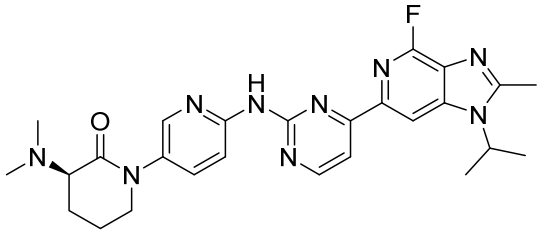
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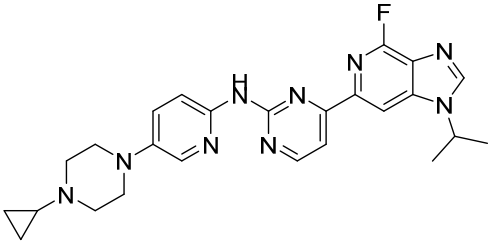
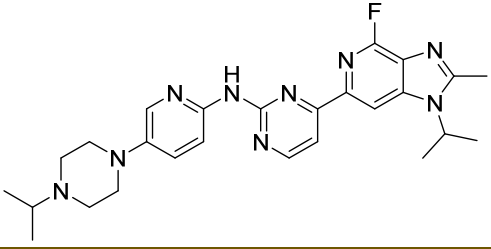
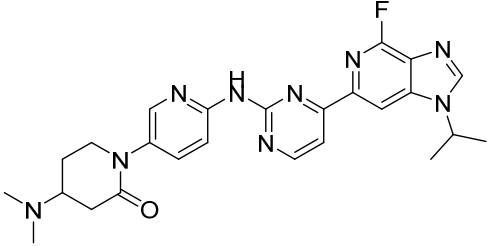
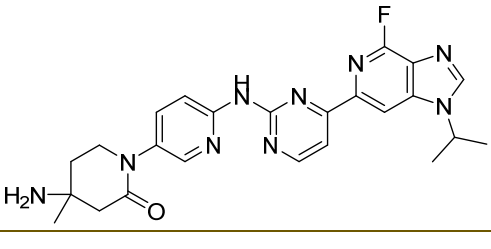
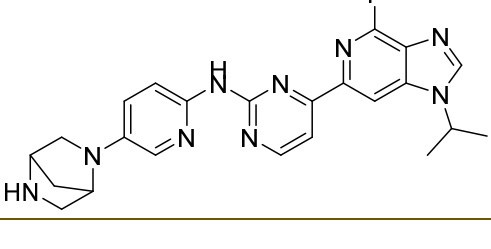
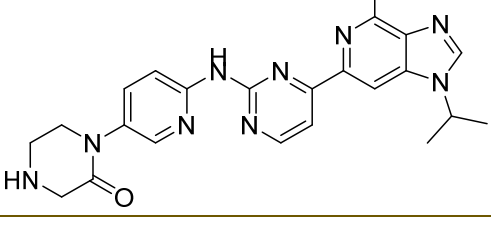
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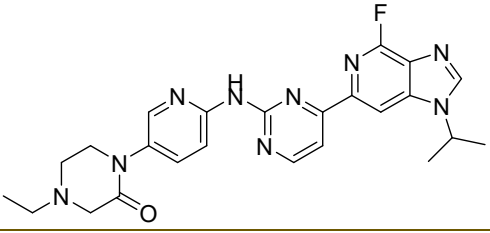
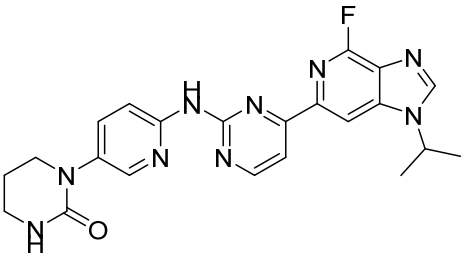
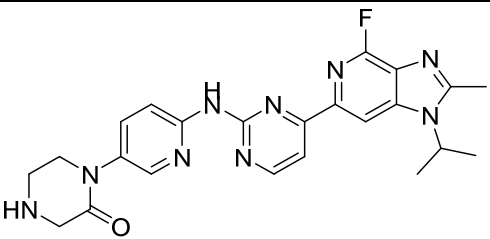
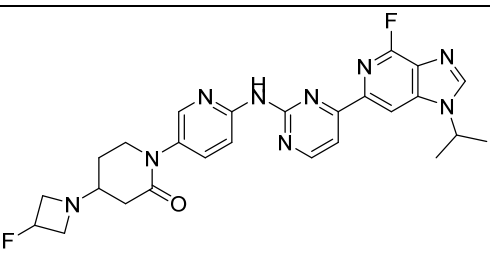
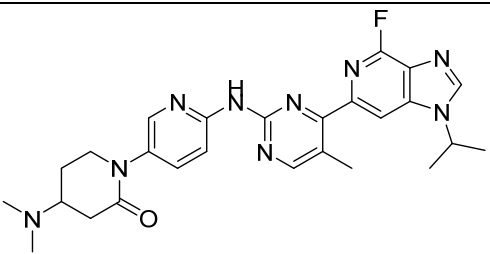
