

CDK INHIBITORS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of priority to International Patent Application Number PCT/CN2019/085494, filed on May 5, 2019. The entire contents of the aforementioned application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Cyclin-Dependent Kinases (CDKs) are a family of protein kinases first discovered for their roles in regulating cell cycle. They have since been identified to play roles in regulating a number of other biological functions such as transcription, mRNA processing, and the differentiation of nerve cells.

CDKs are relatively small proteins with molecular weights between about 34-40 kDa. They contain little more than the kinase domain, and are essentially inactive when not in complex with a class of regulatory proteins called cyclins. CDK levels remain relatively constant throughout the cell cycle, and most regulation is post-translational, most prominently by binding to cyclins.

Like all kinases, the active site, or the ATP-binding site, of CDKs is a cleft between a small amino-terminal lobe and a larger carboxy-terminal lobe. The structure of human CDK2 revealed that CDKs have a modified ATP-binding site that can be regulated by cyclin binding. Phosphorylation by CDK-activating kinase (CAK) at Thr 161 on the T-loop increases the complex activity. Without cyclin, a flexible loop called the activation loop or T-loop blocks the cleft, and the position of several key amino acid residues is not optimal for ATP-binding. With cyclin, two alpha helices change position to permit ATP binding. One of them, the L12 helix that comes just before the T-loop in the primary sequence, becomes a beta strand and helps rearrange the T-loop, so it no longer blocks the active site. The other alpha helix called the PSTAIRE helix rearranges and helps change the position of the key amino acid residues in the active site.

Thus only the cyclin-CDK complex has active kinase activity, and most of known cyclin-CDK complexes regulate the progression through the cell cycle. The CDKs are ubiquitous in all known eukaryotes, and their regulatory function in the cell cycle has been evolutionarily conserved. For example, yeast cells can proliferate normally when their CDK gene has been replaced with the homologous human gene. CDKs exert their regulatory

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.

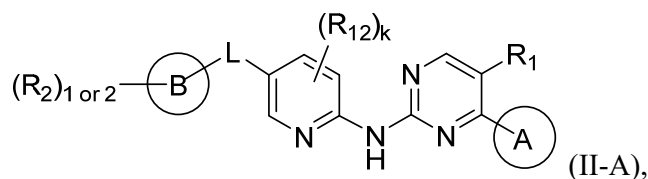
The highly homologous Cyclin-dependent kinases (CDKs) CDK4 and CDK6 in combination with Cyclin D are key regulators of the transition through the restriction point R between the G1 (growth) and S (DNA replication) phases of the cell cycle. CDK4/6 exert their effects via phosphorylation of the retinoblastoma 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.

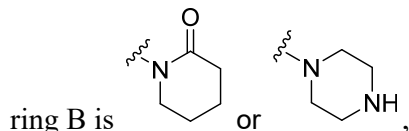
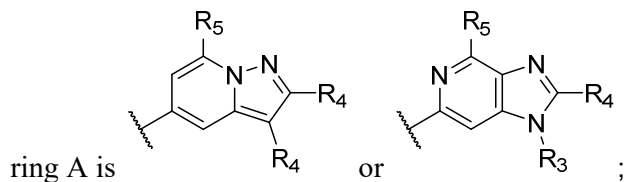
There remains a need to provide CDK4/6 inhibitors which can be used in the treatment of cell proliferative disorders such as cancer.

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



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;

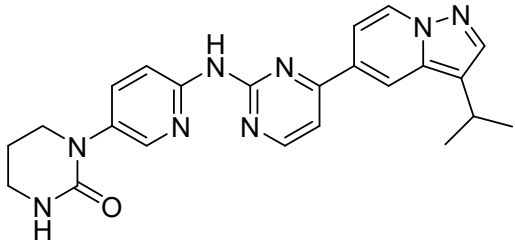
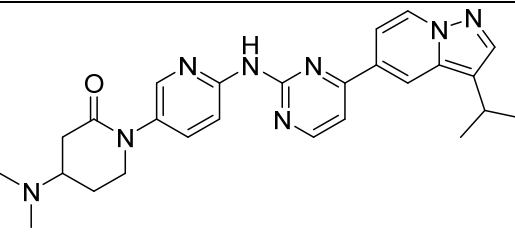
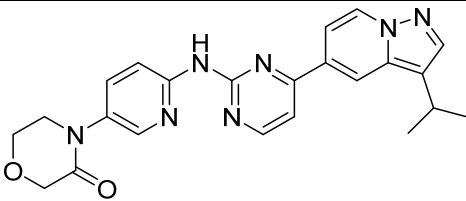
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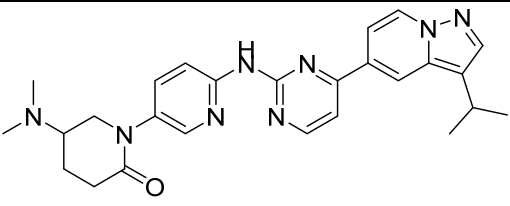
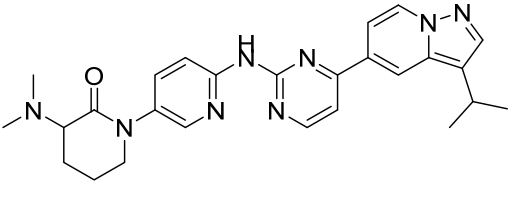
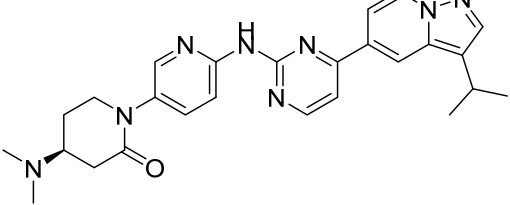
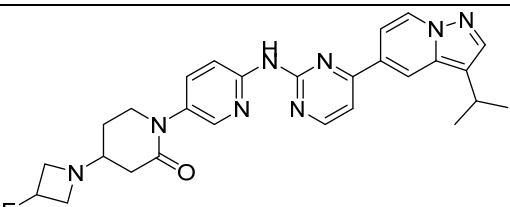
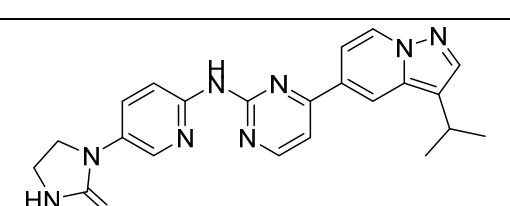
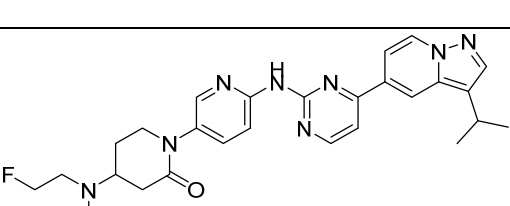
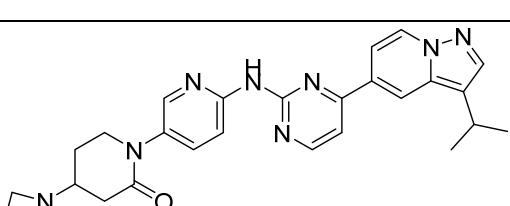
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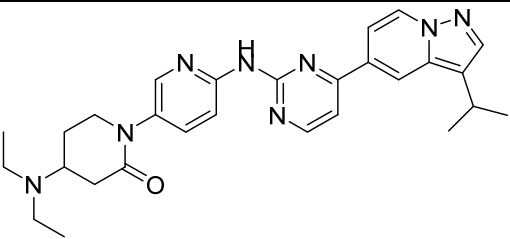
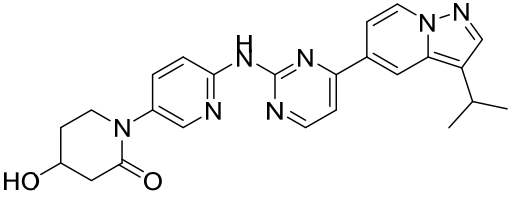
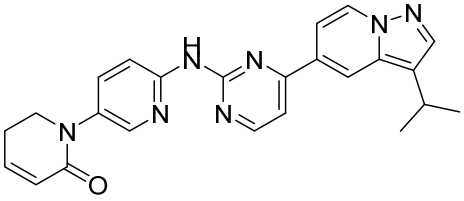
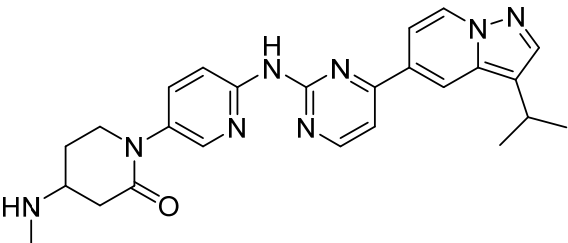
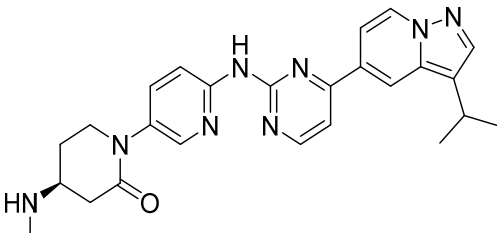
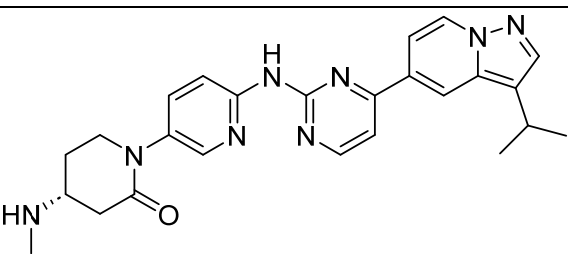
n is 0, 1, 2, 3, 4, or 5; and

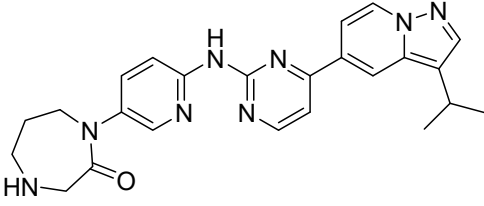
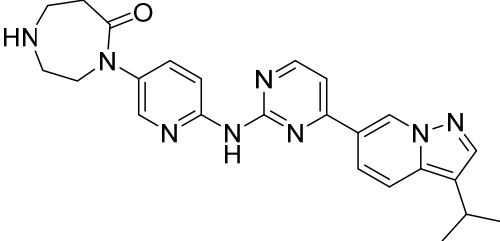
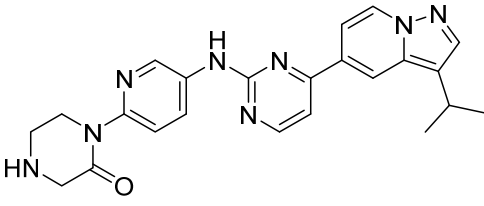
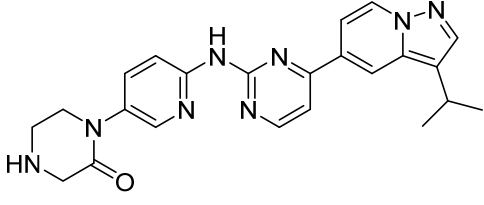
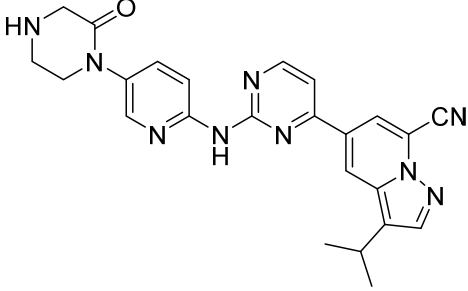
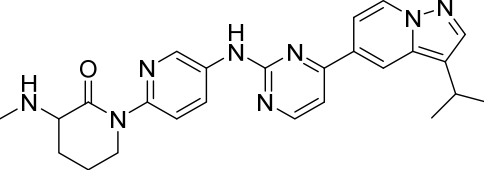
m is 0, 1, or 2.

In another aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein the compound is:

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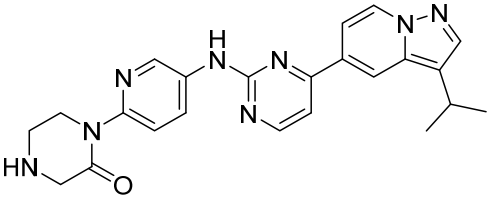
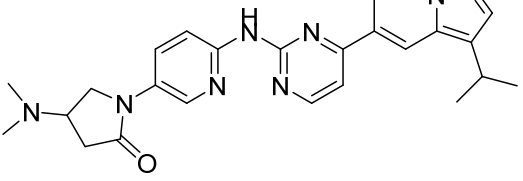
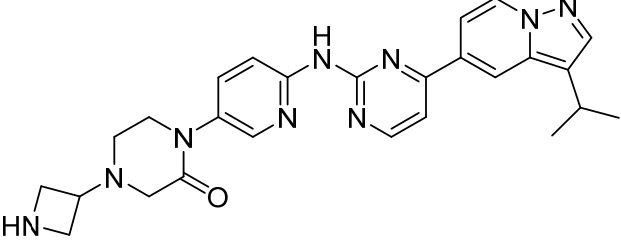
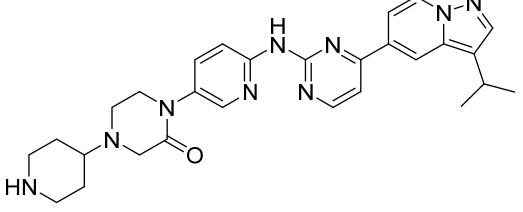
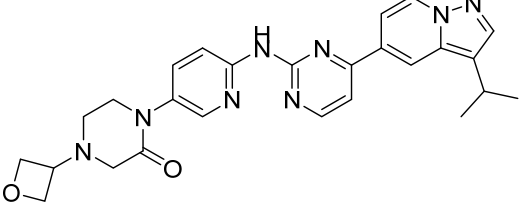
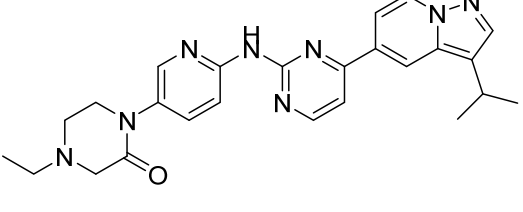
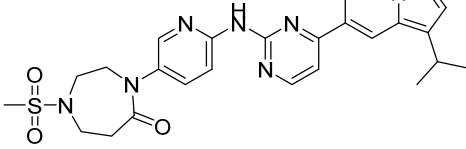
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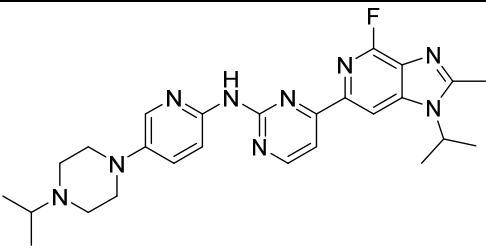
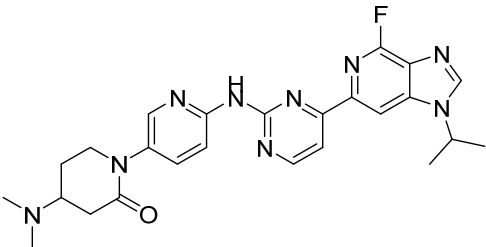
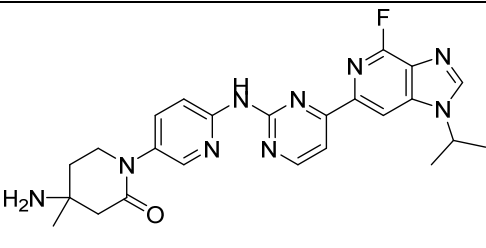
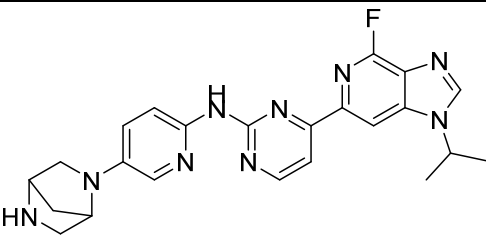
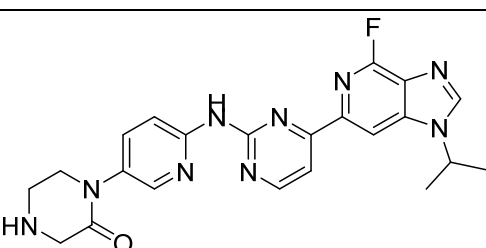
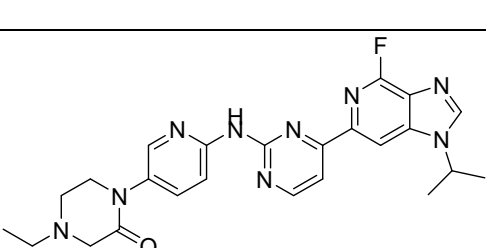
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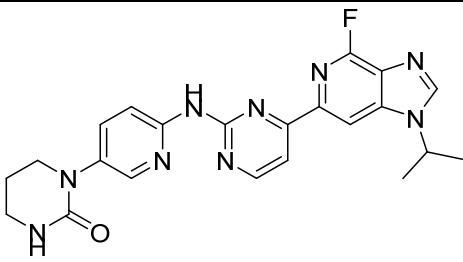
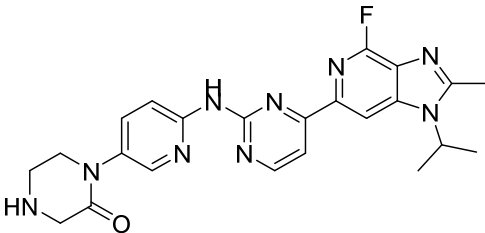
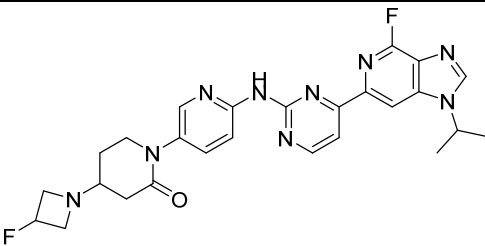
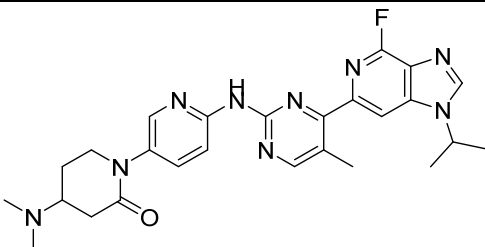
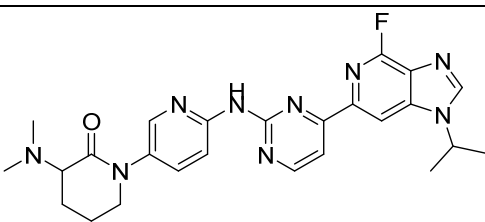
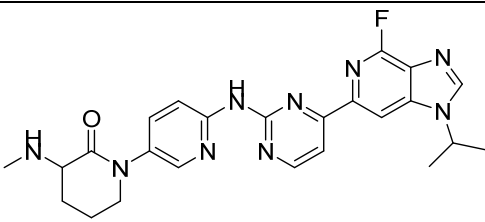
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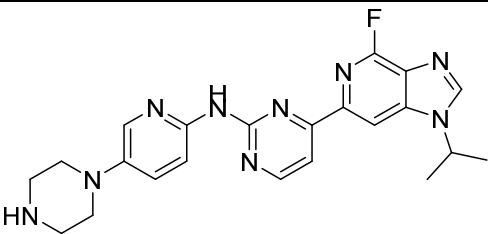
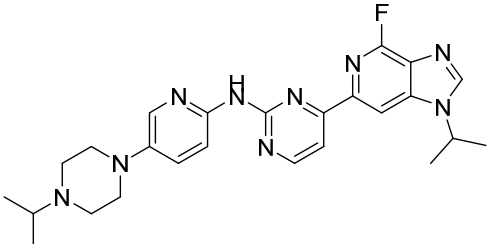
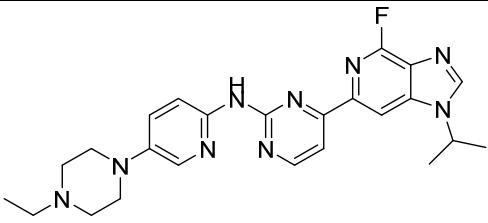
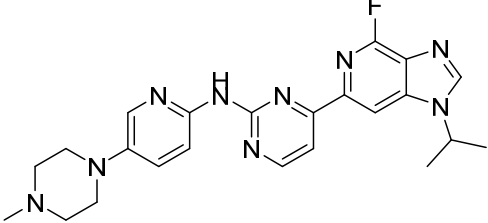
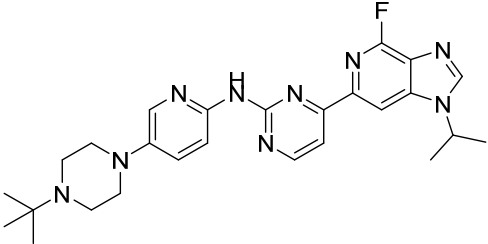
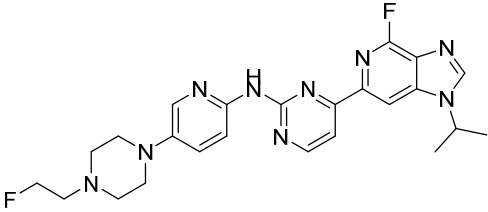
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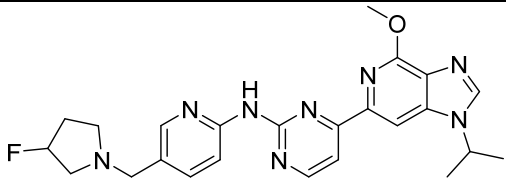
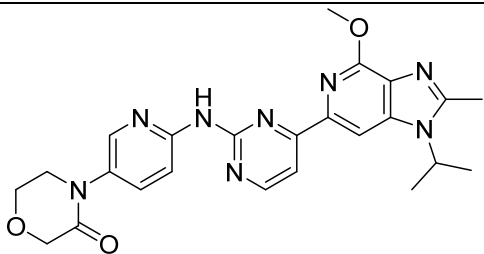
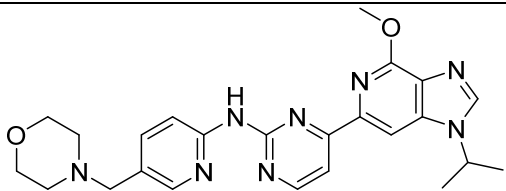
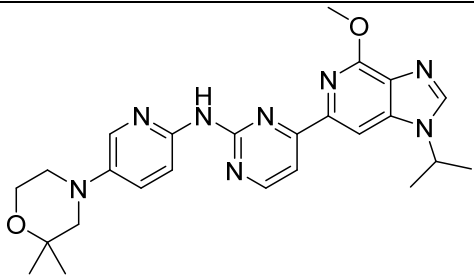
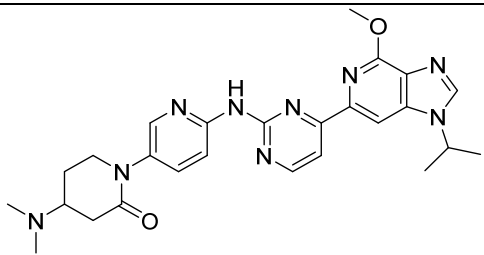
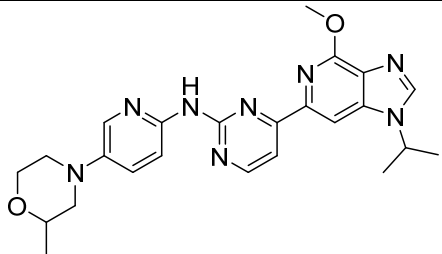
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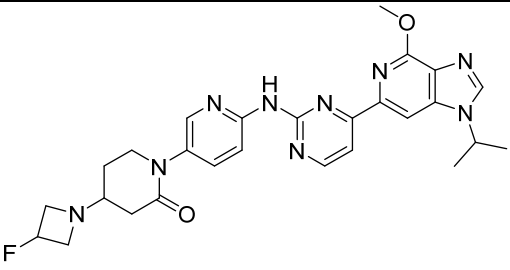
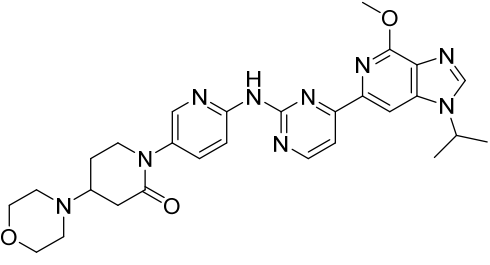
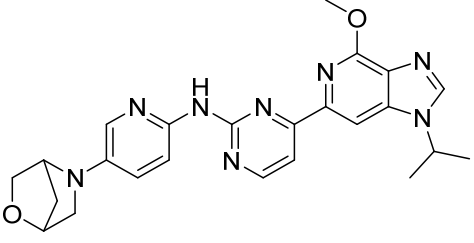
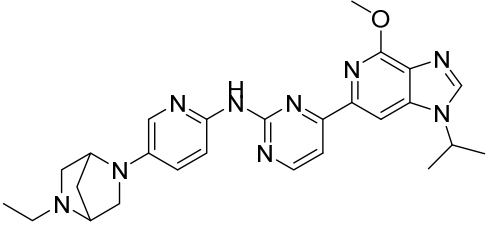
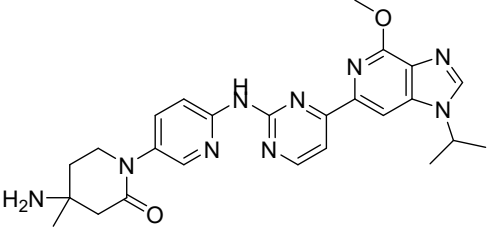
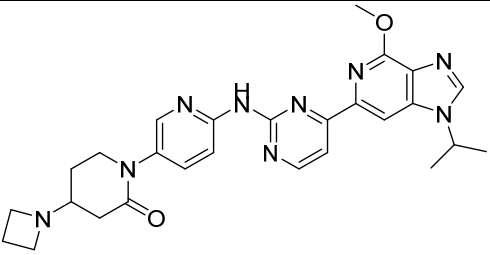
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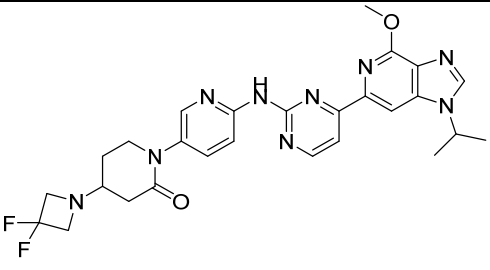
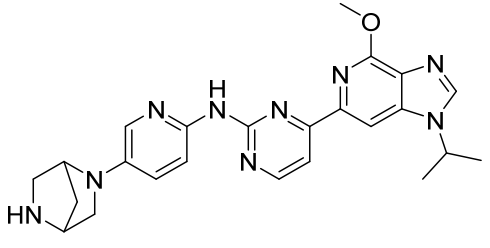
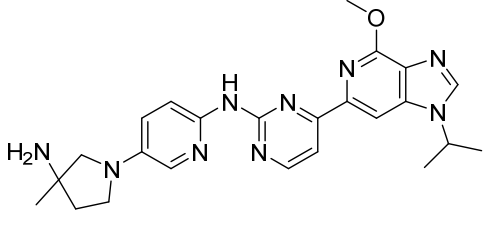
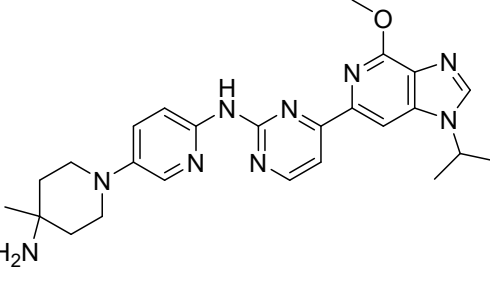
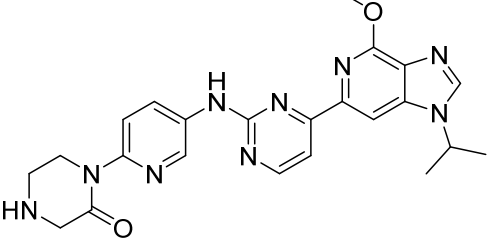
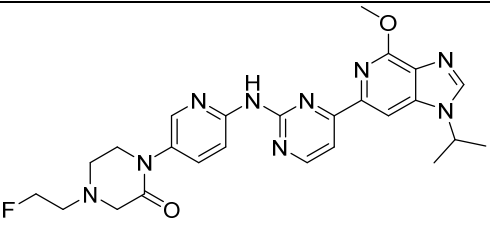
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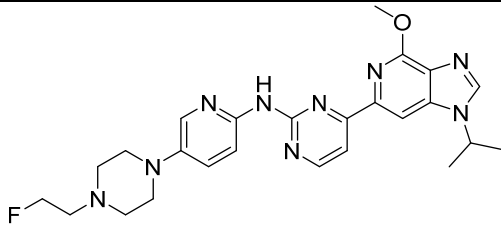
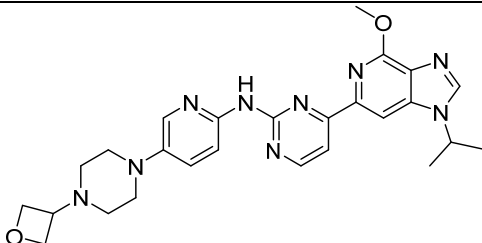
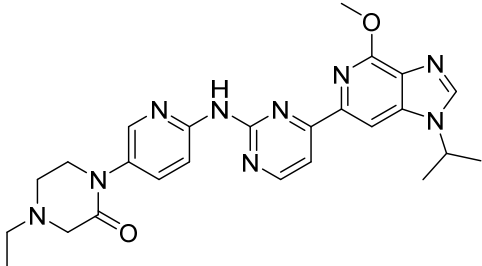
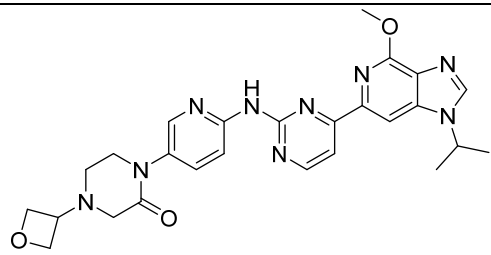
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In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising an effective amount of the compound disclosed herein or a pharmaceutically acceptable salt, or a stereoisomer thereof, and a pharmaceutically acceptable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

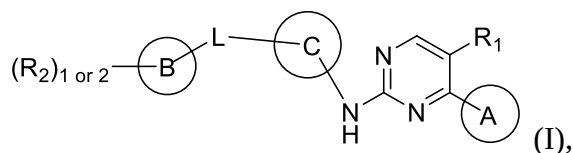
In another aspect of the present disclosure, there is provided a use of a compound

disclosed herein, in the manufacture of a medicament for treating a cancer by inhibiting a cyclin-dependent kinase (CDK) 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; keratoacanthoma; or Kaposi's sarcoma.

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.

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:



wherein R₁, R₂, ring A, ring B, ring C, and linker L are as defined herein.

In one example, the compound or pharmaceutically acceptable salt, or a stereoisomer thereof is selected from the compounds of the examples provided herein.

Also provided are pharmaceutical compositions comprising the compounds of the present disclosure, or a pharmaceutically acceptable salt, or a stereoisomer thereof and a pharmaceutically acceptable carrier.

The present disclosure further provides a method of treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of (1) the compound of the present disclosure or a pharmaceutically acceptable salt, or a stereoisomer thereof; or (2) a pharmaceutically acceptable composition comprising the compound of the present disclosure or a pharmaceutically acceptable salt, or a stereoisomer thereof, and a pharmaceutically acceptable carrier. In certain examples, the cancer is selected from the group consisting of colorectal cancer, breast cancer (such as hormone receptor positive, HER2/neu negative advanced or metastatic breast cancer in postmenopausal women), lung cancer, prostate cancer, glioblastoma, mantle cell lymphoma, chronic myeloid leukemia and acute myeloid leukemia.

In certain examples of the methods of the present disclosure, the cancer can be treated by inhibiting the activity of a cyclin-dependent kinase (CDK), *e.g.*, CDK2, CDK4, and/or CDK6.

In certain examples of the methods of the present disclosure, 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; keratocanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

In certain examples of the methods of the present disclosure, the compounds of the present disclosure are administered with any one of a second therapeutic agent as described herein that also treats the same cancer.

The present disclosure also provides a use of the compound of the present disclosure or a pharmaceutically acceptable salt, or a stereoisomer thereof or a pharmaceutical composition

comprising the same in any of the methods of the present disclosure described above. In one example, provided is the compound of the present disclosure or a pharmaceutically acceptable salt, or a stereoisomer thereof or a pharmaceutical composition comprising the same for use in any of the method of the present disclosure described above. In another example, provided is use of the compound of the present disclosure or a pharmaceutically acceptable salt, or a stereoisomer thereof or a pharmaceutical composition comprising the same for the manufacture of a medicament for any of the method of the present disclosure described.

DETAILED DESCRIPTION OF THE INVENTION

1. *Overview*

The present invention provides a compound of the present invention or a pharmaceutically acceptable salt thereof for use in therapy, such as cancer therapy.

The present also invention provides a pharmaceutical formulation comprising a compound of the present invention or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

The present invention provides a compound of the present invention or a pharmaceutically acceptable salt thereof for use in the treatment of cancer. In particular, those cancers may be any of the cancers described herein below, such as colorectal cancer, breast cancer (including ER⁺HER2⁻ advanced or metastatic or recurrent breast cancer is in an adult woman, or a postmenopausal woman), lung cancer, especially non-small cell lung cancer (NSCLC), prostate cancer, glioblastoma, mantel cell lymphoma (MCL), chronic myeloid leukemia (CML) and acute myeloid leukemia (AML).

This invention further provides a method of treating cancer selected from the group consisting of colorectal cancer, breast cancer (including ER⁺HER2⁻ advanced or metastatic or recurrent breast cancer is in an adult woman, or a postmenopausal woman), lung cancer, especially non-small cell lung cancer (NSCLC), prostate cancer, glioblastoma, mantel cell lymphoma, chronic myeloid leukemia and acute myeloid leukemia in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof.

Additionally, this invention provides the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of cancer. In particular those cancers are selected from the group consisting of colorectal cancer, breast cancer (including ER⁺HER2⁻ advanced or metastatic or recurrent

breast cancer is in an adult woman, or a postmenopausal woman), lung cancer, especially non-small cell lung cancer (NSCLC), prostate cancer, glioblastoma, mantel cell lymphoma, chronic myeloid leukemia and acute myeloid leukemia.

Furthermore, this invention provides a pharmaceutical formulation for use in therapy comprising a compound of the present invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent, or excipient. The invention also provides a pharmaceutical formulation for treating colorectal cancer, breast cancer (including ER⁺HER2⁻ advanced or metastatic or recurrent breast cancer is in an adult woman, or a postmenopausal woman), lung cancer, especially non-small cell lung cancer (NSCLC), prostate cancer, glioblastoma, mantel cell lymphoma, chronic myeloid leukemia and acute myeloid leukemia comprising a compound of the present invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent, or excipient.

Treatable disease indications and potential second therapeutic agent useful for combination therapy are described in further detail in the sections below.

It should be understood that any embodiment described herein, including those described only in one of the sections below or only in the examples, may be combined with any one or more additional embodiments of the invention, unless expressly disclaimed or otherwise improper / inapplicable.

2. Definitions

The term “halo” or “halogen” as used herein means halogen and includes chloro, fluoro, bromo and iodo.

The term “alkyl” used alone or as part of a larger moiety, such as “alkoxy” or “haloalkyl” and the like, means saturated aliphatic straight-chain or branched monovalent hydrocarbon radical. Unless otherwise specified, an alkyl group typically has 1-4 carbon atoms, *i.e.* (C₁-C₄)alkyl. As used herein, a “(C₁-C₄)alkyl” group means a radical having from 1 to 4 carbon atoms in a linear or branched arrangement. Examples include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, isobutyl, sec-butyl and tert-butyl.

The term “alkenyl” means branched or straight-chain monovalent hydrocarbon radical containing at least one double bond. Alkenyl may be mono or polyunsaturated, and may exist in the E or Z configuration. Unless otherwise specified, an alkenyl group typically has 2-6 carbon atoms, *i.e.* (C₂-C₆)alkenyl. For example, “(C₂-C₆)alkenyl” means a radical having

from 2-6 carbon atoms in a linear or branched arrangement.

The term “alkynyl” means branched or straight-chain monovalent hydrocarbon radical containing at least one triple bond. Unless otherwise specified, an alkynyl group typically has 2-6 carbon atoms, *i.e.* (C₂-C₆)alkynyl. For example, “(C₂-C₆)alkynyl” means a radical having from 2-6 carbon atoms in a linear or branched arrangement.

The term “alkoxy” means an alkyl radical attached through an oxygen linking atom, represented by -O-alkyl. For example, “(C₁-C₄)alkoxy” includes methoxy, ethoxy, propoxy, and butoxy.

The terms “haloalkyl” and “haloalkoxy” means alkyl or alkoxy, as the case may be, substituted with one or more halogen atoms. Examples of haloalkyl, include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl and the like.

The terms “hydroxyalkyl” and “hydroxyalkoxy” means alkyl or alkoxy, as the case may be, substituted with one or more hydroxy groups.

The term “cycloalkyl” as employed herein includes saturated cyclic, bicyclic, tricyclic, or polycyclic hydrocarbon groups having 3 to 14 carbons containing the indicated number of rings and carbon atoms (for example a C₃-C₁₄ monocyclic, C₄-C₁₄ bicyclic, C₅-C₁₄ tricyclic, or C₆-C₁₄ polycyclic cycloalkyl). In some embodiments “cycloalkyl” is a monocyclic cycloalkyl. Examples of monocyclic cycloalkyl groups include cyclopentyl (C₅), cyclohexyl (C₆), cyclopropyl (C₃) cyclobutyl (C₄), cycloheptyl (C₇) and cyclooctyl (C₈). In some embodiments “cycloalkyl” is a bicyclic cycloalkyl. Examples of bicyclic cycloalkyls include bicyclo[1.1.0]butane (C₄), bicyclo[1.1.1]pentane (C₅), spiro[2.2] pentane (C₅), bicyclo[2.1.0]pentane (C₅), bicyclo[2.1.1]hexane (C₆), bicyclo[3.3.3]undecane (C₁₁), decahydronaphthalene (C₁₀), bicyclo[4.3.2]undecane (C₁₁), spiro[5.5]undecane (C₁₁) and bicyclo[4.3.3]dodecane (C₁₂). In some embodiments “cycloalkyl” is a tricyclic cycloalkyl. Examples of tricyclic cycloalkyls include adamantane (C₁₂). Unless otherwise described, a “cycloalkyl” has from three to six carbon atoms.

The term “aryl group” used alone or as part of a larger moiety as in “aralkyl”, “aralkoxy”, or “aryloxyalkyl”, means a carbocyclic aromatic ring. The term “aryl” may be used interchangeably with the terms “aryl ring” “carbocyclic aromatic ring”, “aryl group” and “carbocyclic aromatic group”. An aryl group typically has six to fourteen ring atoms. Examples includes phenyl, naphthyl, anthracenyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indanyl, indenyl and the like. A “substituted aryl group” is substituted at any one or more substitutable ring atom, which is a ring carbon atom bonded to

a hydrogen.

The term “heterocyclyl group” or “heterocyclic group” means a monocyclic, non-aromatic ring with 3 to 10-members containing from 1-4 ring heteroatoms or a polycyclic ring with ring with 7 to 20-members and from 1 to 4 ring heteroatoms, wherein the polycyclic ring having one or more monocyclic non-aromatic heterocyclic ring fused with one or more aromatic or heteroaromatic ring. Each heteroatom is independently selected from nitrogen, quaternary nitrogen, oxidized nitrogen (*e.g.*, NO); oxygen; and sulfur, including sulfoxide and sulfone. In one embodiment, the heterocyclyl group is a bicyclic ring having a monocyclic non-aromatic heterocyclic ring fused with a phenyl group. Exemplary polycyclic heterocyclic group includes tetrahydroisoquinolinyl (such as 1,2,3,4-tetrahydroisoquinolin-7-yl, 2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl, 1,2,3,4-tetrahydroisoquinolin-6-yl and 2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl), isoindolinyl (such as 2-ethylisoindolin-5-yl, 2-methylisoindolin-5-yl), indolinyl, tetrahydrobenzo[f]oxazepinyl (such as 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl). The term “heterocycle,” “heterocyclyl,” or “heterocyclic” whether saturated or partially unsaturated, also refers to rings that are optionally substituted. In some embodiments, a heterocyclyl group is a 3-14 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“3-14 membered heterocyclyl”).

The term “heteroaryl”, “heteroaromatic”, “heteroaryl ring”, “heteroaryl group”, “heteroaromatic ring”, and “heteroaromatic group”, used alone or as part of a larger moiety as in “heteroaralkyl” or “heteroarylalkoxy”, refers to aromatic ring groups having five to fourteen ring atoms selected from carbon and at least one (typically 1 to 4, more typically 1 or 2) heteroatoms (*e.g.*, oxygen, nitrogen or sulfur). “Heteroaryl” includes monocyclic rings and polycyclic rings in which a monocyclic heteroaromatic ring is fused to one or more other carbocyclic aromatic or heteroaromatic rings. As such, “5-14 membered heteroaryl” includes monocyclic, bicyclic or tricyclic ring systems.

Examples of monocyclic 5-6 membered heteroaryl groups include furanyl (*e.g.*, 2-furanyl, 3-furanyl), imidazolyl (*e.g.*, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), isoxazolyl (*e.g.*, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (*e.g.*, 2-oxadiazolyl, 5-oxadiazolyl), oxazolyl (*e.g.*, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), pyrazolyl (*e.g.*, 3-pyrazolyl, 4-pyrazolyl), pyrrolyl (*e.g.*, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), pyridyl (*e.g.*, 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (*e.g.*, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl),

pyridazinyl (*e.g.*, 3-pyridazinyl), thiazolyl (*e.g.*, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), triazolyl (*e.g.*, 2-triazolyl, 5-triazolyl), tetrazolyl (*e.g.*, tetrazolyl), thienyl (*e.g.*, 2-thienyl, 3-thienyl), pyrimidinyl, pyridinyl and pyridazinyl. Examples of polycyclic aromatic heteroaryl groups include carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, indolyl, isoindolyl, acridinyl, or benzisoxazolyl. A “substituted heteroaryl group” is substituted at any one or more substitutable ring atom, which is a ring carbon or ring nitrogen atom bonded to a hydrogen.

The term “bridged bicyclic group” refers to a ring system which includes two rings that share at least three adjacent ring atoms.

As used herein, many moieties (*e.g.*, alkyl, alkylene, cycloalkyl, aryl, heteroaryl, or heterocyclyl) are referred to as being either “substituted” or “optionally substituted”. When a moiety is modified by one of these terms, unless otherwise noted, it denotes that any portion of the moiety that is known to one skilled in the art as being available for substitution can be substituted, which includes one or more substituents. Where if more than one substituent is present, then each substituent may be independently selected. Such means for substitution are well-known in the art and/or taught by the instant disclosure. The optional substituents can be any substituents that are suitable to attach to the moiety.

Where suitable substituents are not specifically enumerated, exemplary substituents include, but are not limited to: (C₁-C₅)alkyl, (C₁-C₅)hydroxyalkyl, (C₁-C₅)haloalkyl, (C₁-C₅)alkoxy, (C₁-C₅) haloalkoxy, halogen, hydroxyl, cyano, amino, -CN, -NO₂, -OR^{cl}, -NR^{al}R^{bl}, -S(O)_iR^{al}, -NR^{al}S(O)_iR^{bl}, -S(O)_iNR^{al}R^{bl}, -C(=O)OR^{al}, -OC(=O)OR^{al}, -C(=S)OR^{al}, -O(C=S)R^{al}, -C(=O)NR^{al}R^{bl}, -NR^{al}C(=O)R^{bl}, -C(=S)NR^{al}R^{bl}, -C(=O)R^{al}, -C(=S)R^{al}, NR^{al}C(=S)R^{bl}, -O(C=O)NR^{al}R^{bl}, -NR^{al}(C=S)OR^{bl}, -O(C=S)NR^{al}R^{bl}, -NR^{al}(C=O)NR^{al}R^{bl}, -NR^{al}(C=S)NR^{al}R^{bl}, phenyl, or 5-6 membered heteroaryl. Each R^{al} and each R^{bl} are independently selected from -H and (C₁-C₅)alkyl, optionally substituted with hydroxyl or (C₁-C₃)alkoxy; R^{cl} is -H, (C₁-C₅)haloalkyl or (C₁-C₅)alkyl, wherein the (C₁-C₅)alkyl is optionally substituted with hydroxyl or (C₁-C₃)alkoxy.

Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer.

Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and diastereomers can also be obtained from diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

When a compound is designated by a name or structure that indicates a single enantiomer, unless indicated otherwise, the compound is at least 60%, 70%, 80%, 90%, 99% or 99.9% optically pure (also referred to as “enantiomerically pure”). Optical purity is the weight in the mixture of the named or depicted enantiomer divided by the total weight in the mixture of both enantiomers.

When the stereochemistry of a disclosed compound is named or depicted by structure, and the named or depicted structure encompasses more than one stereoisomer (*e.g.*, as in a diastereomeric pair), it is to be understood that one of the encompassed stereoisomers or any mixture of the encompassed stereoisomers are included. It is to be further understood that the stereoisomeric purity of the named or depicted stereoisomers is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight. The stereoisomeric purity in this case is determined by dividing the total weight in the mixture of the stereoisomers encompassed by the name or structure by the total weight in the mixture of all of the stereoisomers.

When a geometric isomer is depicted by name or structure, it is to be understood that the geometric isomeric purity of the named or depicted geometric isomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% pure by weight. Geometric isomeric purity is determined by dividing the weight of the named or depicted geometric isomer in the mixture by the total weight of both geometric isomers in the mixture.

Racemic mixture means 50% of one enantiomer and 50% of its corresponding enantiomer. The invention encompasses all enantiomerically-pure, enantiomerically-enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures, and

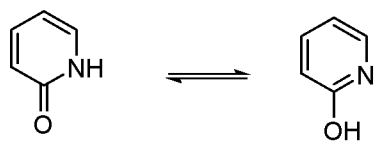
diastereomeric mixtures of the compounds of the invention.

The compounds described herein may also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of the compound disclosed herein will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. *See, for instance, Wada, E et al., Seikagaku, 1994, 66:15; Gannes, LZ et al., Comp Biochem Physiol Mol Integr Physiol, 1998, 119:725.*

The compounds described herein may exist in various tautomeric forms. The term “tautomers” or “tautomeric” refers to two or more interconvertible compounds/ substituents resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a single bond, or vice versa). Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations. The present teachings encompass compounds in the form of tautomers, which includes forms not depicted structurally. All such isomeric forms of such compounds are expressly included. If a tautomer of a compound is aromatic, this compound is aromatic. Similarly, if a tautomer of a compound is a heteroaryl, this compound is heteroaryl.

In certain instances tautomeric forms of the disclosed compounds exist, such as the tautomeric structures shown below:



It is to be understood that when a compound herein is represented by a structural formula or designated by a chemical name herein, all other tautomeric forms which may exist for the compound are encompassed by the structural formula.

The compounds of this invention can exist in free form for treatment, or where

appropriate, as a pharmaceutically acceptable salt form.

The term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art, for example, Berge *et al.* describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4} \text{ alkyl})_4^-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

Such pharmaceutically acceptable acid addition salts and common methodology for preparing them are well known in the art. *See, e.g.,* Stahl *et al.*, HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION AND USE, (VCHA/Wiley-VCH, 2002); Bighley *et al.*, in “*Encyclopedia of Pharmaceutical Technology.*” Eds. Swarbrick and Boylan, Vol. 13, Marcel Dekker, Inc., New York, Basel, Hong Kong 1995, pp.

453-499; Berge *et al.*, “Pharmaceutical Salts,” *Journal of Pharmaceutical Sciences*, 66(1): 1977.

The terms “composition” and “formulation” are used interchangeably.

A “subject” is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like).

The term “administer,” “administering,” or “administration” refers to methods introducing a compound of the invention, or a composition thereof, in or on a subject. These methods include, but are not limited to, intraarticular (in the joints), intravenous, intramuscular, intratumoral, intradermal, intraperitoneal, subcutaneous, orally, topically, intrathecally, inhalationally, transdermally, rectally, and the like. Administration techniques that can be employed with the agents and methods described herein are found in *e.g.*, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.; Pergamon; and Remington’s, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa.

The terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed (*i.e.*, therapeutic treatment). In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*i.e.*, prophylactic treatment) (*e.g.*, in light of a history of symptoms and/or in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

The terms “condition,” “disease,” and “disorder” are used interchangeably.

Generally, an effective amount of a compound taught herein varies depending upon various factors, such as the given drug or compound, the pharmaceutical formulation, the route of administration, the type of disease or disorder, the identity of the subject or host being treated, and the like, but can nevertheless be routinely determined by one skilled in the art. An effective amount of a compound of the present teachings may be readily determined by one of ordinary skill by routine methods known in the art.

The term “an effective amount” means an amount when administered to the subject

which results in beneficial or desired results, including clinical results, *e.g.*, inhibits, suppresses or reduces the symptoms of the condition being treated in the subject as compared to a control. For example, an effective amount can be given in unit dosage form (*e.g.*, from 1 mg to about 50 g per day, *e.g.*, from 1 mg to about 5 grams per day).

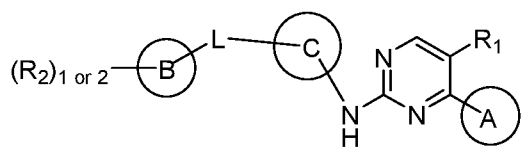
A “therapeutically effective amount” is that amount effective for detectable killing or inhibition of the growth or spread of cancer cells; the size or number of tumors; or other measure of the level, stage, progression or severity of the cancer. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular anticancer agent, its mode of administration, combination treatment with other therapies, and the like.

The general chemical terms used in the formulae above have their usual meanings.

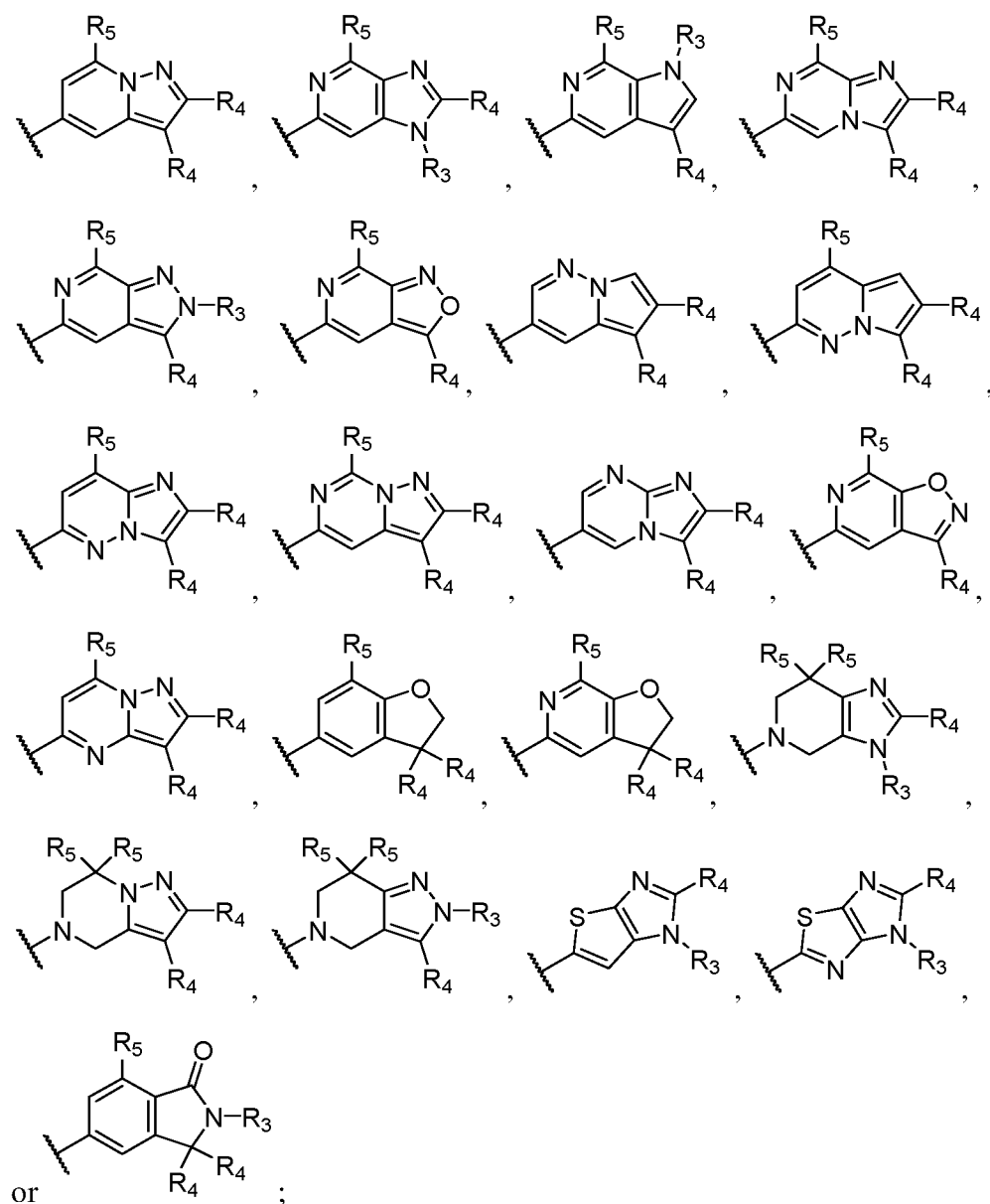
As used herein, “h” refers to hour or hours, “min” refers to minutes or minutes, “Cdk” or “CDK” refers to cyclin dependent kinase, “pRb” refers to retinoblastoma protein, “MCL” refers to mantle cell lymphoma, “AML” refers to acute myeloid leukemia, “CML” refers to chronic myeloid leukemia, “Boc” refers to N-tert-butoxycarbonyl, “EA” refers to ethyl acetate, “DCM” refers to dichloromethane, “DMSO” refers to dimethylsulfoxide, “DMA” refers to dimethylacetamide, “THF” refers to tetrahydrofuran, “MtBE” refers to methyl tert-butyl ether, “TEA” refers to triethylamine, “FBS” refers to fetal bovine serum, “PBS” refers to phosphate buffered saline, “BSA” refers to bovine serum albumin, “RT” refers to room temperature, “mpk” means milligrams per kilogram, “po” refers to per os (oral), “qd” means once daily dosing, “HPLC” means high pressure liquid chromatography, “q2d” means a single dose every 2 days, “q2dx10” means a single dose every 2 days times 10, “VSMC” refers to vascular smooth muscle cell and “XRD” refers to X-ray diffraction.

3. Compounds

In a first embodiment of the invention, provided is 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, $-(CH_2)_nOR_6$, $-(CH_2)_nSR_6$, $-(CH_2)_nC(O)R_6$, $-(CH_2)_nC(O)OR_6$,

$-(\text{CH}_2)_n\text{S}(\text{O})_m\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_7\text{R}_8$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}_7\text{R}_8$, $-(\text{CH}_2)_n\text{NR}_7\text{C}(\text{O})\text{R}_6$,
 $-(\text{CH}_2)_n\text{NR}_7\text{S}(\text{O})_m\text{R}_6$, C_{3-8} 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 R_2 is each optionally substituted with one or more groups selected from deuterium, halogen, CN, -OH, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, and NR_7R_8 ; or

when ring B is 3-10 membered heterocyclyl, two R_2 attached to the same ring atom of ring B may form C_{3-6} cycloalkyl or 3-6 membered heterocyclyl optionally substituted with one or more groups selected from deuterium, halogen, CN, -OH, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, and NR_7R_8 ;

each instance of R_3 is independently selected from H, deuterium, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, or 3-10 membered heterocyclyl; wherein the C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, or 3-10 membered heterocyclyl represented by R_3 is optionally substituted with one or more groups selected from deuterium, halogen, CN, -OH, C_{1-8} alkyl, and C_{1-8} haloalkyl;

each instance of R_4 is independently selected from H, deuterium, halogen, CN, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, $\text{C}(\text{O})\text{C}_{1-8}$ alkyl, C_{3-8} cycloalkyl, or 3-10 membered heterocyclyl; wherein the C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, or 3-10 membered heterocyclyl represented by R_4 or in the group represented by R_4 is each optionally substituted with one or more groups selected from deuterium, halogen, -OH, C_{1-8} alkyl and C_{1-8} haloalkyl; 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 deuterium, halogen, CN, -OH, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, and NR_7R_8 ;

each instance of R_5 is H, deuterium, halogen, -OH, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $\text{C}(\text{O})\text{C}_{1-4}$ alkyl, or 3-6 membered heterocyclyl;

each instance of R_6 is independently H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, 3-10 membered heterocyclyl, 6-14 membered aryl, 5-14 membered heteroaryl, wherein the C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, 3-10 membered heterocyclyl, 6-14 membered aryl, 5-14 membered heteroaryl represented by R_6 is each optionally substituted with one or more groups selected from halogen, CN, -OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and NR_7R_8 ;

each instance of R_7 and R_8 is independently H, C_{1-4} alkyl or cyclopropyl;

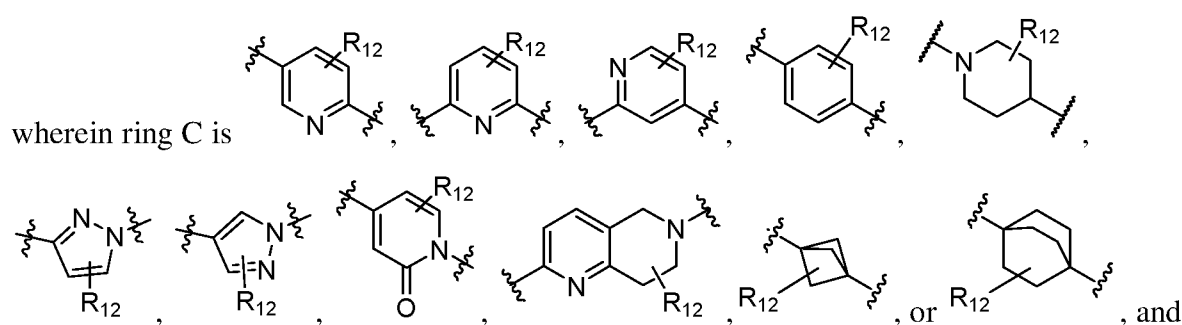
each instance of R₁₂ is H, deuterium, halogen, -OH, CN, NH₂, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl; wherein the C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, C₃₋₈ cycloalkyl, or 3-10 membered heterocyclyl represented by R₁₂ is optionally 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

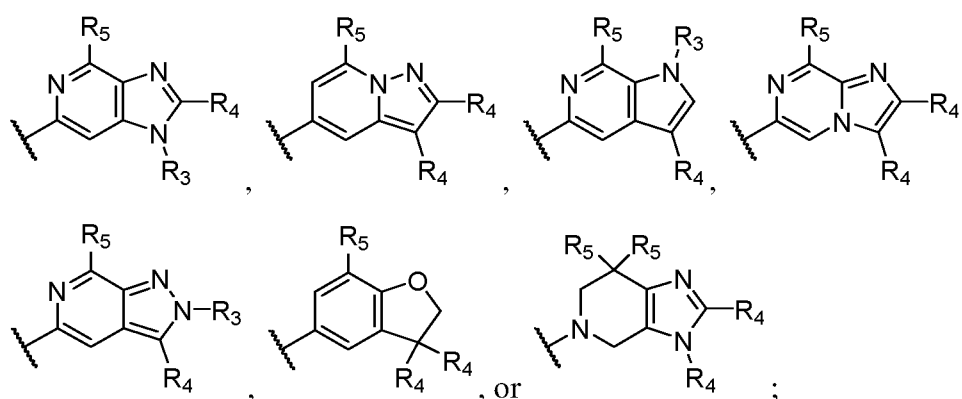
m is 0, 1, or 2.

In a second embodiment of the invention, provided is a compound represented by structural formula (I), or a pharmaceutically acceptable salt, or a stereoisomer thereof,



the remaining variables are as defined in the first embodiment.