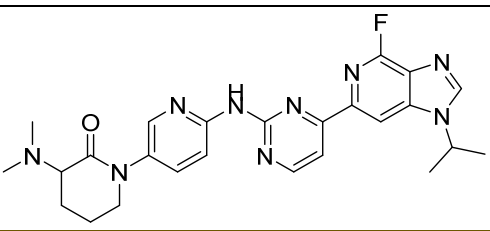
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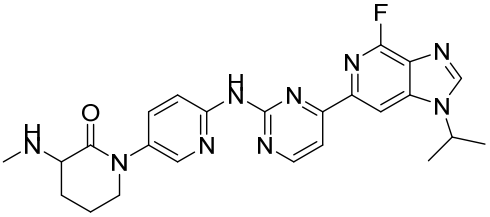
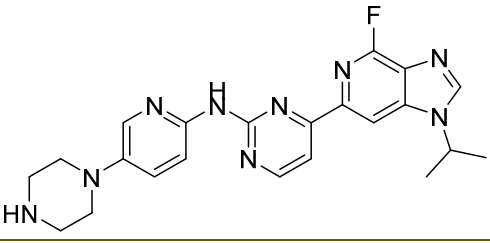
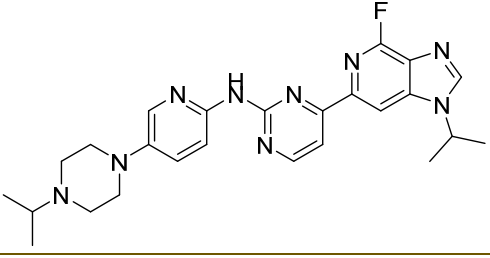
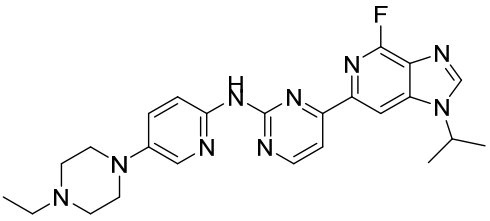
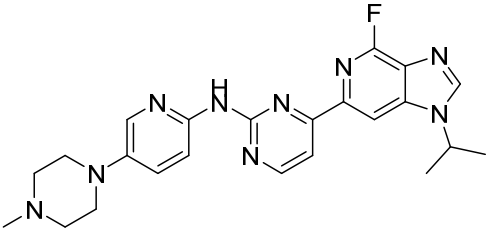
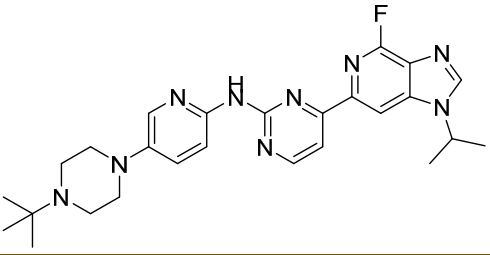
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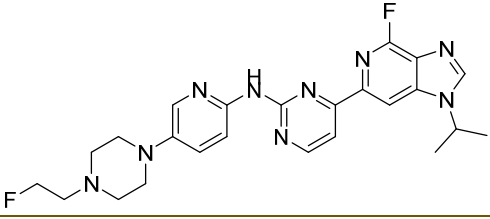
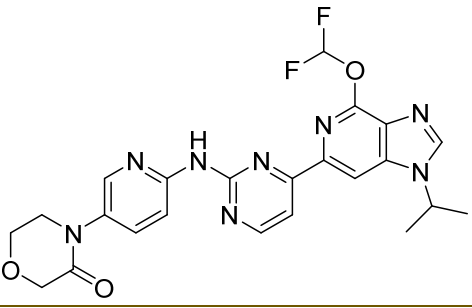
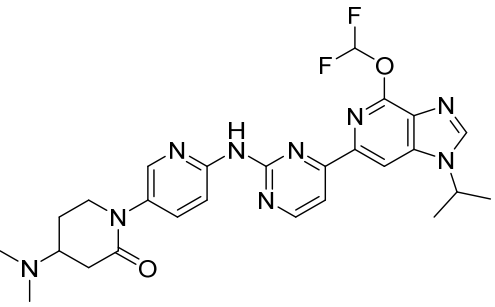
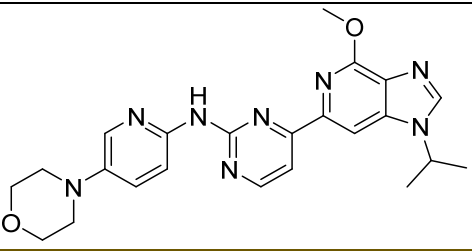
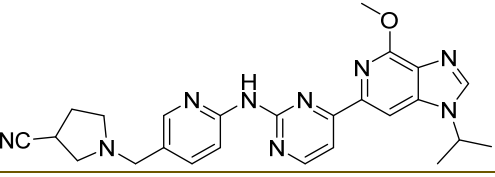