In a third embodiment of the invention, provided is a compound of the first or second embodiment, or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring A is



wherein

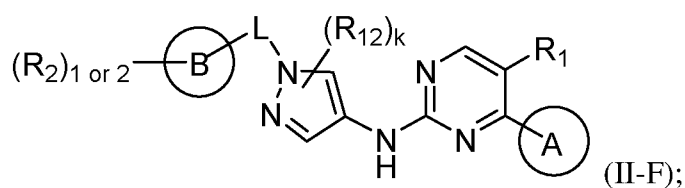
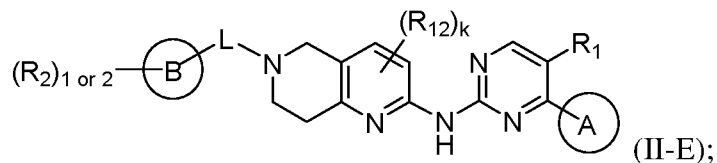
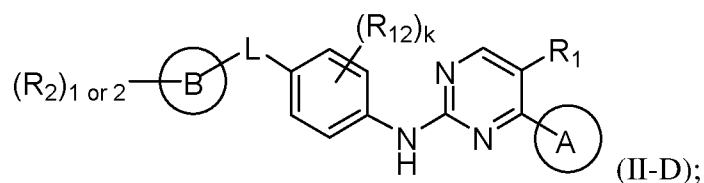
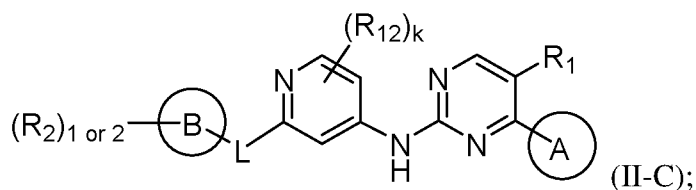
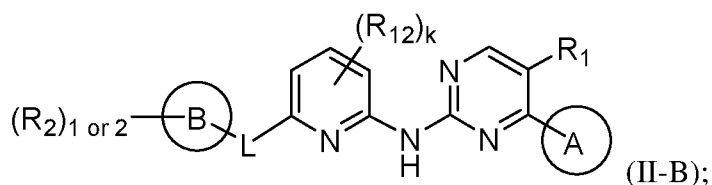
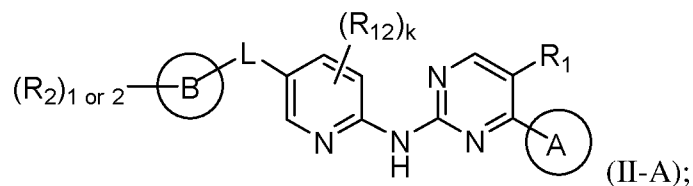
each instance of R₃ is H, deuterium, C₁₋₄ alkyl optionally substituted with -OH, or C₃₋₆ cycloalkyl optionally substituted with -OH;

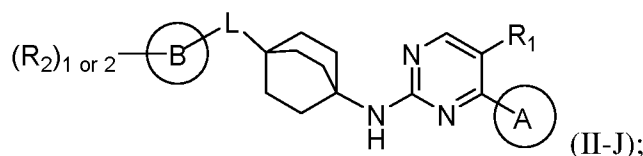
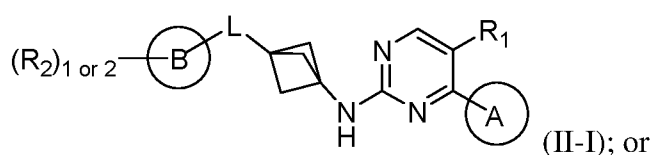
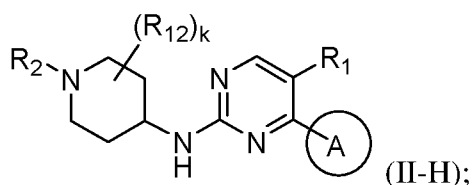
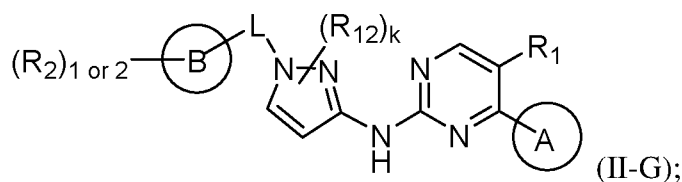
each instance of R₄ is H, deuterium, halogen, C₁₋₄ alkyl optionally substituted with fluoro, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl optionally substituted with methyl, or 3-6 membered

heterocyclyl; or two 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, and the remaining variables are as defined in the first and/or second embodiment.

In a fourth embodiment of the invention, the compound of structural formula (I) 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, and the remaining variables are as defined in the first, second and/or third embodiment(s).

In a fifth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein L is a bond, $-(CH_2)-$, $-O(CH_2)-$, $-C(=O)-$, or $-S(O)_2-$, and the remaining variables are as defined in the first, second, third, and/or fourth embodiment(s).

In a sixth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), 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, and the remaining variables are as defined in the first, second, third, fourth, and/or fifth embodiment(s).

In a seventh embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), 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

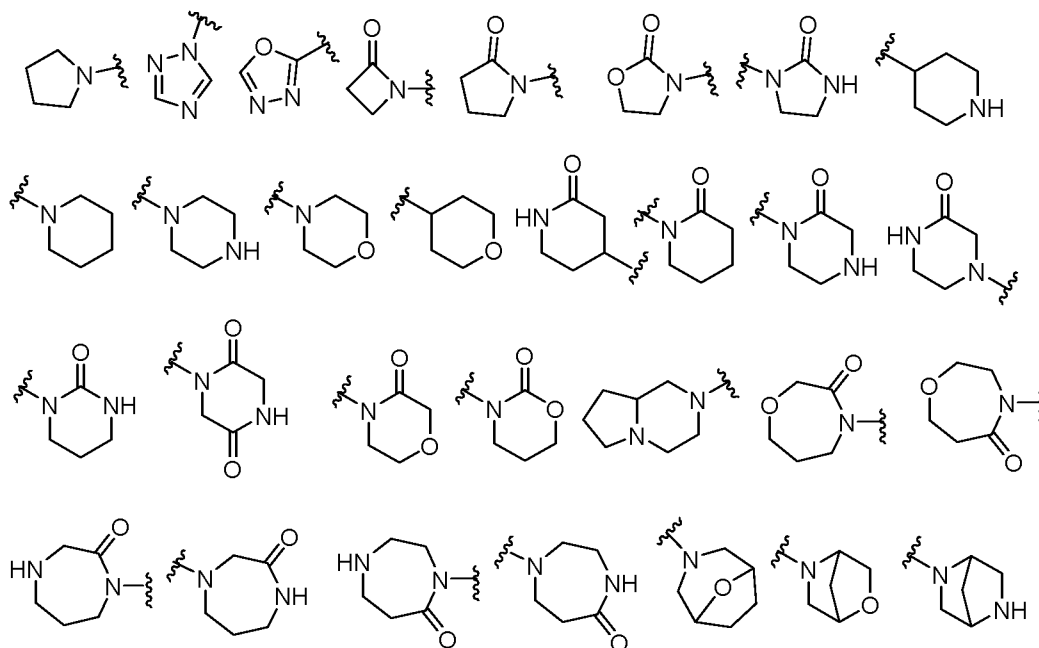
two R_2 attached to the same ring atom of ring B form 3-6 heterocyclyl (when ring B is 3-10 membered heterocyclyl) optionally substituted with one or more groups selected from halogen, $-OH$, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, C_{1-2} haloalkoxy, and NR_7R_8 ;

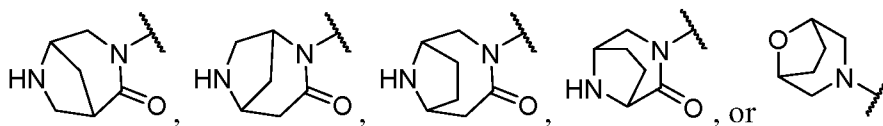
each instance of R_6 is independently H, C_{1-4} alkyl, C_{3-6} cycloalkyl, 3-7 membered heterocyclyl, phenyl, 5-6 membered heteroaryl, wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, 3-7 membered heterocyclyl, phenyl, 5-6 membered heteroaryl represented by R_6 is each optionally substituted with halogen, 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, and the remaining variables are as defined in the first, second, third, fourth, fifth, and/or sixth embodiment(s).

In an eighth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein R_1 is H, F, Cl, or CH_3 , and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, and/or seventh embodiment(s).

In a ninth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring B is

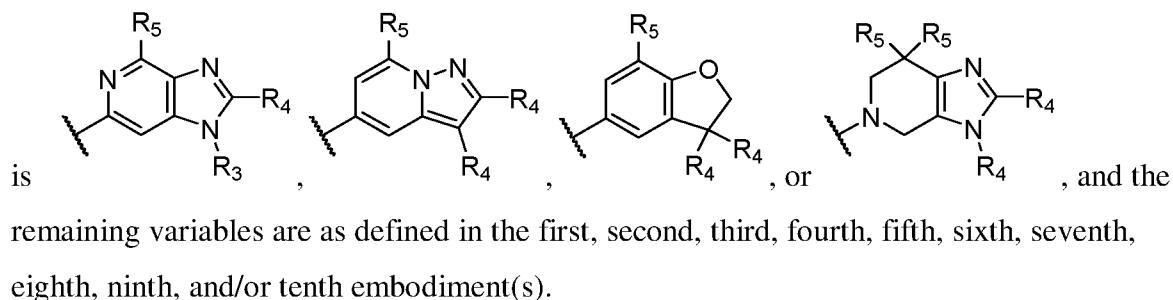




, each of which is optionally substituted with one or two R_2 groups, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, and/or eighth embodiment(s).

In a tenth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), 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, $-(CH_2)_nS(O)_2C_{1-4}$ alkyl, $-(CH_2)_nNR_7R_8$, C_{3-4} cycloalkyl, or 3-6 membered heterocyclyl; and n is 0, 1, or 2; or two R_2 attached to the same ring atom of ring B form 3-6 heterocyclyl when ring B is 4-7 membered heterocyclyl, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, and/or ninth embodiment(s).

In an eleventh embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring A



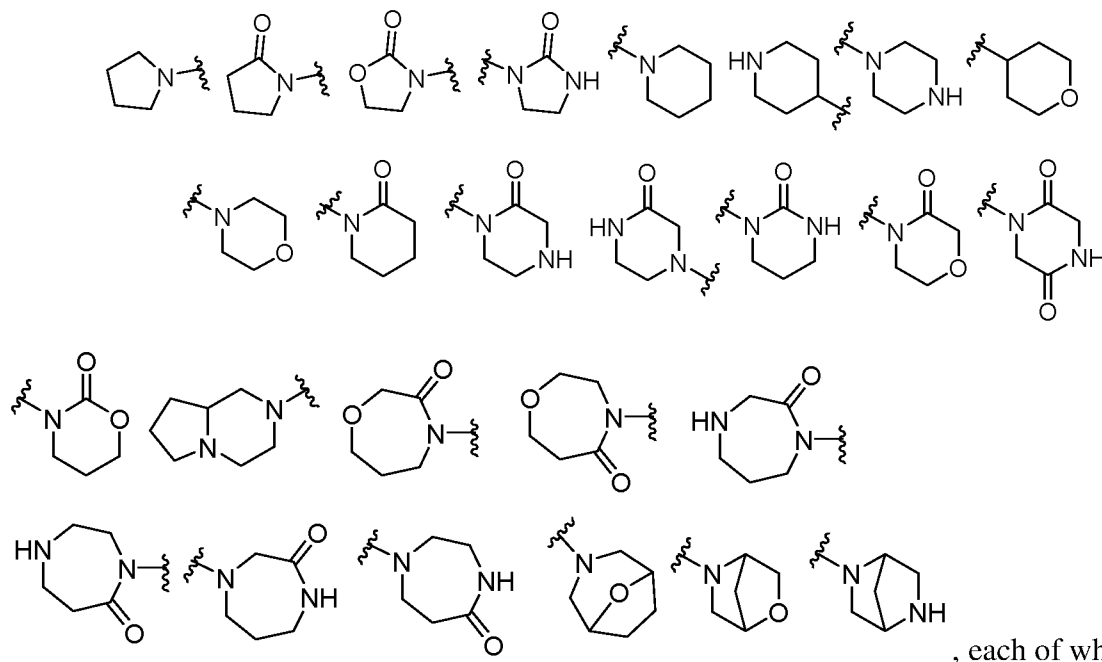
In a twelfth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein R_1 is H or F, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, and/or eleventh embodiment(s).

In a thirteenth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein each instance of R_3 is H, C_{1-3} alkyl optionally substituted with -OH, or C_{3-6} cycloalkyl optionally substituted with -OH; each instance of R_4 is H, halogen, C_{1-3} alkyl, C_{2-4} alkenyl, cyclopentyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl; and each instance of R_5 is H, F, CN, methoxy, $OCHF_2$, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, and/or twelfth embodiment(s).

In a fourteenth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein L is a

bond, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, and/or thirteenth embodiment(s).

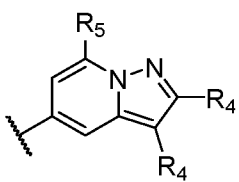
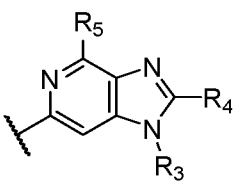
In a fifteenth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring B is



, each of which is optionally substituted with one or two R_2 groups, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, and/or fourteenth embodiment(s).

In a sixteenth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein each instance of R_2 is H, halogen, CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, NH_2 , $N(CH_3)_2$, NH cyclopropyl, $-(CH_2)_nS(O)_2C_{1-3}$ alkyl, cyclopropyl, azetidiny optionally substituted with F, oxetanyl, morpholinyl, piperidinyl, tetrahydro-2H-pyran, or two R_2 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, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, and/or fifteenth embodiment(s).

In a seventeenth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring A

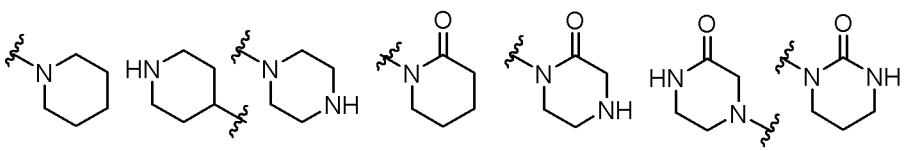
is  or , and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, and/or sixteenth embodiment(s).

In an eighteenth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein each instance of R_3 is H or C_{1-3} alkyl; each instance of R_4 is H or C_{1-3} alkyl; and each instance of R_5 is H, F, or OMe, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, and/or seventeenth embodiment(s).

In a nineteenth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein R_1 is H, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, and/or eighteenth embodiment(s).

In a twentieth embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring C is unsubstituted, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, and/or nineteenth embodiment(s).

In a twenty-first embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring B

is , each of which is optionally substituted with one or two R_2 groups, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, and/or twentieth embodiment(s).

In a twenty-second embodiment of the invention, the compound of structural formula (I), (II-A)-(II-J), or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein R_2 is H, halogen, CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, NH_2 , $N(CH_3)_2$,

NHcyclopropyl, and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, and/or twenty-first embodiment(s).

In one embodiment, the compound or a pharmaceutically acceptable salt, or a stereoisomer thereof, is selected from the compounds of Formulae (I), (II-A)-(II-J), in the examples.

Another aspect of the present disclosure relates to labeled compounds of the invention (radio-labeled, fluorescent-labeled, *etc.*) that would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating CDK in tissue samples, including human, and for identifying CDK ligands by inhibition binding of a labeled compound. Accordingly, the present disclosure includes such labeled compounds.

The present disclosure further includes isotopically-labeled compounds of the invention. An “isotopically” or “radio-labeled” compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (*i.e.*, naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^2H (also written as D for deuterium), ^3H (also written as T for tritium), ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}Cl , ^{82}Br , ^{75}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I and ^{131}I . The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound.

The present invention can further include synthetic methods for incorporating radio-isotopes into compounds of the invention. Synthetic methods for incorporating radio-isotopes into organic compounds are well known in the art, and an ordinary skill in the art will readily recognize the methods applicable for the compounds of invention.

A labeled compound of the invention can be used in a screening assay to identify/evaluate compounds. For example, a newly synthesized or identified compound (*i.e.*, test compound) which is labeled can be evaluated for its ability to bind a CDK by monitoring its concentration variation when contacting with the CDK, through tracking of the labeling. For example, a test compound (labeled) can be evaluated for its ability to reduce binding of another compound which is known to bind to a CDK (*i.e.*, standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the CDK directly correlates to its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the

concentration of the labeled standard compound is monitored in order to evaluate the competition between the standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

In one embodiment, the compound or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein one or more hydrogen atoms are replaced by deuterium.

4. *Treatable Diseases and Method of Treatment*

Certain compounds of the present invention are selective inhibitors of CDK2, CDK4, and/or CDK6, and are therefore useful in the treatment of a disease or disorder characterised by abnormal cell proliferation that can be inhibited by a reduced activity of CDK-cyclin complexes encompassing CDK2, CDK4, and/or CDK6.

In certain embodiments, compounds of the invention selectively inhibit CDK4/6 over CDK2, with a ratio of IC_{50} values for the latter (CDK2) against the former (CDK4/6) of at least about 10, 20, 50, 100, 200, 300, 400, 500, 800, 1,000, 2,000 or more.

In certain embodiments, compounds of the invention selectively inhibit CDK4 over CDK6, with a ratio of IC_{50} values for the latter (CDK6) against the former (CDK4) of at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 50 or more.

In certain embodiments, compounds of the invention selectively inhibit CDK2 over CDK4, with a ratio of IC_{50} values for the latter (CDK4) against the former (CDK2) of at least about 2, 5, 10, 15, 20, 40, 50, 60, 80, 100 or more.

In certain embodiments, compounds of the invention inhibits CDK2/4/6 with similar IC_{50} values, *e.g.*, IC_{50} values within 10-, 5-, 3-, or 2-fold. Such compounds of the invention are useful for treating cancers with cyclin D1 or E1 or E2 amplification or enhanced expression.

CDK2 is the catalytic subunit of the CDK-cyclin complex whose activity is restricted to the G1-S phase of the cell cycle, where cells make proteins necessary for mitosis and replicate their DNA. CDK2 is complexed with cyclin E or A. Cyclin E binds G1 phase CDK2, which is required for G1 to S phase transition. On the other hand, CDK2 binding with Cyclin A is required to progress through the S phase.

Although CDK2 is mostly dispensable in the cell cycle of normally functioning cells, it is critical to the abnormal growth processes of cancer cells. Overexpression of cyclin E occurs in many tumor cells, causing the cells to become dependent on CDK2 and cyclin E.

Abnormal cyclin E activity is observed in breast, lung, colorectal, gastric, and bone cancers, as well as in leukemia and lymphoma. Likewise, abnormal expression of cyclin A2 is associated with chromosomal instability and tumor proliferation, while inhibition leads to decreased tumor growth. Therefore, CDK2 and its cyclin binding partners represent possible therapeutic targets for new cancer therapeutics. Pre-clinical models have shown preliminary success in limiting tumor growth, and have also been observed to reduce side effects of current chemotherapy drugs.

For example, Caldon *et al.* (*Mol Cancer Ther* 11(7):1488-1499, 2012) reported that Cyclin E2 is included in several gene signatures that predict disease progression in either tamoxifen-resistant or metastatic breast cancer, and high expression of CycE2 was characteristic of the luminal B and HER2 subtypes of breast cancer and was strongly predictive of shorter distant metastasis-free survival following endocrine therapy. Further, tamoxifen-resistant (MCF-7 TAMR) breast cancer cells overexpressed cyclin E2; and expression of either cyclin E1 or E2 in T-47D breast cancer cells conferred acute antiestrogen resistance, suggesting that cyclin E overexpression contributes to the antiestrogen resistance of tamoxifen-resistant cells. Proliferation of tamoxifen-resistant cells was inhibited by RNAi-mediated knockdown of cyclin E1, cyclin E2, or CDK2. Besides, ectopic expression of cyclin E1 or E2 also reduced sensitivity to CDK4, but not CDK2, inhibition. Furthermore, CDK2 inhibition of E-cyclin overexpressing cells and tamoxifen-resistant cells restored sensitivity to tamoxifen or CDK4 inhibition.

These data demonstrate that Cyclin E2 overexpression is a potential mechanism of resistance to both endocrine therapy and CDK4 inhibition, and CDK2 inhibitors may in turn overcome such resistance, and may be beneficial as a component of combination therapies in endocrine-resistant disease as they effectively inhibit cyclin E1 and E2 overexpressing cells and enhance the efficacy of other therapeutics. Likewise, the subject compounds with potent inhibitory activities against both CDK2 and CDK4 are expected to be effective against cancer cells that are both non-resistant and resistant to endocrine therapy or CDK4 inhibition.

Thus in certain embodiments, the compounds of the invention may have potent inhibitory effects against both CDK2 and CDK4 (*e.g.*, independently <10 nM, < 5 nM, <1 nM level of IC₅₀ values), and thus are effective to treat tamoxifen-resistant or metastatic breast cancers, such as tamoxifen-resistant or metastatic breast cancers with CycE overexpression.

IC₅₀ values of the compounds of the invention against CDK2/4/6 can be measured

using, for example, the methods described in Examples 1-3 (incorporated herein by reference).

In particular, the compounds of the present invention are useful in the treatment of cancer. In other embodiments, the compounds of the present invention are useful in the treatment of chronic inflammation diseases such as arthritis and cystic fibrosis.

Thus in one aspect, the present invention provides a method of treating cancer, in particular the cancers described herein, in a mammal, comprising administering to a mammal in need of such treatment an effective amount of a compound of the present invention.

In a related aspect, the invention is directed to a use of a compound of the present invention in the manufacture of a medicament for treating cancer, in particular, the cancers described herein.

In another related aspect, the compounds of the present invention can be used in the manufacture of a medicament for the treatment of cancer, in particular, the cancers described herein.

In another related aspect, the invention provides a compound of the present invention for use in treating cancer, in particular, the cancers described herein.

According to any of the above related aspects of the invention, CDK4 and CDK6 may modulate their effects on the cell cycle partly through pRb phosphorylation. Thus, certain compounds of the present invention may inhibit pRb phosphorylation through inhibiting CDK4/6 activity, and thus inhibiting cell proliferation and/or tumor growth, in any cancer type where the cells are proliferating and contain a functional, intact Rb1 gene that encodes pRb.

Thus in certain embodiments, the compounds of the invention are useful in the treatment of pRb⁺ cancers, such as colorectal cancer, breast cancer, lung cancer, prostate cancer, chronic myeloid leukemia, acute myeloid leukemia (Fry *et al.*, *Mol. Cancer Ther.* 3(11):1427, 2004), mantle cell lymphoma (Marzec *et al.*, *Blood* 108(5):1744, 2006), ovarian cancer (Kim *et al.*, *Cancer Research* 54:605, 1994), pancreatic cancer (Schutte *et al.*, *Cancer Research* 57:3126, 1997), malignant melanoma and metastatic malignant melanoma (Maelandsmo *et al.*, *British Journal of Cancer* 73:909, 1996) in mammals. The compounds of the invention are also expected to be useful in the treatment of rhabdomyosarcoma (Saab *et al.*, *Mol. Cancer Ther.* 5(5):1299, 2006) and multiple myeloma (Baughn *et al.*, *Cancer Res.* 66(15):7661, 2006), including relapsed refractory multiple myeloma, in mammals (*e.g.*, human).

Meanwhile, Zhang *et al.* ([Nature dx.doi.org/10.1038/nature25015](https://doi.org/10.1038/nature25015), 2017) reported that inhibition of CDK4/6 *in vivo* may lead to decreased phosphorylation and therefore increased degradation of Cullin 3^{SPOP} E3 ligase (by APC/C^{Cdh1}), which in turn leads to increased PD-L1 levels on tumor cell surface, and reduced numbers of tumor-infiltrating lymphocytes (TILs) in mouse tumors and in primary human prostate cancer specimens. In other words, inhibition of CDK4/6 *in vivo* elevates PD-L1 protein levels, and contributes to increased resistance to immune checkpoint therapy targeting PD-1 (programmed cell death protein 1) and PD-L1 (ligand for PD-1). On the other hand, combining CDK4/6 inhibitor treatment with anti-PD-1 immunotherapy enhances tumor regression, and dramatically improves overall survival rates in mouse tumor models.

Thus in certain embodiments, the compounds of the invention can be used in combination with PD-1/PD-L1 immune checkpoint inhibitors to enhance therapeutic efficacy for human cancers.

PD-1 and PD-L1 inhibitors that can be used with the compounds of the invention are known in the art. PD-1 inhibitors include monoclonal antibodies or antigen binding fragment thereof specific for PD-1. Exemplary PD-1 inhibitors include Pembrolizumab (Keytruda), Nivolumab (Opdivo), and Cemiplimab (Libtayo). PD-L1 inhibitors include monoclonal antibodies or antigen binding fragment thereof specific for PD-L1. Exemplary PD-L1 inhibitors include Atezolizumab (Tecentriq), Avelumab (Bavencio), and Durvalumab (Imfinzi).

Additional immune checkpoint inhibitor that may be used with the compounds of the invention for enhancing therapeutic efficacy for human cancers include monoclonal antibodies or antigen binding fragments thereof specific for CTLA-4 such as Ipilimumab (Yervoy).

Further immune checkpoint inhibitor that may be used with the compounds of the invention for enhancing therapeutic efficacy for human cancers include bispecific monoclonal antibodies or antigen binding fragments thereof specific for PD-1 and PD-L1, or combination of monoclonal antibodies or antigen binding fragments thereof specific for PD-1 and PD-L1, or PD-1 and CTLA-4, etc.

In certain embodiments, the compounds of the invention can be used in combination with Tyr kinase inhibitor, *e.g.*, receptor Tyr kinase (RTK) inhibitors, to enhance therapeutic efficacy for human cancers. Exemplary Tyr kinase inhibitors include ALK inhibitors (such as Crizotinib, Ceritinib, Alectinib, Brigatinib), Bcr-Abl inhibitors (such as Bosutinib,

Dasatinib, Imatinib, Nilotinib, Ponatinib), BTK inhibitor (such as Ibrutinib), c-Met inhibitor (such as Crizotinib, Cabozantinib), EGFR inhibitor (such as Gefitinib, Erlotinib, Lapatinib, Vandetanib, Afatinib, Osimertinib), JAK inhibitor (such as Ruxolitinib, Tofacitinib), MEK1/2 inhibitor (such as Trametinib), PDGFR inhibitor (such as Axitinib, Gefitinib, Imatinib, Lenvatinib, Nintedanib, Pazopanib, Regorafenib, Sorafenib, Sunitinib), RET inhibitor (such as Vandetanib), Src family kinase inhibitors (such as Bosutinib, Dasatinib, Ponatinib, Vandetanib), and VEGFR family inhibitors (such as Axitinib, Lenvatinib, Nintedanib, Regorafenib, Pazopanib, Sorafenib, Sunitinib).

Additional suitable kinase inhibitors that can be used in combination with the subject compounds, as well as the treatable cancer indications, are described in Bhullar *et al.*, *Molecular Cancer* 17:48, 2018 (incorporated herein by reference in its entirety).

Further additional RTK inhibitors include monoclonal antibodies and antigen-binding fragments thereof, including the anti-EGFR mAb such as cetuximab (effective in treating, *e.g.*, lung, colorectal, and head and neck cancer), and the anti-HER2 mAb such as trastuzumab (effective to treat, for example, breast cancer).

In certain embodiments, the compounds of the invention can be used in combination with an antagonist of hormonal receptor signaling, such as the ones described before for breast cancer treatment.

Cancers treatable with the compounds of the invention include: Non-Hodgkin's lymphoma; malignant mesothelioma; non-small cell lung cancer; cholangiocarcinoma; soft tissue sarcoma; glioblastoma; (recurrent) brain tumor; brain metastases secondary to hormone receptor positive breast cancer, non-small cell lung cancer, melanoma (including melanoma positive for cyclin D1 expression); (recurrent or persistent) endometrial cancer; (recurrent or metastatic) Head and Neck Squamous Cell Carcinoma (HNSCC); hepatocellular carcinoma; esophageal squamous cell carcinoma (SCC); esophageal adenocarcinoma (ADC); renal cell carcinoma, and urothelial cancer.

In certain embodiments, the treatable cancers include: carcinoma of the bladder, breast, colon, kidney, epidermis, liver, lung (including SCLC and NSCLC), esophagus, 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; familial melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratoanthoma; thyroid follicular cancer; Kaposi's sarcoma,

squamous cancer, sarcoma; or a tumor of mesenchymal origin.

In certain embodiments, 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.

In certain embodiments, the tumor of the central or peripheral nervous system is astrocytoma, neuroblastoma, glioma or schwannoma.

In certain embodiments, the cancer is small cell lung cancer, non-small cell lung cancer, pancreatic cancer, breast cancer, glioblastoma multiforme, T cell ALL and mantle cell lymphoma.

In certain embodiments, the cancer is selected from the group consisting of: colorectal cancer, mantel cell lymphoma, breast cancer (including advanced or metastatic or recurrent breast cancer), pancreatic cancer, ovarian cancer, glioblastoma, acute myeloid leukemia, and lung cancer, especially NSCLC.

In certain embodiments, the cancer is NSCLC, pancreatic cancer, ovarian cancer or metastatic breast cancer, and the treatment comprising administering to a mammal in need thereof a therapeutically effective combination of a compound of the present invention and gemcitabine HCl.

In certain embodiments, the cancer is NSCLC, pancreatic cancer, ovarian cancer or metastatic breast cancer, wherein the medicament comprising the compound of the present invention also comprises gemcitabine HCl, or is to be administered simultaneously, separately or sequentially with gemcitabine HCl.

In certain embodiments, the compounds of the present invention can be used in combination with other agents for the treatment of NSCLC, pancreatic cancer, ovarian cancer and metastatic breast cancer. For example, the compound of the present invention may be used in simultaneous, separate or sequential combination with gemcitabine HCl in the treatment of NSCLC, pancreatic cancer, ovarian cancer or metastatic breast cancer.

In certain embodiments, the cancer is selected from the group consisting of colorectal cancer, glioblastoma, acute myeloid leukemia and lung cancer.

In certain embodiments, the cancer is glioblastoma or astrocytoma, and the treatment utilizes a therapeutically effective combination of a compound of the invention and temozolomide. The compound of the invention may be administered simultaneously,

separately or sequentially with temozolomide.

Breast Cancer Treatment

In certain embodiments, the compounds of the invention can be used to treat breast cancer.

Breast cancer presents a significant health burden worldwide, and it alone accounted for ~7% of all US cancer-related deaths in 2016. Of all breast cancers, about 75% are diagnosed as hormone receptor-positive (HR⁺) breast cancer, which expresses the estrogen receptor (ER) and/or the progesterone receptor (PgR), and is typically dependent on the ER signaling pathway for growth and survival. That is, the HR⁺ breast cancers harness the biological functions of the ER pathway to promote breast cancer growth, development, and progression. Meanwhile, the reliance of HR⁺ breast cancer on ER signaling made such breast cancer a therapeutic target for endocrine therapy agents that target the estrogen signaling pathway, such as aromatase inhibitors (AIs; including letrozole, anastrozole, and exemestane), selective ER modulators (tamoxifen), and selective ER down-regulators (fulvestrant), etc.

Although endocrine therapy makes up the treatment backbone for HR⁺ breast cancer, the efficacy of endocrine therapy is limited by high rates of both pre-existing *de novo* resistance, and resistance acquired during treatment, due to the presence of alternative survival or “escape” pathway. The ER pathway and many of the known escape pathways act through the cyclin D–CDK4/6–inhibitor of CDK4 (INK4)–retinoblastoma (Rb) pathway to promote tumor growth. As such, targeting both the ER and the cyclin D–CDK4/6–INK4–Rb pathways in combination usually lead to a more extensive inhibition of tumor growth and prevent the activation of escape pathways, precluding the development of endocrine therapy resistance. See Sammons *et al.*, *Current Cancer Drug Targets* 17:637-649, 2017.

Thus in certain embodiments, the breast cancer is a pRb⁺ breast cancer. In certain embodiments, the breast cancer is a hormone receptor (HR)-positive (*e.g.*, estrogen receptor positive (ER⁺), progesterone receptor positive (PR⁺), or ER⁺PR⁺), HER2/neu-negative cancer, including HR⁺HER2⁻ or ER⁺HER2⁻, advanced or metastatic or recurrent breast cancer. In certain embodiments, the HR⁺HER2⁻ or ER⁺HER2⁻ advanced or metastatic or recurrent breast cancer is in an adult woman, or a postmenopausal woman.

In certain embodiments, the compounds of the invention is either used alone, or used with an aromatase inhibitor (that inhibits estrogen production), to treat HR-positive, HER2-negative advanced or metastatic or recurrent breast cancer. In certain embodiments, the aromatase inhibitor temporarily inactivate aromatase (such as anastrozole (ARIMIDEX[®]) and

letrozole (FEMARA[®])). In certain embodiments, the aromatase inhibitor permanently inactivate aromatase (such as exemestane (AROMASIN[®])).

In certain embodiments, the compound(s) of the invention is used with a compound that interferes with estrogen's ability to stimulate the growth of breast cancer cells, such as a Selective Estrogen Receptor Modulator (SERM) that binds to the estrogen receptor to prevent estrogen binding, such as tamoxifen (NOLVADEX[®]) and toremifene (FARESTON[®]). Tamoxifen has been used for more than 30 years to treat HR⁺ breast cancer.

In certain embodiments, the compound(s) of the invention is used with a pure antiestrogen with no estrogen agonist activity, such as fulvestrant (FASLODEX[®]).

In certain embodiments, the HR-positive, HER2-negative advanced or metastatic or recurrent breast cancer is in a postmenopausal woman. In certain embodiments, the HR-positive, HER2-negative advanced or metastatic or recurrent breast cancer has progressed after taking therapy that alters a patient's hormones (*e.g.*, estrogen and/or progesterone), or has worsened after treatment with another hormone therapy.

In certain embodiments, the compound(s) of the invention is used in a patient undergoing ovarian ablation, or has received ovarian ablation. In certain embodiments, the ovarian ablation is through oophorectomy or radiation treatment.

In certain embodiments, the compound(s) of the invention is used with a compound that temporarily suppresses ovarian function (*e.g.*, estrogen and/or progesterone production). Such compound includes gonadotropin-releasing hormone (GnRH) agonists or luteinizing hormone-releasing hormone (LH-RH) agonists, including goserelin (ZOLADEX[®]) and leuprolide (LUPRON[®]).

In certain embodiments, the compound(s) of the invention is used with a compound that inhibits CYP3A4, such as ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin, telithromycin, chloramphenicol, ketoconazole, itraconazole, posaconazole, voriconazole, nefazodone, cobicistat, amiodarone, aprepitant, verapamil, diltiazem, erythromycin, fluconazole, miconazole, bergamottin, cimetidine, ciprofloxacin, cyclosporine, donedarone, fluvoxamine, imatinib, Valerian, buprenorphine, cafestol, cilostazol, fosaprepitant, gabapentin, lomitapide, orphenadrine, ranitidine, ranolazine, tacrolimus, ticagrelor, valproic acid, amlodipine, cannabidiol, dithiocarbamate, mifepristone, norfloxacin, delavirdine, gestodene, mibefradil, star fruit, milk thistle, niacinamide, ginkgo biloba, piperine, isoniazid, and quercetin.

In certain embodiments, the compound(s) of the invention is used with an inhibitor of

IGF-1/IGF-2, such as a monoclonal antibody or an antigen-binding fragment thereof against IGF-1/IGF-2. Exemplary antibodies include xentuzumab, a humanized IgG1 mAb.

In certain embodiments, the compound(s) of the invention is used with a compound that inhibits PI3K. It is believed that inhibition of PI3K reduces the levels of cyclin D1 and other G1-S cyclins, abolishes pRb phosphorylation, and inhibits activation of S-phase transcriptional programs. Representative PI3K inhibitors for use with the compounds of the invention includes idelalisib, copanlisib, duvelisib, taselisib, perifosine, buparlisib, alpelisib, umbralisib, copanlisib, dactolisib, and voxalisib.

In certain embodiments, the mammal to be treated is a human, such as an adult woman having breast cancer (*e.g.*, postmenopausal woman or adult woman having hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic or recurrent breast cancer that has progressed after taking therapy that alters a patient's hormones).

Additionally, certain compounds of the present invention exhibit the advantageous property that they are able to cross the blood-brain barrier. Such compounds are therefore able to penetrate the brain and are thus useful in the treatment of primary and metastatic brain tumors where the cells are proliferating and contain a functional, intact Rb1 gene. Examples of such pRb⁺ brain tumors include glioblastoma, as well as medulloblastoma and astrocytoma (Lee *et al.*, Science 235:1394, 1987).

Temozolomide is a cytotoxic, DNA alkylating agent used for the treatment of brain tumors including glioblastoma and astrocytoma (Friedman *et al.*, Clin. Cancer Res. 6(7):2585-2597, 2000) including brain metastases from melanoma, breast cancer and NSCLC (Siena *et al.*, Annals of Oncology, doi:10.1093/annonc/mdp343, 2009). Temozolomide interacts with DNA causing chemical modification/damage (Marchesi *et al.*, Pharmacol. Res. 56(4):275-287, 2007). Thus, in some embodiments, the compounds of the present invention can be used in combination with temozolomide for the treatment of primary and metastatic pRb⁺ brain tumors such as glioblastoma and astrocytoma, for example, where such metastases are derived from melanoma, breast cancer or NSCLC.

5. *Pharmaceutical Compositions*

The invention provides pharmaceutical compositions which comprise any one of the compounds described herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients.

“Pharmaceutically acceptable excipient” and “pharmaceutically acceptable carrier” refer to a substance that aids the formulation and/or administration of an active agent to and/or absorption by a subject and can be included in the compositions of the present disclosure without causing a significant adverse toxicological effect on the subject. Non-limiting examples of pharmaceutically acceptable carriers and excipients include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer’s solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with or interfere with the activity of the compounds provided herein. One of ordinary skill in the art will recognize that other pharmaceutical carriers and excipients are suitable for use with disclosed compounds.

These compositions optionally further comprise one or more additional therapeutic agents. Alternatively, a compound of the invention may be administered to a patient in need thereof in combination with the administration of one or more other therapeutic regimens (*e.g.* Gleevec or other kinase inhibitors, interferon, bone marrow transplant, farnesyl transferase inhibitors, bisphosphonates, thalidomide, cancer vaccines, hormonal therapy, antibodies, radiation, *etc.*). For example, additional therapeutic agents for conjoint administration or inclusion in a pharmaceutical composition with a compound of this invention may be another one or more anticancer agents.

As described herein, the compositions of the present invention comprise a compound of the invention together with a pharmaceutically acceptable carrier, which, as used herein, includes any and all solvents, diluents, or other vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington’s Pharmaceutical Sciences, Fifteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1975) discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other

component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition.

6. *Formulations*

This invention also encompasses a class of compositions comprising the active compounds of this invention in association with one or more pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients.

In certain embodiments, the invention provides a pharmaceutical formulation for treating cancer, in particular the cancers described herein, comprising a compound of the present invention or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

In certain embodiments, the invention provides a pharmaceutical formulation for treating a cancer selected from the group consisting of colorectal cancer, mantle cell lymphoma, breast cancer (including ER⁺HER2⁻ advanced or metastatic or recurrent breast cancer in an adult woman, or a postmenopausal woman), glioblastoma, acute myeloid leukemia and lung cancer, especially NSCLC, comprising a compound of the present invention or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

In certain embodiments, the invention provides a pharmaceutical formulation for treating glioblastoma or astrocytoma, comprising a compound of the invention and temozolomide, together with a pharmaceutically acceptable carrier.

In certain embodiments, the invention also provides a pharmaceutical formulation,

comprising a compound of the invention or a pharmaceutically acceptable salt thereof and temozolomide, together with a pharmaceutically acceptable carrier, diluent, or excipient.

In certain embodiments, the invention provides a pharmaceutical formulation for treating NSCLC, pancreatic cancer, ovarian cancer or metastatic breast cancer (including ER⁺HER2⁻ advanced or metastatic or recurrent breast cancer in an adult woman, or a postmenopausal woman), comprising a compound of the invention and gemcitabine HCl, together with a pharmaceutically acceptable carrier.

In certain embodiments, the invention also provides a pharmaceutical formulation, comprising a compound of the invention or a pharmaceutically acceptable salt thereof and gemcitabine HCl, together with a pharmaceutically acceptable carrier, diluent, or excipient.

The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly, intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient.

Examples of such dosage units are tablets or capsules. For example, a suitable daily dose for a human or other mammal may vary depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The amount of compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary

widely, but can be determined routinely using standard methods. As mentioned previously, the daily dose can be given in one administration or may be divided between 2, 3, 4 or more administrations.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants, excipients or carriers appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (*e.g.*, liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, *e.g.*, from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

The compounds of this invention can also be administered by a transdermal device. Preferably transdermal administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered - continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner.

While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without

stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required.

Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients.

The active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (*i.e.* Captisol), cosolvent solubilization (*i.e.* propylene glycol) or micellar solubilization (*i.e.*

Tween 80).

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers *etc.* Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents. Pharmaceutical compositions of this invention comprise a compound of the formulas described herein or a pharmaceutically acceptable salt thereof; an additional agent selected from a kinase inhibitory agent (small molecule, polypeptide, antibody, *etc.*), an immunosuppressant, an anticancer agent, an anti-viral agent, antiinflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation compound; and any pharmaceutically acceptable carrier, adjuvant or vehicle.

Alternate compositions of this invention comprise a compound of the formulae described herein or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier, adjuvant or vehicle. Such compositions may optionally comprise one or more additional therapeutic agents, including, for example, kinase inhibitory agents (small molecule, polypeptide, antibody, *etc.*), immunosuppressants, anti-cancer agents, anti-viral agents, antiinflammatory agents, antifungal agents, antibiotics, or anti-vascular hyperproliferation compounds.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or

adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, selfemulsifying drug delivery systems (SEDDS) such as d-atocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α -, β -, and γ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2 and 3-hydroxypropyl-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

The pharmaceutical compositions may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents.

If desired, certain sweetening, flavoring and/or coloring agents may be added. The pharmaceutical compositions may comprise formulations utilizing liposome or microencapsulation techniques, various examples of which are known in the art.

The pharmaceutical compositions may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability,

fluorocarbons, and/or other solubilizing or dispersing agents, examples of which are also well known in the art.

7. *Treatment Kits*

One aspect of the present invention relates to a kit for conveniently and effectively carrying out the methods or uses in accordance with the present invention. In general, the pharmaceutical pack or kit comprises one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages, and may also include a card having the dosages oriented in the order of their intended use. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The following representative examples contain important additional information, exemplification and guidance which can be adapted to the practice of this invention in its various embodiments and the equivalents thereof. These examples are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit its scope. Indeed, various modifications of the invention, and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art upon review of this document, including the examples which follow and the references to the scientific and patent literature cited herein.

The contents of the cited references are incorporated herein by reference to help illustrate the state of the art.

In addition, for purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry," Thomas Sorrell, University Science Books, Sausalito: 1999, and "Organic Chemistry," Morrison & Boyd (3d Ed), the entire contents of both of which are incorporated herein by reference.

8. *Synthesis Schemes*

The compounds of Formula I can be prepared by one of ordinary skill in the art following art recognized techniques and procedures. More specifically, compounds of Formula I can be prepared as set forth in the schemes, methods, and examples set forth below. It will be recognized by one of skill in the art that the individual steps in the following schemes may be varied to provide the compounds of Formula I. The reagents and starting materials are readily available to one of ordinary skill in the art. All substituents, unless otherwise specified, are as previously defined.

EXAMPLES

Biological Example 1. Assay for Inhibition of CDK4/CyclinD1

The CDK4 enzyme assay for IC₅₀ determination was performed as follows. Microfluidic kinase detection technology (Caliper) was used to monitor the phosphorylation of peptide substrate by CDK4/CyclinD1. The total reaction volume was 15 μ L containing buffer A (100 mM HEPES (pH 7.5), 0.1% BSA, 0.01% Triton X-100, 1 mM DTT, 10 mM MgCl₂, 10 μ M Sodium Orthovanadate, 10 μ M Beta-Glycerophosphate), 200 μ M ATP, 1 nM CDK4/CyclinD1 (Thermofisher, PR8064A), 1 μ M FL-34 (5-FAM-RRRFRPASPLRGPPK), and the test compound at appropriate dilutions in DMSO. All components were added to the 384-well plate (Corning, 4514), and incubated at Room Temperature for 3 hours. The reaction was terminated by addition of 15 μ L Stop Buffer (180 mM HEPES (pH 7.5), 20 mM EDTA, Coating-3 reagent (PerkinElmer, 760050)). The plate was then loaded on Caliper EZ Reader (EZ Reader II, PerkinElmer, HD-4HYSG2772), and the reaction mixtures including substrate and product were sipped into the microfluidic chip for separation and detection. The IC₅₀ values of the test compound were determined by fitting the inhibition curves by 4 parameter sigmoidal dose-response model using the Xlfit5/GraphPad Prism 5 software.

Biological Example 2. Assay for Inhibition of CDK6/CyclinD3

The CDK6 enzyme assay for IC₅₀ determination was performed as follows. Microfluidic kinase detection technology (Caliper) was used to monitor the phosphorylation of peptide substrate by CDK6/CyclinD3. The total reaction volume is 15 μ L containing buffer A (100 mM HEPES (pH 7.5), 0.1% BSA, 0.01% Triton X-100, 1 mM DTT, 10 mM

MgCl₂, 10 μM Sodium Orthovanadate, 10 μM Beta-Glycerophosphate), 300 μM ATP, 2 nM CDK6/CyclinD3 (Carna, 04-107), 1 μM FL-34 (5-FAM-RRRFRPASPLRGPPK), and the test compound at appropriate dilutions in DMSO. All components were added to the 384-well plate (Corning, 4514), and incubated at Room Temperature for 3 hours. The reaction was terminated by addition of 15 μL Stop Buffer (180 mM HEPES (pH 7.5), 20 mM EDTA, Coating-3 reagent (PerkinElmer, 760050)). The plate was then loaded on Caliper EZ Reader (EZ Reader II, PerkinElmer, HD-4HYSG2772), and the reaction mixtures including substrate and product were sipped into the microfluidic chip for separation and detection. The IC₅₀ values of the test compound were determined by fitting the inhibition curves by 4 parameter sigmoidal dose-response model using the Xlfit5/GraphPad Prism 5 software.

Biological Example 3. Assay for Inhibition of CDK2/CyclinE1

The CDK2 enzyme assay for IC₅₀ determination was performed as follows. Microfluidic kinase detection technology (Caliper) was used to monitor the phosphorylation of peptide substrate by CDK2/CyclinE1. The total reaction volume was 15 μL containing buffer A (100 mM HEPES (pH 7.5), 0.1% BSA, 0.01% Triton X-100, 1 mM DTT, 10 mM MgCl₂, 10 μM Sodium Orthovanadate, 10 μM Beta-Glycerophosphate), 100 μM ATP, 5 nM CDK2/CyclinE1 (SignalChem, C29-18G), 5 μM FL-18 (5-FAM-QSPKKG-NH₂), and the test compound at appropriate dilutions in DMSO. All components were added to the 384-well plate (Corning, 4514), and incubate at Room Temperature for 3 hours. The reaction was terminated by addition of 15 μL Stop Buffer (180 mM HEPES (pH 7.5), 20 mM EDTA, Coating-3 reagent (PerkinElmer, 760050)). The plate was loaded on Caliper EZ Reader (EZ Reader II, PerkinElmer, HD-4HYSG2772), and the reaction mixtures including substrate and product were sipped into the microfluidic chip for separation and detection. The IC₅₀ values of the test compound were determined by fitting the inhibition curves by 4 parameter sigmoidal dose-response model using the Xlfit5/GraphPad Prism 5 software.

The IC₅₀ values of each exemplified compound against CDK2, CDK4 and CDK6 are provided in the synthetic examples below. The IC₅₀ values are indicated as "A," "B," "C," and "D," for values less than or equal to 10 nM; less than or equal to 100 nM; less than or equal to 1 μM; and greater than 1 μM, respectively.

Biological Example 4. Anti-proliferation Assay in T47D Cell

T47D is a human breast cancer cell line commonly used in biomedical research involving the hormonal expression of cancer cells. T47D cells are distinct from other human breast cancer cells in that their progesterone receptors (PR) are not regulated by estradiol, a hormone that is abundant within the cells themselves. T47D cells have been employed in studies of the effects of progesterone on breast cancer and the corresponding transcriptional regulation caused by introduced drugs. The cells have been noted to be extremely resistant to estrogens and antiestrogens.

T47D breast cancer cells from American Type Culture Collection (ATCC, HTB-133) were plated at 3000 cells/well in 96-well plates, and were incubated in RPMI 1640 medium (Gibco, 31800105) with 10% Fetal Bovine Serum (FBS, Biowest, FB-1058) at 37 °C, 5% CO₂. After overnight incubation, baseline values were measured of the samples from one plate using Cyquant reagent (Invitrogen, C35011) following manufacturer's recommendations. Cells were incubated with the detection reagent for 1 hour at 37 °C, and then the fluorescence was measured with excitation at 485 nm and emission at 535 nm using Spectra Max M5 (Molecular Devices, HD-4HYSG3196). Other plates were dosed with compounds at a ten-point dose concentration from 10 µM to 0.51 nM in a 3-fold dilution scheme. On day 6 after compound addition, Cyquant reagent was added and the fluorescence was measured using Spectra Max M5. The IC₅₀ values of the test compound's anti-proliferation activity were determined from the baseline subtracted viability readout curve using Xlfit5/GraphPad Prism 5 software.

Biological Example 5. Inhibition of Phosphorylation of Retinoblastoma Protein (pRb) in T47D Cell

T47D breast cancer cells from American Type Culture Collection (ATCC, HTB-133) were plated at 40,000 cells/well in 96-well plates, and were incubated in RPMI 1640 medium (Gibco, 31800105) with 10% Fetal Bovine Serum (FBS, Biowest, FB-1058). Cells were then allowed to adhere overnight at 37 °C, 5% CO₂. The following day, compounds were titrated in a 3-fold dilution scheme, and the highest compound concentration tested was 10 µM. After 24 hours incubation with compounds, cells were lysed in ice-cold lysis buffer containing phosphatase inhibitor cocktail and 1 mM PMSF. Cell lysates (50 µL /well) were then transferred to ELISA plates (pRb Ser807/811 ELISA kit, Cell Signaling, 13152 or pRb

Ser780 ELISA kit, Cell Signaling, 13016)). Plates were incubated overnight at 4 °C, with constant slow speed shaking. After incubation, plates were washed following manufacturer's recommendations, and then 100 µL reconstituted detection antibody was added to each well and incubated for 1 hour at 37 °C. After incubation, plates were washed, and then 100 µL reconstituted HRP-linked secondary antibody was added to each well and incubated for 30 mins at 37 °C. After incubation, plates were washed. Then, 100 µL TMB substrate was added to each well and incubated for 10 min at 37 °C or 30 min at 25 °C. Finally, 100 µL of STOP solution was added to each well and mixed gently for a few seconds. Plates were read on the Envision plate reader (PerkinElmer, 2104-0010) using the 96-well luminescence mode. IC₅₀ values were calculated using 4 parameter sigmoidal dose-response model of Xlfit5/GraphPad Prism 5 software.

The cellular data obtained from biological examples 4 and 5 are listed in the Table A below. The IC₅₀ values are indicated as "++++", for values less than or equal to 100 nM; "+++ ", for values less than or equal to 500 nM; "++", for values less than or equal to 1 µM; and "+", for values greater than 1 µM, respectively.

Synthetic Examples

Equipment Description

¹H NMR spectra were recorded on a Bruker Ascend 400 spectrometer. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).

The analytical low-resolution mass spectra (MS) were recorded on Waters ACQUITY UPLC with SQ Detectors using a Waters CORTECS C18+, 2.7 µm 4.6×30 mm using a gradient elution method.

Solvent A: 0.1% formic acid (FA) in water

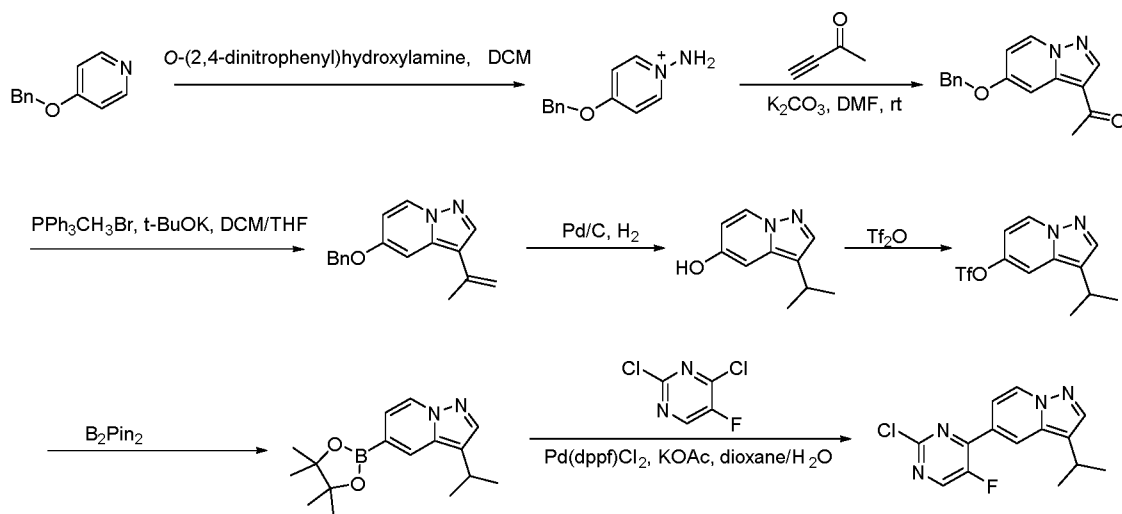
Solvent B: 0.1% FA in acetonitrile

5% ACN to 95% ACN in 1.0 min, hold 1.0 min,

Total 2.5 min; Flow rate: 1.8 mL/min; Column Temp 40 degree.

Intermediate

Intermediate 1



Step 1

To a solution of 4-benzyloxypyridine (185 mg, 998 μmol) in DCM (10 mL) was added amino 2,4,6-trimethylbenzenesulfonate (236 mg, 1.1 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 14 h. The mixture was concentrated under reduced pressure to get crude desired product (400 mg, 99% yield) as colorless oil. LC-MS: m/z 202 $[\text{M}+\text{H}]^+$.

Step 2

To a solution of 4-benzyloxypyridin-1-ium-1-amine (187 mg, 929 μmol) in DMF (10 mL) was added Cs_2CO_3 (192 mg, 1.4 mmol) and but-3-yn-2-one (94 mg, 1.4 mmol). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with water (50 mL) and extracted with DCM (2×25 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (eluting with PE/EA=10/1) to get desired product (90 mg, 35% yield) as yellow solid. LC-MS: m/z 267 $[\text{M}+\text{H}]^+$.

Step 3

To a solution of methyl(triphenyl)phosphonium bromide (241 mg, 675 μmol) in THF (10 mL) was added butyllithium (43.3 mg, 675 μmol) dropwise under N_2 at -20 °C. The reaction was stirred at -20 °C for 1 h. Then a solution of 1-(5-benzyloxypyrazolo[1,5-a]pyridin-3-yl)ethanone (90 mg, 338 μmol) in THF (15 mL) was added dropwise at -20 °C. The reaction mixture was stirred at 10 °C for 3 h. The reaction mixture was quenched with MeOH (3 mL)

and concentrated under reduced pressure. The residue was purified by prep-HPLC (eluting with PE: EA =1/1) to get crude desired product (41.0 mg, 46% yield) as yellow solid. LC-MS: m/z 265 [M+H]⁺.

Step 4

To a solution of 5-benzyloxy-3-isopropenyl-pyrazolo[1,5-a] pyridine (600 mg, 2.3 mmol) in methanol (50 mL) was added Pd/C (60 mg). The reaction mixture was stirred at 30 °C under H₂ for 48 h. The reaction mixture was filtrated and concentrated under reduced pressure to get desired product (380 mg, 95% yield) as yellow solid. LC-MS: m/z 177 [M+H]⁺.

Step 5

To a solution of 3-isopropylpyrazolo[1,5-a] pyridin-5-ol (650 mg, 3.7 mmol) and DIPEA (410 mg, 4.1 mmol) in DCM (15 mL) was added Tf₂O (1.1 g, 4.1 mmol) under N₂ at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was washed with brine (15 mL) and dried over Na₂SO₄. The organic layer was filtrated, and the filtrate was concentrated to get desired product (1.1 g, 92% yield) as colorless oil. LC-MS: m/z 309 [M+H]⁺.

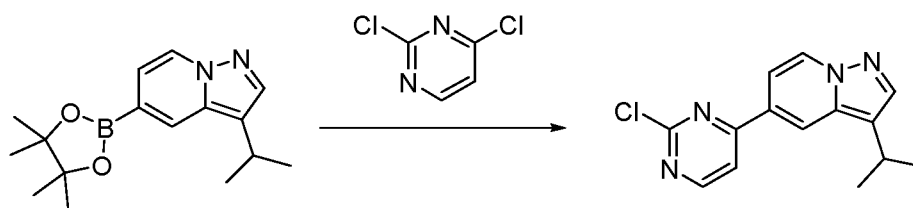
Step 6

To a solution of (3-isopropylpyrazolo[1,5-a]pyridin-5-yl) trifluoromethanesulfonate (1.1 g, 3.4 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.3 g, 5.1 mmol) in dioxane (10 mL) were added Pd(dppf)Cl₂ (249 mg, 340 μmol) and KOAc (1.0 g, 10.2 mmol). The reaction mixture was stirred at 110 °C for 2 h under N₂. The mixture was filtrated, and the filtrate was concentrated under reduced pressure to obtained crude desired product (950 mg, 97% yield) as dark solid. LC-MS: m/z 287 [M+H]⁺.

Step 7

To a solution of 3-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (950 mg, 3.3 mmol) and 2,4-dichloro-5-fluoro-pyrimidine (665 mg, 4.0 mmol) in H₂O (1 mL) and 1,4-dioxane (15 mL) were added Na₂CO₃ (1.2 g, 10.0 mmol) and Pd(dppf)Cl₂ (242 mg, 332 μmol). The mixture was stirred under N₂ at 110 °C for 6 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (20 g silica gel column, PE/EA with EA 0-50%) to afford desired product (650 mg, 67% yield) as yellow solid. LC-MS: m/z 291 [M+H]⁺.

Intermediate 2

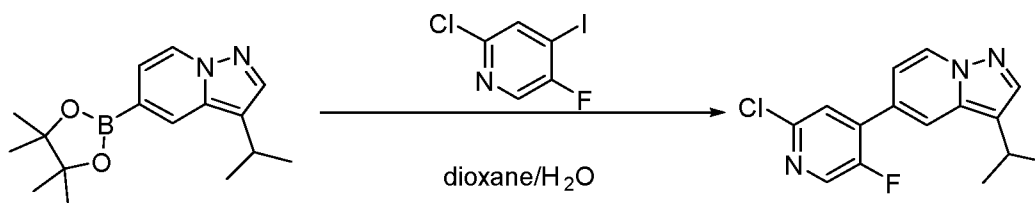


To a solution of 3-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (3.5 g, 12.2 mmol) and 2,4-dichloropyrimidine (2.7 g, 18.4 mmol) in water (3 mL) and 1,4-dioxane (60 mL) were added Pd(dppf)Cl₂ (0.9 g, 1.2 mmol) and Na₂CO₃ (1.52 g, 14 mmol). The reaction mixture was stirred under N₂ at 110 °C for 6 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (20 g silica gel column, PE with EA 0-50%) to afford desired product (2.1 g, 62% yield) as yellow solid. LC-MS: m/z 273 [M+H]⁺.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

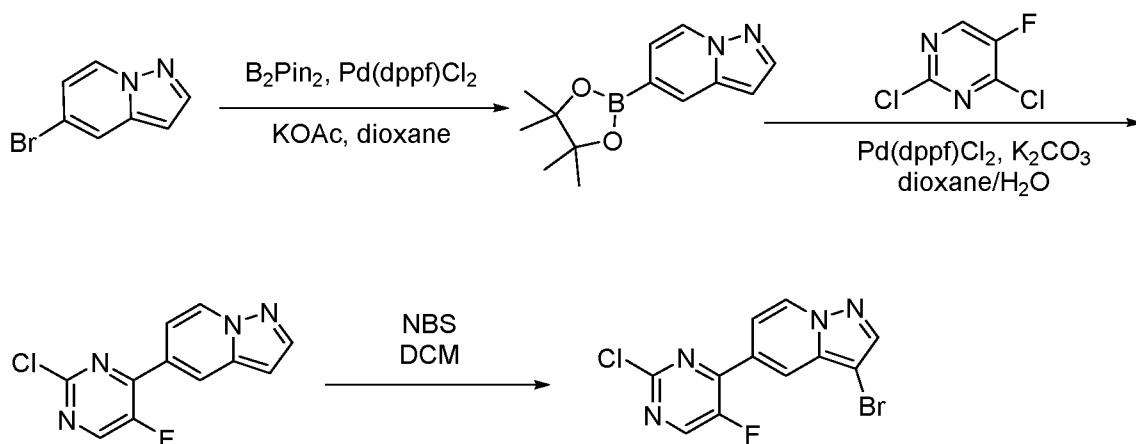
ID	Structure	LC-MS: m/z [M+H] ⁺
Intermediate 3		321
Intermediate 4		305

Intermediate 5



To a solution of 3-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (200 mg, 698 μ mol) and 2-chloro-5-fluoro-4-iodo-pyridine (269 mg, 1.1 mmol) in H₂O (1 mL) and 1,4-dioxane (20 mL) were added Na₂CO₃ (260 mg, 2.1 mmol) and Pd(dppf)Cl₂ (51.1 mg, 69.9 μ mol). The reaction mixture was stirred under N₂ at 110 °C for 6 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (20 g silica gel column, PE/EA with EA 0-50%) to afford desired product (140 mg, 69% yield) as yellow solid. LC-MS: m/z 290 [M+H]⁺.

Intermediate 6



Step 1

To a solution of 5-bromopyrazolo[1,5-a]pyridine (0.9 g, 4.6 mmol) in dried dioxane (40 mL) was added B₂Pin₂ (1.8 g, 6.9 mmol), Pd(dppf)Cl₂ (0.7 g, 0.9 mmol) and potassium acetate (1.4 g, 13.9 mmol). The mixture was stirred at 110 °C for 8 hours in a nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0–50% Petroleum ether / EtOAc) to afford desired product (1.1 g, 75% yield) as a white solid. LC-MS: m/z 245 [M+H]⁺.

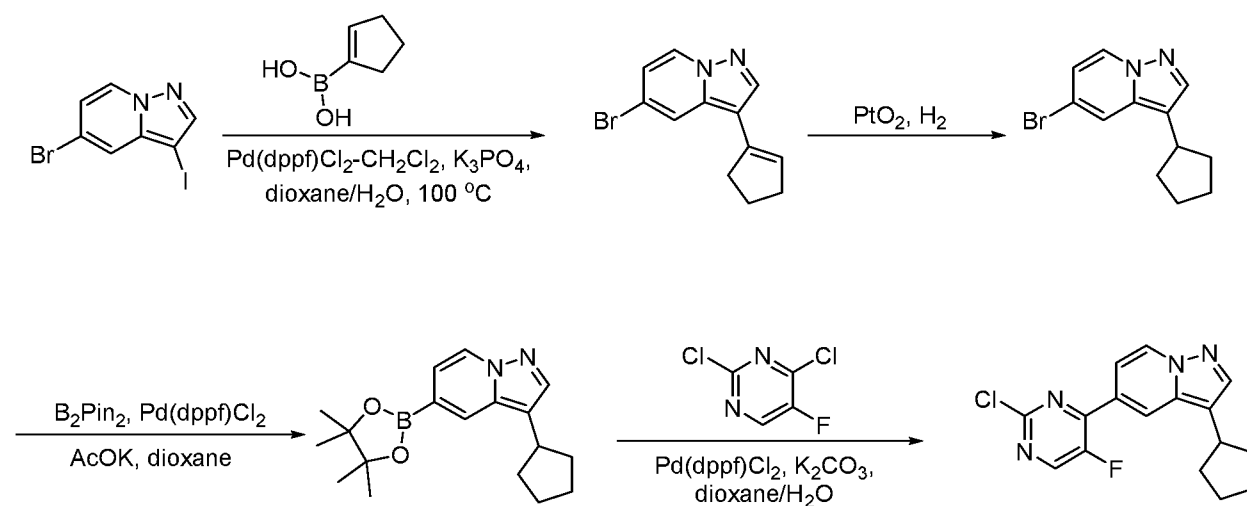
Step 2

To a solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (1.0 g, 4.0 mmol) in dioxane (45 mL) was added 2,4-dichloro-5-fluoropyrimidine (1.0 g, 6.0 mmol), Pd(dppf)Cl₂ (0.6 g, 0.8 mmol) and K₂CO₃ (1.7 g, 12.0 mmol). Then 5 mL H₂O was added. The mixture was stirred at 110 °C for 8 hours. The mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0–50% EtOAc in petroleum ether) to afford desired product (0.7 g, 66% yield) as a white solid. LC-MS: m/z 249 [M+H]⁺.