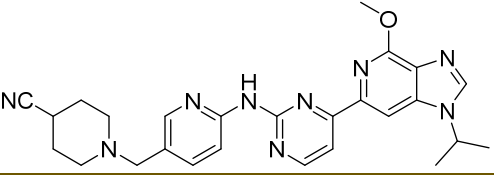
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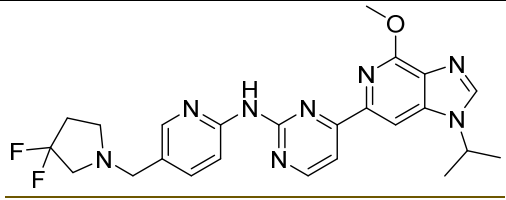
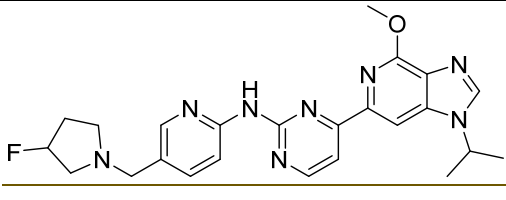
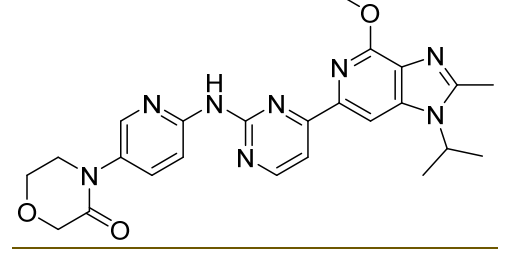
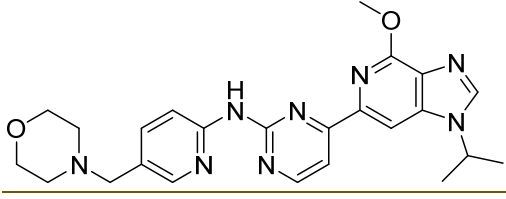
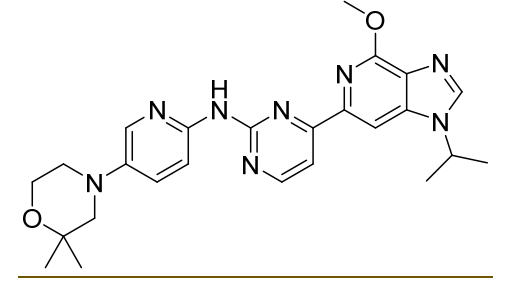
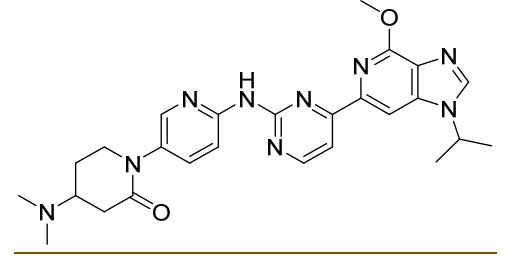
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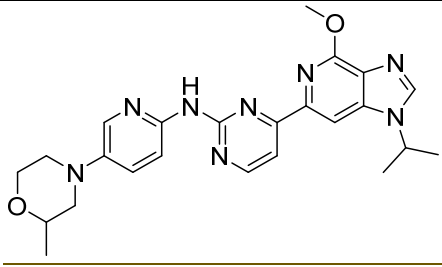
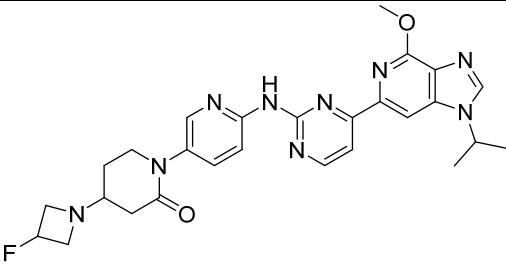
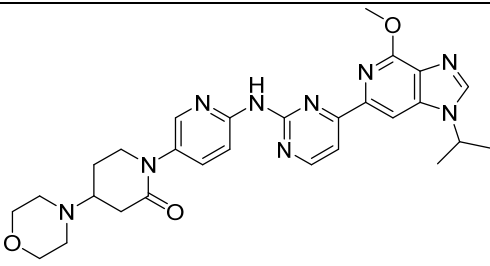
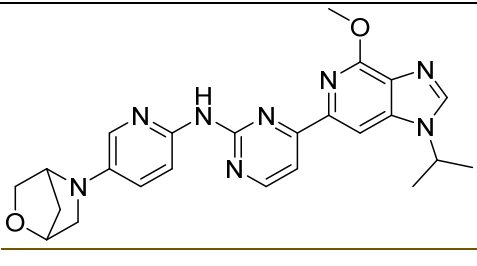
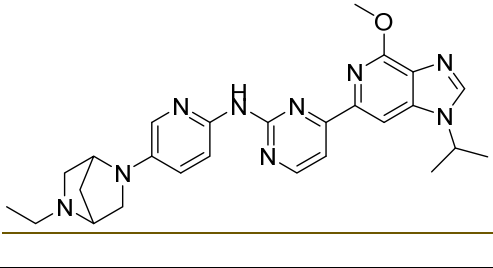