Step 3

To a solution of 5-(2-chloro-5-fluoropyrimidin-4-yl) pyrazolo[1,5-a] pyridine (610 mg, 2.5 mmol) in DCM (20 mL) was added NBS (482 mg, 2.7 mmol). The mixture was stirred at 25 °C for 4 hours. The mixture was concentrated under reduced and purified by silica gel chromatography (0–50% EtOAc/PE) to afford desired product (680 mg, 84% yield) as a white solid. LC-MS: m/z 327 $[M+H]^+$.

Intermediate 7



Step 1

To a solution of 5-bromo-3-iodo-pyrazolo[1,5-a]pyridine (1.0 g, 3.1 mmol) and cyclopent-1-en-1-ylboronic acid (0.4 g, 3.4 mmol) in dioxane (20 mL) and water (5 mL) were added cyclopentyl(diphenyl)phosphane dichloromethane dichloropalladium iron (0.8 g, 0.9 mmol), tripotassium phosphate (2.0 g, 9.3 mmol). The reaction mixture was stirred at 100 °C under N_2 atmosphere for 5 hours. The reaction mixture was extracted with EtOAc (3×10 mL). The organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4 , it was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography to afford desired product (0.3 g, 38% yield) as a white solid. LC-MS: m/z 265.1 $[M+H]^+$.

Step 2

To a solution of 5-bromo-3-(cyclopent-1-en-1-yl) pyrazolo[1,5-a] pyridine (270 mg, 1.0 mmol) in methanol (10 mL) was added PtO_2 (46.6 mg, 205.2 μ mol). The mixture was stirred at 25 °C under hydrogen atmosphere for 2 hours. The mixture was filtered through a Celite pad.

The filtrate was concentrated to afford desired product (190 mg, 69% yield) as a white solid, which was used directly in the next step without further purification. LC-MS: m/z 267.1 $[M+H]^+$.

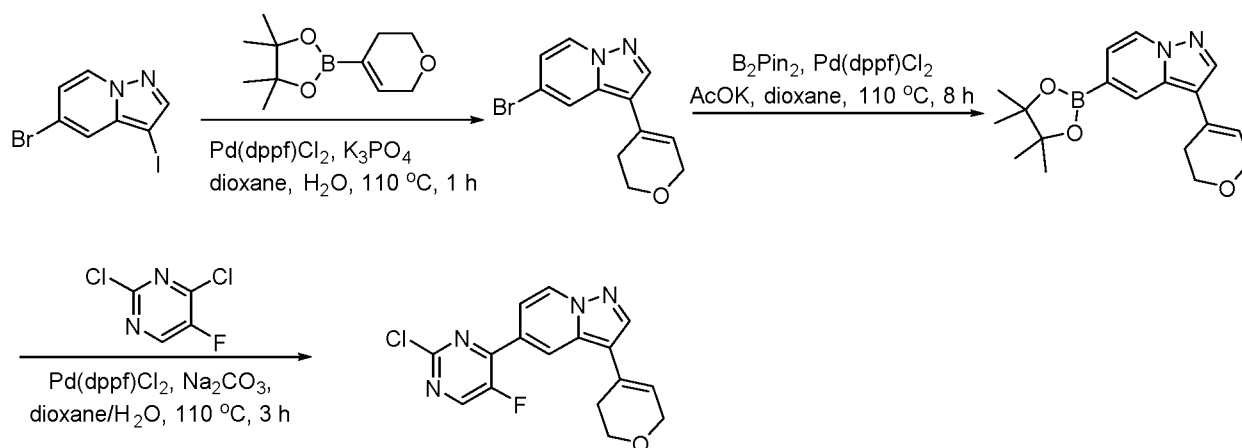
Step 3

To a stirred solution of 5-bromo-3-cyclopentyl-pyrazolo[1,5-a]pyridine (210 mg, 792 μ mol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (301 mg, 1.2 mmol) at 25 °C were added cyclopentyl (diphenyl) phosphane dichloropalladium iron (57.9 mg, 79.2 μ mol) and potassium acetate (233 mg, 2.4 mmol). The reaction mixture was stirred at 110 °C for 2 hours. The mixture was filtered and concentrated in vacuo to afford desired product as a black solid, which was used directly in the next step without further purification. LC-MS: m/z 313.1 $[M+H]^+$.

Step 4

To a mixture of 3-cyclopentyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (210 mg, 672 μ mol) and 2,4-dichloro-5-fluoro-pyrimidine (134 mg, 807 μ mol) in dioxane (5 mL) and water (1 mL) were added cyclopentyl(diphenyl)phosphane dichloropalladium iron (49.2 mg, 67.2 μ mol), dipotassium carbonate (278 mg, 2.0 mmol). The resulting mixture was stirred under N_2 atmosphere at 105 °C for 3 hours. The reaction mixture was diluted with water (10 mL) and then extracted with EtOAc (3×10 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4 , it was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography to afford desired product (40 mg, 19% yield) as a white solid. LC-MS: m/z 317.1 $[M+H]^+$.

Intermediate 8



Step 1

To a solution of 5-bromo-3-iodo-pyrazolo[1,5-a] pyridine (1.0 g, 3.1 mmol) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (845.7 mg, 4.0 mmol) in anhydrous dioxane (20 mL) was added Pd(dppf)Cl₂ (758 mg, 929 μmol), K₃PO₄ (2.0 g, 9.3 mmol) and water (5 mL) under the atmosphere of N₂. Then the reaction mixture was stirred at 110 °C for 1 hour. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (80 g silica gel column, petrol ether/EtOAc with EtOAc 0-30%) to afford the product desired product (508 mg, 59% yield) as a brown solid. LC-MS: m/z 279 [M+H]⁺.

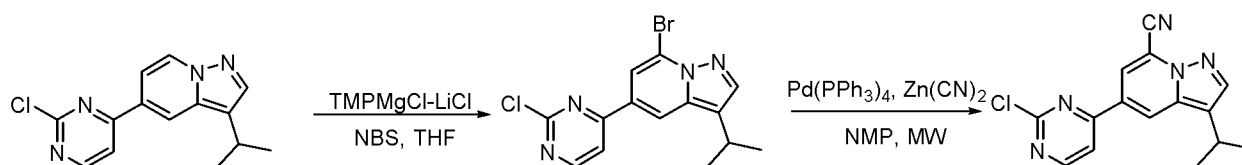
Step 2

To a solution of 5-bromo-3-(3,6-dihydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyridine (360 mg, 1.3 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (425 mg, 1.7 mmol) in dioxane (15 mL) was added cyclopentyl(diphenyl)phosphane dichloropalladium iron (188 mg, 257 μmol), potassium acetate (379 mg, 3.8 mmol) under the atmosphere of N₂. Then the reaction mixture was stirred at 110 °C for 8 hours. The mixture was filtered and concentrated under reduced pressure to afford the crude desired product as a yellow oil which was used for next step without further purification. LC-MS: m/z 327 [M+H]⁺.

Step 3

To a solution of 3-(3,6-dihydro-2H-pyran-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (430 mg, 1.3 mmol) and 2,4-dichloro-5-fluoro-pyrimidine (242 mg, 1.5 mmol) in dioxane (15 mL) added cyclopentyl(diphenyl)phosphane dichloropalladium iron (192 mg, 263 μmol), disodium carbonate (419 mg, 3.9 mmol) and water (1 mL) under the atmosphere of N₂. Then the reaction mixture was stirred at 110 °C for 3 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (40 g silica gel column, petrol ether/EtOAc with EtOAc 0-30%) to afford desired product (360 mg, 82% yield) as an orange solid. LC-MS: m/z 331.1 [M+H]⁺.

Intermediate 9



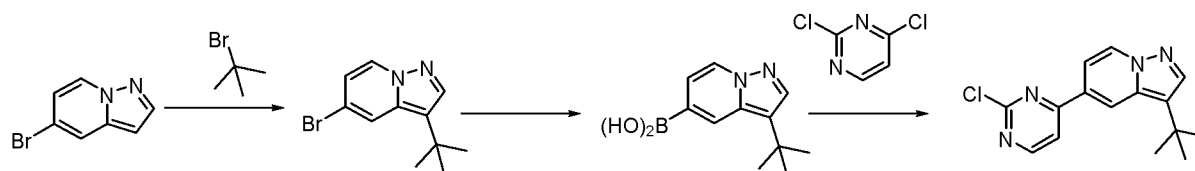
Step 1

To a solution of 5-(2-chloropyrimidin-4-yl)-3-isopropyl-pyrazolo[1,5-a] pyridine (100 mg, 366 μ mol) in THF (8 mL) was added TMPMgCl-LiCl (1 M, 916 μ L) at -78 $^{\circ}$ C under N₂. The reaction was stirred at -78 $^{\circ}$ C for 0.5 h. Then NBS (78.3 mg, 439 μ mol) was added. The mixture was warmed to 25 $^{\circ}$ C and stirred for 1.5 h. The mixture was quenched with NH₄Cl aq. (10 mL), extracted with EA (2 $\times$ 15 mL). The combined organic phases were concentrated under reduced pressure. The residue was purified by FCC (12 g silica gel, 0-30% EtOAc in PE) to give desired product (45.0 mg, 34% yield) as a yellow solid. LC-MS: m/z 351.0 [M+H]⁺.

Step 2

A solution of 7-bromo-5-(2-chloropyrimidin-4-yl)-3-isopropyl-pyrazolo[1,5-a]pyridine (45.0 mg, 127 μmol), $\text{Pd}(\text{PPh}_3)_4$ (14.7 mg, 12.8 μmol) and $\text{Zn}(\text{CN})_2$ (22.5 mg, 191 μmol) in NMP (5 mL) was irradiated in a microwave reactor at 110 $^\circ\text{C}$ under N_2 for 0.5 h. The mixture was concentrated under reduced pressure. The residue was purified by FCC (4 g silica gel, 0-30% EtOAc in PE) to give desired product (15.0 mg, 39% yield) as a yellow solid. LC-MS: m/z 298.1 $[\text{M}+\text{H}]^+$.

Intermediate 84



Step 1

To a suspension of trichloroalumane (2.7 g, 20.3 mmol) in DCM (10 mL) was added 2-bromo-2-methyl-propane (4.1 g, 30.4 mmol) at 0 °C under the atmosphere of N₂. The reaction mixture was stirred at 0 °C under the atmosphere of N₂ for 10 mins. Then 5-bromopyrazolo[1,5-a]pyridine (2 g, 10.1 mmol) was added to the reaction mixture. The reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was quenched with ice water (50 mL). Then the mixture was extracted with DCM (3 × 50 mL), the combined organic layer was dried over anhydrous Na₂SO₄, filtered and cocentrated under reduced pressure. The residue was purified by flash column chromatography to afford the desired product 5-bromo-3-tert-butyl-pyrazolo[1,5-a]pyridine (1.2 g, 46% yield) as a yellow oil. LC-MS: m/z 253.1 [M+H]⁺.

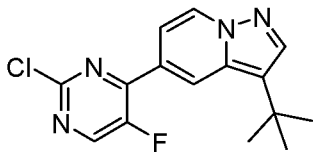
Step 2

To a solution of 5-bromo-3-tert-butyl-pyrazolo[1,5-a]pyridine (200 mg, 790 μmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (300 mg, 1.2 mmol) in dioxane (8 mL) was added cyclopentyl(diphenyl)phosphane dichloropalladium iron (173 mg, 237 μmol) and potassium acetate (232 mg, 2.4 mmol) under the atmosphere of N_2 . Then the mixture was stirred at 110 $^\circ\text{C}$ under the atmosphere of N_2 for 13 hours. The mixture was filtered and concentrated under reduced pressure to afford desired product as a yellow oil which was used in the next step without further purification.

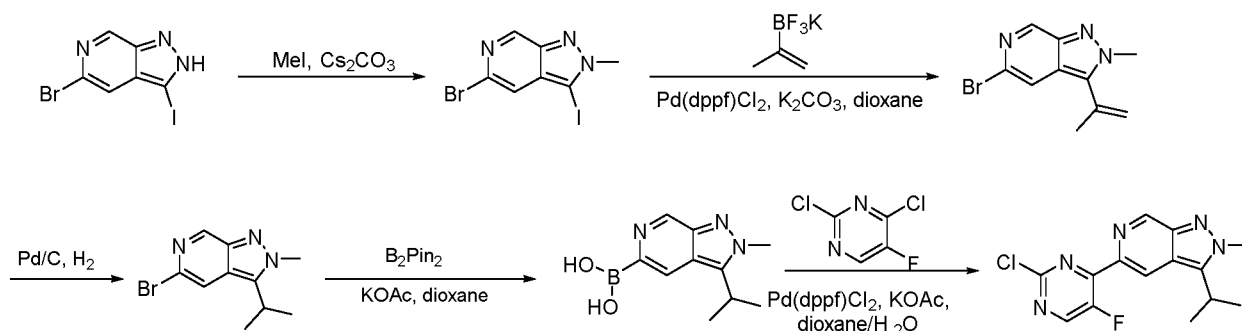
Step 3

To a solution of (3-tert-butylpyrazolo[1,5-a]pyridin-5-yl)boronic acid (180 mg, 825 μmol) and 2,4-dichloropyrimidine (147 mg, 990 μmol) in dioxane (12 mL) was added cyclopentyl(diphenyl)phosphane dichloropalladium iron (72 mg, 99 μmol), disodium carbonate (174 mg, 1.6 mmol) and water (0.5 mL) under the atmosphere of N_2 . Then the reaction mixture was stirred at 110 $^\circ\text{C}$ under the atmosphere of N_2 for 5 hours. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography to afford desired product (220 mg, 92% yield) as yellow solid. LC-MS: m/z 287.1 $[\text{M}+\text{H}]^+$.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

ID	Structure	LC-MS: m/z $[\text{M}+\text{H}]^+$
Intermediate 85		305.1

Intermediate 10



Step 1

To a solution of 5-bromo-3-iodo-2H-pyrazolo[3,4-c] pyridine (200 mg, 617 μmol) and Cs_2CO_3 (500 mg, 1.5 mmol) in DMF (8 mL) was added MeI (99 mg, 679 μmol) at 0 °C. The reaction mixture was stirred at 25 °C for 1.5 hours. The mixture was quenched with water (20 mL) and then extracted with ethyl acetate (2×50 mL). The combined organic phase was dried over anhydrous Na_2SO_4 . The filtrate was concentrated. The residue was purified by flash column chromatography (24 g silica gel column, EA in DCM 0 to 10% in 20 minutes) to give desired product (20.0 mg) as a light-purple solid. LC-MS: m/z 337.9 $[\text{M}+\text{H}]^+$.

Step 2

A solution of 5-bromo-3-iodo-2-methyl-pyrazolo[3,4-c] pyridine (167 mg, 494 μmol), potassium isopropenyltrifluoroborate (90.0 mg, 600 μmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (90.0 mg, 100 μmol) and K_2CO_3 (140 mg, 1 mmol) in dioxane (10 mL) was stirred at 80 °C for 72 hours. The reaction mixture was quenched with water (50 mL) and then extracted with ethyl acetate (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (24 g silica gel column, EA in PE 0 to 70% in 20 minutes) to give desired product (30.0 mg) as a yellow solid. LC-MS: m/z 252.1 $[\text{M}+\text{H}]^+$.

Step 3

To a solution of 5-bromo-3-isopropenyl-2-methyl-pyrazolo[3,4-c] pyridine (40.0 mg, 158 μmol) in THF (12 mL) was added PtO_2 (18.1 mg, 79.3 μmol), the mixture was stirred under hydrogen atmosphere at 25 °C for 2 hours. The reaction mixture was filtered and then washed with methanol (5 mL). The filtrate was concentrated to give desired product (30.0 mg, 74%

yield) as a white solid, which was used directly without further purification. LC-MS: m/z 254.1 $[M+H]^+$.

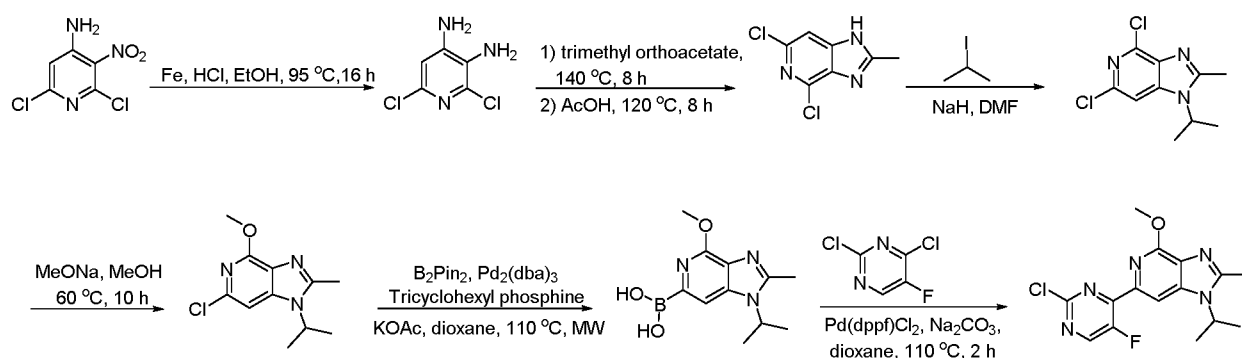
Step 4

A solution of 5-bromo-3-isopropyl-2-methyl-pyrazolo[3,4-c]pyridine (30.0 mg, 118 μ mol), B_2Pin_2 (46.0 mg, 181 μ mol), $Pd_2(dba)_3$ (22.0 mg, 24.0 μ mol), KOAc (35.0 mg, 357 μ mol) and tricyclohexylphosphane (14.0 mg, 0.05 mmol) in dioxane (2 mL) was stirred under microwave condition at 120 °C for 1 hour. The reaction mixture was filtered and washed with DCM (5 mL). The filtrate was concentrated under reduced pressure to give crude desired product (25.0 mg) as a black solid. LC-MS: m/z 220.1 $[M+H]^+$.

Step 5

A solution of (3-isopropyl-2-methyl-pyrazolo[3,4-c]pyridin-5-yl)boronic acid (26.0 mg, 118 μ mol), 2,4-dichloro-5-fluoro-pyrimidine (24.0 mg, 14 μ mol), $Pd(dppf)Cl_2$ (9.0 mg, 12.3 μ mol) and K_2CO_3 (33.0 mg, 239 μ mol) in dioxane (3 mL) and water (1.5 mL) was stirred under N_2 atmosphere at 100 °C for 16 hours. The reaction mixture was quenched with water (50 mL) and then extracted with ethyl acetate (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (24 g, EA in PE from 0 to 90 % in 20 minutes) to give desired product (30.0 mg) as a yellow solid. LC-MS: m/z 306.1 $[M+H]^+$.

Intermediate 11



Step 1

Iron powder (2.6 g, 46.5 mmol), water (9 mL), and concentrated HCl (2 mL) were added to 4-amino-2,6-dichloro-3-nitropyridine (2.0 g, 9.6 mmol) in ethanol (50 mL). The mixture was heated at reflux for 16 h. The mixture was cooled to room temperature, then it was

neutralized with sodium hydrogen carbonate (saturated aq.). The mixture was filtered, and the residue was washed with ethyl acetate. The filtrate was concentrated. The residue was dissolved in ethyl acetate and washed with water (30 mL). The organic layer was dried over Na_2SO_4 and evaporated to afford desired product (1.9 g, 99% yield) as a yellow solid. LC-MS: m/z 177.9 $[\text{M}+\text{H}]^+$.

Step 2

The solution of 2,6-dichloropyridine-3,4-diamine (1.8 g, 8.4 mmol) in trimethyl orthoacetate (20 mL) was stirred at 140 °C for 5 hours. Then the mixture was concentrated under reduced pressure, the residue was dissolved in AcOH (20 mL). Then the mixture was stirred at 120 °C for 5 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (40 g silica gel column, petrol ether/EtOAc with EtOAc 0-50%) to afford desired product (1.3 g, 67% yield) as a yellow solid. LC-MS: m/z 201.9 $[\text{M}+\text{H}]^+$.

Step 3

To a solution of 4,6-dichloro-2-methyl-1H-imidazo[4,5-c] pyridine (1.9 g) in anhydrous DMF (5 mL) was added NaH (772 mg, 32.1 mmol) at 0 °C. Then 2-iodopropane (3.3 g, 19.3 mmol) was added to the reaction mixture. The mixture was allowed warm to room temperature and stirred for 13 hours. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (80 g silica gel column, MeOH in DCM 0-10%) to afford desired product (487 mg, 31% yield) as a yellow solid. LC-MS: m/z 244 $[\text{M}+\text{H}]^+$.

Step 4

To a solution of 4,6-dichloro-1-isopropyl-2-methyl-1H-imidazo[4,5-c] pyridine (200 mg, 0.8 mmol) in MeOH (5 mL) was added the solution of MeONa (5.4 N, 5 mL in MeOH). The mixture was heated at reflux (65 °C) for 10 h. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (40 g silica gel column, petrol ether/EtOAc with EtOAc 0-100%) to afford desired product (140 mg, 71% yield) as a white solid. LC-MS: m/z 240 $[\text{M}+\text{H}]^+$.

Step 5

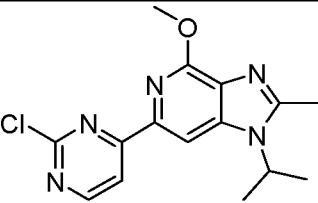
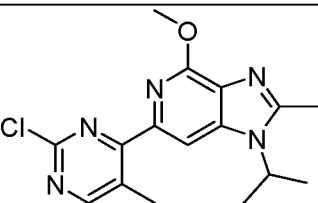
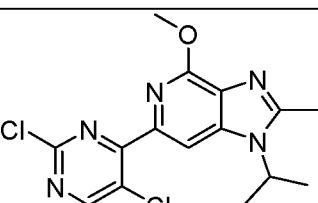
To a solution of 6-chloro-1-isopropyl-4-methoxy-2-methyl-1H-imidazo[4,5-c]pyridine (120 mg, 0.5 mmol) and Pin_2B_2 (153 mg, 0.6 mmol) in anhydrous dioxane (8 mL) was added

$\text{Pd}_2(\text{dba})_3$ (137 mg, 0.15 mmol), tricyclohexyl phosphine (84.1 mg, 0.3 mmol), AcOK (147 mg, 1.5 mmol) under the atmosphere of N_2 . Then the mixture was stirred at 110 °C (microwave) for 1.5 hours. The mixture was filtered and concentrated under reduced pressure to afford crude desired product as a brown oil which was used in next step without further purification. LC-MS: m/z 250 $[\text{M}+\text{H}]^+$.

Step 6

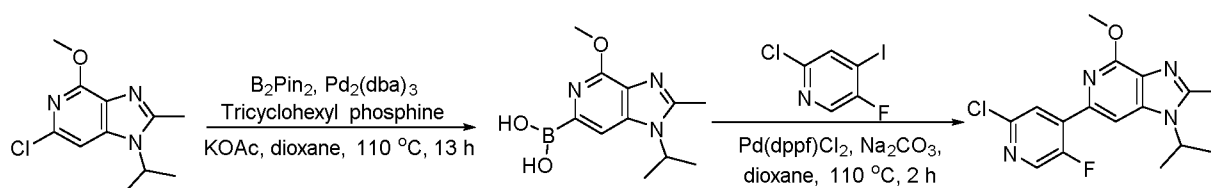
To a solution of (1-isopropyl-4-methoxy-2-methyl-1H-imidazo[4,5-c]pyridin-6-yl)boronic acid (300 mg) and 2,4-dichloro-5-fluoropyrimidine (83.5 mg, 0.5 mmol) in anhydrous dioxane/water (8 mL/2 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (122 mg, 0.2 mmol), Na_2CO_3 (159 mg, 1.5 mmol) under the atmosphere of N_2 . Then the mixture was stirred at 110 °C for 3 hours. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (40 g silica gel column, petrol ether/EtOAc with EtOAc 0-50%) to afford desired product (139 mg, 82% yield) as a yellow solid. LC-MS: m/z 336 $[\text{M}+\text{H}]^+$.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

ID	Structure	LC-MS: m/z $[\text{M}+\text{H}]^+$
Intermediate 12		318.1
Intermediate 13		332.1
Intermediate 14		352.0

Intermediate 15		322.0
Intermediate 16		304.1
Intermediate 17		308.0

Intermediate 18



Step 1

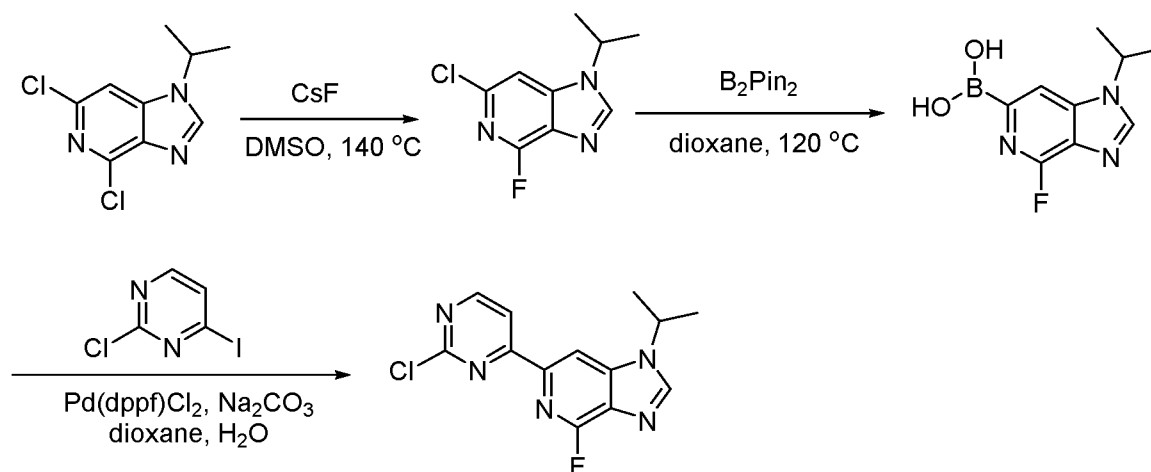
To a sealed tube was charged with the solution of 6-chloro-1-isopropyl-4-methoxy-2-methylimidazo[4,5-c]pyridine (170 mg, 709 μ mol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (270 mg, 1.1 mmol) in dioxane (5 mL). Then tris(dibenzylideneacetone)dipalladium(0) (194 mg, 212 μ mol), tricyclohexylphosphane (119 mg, 425 μ mol) and potassium acetate (208 mg, 2.1 mmol) were added under the atmosphere of N_2 . Then the reaction mixture was stirred at 110 $^{\circ}C$ for 5 hours. The mixture was filtered, and the filtrate was concentrated under reduced pressure to afford crude desired product which was used for next step without further purification. LC-MS: m/z 250 $[M+H]^+$.

Step 2

To a solution of (1-isopropyl-4-methoxy-2-methylimidazo[4,5-c]pyridin-6-yl)boronic acid (190 mg, 762 μ mol) and 2-chloro-5-fluoro-4-iodopyridine (216 mg, 839 μ mol) in dioxane (8

mL) was added cyclopentyl(diphenyl)phosphane dichloropalladium iron (167 mg, 228 μ mol), disodium carbonate (242 mg, 2.2 mmol) and water (2 mL) under the atmosphere of N_2 . Then the reaction mixture was stirred at 110 $^{\circ}C$ for 5 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (40 g silica gel column, petrol ether/EtOAc with EtOAc 0-100%) to afford desired product (160 mg, 62% yield) as a yellow solid. LC-MS: (ESI) m/z 335 $[M+H]^+$.

Intermediate 19



Step 1

To the mixture of 4,6-dichloro-1-isopropyl-imidazo[4,5-c] pyridine (250 mg, 1.1 mmol) in DMSO (10 mL) was added CsF (510 mg, 3.4 mmol), then the mixture stirred at 140 $^{\circ}C$ for 1.5 hours. The resulting mixture were poured into water (100 mL) and extracted with EA (3 $\times$ 30 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated. The residue was purified by flash column (80 g 200-300 mesh sic-gel, PE/EA=5/1-2/1) to afford desired product (210 mg, 75% yield) as a cream white solid. LC-MS: (ESI) m/z 214.1 $[M+H]^+$.

Step 2

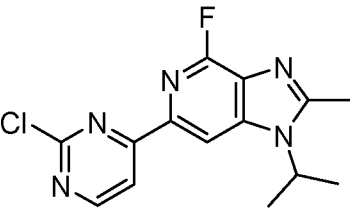
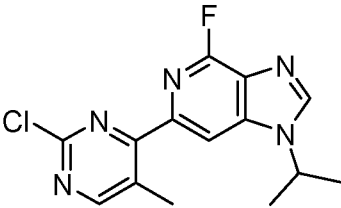
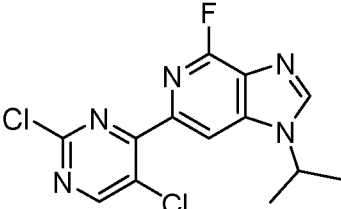
To a solution of 6-chloro-4-fluoro-1-isopropyl-imidazo[4,5-c] pyridine (30.0 mg, 140 μ mol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (35.6 mg, 140 μ mol) in dioxane (5 mL) were added potassium acetate (41.3 mg, 421 μ mol) and cyclopentyl(diphenyl) phosphane dichloropalladium iron (15.4 mg, 21.1 μ mol). The mixture was degassed with N_2 and stirred at 110 $^{\circ}C$ for 16 hours. The mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to crude desired

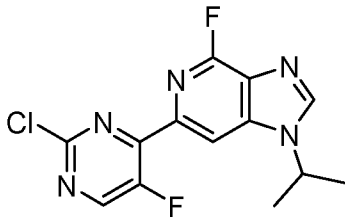
product (50 mg) as black oil, which was used directly in the next step. LC-MS: (ESI) m/z 224.2 $[M+H]^+$.

Step 3

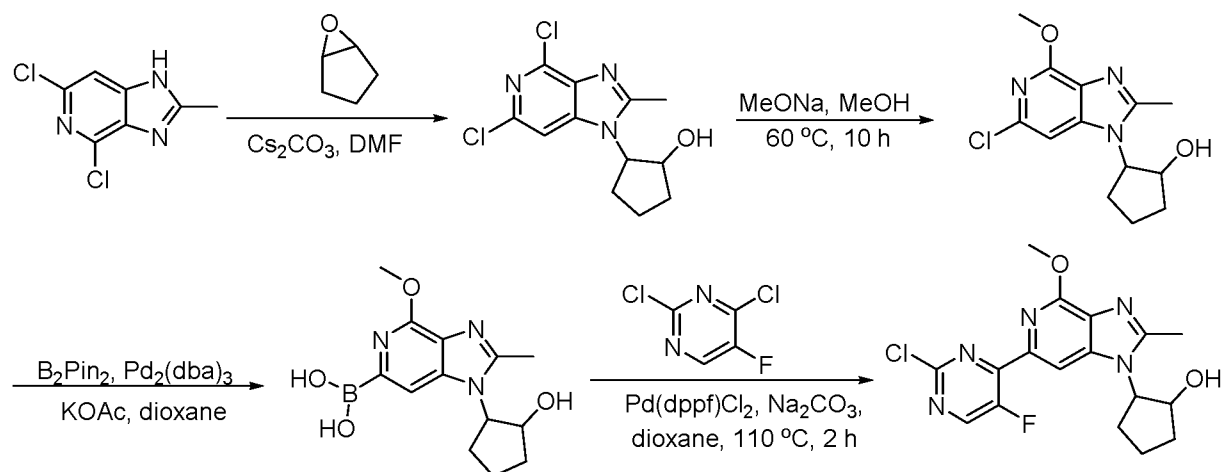
To a solution of (4-fluoro-1-isopropyl-imidazo[4,5-c] pyridin-6-yl) boronic acid (50.0 mg, 224 μmol) and 2-chloro-4-iodo-pyrimidine (53.9 mg, 224 μmol) in dioxane (3 mL) were added cyclopentyl (diphenyl) phosphane dichloropalladium iron (24.6 mg, 33.6 μmol) and potassium acetate (66.0 mg, 672 μmol). The mixture was degassed with N_2 and stirred at 110 °C for 16 hours. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate in petroleum ether 0-60% to give desired product (30.0 mg, 46% yield) as white solid. LC-MS: (ESI) m/z 292.1 $[M+H]^+$.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

ID	Structure	LC-MS: m/z $[M+H]^+$
Intermediate 86		306.0
Intermediate 87		306.0
Intermediate 88		326.0

Intermediate 89		310.0
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Intermediate 20



Step 1

To a solution of 4,6-dichloro-2-methyl-3H-imidazo[4,5-c] pyridine (4.0 g, 19.8 mmol) and 6-oxabicyclo[3.1.0] hexane (6.6 g, 79.1 mmol) in DMF (50 mL) was added cesium carbonate (16.1 g, 49.5 mmol). The reaction mixture was stirred at 100° C for 48 h. Then the reaction mixture was quenched with H₂O (50 mL) and extracted with EA (3 × 10 mL). The organic layer was concentrated under reduced pressure. The residue was purified by flash column chromatography (20 g silica gel column, DCM with MeOH 0-10%) to afford desired product (650 mg, 11% yield) as yellow solid. LC-MS: m/z 286 [M+H]⁺.

Step 2

To a solution of 2-(4,6-dichloro-2-methyl-imidazo[4,5-c] pyridin-1-yl) cyclopentanol (650 mg, 2.2 mmol) in methanol (10 mL) was added sodium methanolate (5.4 M, 841 μL) at 25 °C. The reaction mixture was stirred at 60 °C for 48 hr. The mixture was quenched with water (20 mL) and then extracted with ethyl acetate (2 × 20 mL). The combined organic phase was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure.

The residue was purified by silica gel chromatography eluting with EA in PE 10-60% to give desired product (600 mg, 94% yield) as a light-yellow oil. LC-MS: (ESI) m/z 282.2 $[M+H]^+$.

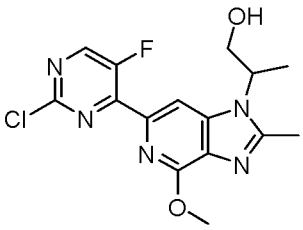
Step 3

To a mixture of 2-(6-chloro-4-methoxy-2-methyl-imidazo[4,5-c]pyridin-1-yl) cyclopentanol (200 mg, 709 μmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (270 mg, 1.1 mmol) in dioxane (8 mL) was added $\text{Pd}_2(\text{dba})_3$ (97.5 mg, 106 μmol), potassium acetate (209 mg, 2.1 mmol) and tricyclohexylphosphane (59.7 mg, 212 μmol). The resulting mixture was stirred under nitrogen atmosphere at 110 °C for 6 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure to afford crude desired product (200 mg, 96% yield) as a brown oil which was used for next step without further purification. LC-MS: (ESI) m/z 292.2 $[M+H]^+$.

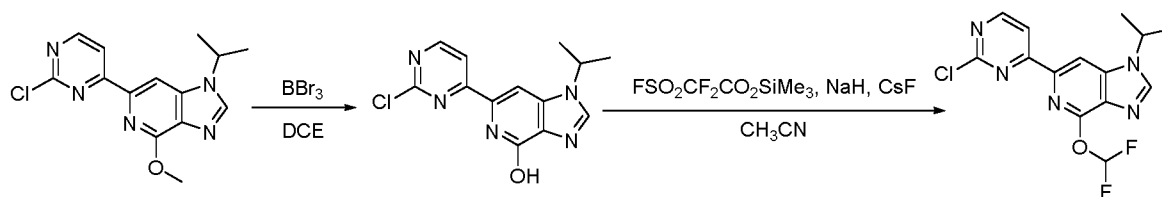
Step 4

To a solution of [1-(2-hydroxycyclopentyl)-4-methoxy-imidazo[4,5-c]pyridin-6-yl]boronic acid (250 mg, 902 μmol) and 2,4-dichloro-5-fluoro-pyrimidine (165 mg, 992 μmol) in dioxane (3 mL) was added disodium carbonate (239 mg, 2.3 mmol) and cyclopentyl(diphenyl)phosphane dichloropalladium iron (132 mg, 180 μmol) under the atmosphere of N_2 . Then the reaction mixture was stirred at 110 °C for 5 hours. The mixture was concentrated under reduced pressure and the residue was purified to give desired product (250 mg, 76% yield) as a yellow solid. LC-MS: m/z 378.1 $[M+H]^+$.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

ID	Structure	LC-MS: m/z $[M+H]^+$
Intermediate 21		352.1

Intermediate 22



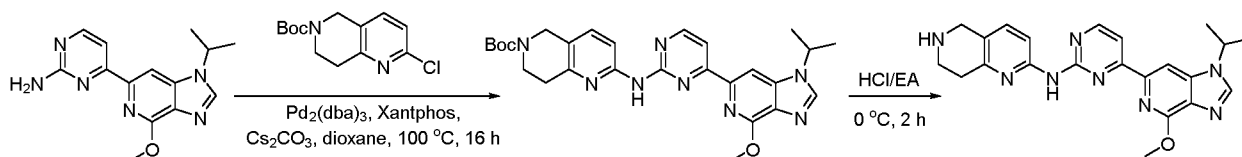
Step 1

To a solution of 6-(2-chloropyrimidin-4-yl)-1-isopropyl-4-methoxy-imidazo[4,5-c] pyridine (150 mg, 493 μ mol) in DCE (5 mL) was added tribromoborane (618 mg, 2.4 mmol) at 0 °C. The mixture was stirred at 60 °C for 12 h. The mixture was quenched by aqueous NaHCO_3 (10 mL), extracted with DCM (2×10 mL). The organic layers were combined and dried over Na_2SO_4 , filtered and concentrated to get crude desired product (140 mg) as a yellow solid, which was used in next step directly without any other purification. LC-MS: m/z 290.1 $[\text{M}+\text{H}]^+$.

Step 2

To a solution of 6-(2-chloropyrimidin-4-yl)-1-isopropyl-imidazo[4,5-c] pyridin-4-ol (0.1 g, 345 μ mol) and trimethylsilyl 2,2-difluoro-2-fluorosulfonyl-acetate (129 mg, 517 μ mol) in CH_3CN (5 mL) was added NaH (16.5 mg, 690 μ mol) and CsF (78.6 mg, 517 μ mol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was quenched with water (5 mL), extracted with EtOAc (2×10 mL). The organic layers were combined and dried over Na_2SO_4 , filtered and concentrated to get a residue, which was purified by flash column chromatography (SiO_2 , hexanes/ethyl acetate 1:1) to afford desired product (105 mg, 89% yield) as a white solid. LC-MS: m/z 340.1 $[\text{M}+\text{H}]^+$.

Intermediate 23



Step 1

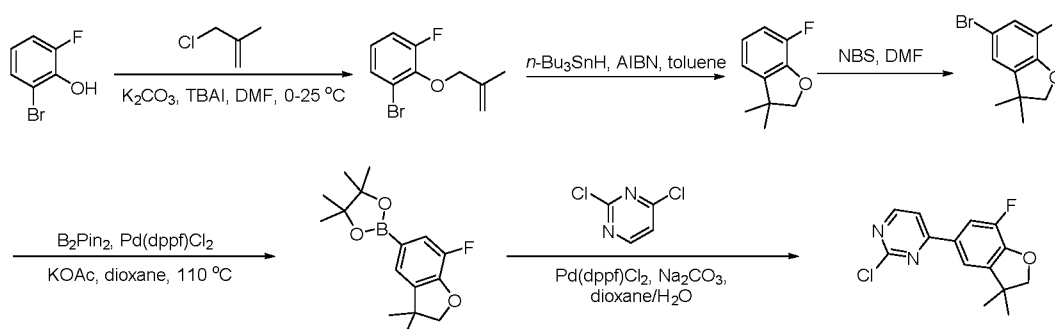
To the mixture of tert-butyl 2-chloro-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (302 mg, 2.3 mmol) in dioxane (10 mL) were added 4-(1-isopropyl-4-methoxy-imidazo[4,5-c]pyridin-6-yl)pyrimidin-2-amine (322 mg, 1.1 mmol),

tris(dibenzylideneacetone)dipalladium(0) (100 mg, 109 μmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (190 mg, 328 μmol), cesium carbonate (2.0 g, 6.1 mmol) in sequence. The mixture was degassed by N_2 for 5 times. The mixture was stirred at 110 $^\circ\text{C}$ for 16 hours. The reaction mixture was diluted with water (100mL) and extracted with EA ($3 \times 30\text{mL}$). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated. The residue was purified by flash column to afford desired product (611 mg, 92% yield) as a yellow solid. LC-MS: (ESI) m/z 517.3 $[\text{M}+\text{H}]^+$.

Step 2

In an ice bath, HCl/EtOAc (2 M, 7 mL) was added into tert-butyl 2-[[4-(1-isopropyl-4-methoxy-1H-imidazo[4,5-c]pyridin-6-yl)pyrimidin-2-yl]amino]-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (152 mg, 280 μmol), the mixture was stirred in ice bath for 2 hours. The mixture was concentrated and dried in vacuo to afford desired product (1220 mg, 91% yield) as a yellow solid. LC-MS: (ESI) m/z 417.2 $[\text{M}+\text{H}]^+$.

Intermediate 24



Step 1

To a solution of 2-bromo-6-fluorophenol (4.0 g, 21.1 mmol) in DMF (50 mL) was added K_2CO_3 (5.8 g, 42.2 mmol), TBAI (0.4 g, 1.1 mmol) and 3-chloro-2-methylprop-1-ene (2.8 g, 31.6 mmol) at 0 $^\circ\text{C}$. The reaction mixture was stirred at 25 $^\circ\text{C}$ for 14 h. The mixture was concentrated under reduced pressure and purified to get desired product (4.5 g, 88% yield). LC-MS: m/z 245.0 $[\text{M}+\text{H}]^+$.

Step 2

To a solution of 1-bromo-3-fluoro-2-((2-methylallyl)oxy)benzene (2.5 g, 10.2 mol) in toluene (50 mL) was added $n\text{-Bu}_3\text{SnH}$ (3.6 g, 12.3 mmol) and AIBN (2.0 g, 2.3 mmol) under N_2 . The reaction mixture was stirred at 90 $^\circ\text{C}$ for 12 h. The reaction mixture was quenched with water (50 mL) and extracted with DCM ($2 \times 50\text{ mL}$). The organic layer was washed

with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (eluting with PE/EA=10/1) to get desired product (1.4 g, 81% yield). LC-MS: m/z 167.1 $[\text{M}+\text{H}]^+$.

Step 3

To a solution of 7-fluoro-3,3-dimethyl-2,3-dihydrobenzofuran (1.4 g, 8.4 mmol) in DMF (30 mL) was added NBS (1.8 g, 10.1 mmol) under N_2 at 25 °C. The reaction was stirred for 15 h. The reaction mixture was quenched with water (3 mL) and concentrated under reduced pressure. The residue was purified (eluting with PE: EA =1/1) to get desired product (450 mg, 22% yield). LC-MS: m/z 245.0 $[\text{M}+\text{H}]^+$.

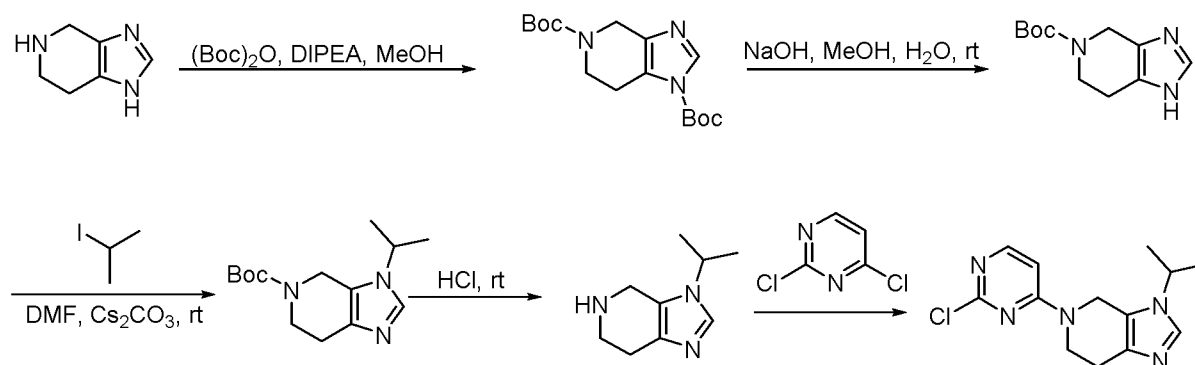
Step 4

To a solution of 5-bromo-7-fluoro-3,3-dimethyl-2,3-dihydrobenzofuran (100 mg, 0.4 mmol) and Pin_2B_2 (122 mg, 0.5 mmol) in anhydrous dioxane (10 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (98.0 mg, 0.16 mmol) and KOAc (117 mg, 1.2 mmol) under the atmosphere of N_2 . Then the mixture was stirred at 110 °C (microwave) for 1.5 hours. The mixture was filtered and concentrated under reduced pressure to afford crude desired product (150 mg) as a brown oil which was used in next step without further purification. LC-MS: m/z 293.2 $[\text{M}+\text{H}]^+$.

Step 5

To a solution of above 2-(7-fluoro-3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolan (150 mg) and 2,4-dichloropyrimidine (61.0 mg, 0.4 mmol) in anhydrous dioxane/water (8 mL/2 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (98.0 mg, 0.16 mmol), Na_2CO_3 (127 mg, 1.2 mmol) under the atmosphere of N_2 . Then the mixture was stirred at 110 °C for 3 hours. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (40 g silica gel column, petrol ether/EtOAc with EtOAc 0-50%) to afford desired product (60.0 mg, 51% yield). LC-MS: m/z 279.1 $[\text{M}+\text{H}]^+$.

Intermediate 25



Step 1

To a mixture of 4,5,6,7-tetrahydro-1H-imidazo[4,5-c] pyridine (2.3 g, 17.3 mmol) and DIPEA (4.4 g, 34 mmol) in methanol (30 mL) was added Boc_2O (5.5 g, 43.2 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 18 hours. The reaction mixture was quenched with water (50 mL) and then extracted with EtOAc (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (24g, EtOAc in PE 0-100% in 20 minutes) to give desired product (4.7 g, 14.5 mmol) as a yellow oil. LC-MS: m/z 346.2 $[\text{M}+\text{Na}]^+$.

Step 2

A mixture of ditert-butyl 6,7-dihydro-4H-imidazo[4,5-c] pyridine-1,5-dicarboxylate (4.7 g, 14.5 mmol) and sodium hydroxide (1 M in water, 29.0 mL) in dioxane (36 mL) was stirred at 25 °C for 1 hour. The reaction mixture was quenched with water (50 mL) and then extracted with EtOAc (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then was filtered. The filtrate was concentrated. The residue was purified by flash column chromatography to give desired product (2.7 g, 12.1 mmol) as a colorless oil. LC-MS: m/z 224.3 $[\text{M}+\text{H}]^+$.

Step 3

A mixture of tert-butyl 1,4,6,7-tetrahydroimidazo[4,5-c] pyridine-5-carboxylate (500 mg, 2.2 mmol) and cesium carbonate (2.1 g, 6.7 mmol) in DMF (20 mL) was stirred under N_2 atmosphere at 25 °C for 16 hours. The reaction mixture was quenched with water (50 mL) and then extracted with EtOAc (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then was filtered. The filtrate was concentrated. The residue was

purified by flash column chromatography (24g, MeOH in DCM 0-20% in 20 minutes) to give desired product (330 mg, 55% yield) as a yellow oil. LC-MS: m/z 266.2 $[M+H]^+$.

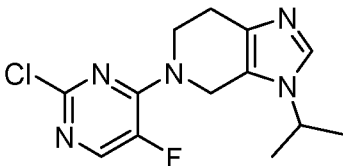
Step 4

A mixture of tert-butyl 3-isopropyl-6,7-dihydro-4H-imidazo[4,5-c]pyridine-5-carboxylate (530 mg, 2.0 mmol), HCl (2 N, 2 mL) in ethyl acetate (2 mL) was stirred at 25 °C for 1 hour. The reaction mixture was quenched with water (50 mL) and then extracted with EtOAc (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then was filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (24g, EtOAc in PE 0-100% in 20 minutes) to give desired product (300 mg, 90% yield) as a yellow solid. LC-MS: m/z 166.3 $[M+H]^+$.

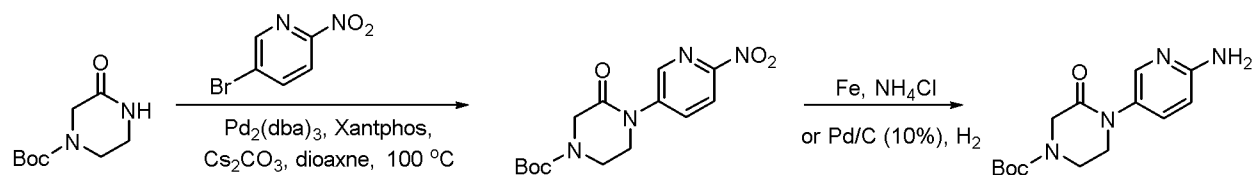
Step 5

A mixture of 3-isopropyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (165 mg, 998 μ mol) 2,4-dichloropyrimidine (178 mg, 1.2 mmol) and potassium carbonate (690 mg, 4.9 mmol) in methanol (10 mL) was stirred under N_2 atmosphere at 40 °C for 2 hours. The reaction mixture was quenched with water (50 mL) and then extracted with EtOAc (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then was filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (24g, MeOH in DCM 0-20% in 20 minutes) to give desired product (66.0 mg) as a colorless oil. LC-MS: m/z 278.1 $[M+H]^+$.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

ID	Structure	LC-MS: m/z $[M+H]^+$
Intermediate 90		296.1

Intermediate 26



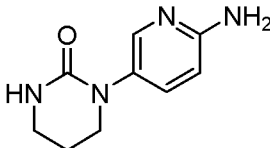
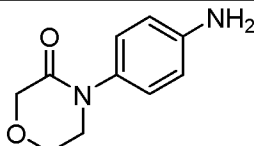
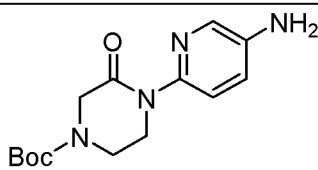
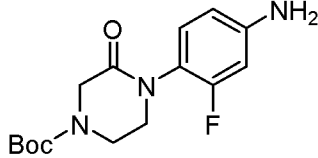
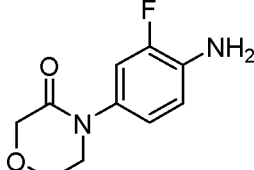
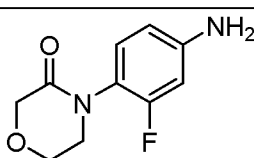
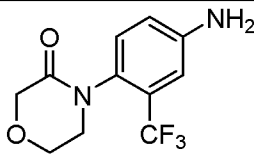
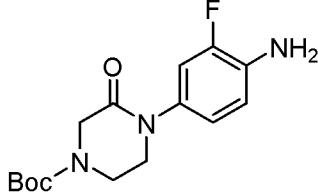
Step 1

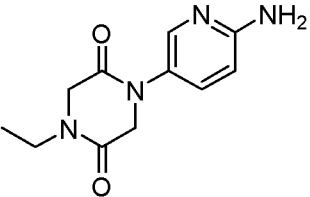
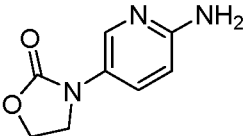
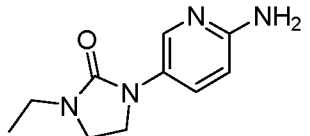
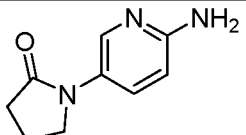
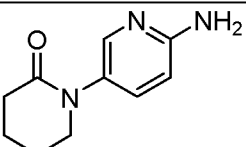
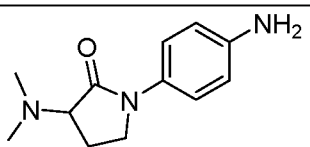
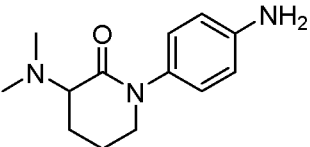
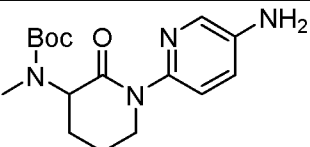
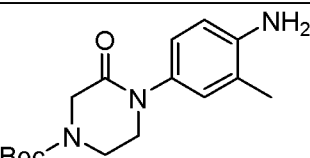
To a solution of 5-bromo-2-nitro-pyridine (10.0 g, 49.2 mmol) and tert-butyl 3-oxopiperazine-1-carboxylate (10.8 g, 54.1 mmol) in dioxane (30 mL) was added cesium carbonate (32.1 g, 98.5 mmol), tris(dibenzylideneacetone)dipalladium(0) (4.5 g, 4.9 mmol) and (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (2.8 g, 4.9 mmol) at $25\text{ }^\circ\text{C}$. Then the mixture was stirred at $110\text{ }^\circ\text{C}$ for 8 hours. The solvent was removed under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH in DCM 0-15% in 20 minutes to give desired product (1.5 g, 9% yield) as light-yellow solid. LC-MS: m/z 323.1 $[\text{M}+\text{H}]^+$.

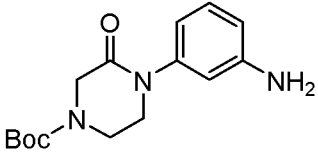
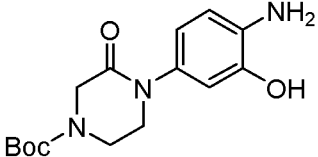
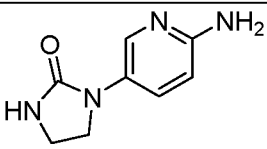
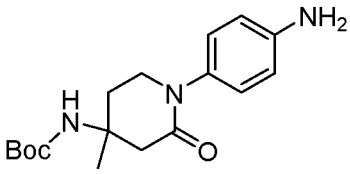
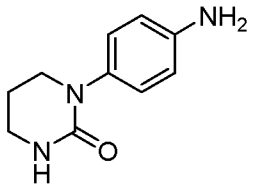
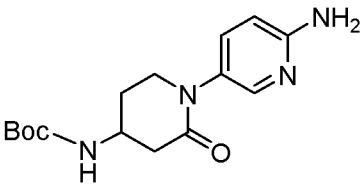
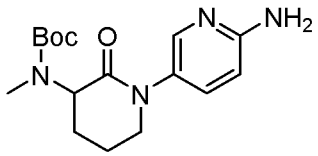
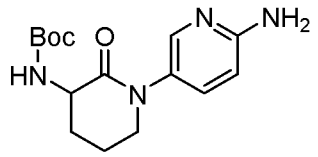
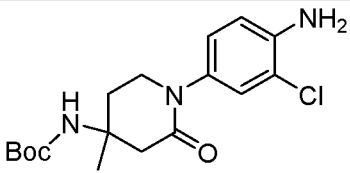
Step 2

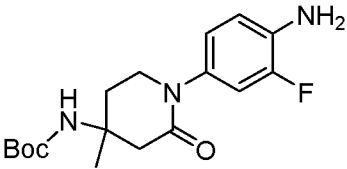
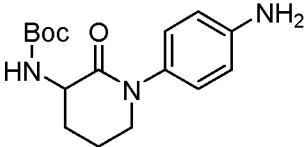
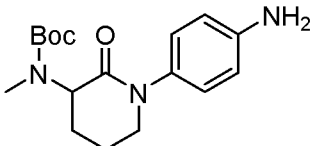
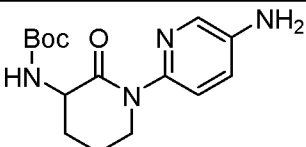
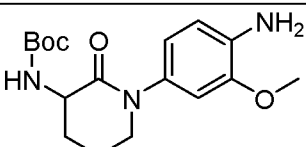
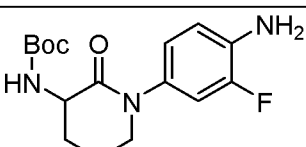
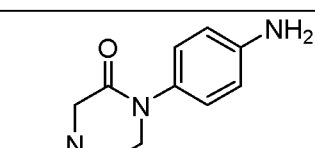
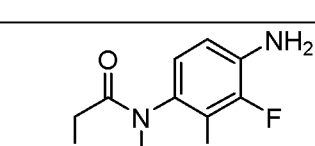
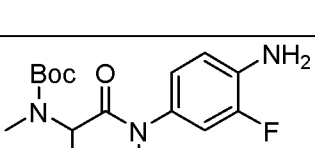
To a stirred solution of tert-butyl 4-(6-nitro-3-pyridyl)-3-oxo-piperazine-1-carboxylate (1.6 g, 4.9 mmol) in ethanol (20 mL) were added iron powder (1.1 g, 19.8 mmol) and ammonia hydrochloride (2.6 g, 49.6 mmol) at $25\text{ }^\circ\text{C}$. The reaction mixture was stirred at $80\text{ }^\circ\text{C}$ under N_2 atmosphere for 2 hours. The mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain desired product which was used directly in the next step without further purification. LC-MS: m/z 293.1 $[\text{M}+\text{H}]^+$.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

ID	Structure	LC-MS: m/z [M+H] ⁺
Intermediate 27		193.1
Intermediate 28		193.0
Intermediate 29		293.2
Intermediate 30		310.2
Intermediate 31		211.1
Intermediate 32		211.1
Intermediate 33		261.0
Intermediate 34		310.2

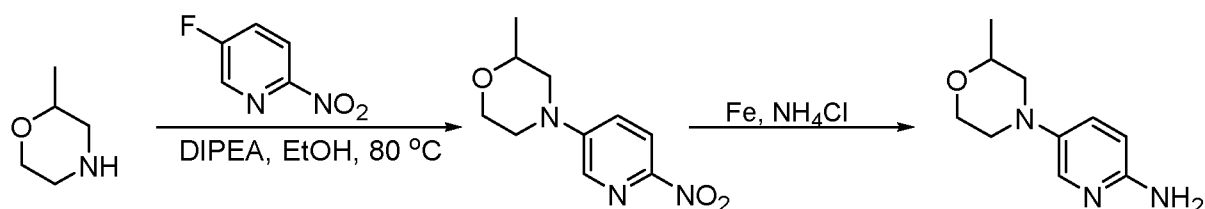
Intermediate 35		235.1
Intermediate 36		180.0
Intermediate 37		207.1
Intermediate 38		178.0
Intermediate 39		192.1
Intermediate 91		220.1
Intermediate 92		234.1
Intermediate 93		321.2
Intermediate 94		306.2

Intermediate 95		292.1
Intermediate 96		308.2
Intermediate 97		179.0
Intermediate 98		320.2
Intermediate 99		192.1
Intermediate 100		307.1
Intermediate 101		321.2
Intermediate 102		307.2
Intermediate 103		354.1

Intermediate 104		338.2
Intermediate 105		306.1
Intermediate 106		320.2
Intermediate 107		307.1
Intermediate 108		336.2
Intermediate 109		324.1
Intermediate 110		292.2
Intermediate 111		328.1
Intermediate 112		338.2

Intermediate 113		208.1
Intermediate 114		190.0

Intermediate 40



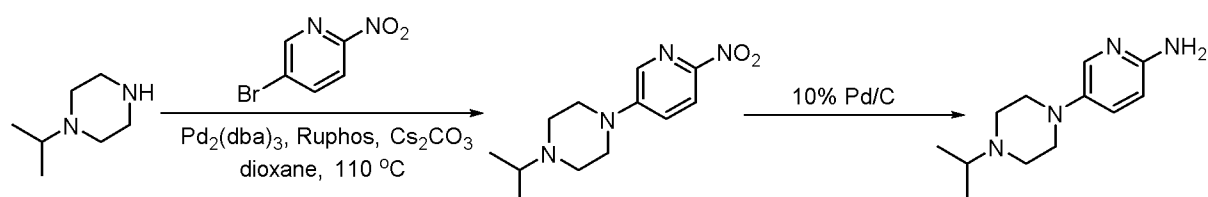
Step 1

To a solution of 2-methylmorpholine (100 mg, 988 μ mol) and 5-fluoro-2-nitropyridine (140 mg, 988 μ mol) in ethanol (15 mL) was added DIPEA (383 mg, 2.9 mmol). The mixture was stirred at 80 °C for 8 hr. The reaction was concentrated under reduced pressure to give desired product (200 mg, 90% yield) as a yellow solid. LC-MS: m/z 224.1 $[M+H]^+$.

Step 2

To a solution of 2-methyl-4-(6-nitro-3-pyridyl)morpholine (200 mg, 895 μ mol) in ethanol (15 mL) were added Iron (250 mg, 4.4 mmol) and ammonia hydrochloride (239 mg, 4.4 mmol). The mixture was stirred at 80 °C for 8 hr. The mixture was concentrated under reduced pressure. The residue was purified silica gel column chromatography eluting with MeOH/DCM 0-10% in 15 mins to afford desired product (150 mg, 86% yield) as a brown solid. LC-MS: m/z 194.1 $[M+H]^+$.