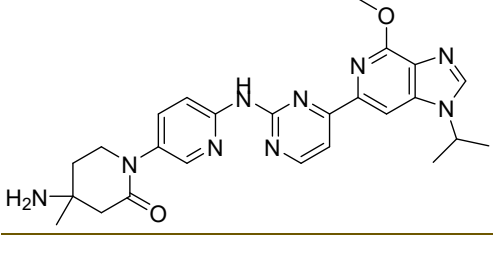
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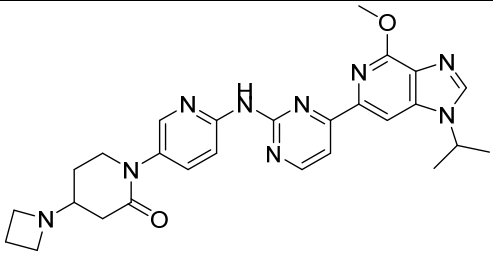
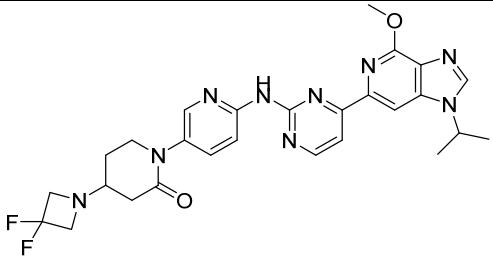
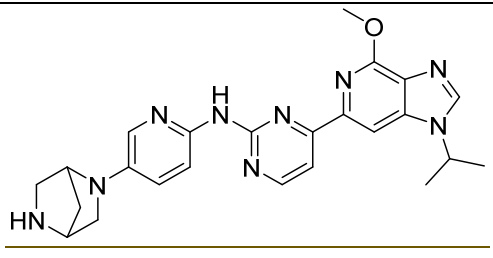
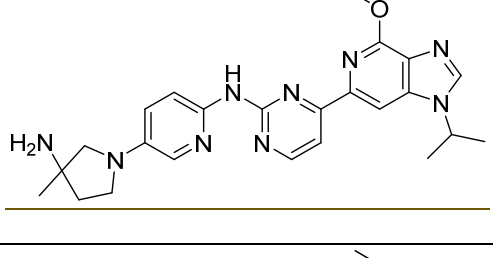
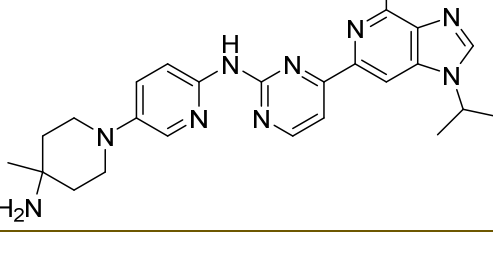
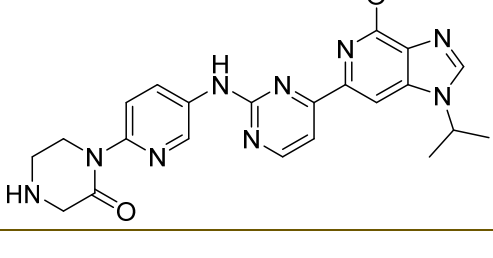
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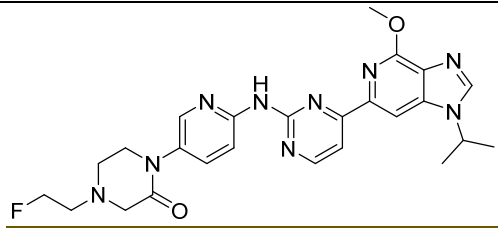
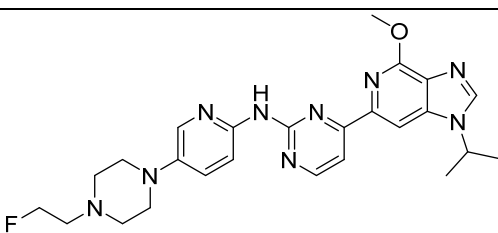
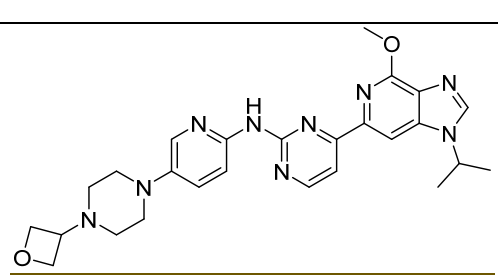
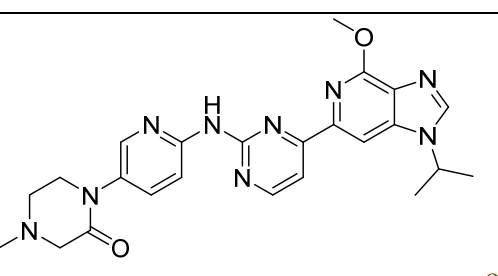
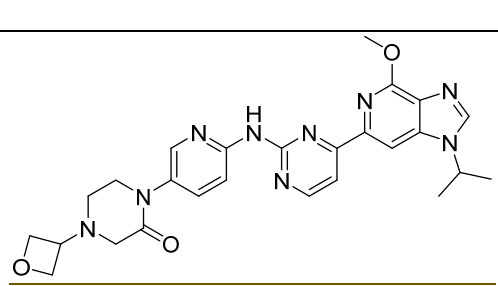
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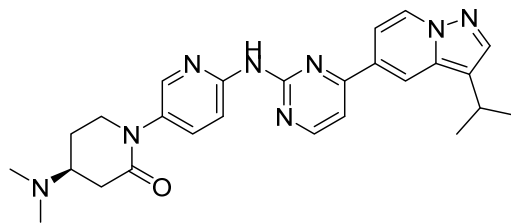
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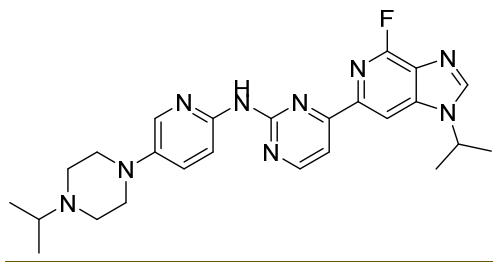
<u>122</u>	
<u>123</u>	
<u>130</u>	
<u>134</u>	 or
<u>137</u>	

-a compound listed in the examples.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is



12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is



2413. A pharmaceutical composition comprising an effective amount of the compound of any one of claims 1-2312 or a pharmaceutically acceptable salt, or a stereoisomer thereof, and a pharmaceutically acceptable carrier.