Intermediate 115



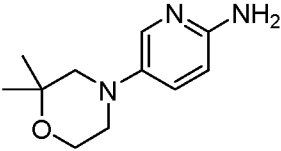
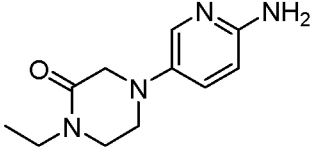
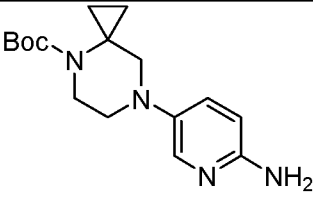
Step 1

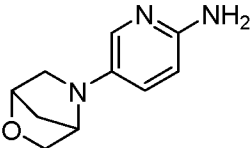
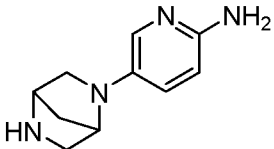
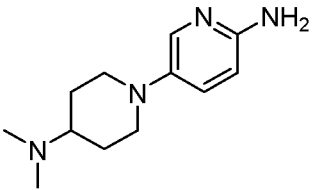
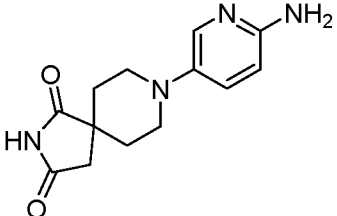
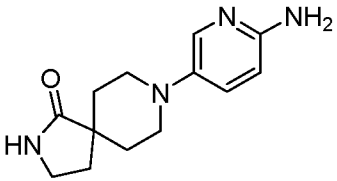
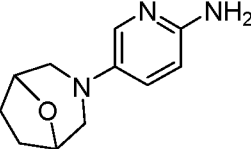
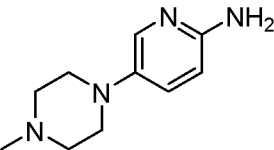
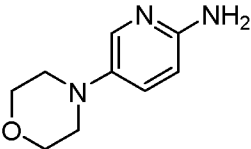
To a solution of 5-bromo-2-nitro-pyridine (1 g, 4.9 mmol) and 1-isopropylpiperazine (631.6 mg, 4.9 mmol) in dioxane (40 mL) was added tris(dibenzylideneacetone)dipalladium(0) (451.1 mg, 492 μ mol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenylphosphane (570 mg, 985 μ mol) and cesium carbonate (4.8 g, 14.8 mmol). Then the reaction mixture was stirred at 110 °C under N₂ for 3 hr. The reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography eluting with ethyl acetate in petroleum ether 1-100% to afford desired product (850 mg, 68% yield) as a yellow solid. LC-MS: m/z 251.1 [M+H]⁺.

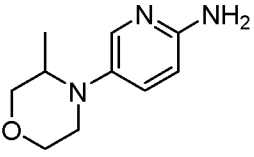
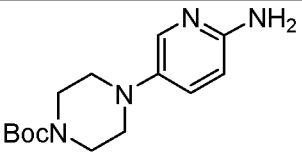
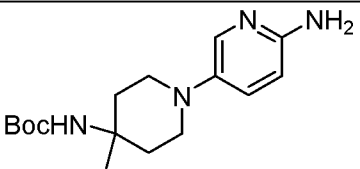
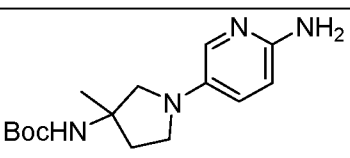
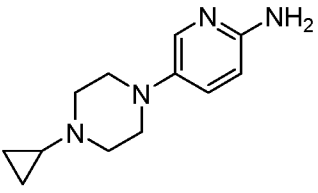
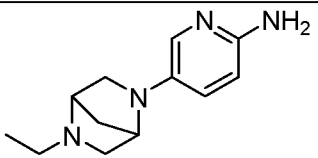
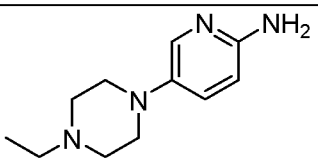
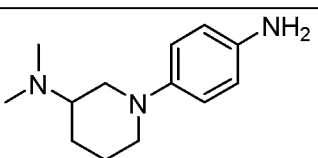
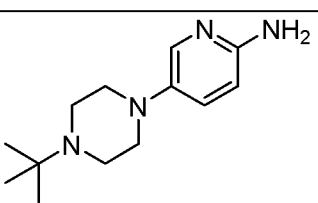
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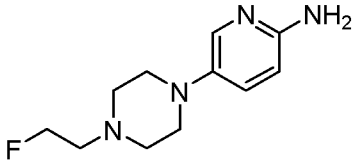
To a solution of 1-isopropyl-4-(6-nitro-3-pyridyl)piperazine (850 mg, 3.4 mmol) in methanol (30 mL) was added Pd/C (412 mg, 10%). Then the reaction mixture was degassed with H₂ for three time and stirred at 25 °C for 3 hr. The reaction mixture was filtered and then washed with methanol (20 mL). The combined solvent was concentrated under reduced pressure to give desired product (620 mg, 82% yield) as a brown solid. LC-MS: m/z 221.2 [M+H]⁺.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

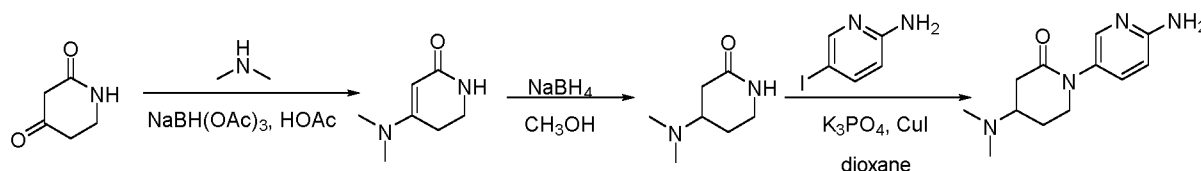
ID	Structure	LC-MS: m/z [M+H] ⁺
Intermediate 41		208.1
Intermediate 42		221.1
Intermediate 43		305.2

Intermediate 44		192.1
Intermediate 45		191.1
Intermediate 46		221.2
Intermediate 47		261.1
Intermediate 48		247.2
Intermediate 49		206.1
Intermediate 50		193.1
Intermediate 51		180.2

Intermediate 52		194.1
Intermediate 53		279.2
Intermediate 54		307.2
Intermediate 55		293.2
Intermediate 116		219.2
Intermediate 117		219.2
Intermediate 118		207.1
Intermediate 119		220.2
Intermediate 120		235.2

Intermediate 121		225.1
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Intermediate 56



Step 1

To a mixture of piperidine-2,4-dione (2.1 g, 18.5 mmol) and N-methylmethanamine (3.4 g, 74.2 mmol) in DCM (36 mL) and THF (18 mL) was added CH₃COOH (10 mL), the resulting mixture was stirred under nitrogen atmosphere at 25 °C for 3 h. Sodium triacetoxyborohydride (7.8 g, 37.1 mmol) was added to this mixture, the resulting mixture was stirred under nitrogen atmosphere at 25 °C for 12 h. The reaction was quenched with water (50 mL) and concentrated in vacuo to remove DCM and THF. The mixture was extracted with DCM (3 × 100 mL). The organic solution was washed with brine (20 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford desired product (2.6 g, 89% yield), which was used in next step without any purification. LC-MS: m/z 141.2 [M+H]⁺.

Step 2

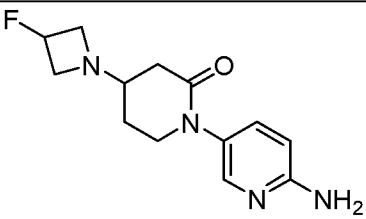
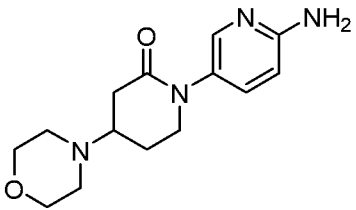
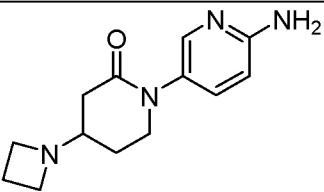
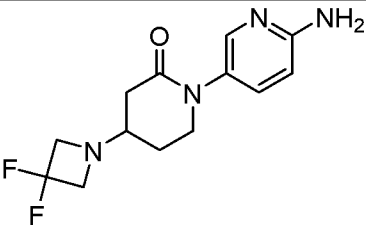
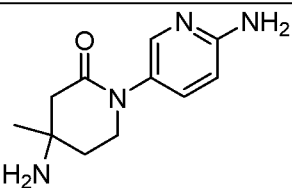
To a mixture of 4-(dimethylamino)-2,3-dihydro-1H-pyridin-6-one (1.0 g, 7.1 mmol) in methanol (15 mL) was added sodium borohydride (539.0 mg, 14.2 mmol), the resulting mixture was stirred under nitrogen atmosphere at 25 °C for 12 h. The reaction was quenched with sat. NH₄Cl aqueous solution (10 mL) and then concentrated in vacuo to remove MeOH. The aqueous solution was purified by reverse phase column (C18, 40 g) eluting with (MeCN/water (0.1% NH₄OH) = 1/10) to give desired product (0.3 g, 32% yield) as light yellow solid. LC-MS: m/z 143.2 [M+H]⁺.

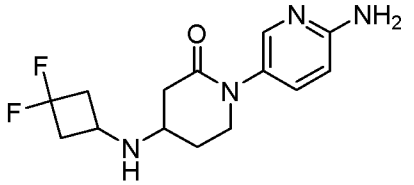
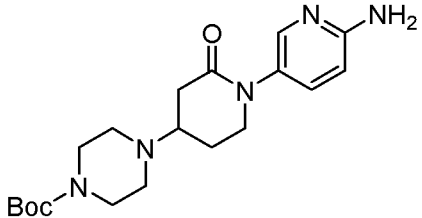
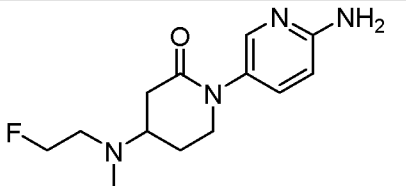
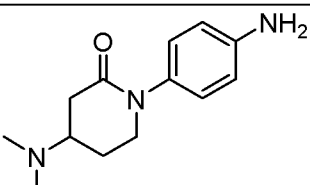
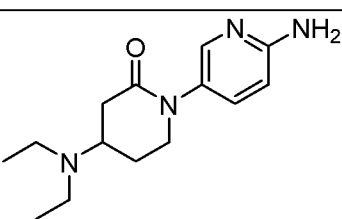
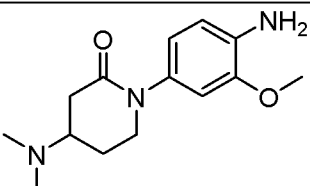
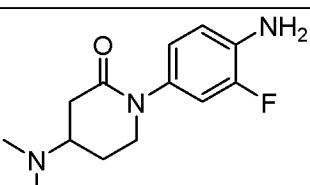
Step 3

To a mixture of 4-(dimethylamino)piperidin-2-one (270 mg, 1.9 mmol), 5-iodopyridin-2-amine (1.0 g, 4.7 mmol) and potassium phosphate (1.2 g, 5.7 mmol) in dioxane (26 mL) was

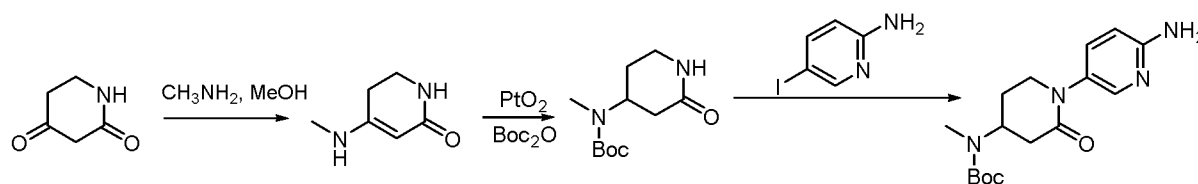
added (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (162 mg, 1.1 mmol) and CuI (108 mg, 569 μ mol), the resulting mixture was stirred under nitrogen atmosphere at 110 °C for 12 h. The reaction was filtered. The filtrate was concentrated in vacuo to give the residue. The residue was purified by reverse phase column (C18, 20 g) eluting with (MeCN/water (0.1% NH_4OH) = 1/10) to give desired product (272 mg, 61% yield) as a light-yellow solid. LC-MS: m/z 235.2 $[\text{M}+\text{H}]^+$.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

ID	Structure	LC-MS: m/z $[\text{M}+\text{H}]^+$
Intermediate 57		265.1
Intermediate 58		277.2
Intermediate 59		247.1
Intermediate 60		283.1
Intermediate 127		221.3

Intermediate 128		297.1
Intermediate 129		376.2
Intermediate 130		267.1
Intermediate 131		234.2
Intermediate 132		263.2
Intermediate 133		264.3
Intermediate 134		252.1

Intermediate 135



Step 1

To a solution of piperidine-2,4-dione (5 g, 44.2 mmol) in methanol (20 mL) was added methanamine (2.7 g, 88.4 mmol, 3.0 mL). The mixture was stirred at 25 °C for 16 hours. The mixture was concentrated in vacuo to afford desired product as brown solid. LC-MS: m/z 127.1 $[M+1]^+$.

Step 2

To a solution of 4-(methanimino)-2,3-dihydro-1H-pyridin-6-one (2.6 g, 20.8 mmol) in methanol (20 mL) was added dioxoplatinum (474.1 mg, 2.0 mmol). Then the mixture was degassed with H_2 . Then the reaction mixture was stirred at 25 °C for 16 hours. The mixture was filtered and concentrated in vacuo to afford desired product as black oil. LC-MS: m/z 129.1 $[M+1]^+$.

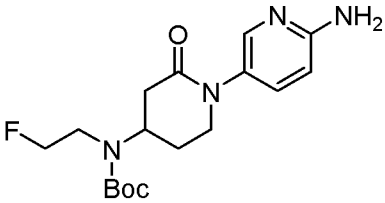
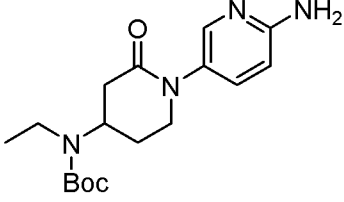
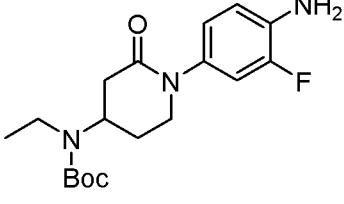
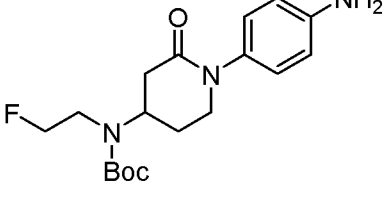
Step 3

To a solution of 4-(methanimino)piperidin-2-one (2.6 g, 20.5 mmol) in DCM (10 mL) was added *N,N*-diethylethanamine (4.1 g, 41.1 mmol) and *tert*-butoxycarbonyl *tert*-butyl carbonate (5.3 g, 24.6 mmol). The reaction mixture was stirred at 25 °C for 3 hours. The mixture was concentrated under reduced pressure and purified by flash chromatography (40 g silica gel, MeOH in DCM 0-10%) to afford desired product (2.9 g, 61% yield) as yellow oil. LC-MS: m/z 229.2 $[M+1]^+$.

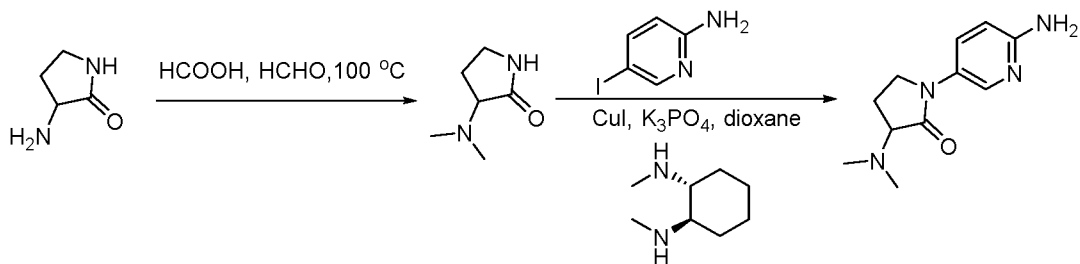
Step 4

To a solution of *tert*-butyl *N*-methyl-*N*-(2-oxo-4-piperidyl)carbamate (2 g, 8.7 mmol) in dry dioxane (20 mL) was added 5-iodopyridin-2-amine (1.9 g, 8.7 mmol), iodocopper (166.8 mg, 876 μ mol), (1*R*,2*R*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (249 mg, 1.7 mmol) and tripotassium phosphate (5.5 g, 26.2 mmol). The reaction mixture was stirred at 105 °C for 16 hours. The mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography (40 g silica gel, MeOH in DCM 0-10%) to afford desired product (1.7 g, 62% yield) as black oil. LC-MS: m/z 321.2 $[M+1]^+$.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

ID	Structure	LC-MS: m/z [M+H] ⁺
Intermediate 136		353.4
Intermediate 137		335.2
Intermediate 138		352.2
Intermediate 139		352.2

Intermediate 61



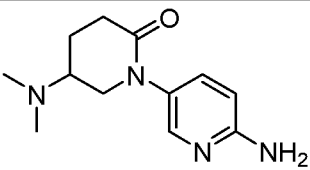
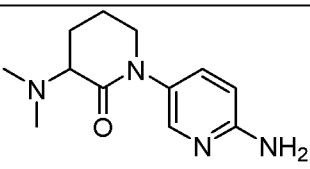
Step 1

In ice bath, to a mixture of 3-aminopyrrolidin-2-one (333 mg, 3.3 mmol) in water (8 mL) were added formic acid (610 mg, 13.2 mmol) and formaldehyde (540 mg, 17.9 mmol), the resulted mixture was stirred at 100 °C for 1.5 hours. The mixture was concentrated. The residue was purified by prep-HPLC and then lyophilized to afford desired product (162 mg) as a yellow oil. LC-MS: m/z 129.3 [M+H]⁺.

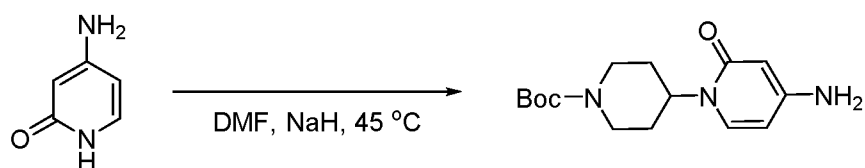
Step 2

To a solution of 3-(dimethyl amino)pyrrolidin-2-one (130 mg, 1.0 mmol) and 5-iodopyridin-2-amine (267 mg, 1.2 mmol) in dioxane (3 mL) was added (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (43 mg, 304 μmol), CuI (28.9 mg, 152 μmol) and tri-potassium phosphate (645 mg, 3.0 mmol) at 25 °C. The reaction mixture was stirred at 110 °C for 16 hours. The mixture was quenched with water (20 mL) and then extracted with ethyl acetate (2 × 10 mL). The combined organic phase was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EA in PE 20-70 % to give desired product (160 mg, 71% yield) as a yellow solid. LC-MS: m/z 221.1 [M+H]⁺.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

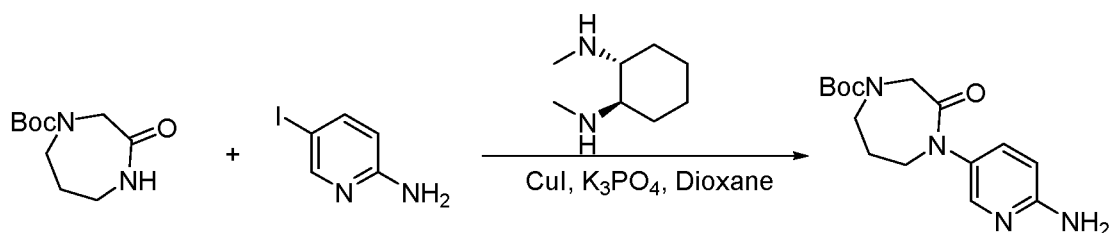
ID	Structure	LC-MS: m/z [M+H] ⁺
Intermediate 140		235.2
Intermediate 141		235.2

Intermediate 62



To a solution of 4-amino-1H-pyridin-2-one (4.0 g, 36.3 mmol) and tert-butyl 4-methylsulfonyloxypiperidine-1-carboxylate (10.1 g, 36.3 mmol) in DMF (10 mL) was added NaH (835 mg, 34.8 mmol) at 25 °C. Then the mixture was stirred at 45 °C for 6 hours. The reaction was quenched with water (200 mL) and then extracted with EA (3 × 100 mL). The organic solution was washed with brine (100 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with methanol in dichloromethane 0-15% in 20 minutes to give desired product (0.4 g, 5% yield) as yellow solid. LC-MS: m/z 294.2 [M+H]⁺.

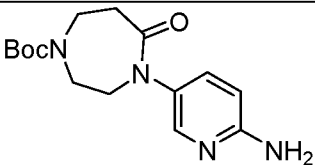
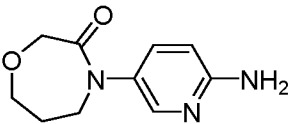
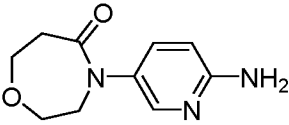
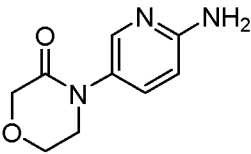
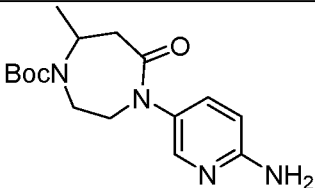
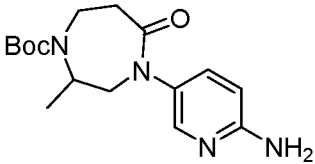
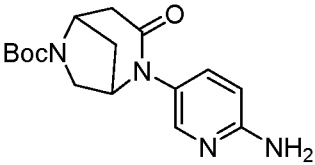
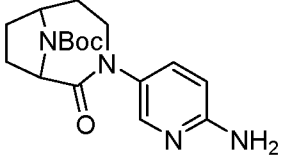
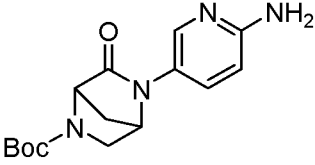
Intermediate 63



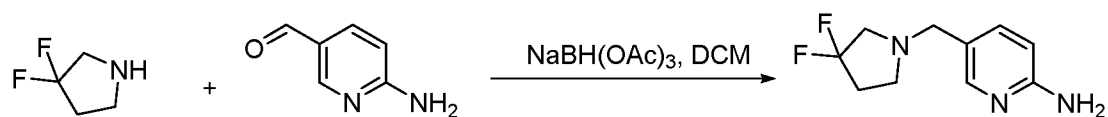
Step 1

To a stirred solution of tert-butyl 3-oxo-1,4-diazepane-1-carboxylate (500 mg, 2.3 mmol) and 5-iodopyridin-2-amine (564 mg, 2.5 mmol) in dioxane (10 mL) was added (1R,2R)-N1, N2-dimethylcyclohexane-1,2-diamine (132 mg, 933 μmol), tri-potassium phosphate (1.5 g, 7.0 mmol) and CuI (28.9 mg, 152 μmol). The reaction mixture was stirred at 110 °C under N₂ atmosphere for 5 hours. The mixture was concentrated under reduced pressure to get the residue, which was purified by flash column chromatography (80 g silica gel column), eluting with MeOH in DCM 0-5%, to obtain desired product (280 mg, 39% yield) as brown solid. LC-MS: m/z 306.2 [M+H]⁺.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

ID	Structure	LC-MS: m/z [M+H] ⁺
Intermediate 64		307.2
Intermediate 65		208.1
Intermediate 66		208.1
Intermediate 67		194.1
Intermediate 142		321.2
Intermediate 143		321
Intermediate 144		319.4
Intermediate 145		333.2
Intermediate 146		305.1

Intermediate 68

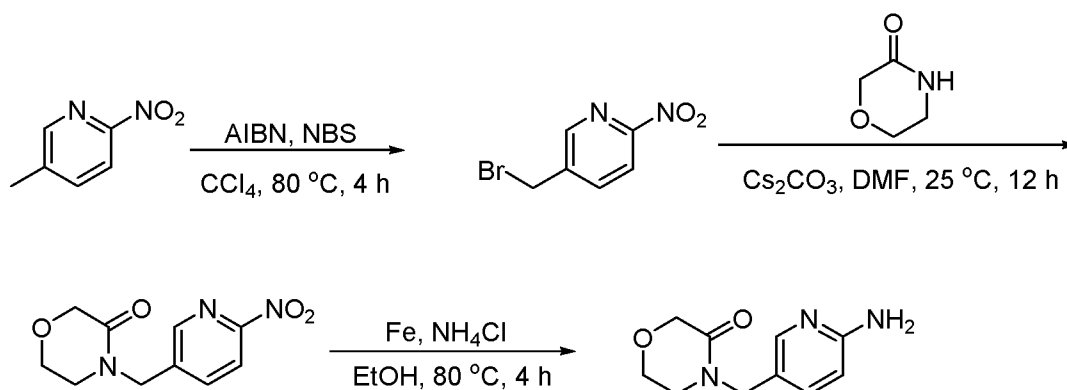


A mixture of 3,3-difluoropyrrolidine (128.0 mg, 1.2 mmol), 3,3-difluoropyrrolidine (128 mg, 1.2 mmol) and $\text{NaBH}(\text{OAc})_3$ (633 mg, 3.0 mmol) in DCM (8 mL) was stirred under N_2 atmosphere at 25 °C for 2 hours. The reaction mixture was quenched with water (50 mL) and then extracted with EtOAc (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then was filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (24 g, MeOH in DCM 0-20% in 20 minutes) to give desired product (156 mg, 73% yield) as a colorless oil. LC-MS: (ESI) m/z 214.2 $[\text{M}+\text{H}]^+$.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

ID	Structure	LC-MS: m/z $[\text{M}+\text{H}]^+$
Intermediate 69		217.1
Intermediate 70		203.1
Intermediate 71		194.1
Intermediate 72		196.1

Intermediate 73



Step 1

To a stirred solution of 5-methyl-2-nitropyridine (5.0 g, 36.2 mmol) were added 1-bromopyrrolidine-2,5-dione (6.7 g, 38.0 mmol) and azo-di-isobutyronitrile (0.6 g, 3.6 mmol). The reaction mixture was stirred at 80 °C under N₂ atmosphere for 4 hours. The mixture was filtered through Celite. The filtrate was concentrated and purified to obtain desired product (4.8 g, 61% yield) as a light-yellow solid. LC-MS: m/z 216.9 [M+H]⁺.

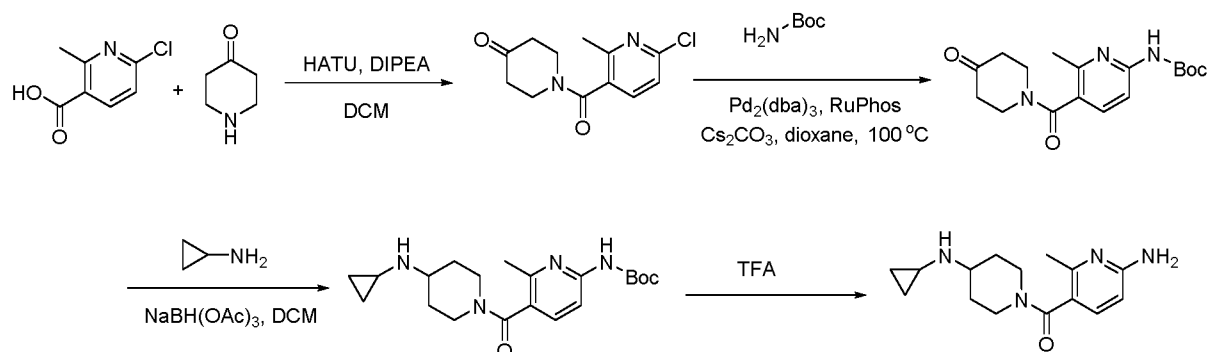
Step 2

A stirred mixture of morpholin-3-one (1.4 g, 13.8 mmol) and cesium carbonate (2.2 g, 6.9 mmol) in DMF (15 mL) was stirred at 25 °C for 12 hours. To the above mixture was added 5-(bromomethyl)-2-nitropyridine (1.0 g, 4.6 mmol) at 25 °C. The resulting mixture was stirred at 25 °C for 4 hours under N₂ atmosphere. The mixture was poured into water (100 mL) and extracted with dichloromethane (5 × 200 mL). The combined organic phase was dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to get the residue, which was purified to obtain desired product (100 mg, 7% yield) as a white solid. LC-MS: m/z 238 [M+H]⁺.

Step 3

To a stirred solution of 4-[(6-nitro-3-pyridyl) methyl] morpholin-3-one (40.0 mg, 168 μmol) in ethanol (2 mL) were added NH₄Cl (100 mg, 2.0 mmol) and iron powder (37.6 mg, 674 μmol) at 25 °C. The reaction mixture was stirred at 80 °C under N₂ atmosphere for 12 hours. The mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain desired product (23.0 mg, 65% yield) as a light-yellow solid, which was used directly in the next step without further purification. LC-MS: m/z 208 [M+H]⁺.

Intermediate 74



Step 1

A mixture of 6-chloro-2-methylpyridine-3-carboxylic acid (2.0 g, 11.6 mmol), piperidin-4-one (1.4 g, 13.9 mmol), N-ethyl-N-isopropylpropan-2-amine (3.8 g, 29.1 mmol) and HATU (5.3 g, 14.0 mmol) in DCM (25 mL) was stirred under N_2 atmosphere at room temperature for 2 hours. The reaction mixture was quenched with water (100 mL) and then extracted with DCM (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (40 g, EtOAc in PE 0-100% in 20 minutes) to give desired product (3.5 g, 95% yield) as a yellow oil. LC-MS: m/z 253.1 $[M+H]^+$.

Step 2

A mixture of 1-(6-chloro-2-methylpyridine-3-carbonyl)piperidin-4-one (760 mg, 3.0 mmol), tert-butyl carbamate (421 mg, 3.6 mmol), $Pd_2(dba)_3$ (137 mg, 149 μ mol), RuPhos (137 mg, 294 μ mol) and Cs_2CO_3 (1.5 g, 4.6 mmol) in dioxane (10 mL) was stirred under N_2 atmosphere at 100 °C for 2 hours. The reaction mixture was quenched with water (50 mL) and then extracted with EtOAc (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (12 g, EtOAc in PE 0-100% in 10 minutes) to give desired product (430 mg, 36% yield) as a yellow solid. LC-MS: m/z 334.1 $[M+H]^+$.

Step 3

A mixture of tert-butyl N-[6-methyl-5-(4-oxopiperidine-1-carbonyl)-2-pyridyl]carbamate (1.9 g, 5.9 mmol), cyclopropanamine (681 mg, 11.9 mmol) and $NaBH(OAc)_3$ (3.8 g, 17.9 mmol) in DCM (100 mL) was stirred at 25 °C for 2 hours. The reaction mixture was quenched with water (200 mL) and then extracted with DCM (3×150 mL). The combined organic phase

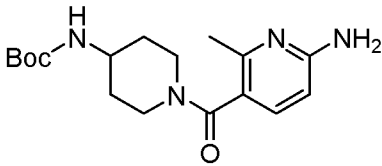
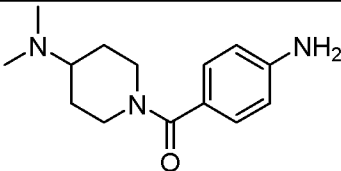
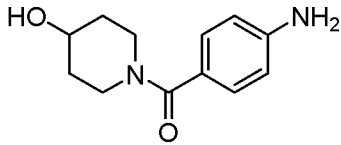
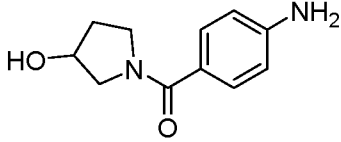
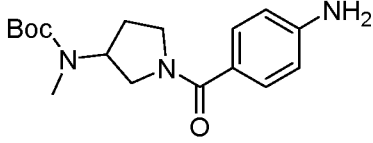
was dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (40 g, EtOAc in PE 0-100% in 25 minutes) to desired product (1.3 g, 30% yield) as a yellow solid. LC-MS: m/z 375.1 $[\text{M}+\text{H}]^+$.