2514. Use of a compound of any one of claims 1-2312, or a pharmaceutically acceptable salt, or a stereoisomer thereof, in the manufacture of a medicament for treating cancer, wherein the cancer is selected from the group consisting of colorectal cancer, breast cancer, lung cancer, prostate cancer, glioblastoma, mantel cell lymphoma, chronic myeloid leukemia and acute myeloid leukemia.
2615. Use of a compound of any one of claims 1-2312, in the manufacture of a medicament for treating a cancer by inhibiting a cyclin-dependent kinase (CDK).
2716. The use of claim 2615, wherein the cancer is carcinoma of the bladder, breast, colon, kidney, epidermis, liver, lung, oesophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, nose, head and neck, prostate, or skin; a hematopoietic tumor of lymphoid lineage; a hematopoietic tumor of myeloid lineage; thyroid follicular cancer; a tumor of mesenchymal origin; a tumor of the central or peripheral nervous system; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratoanthoma; ~~thyroid follicular cancer~~; or Kaposi's sarcoma.
2817. The use of claim 2716, wherein the hematopoietic tumor of lymphoid lineage is leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, B-cell

lymphoma, T-cell lymphoma, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma.

- ~~29~~18. The use according to claim ~~26~~15, wherein the cancer is pRb⁺ breast cancer, or hormone receptor (HR)-positive (*e.g.*, estrogen receptor positive (ER⁺), progesterone receptor positive (PR⁺), or ER⁺PR⁺), HER2/neu-negative cancer.
- ~~30~~19. The use of claim ~~29~~18, wherein the cancer is advanced or metastatic or recurrent breast cancer.
- ~~31~~20. The use of claim ~~30~~19, wherein the breast cancer is in an adult woman, or a postmenopausal woman.
- ~~32~~21. The use of any of claims ~~29-31~~18-20, wherein a second agent selected from: an aromatase inhibitor, a Selective Estrogen Receptor Modulator (SERM), a pure antiestrogen with no estrogen agonist activity, a compound that temporarily suppresses ovarian function (*e.g.*, estrogen and/or progesterone production) such as a gonadotropin-releasing hormone (GnRH) agonist or a luteinizing hormone-releasing hormone (LH-RH) agonist, a compound that inhibits CCYP3A4, or a monoclonal antibody or an antigen-binding fragment thereof against IGF-1/IGF-2 is to be further administered.
- ~~33~~22. The use of any of claims ~~25-32~~14-21, wherein an immune checkpoint inhibitor (such as a PD-1 inhibitor, a PD-L1 inhibitor, or a CTLA-4 inhibitor), a receptor Tyr kinase inhibitor, and/or an ~~antagonist~~antagonist of hormone receptor (such as estrogen receptor) is to be further administered.
- ~~34~~23. A compound of any one of claims 1-~~23~~12, or a pharmaceutically acceptable salt, or a stereoisomer thereof, for use in treating cancer, wherein the cancer is selected from the group consisting of colorectal cancer, breast cancer, lung cancer, prostate cancer, glioblastoma, mantel cell lymphoma, chronic myeloid leukemia and acute myeloid leukemia, or for use in treating a cancer by inhibiting a cyclin-dependent kinase (CDK).