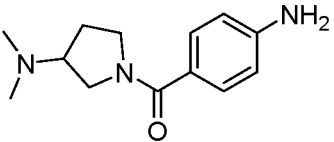
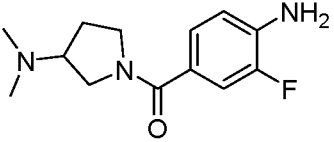
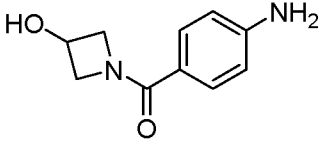
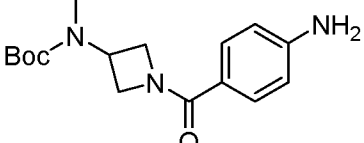
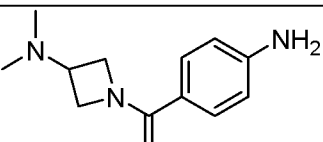
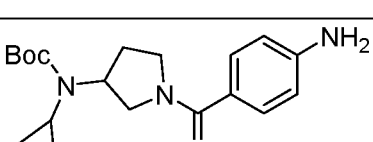
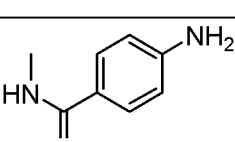
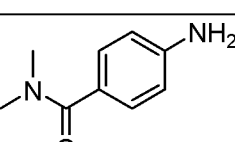
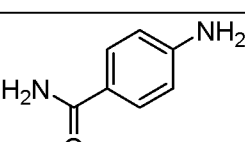
Step 4

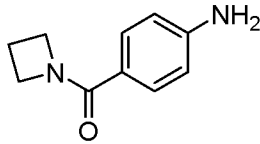
A mixture of tert-butyl N-[5-[4-(cyclopropylamino) piperidine-1-carbonyl]-6-methyl-2-pyridyl] carbamate (1.3 g, 3.4 mmol) in TFA (6 mL) was stirred at room temperature for 2 hours. The reaction mixture was added anhydrous K_2CO_3 and then was filtered. The filtrate was concentrated to give desired product (750 mg, 80% yield) as a yellow solid. LC-MS: m/z 275.1 $[\text{M}+\text{H}]^+$.

Additional intermediate of invention was prepared by using the corresponding derivative.

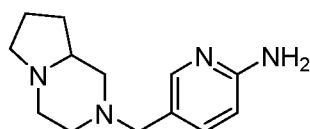
Selected compound and its corresponding characterization data are presented in Table below.

ID	Structure	LC-MS: m/z $[\text{M}+\text{H}]^+$
Intermediate 75		335.2
Intermediate 147		248.1
Intermediate 148		221.3
Intermediate 149		207.1
Intermediate 150		320.2

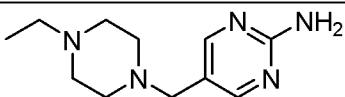
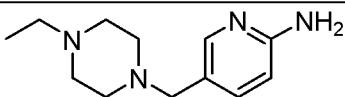
Intermediate 151		234.2
Intermediate 152		252.1
Intermediate 153		193.0
Intermediate 154		306.2
Intermediate 155		220.1
Intermediate 156		346.2
Intermediate 157		151.0
Intermediate 158		165.0
Intermediate 159		137.0

Intermediate 160		177.0
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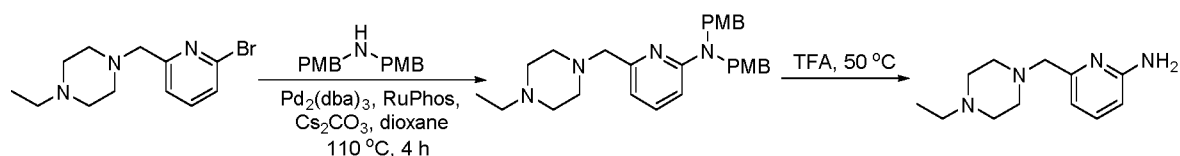
Intermediate 76



To a suspension of 1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-a] pyrazine (2.0 g, 15.8 mmol) oxalate in DCM/MeCN (5/1) was added anhydrous Na_2CO_3 (4.6 g, 43.3 mmol). Then the mixture was stirred at room temperature for 16 hours. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue and 6-aminopyridine-3-carbaldehyde (1.3 g, 10.6 mmol) was dissolved in DCM (20 mL). Then sodium triacetoxyborohydride (6.0 g, 28.3 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 16 hours. The mixture was quenched with 10 mL MeOH. Then the mixture was diluted with EtOAc (200 mL). Then the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (40 g silica gel column, MeOH (5% NH_4OH) in DCM 0-20%) to afford desired product (720 mg, 19% yield). LC-MS: m/z 233.1 $[\text{M}+\text{H}]^+$.

ID	Structure	LC-MS: m/z $[\text{M}+\text{H}]^+$
Intermediate 77		222.2
Intermediate 78		221.2

Intermediate 79



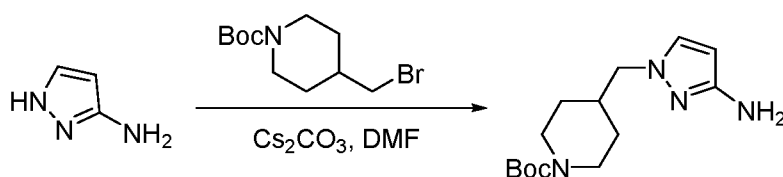
Step 1

A mixture of 1-((6-bromopyridin-2-yl)methyl)-4-ethylpiperazine (300 mg, 1.1 mmol), bis(4-methoxybenzyl)amine (327 mg, 1.3 mmol), $\text{Pd}_2(\text{dba})_3$ (302 mg, 0.3 mmol), RuPhos (306 mg, 0.7 mmol) and Cs_2CO_3 (718 mg, 2.2 mmol) in dioxane (10 mL) was stirred under N_2 protection for 4 h at 110 °C. EtOAc (80 mL) was added to this mixture and filtered. The filtrate was concentrated in vacuo to give the residue. The residue was purified by flash column chromatography (4 g silica gel column, MeOH in DCM 0-10%) to afford desired product (409 mg, 84% yield) as light-yellow solid. LC-MS: (ESI) m/z 461.3 $[\text{M}+\text{H}]^+$.

Step 2

A mixture of 6-[(4-ethylpiperazin-1-yl) methyl]-N,N-bis[(4-methoxyphenyl)methyl]pyridin-2-amine (130 mg, 282 μmol) in 2,2,2-trifluoroacetic acid (2 mL) was stirred at 50 °C for 5 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography eluting methyl alcohol with dichloromethane 0-10 % to give desired product (50.0 mg, 80% yield) as blank solid. LC-MS: (ESI) m/z 221 $[\text{M}+\text{H}]^+$.

Intermediate 80

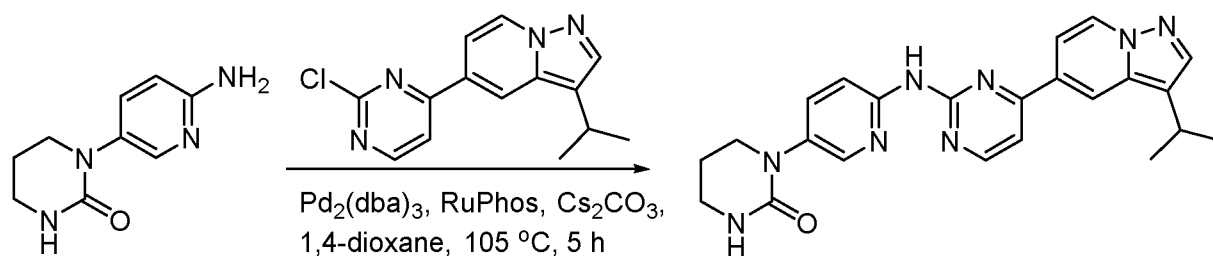


To a solution of 1H-pyrazol-3-amine (1.0 g, 12.0 mmol) and tert-butyl 4-(bromomethyl)piperidine-1-carboxylate (3.3 g, 12.0 mmol) in DMF (10 mL) was added cesium carbonate (11.7 g, 36.1 mmol) at 25 °C. Then the mixture was stirred at 25 °C for 3 hours. The organic phase was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with methanol in dichloromethane 0-15% in 20 minutes to give desired product (1.2 g, 35% yield) as brown solid. LC-MS: m/z 281.2 $[\text{M}+\text{H}]^+$.

Additional intermediates of invention were prepared by using the corresponding derivatives. Selected compounds and their corresponding characterization data are presented in Table below.

ID	structure	LC-MS: m/z [M+H] ⁺
Intermediate 81		308.2
Intermediate 82		308.2
Intermediate 83		281.2

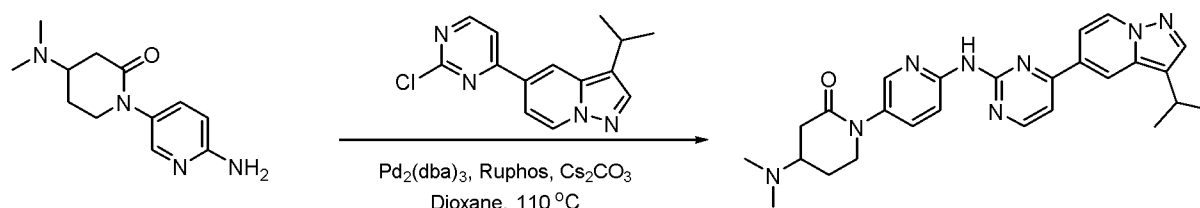
Synthetic Example 1



To a stirred solution of 1-(6-amino-3-pyridyl)hexahydropyrimidin-2-one (38.1 mg, 198 μmol) and 5-(2-chloropyrimidin-4-yl)-3-isopropyl-pyrazolo[1,5-a]pyridine (45.0 mg, 165 μmol) in anhydrous 1,4-dioxane (2 mL) was added $\text{Pd}_2(\text{dba})_3$ (15.1 mg, 16.5 μmol), RuPhos (7.7 mg, 16.5 μmol) and cesium carbonate (161 mg, 494 μmol) at 25 °C under N_2 . The resulting mixture was stirred at 105 °C for 6 h. The reaction was cooled to 25 °C. The mixture was filtered, and the filtrate was concentrated. The residue was purified by prep-HPLC to afford desired product (8.7 mg, 12% yield) as a yellow solid. LC-MS: m/z 429.2 [M+H]⁺.

CDK4 IC₅₀: A; CDK6 IC₅₀: B; CDK2 IC₅₀: C.

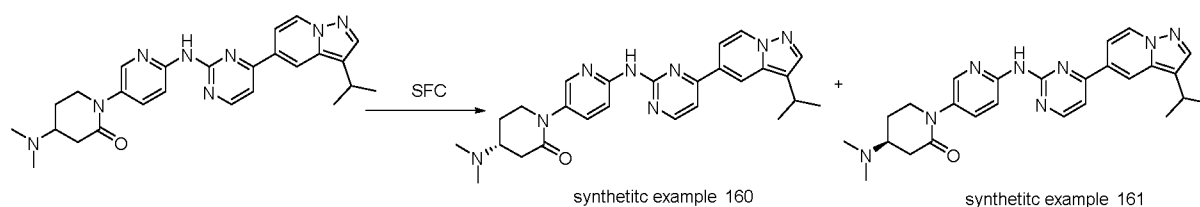
Synthetic Example 16



To a mixture of 1-(6-amino-3-pyridyl)-4-(dimethylamino)piperidin-2-one (30 mg, 128 μ mol) and 5-(2-chloropyrimidin-4-yl)-3-isopropyl-pyrazolo[1,5-a]pyridine (38.4 mg, 140.8 μ mol) in dioxane (5 mL) was added cesium carbonate (125.1 mg, 384.1 μ mol), tris(dibenzylideneacetone)dipalladium(0) (11.7 mg, 12.8 μ mol) and RuPhos (11.9 mg, 25.6 μ mol). The resulting mixture was stirred under nitrogen atmosphere at 110 °C for 4 h. The reaction mixture was extracted with EA (20 mL). The organic phase was washed with water (3 $\times$ 20 mL), brine (3 $\times$ 20 mL) and dried over Na₂SO₄. The mixture was concentrated under reduced pressure and purified by flash column chromatography (DCM/MeOH= 10:1) to afford desired product (23.8 mg, 39% yield) as a yellow solid. LC-MS: m/z 471.2 [M+H]⁺.

CDK4 IC₅₀: A; CDK6 IC₅₀: A; CDK2 IC₅₀: B.

Synthetic Examples 160 and 161

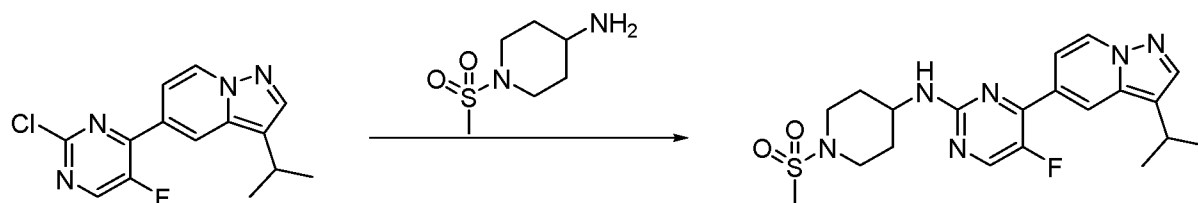


N-[5-[4-(dimethylamino)-1-piperidyl]-2-pyridyl]-4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-amine (210 mg, 459.9 μ mol) was chiral separated by SFC with mobile phase (Hexane/EtOH/DEA=60/40/0.1) (wave length: UV 214 nm, Column: CHIRALCEL OD-H 5.0 cm I.D. $\times$ 25 cm L, Flow rate: 60 mL/min) to give synthetic example 160 (44.2 mg, 21% yield) as a yellow solid (LC-MS: m/z 471.2 [M+H]⁺. ee value >99%) and synthetic example 161 (41.0 mg, 19% yield) as a yellow solid (LC-MS: m/z 471.2 [M+H]⁺. ee value 97%).

Synthetic Example 160, CDK4 IC₅₀: A; CDK6 IC₅₀: B; CDK2 IC₅₀: B.

Synthetic Example 161, CDK4 IC₅₀: A; CDK6 IC₅₀: A; CDK2 IC₅₀: A.

Synthetic Example 10

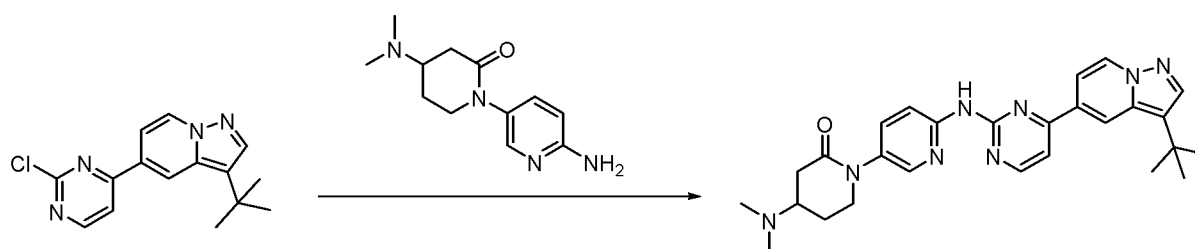


To a solution of 1-methylsulfonylpiperidin-4-amine (20.2 mg, 113.5 μ mol) and 5-(2-chloro-5-fluoro-pyrimidin-4-yl)-3-isopropyl-pyrazolo[1,5-a]pyridine (30 mg, 103.2 μ mol) in

anhydrous dioxane (8 mL) was added tris(dibenzylideneacetone)dipalladium(0) (9.45 mg, 10.3 μ mol), dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane (9.6 mg, 20.6 μ mol) and cesium carbonate (100.8 mg, 309.5 μ mol) under the atmosphere of N₂. Then the reaction mixture was stirred at 110 °C for 5 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography to afford desired product (9 mg, 20% yield) as a pale yellow solid. LC-MS: m/z 433.2 [M+H]⁺.

CDK4 IC₅₀: B; CDK6 IC₅₀: C; CDK2 IC₅₀: B.

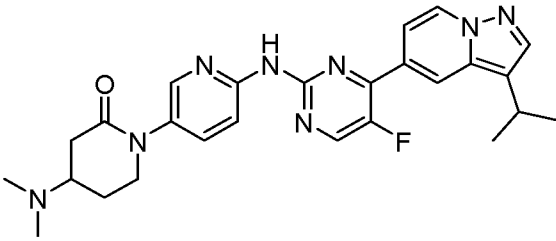
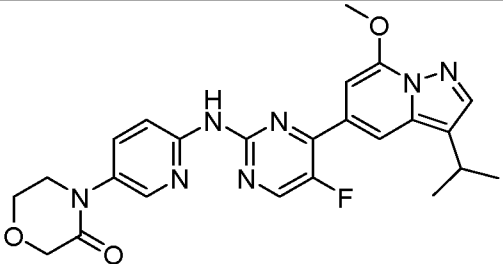
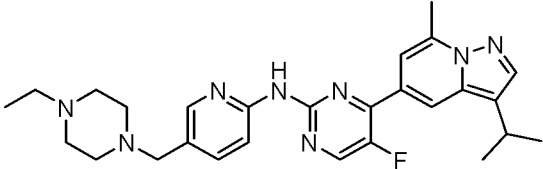
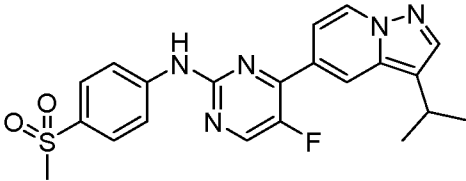
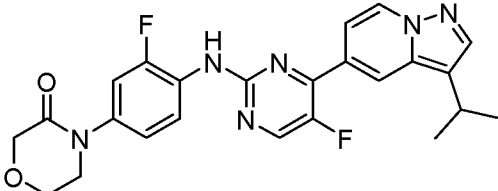
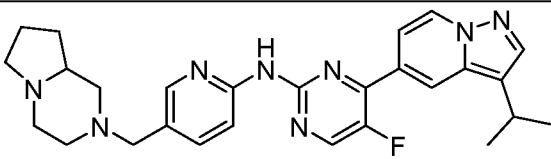
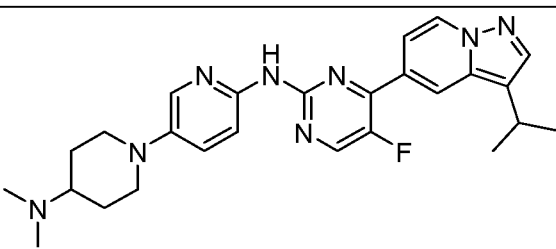
Synthetic Example 175

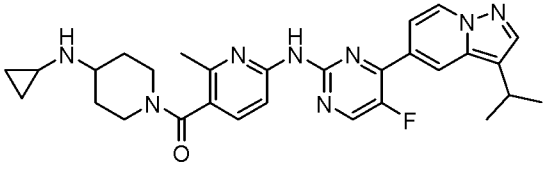
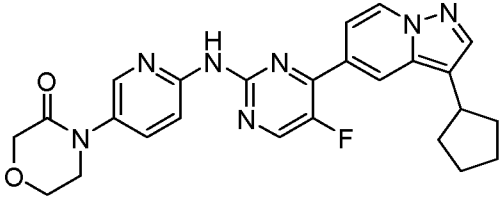
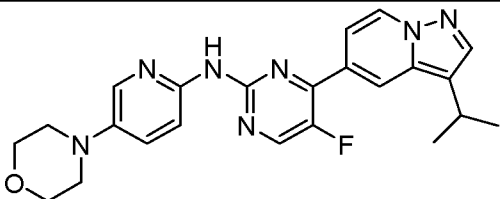
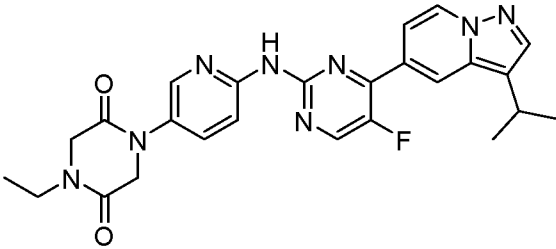
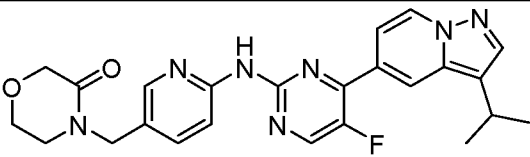
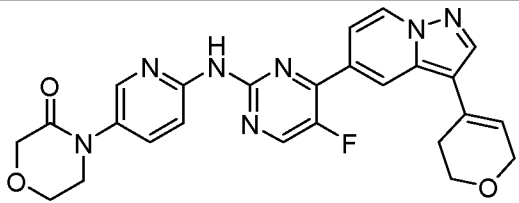
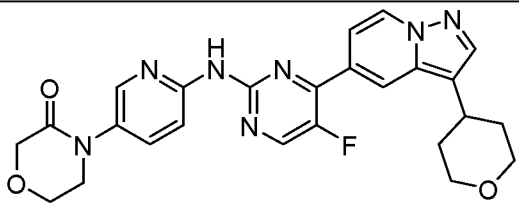
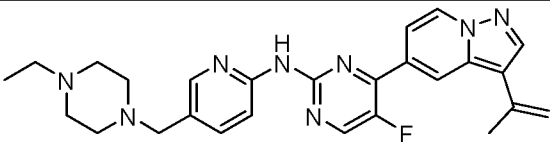


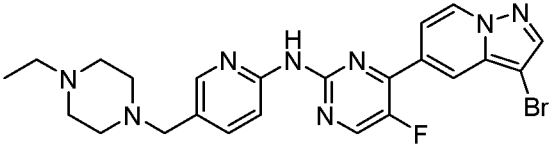
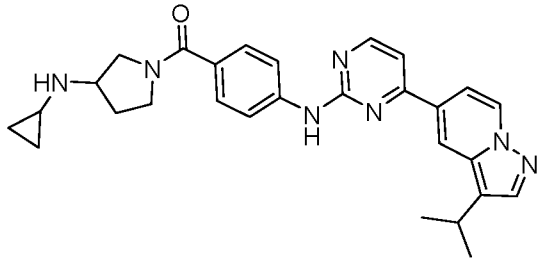
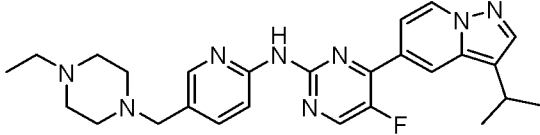
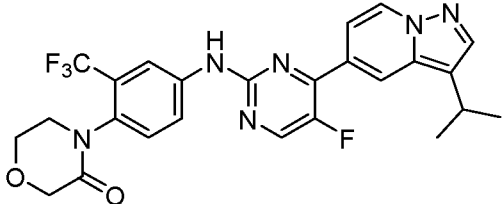
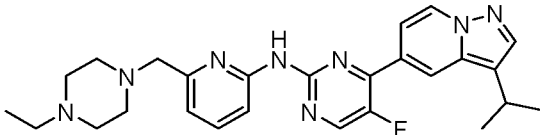
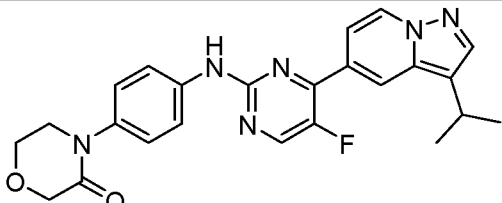
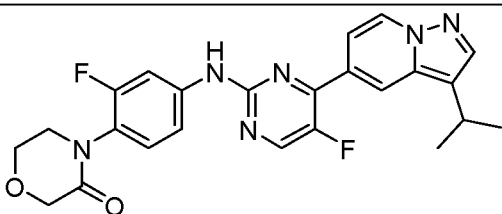
To a solution of 3-tert-butyl-5-(2-chloropyrimidin-4-yl)pyrazolo[1,5-a]pyridine (40 mg, 139.4 μ mol) and 1-(6-amino-3-pyridyl)-4-(dimethylamino)piperidin-2-one (32.6 mg, 139.4 μ mol) in anhydrous dioxane (8 mL) was added tris(dibenzylideneacetone)dipalladium(0) (12.7 mg, 13.95 μ mol), RuPhos (13 mg, 27.9 μ mol) and cesium carbonate (136.3 mg, 418.4 μ mol) under the atmosphere of N₂. Then the reaction mixture was stirred at 110 °C under the atmosphere of N₂ for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (40 g silica gel column, MeOH with DCM 0-10%) to afford desired product (25 mg, 37% yield) as a yellow solid. LC-MS: m/z 485.3 [M+H]⁺.

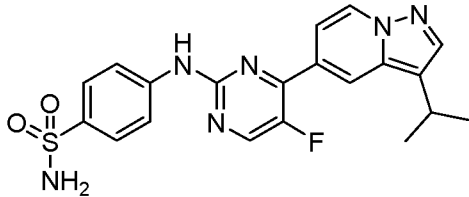
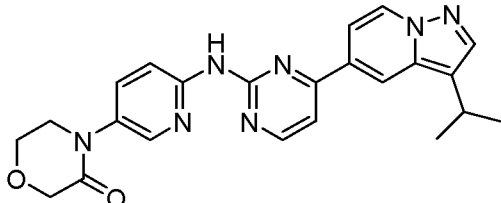
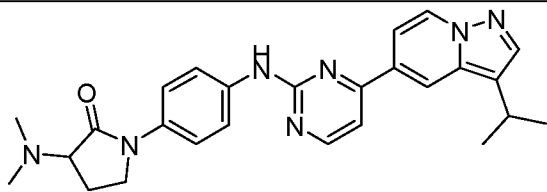
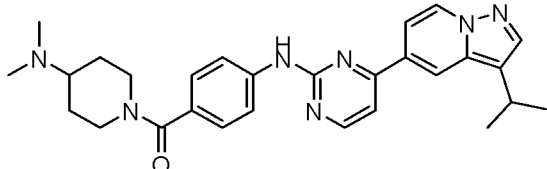
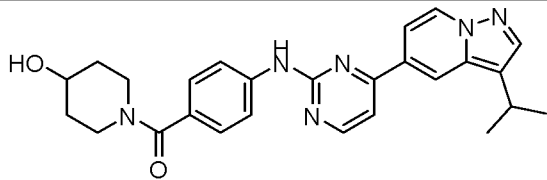
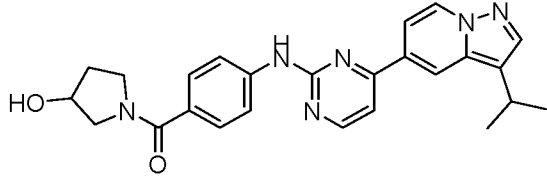
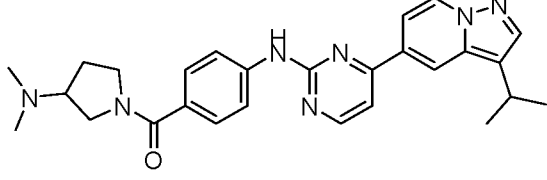
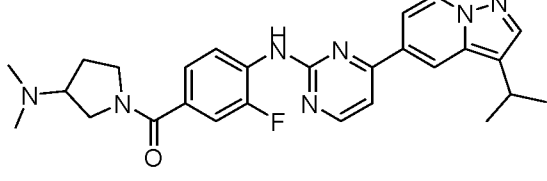
CDK4 IC₅₀: A; CDK6 IC₅₀: A; CDK2 IC₅₀: A.

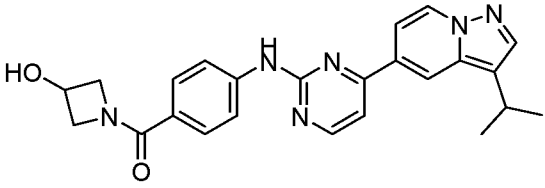
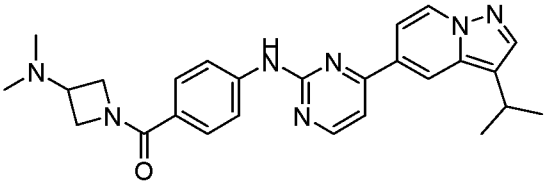
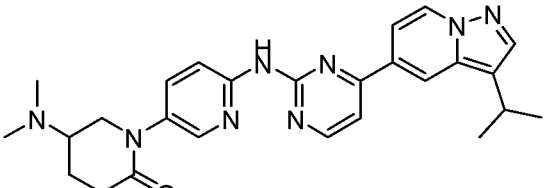
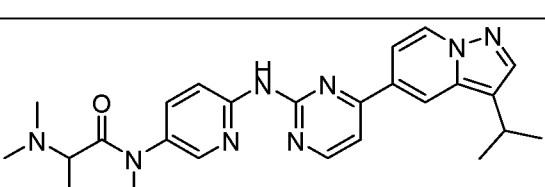
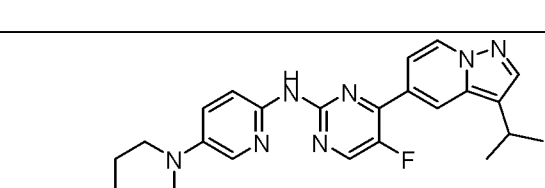
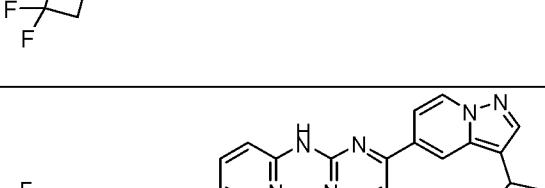
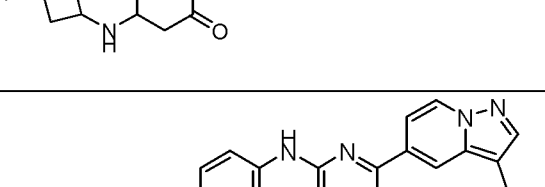
Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC ₅₀	CDK6 IC ₅₀	CDK2 IC ₅₀
2		448.3	A	B	A

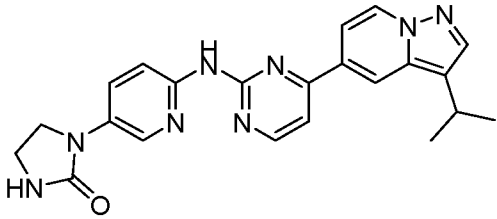
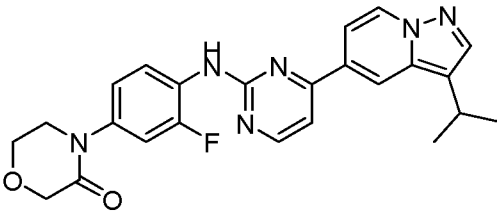
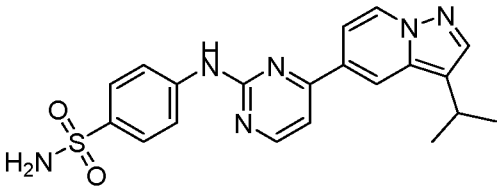
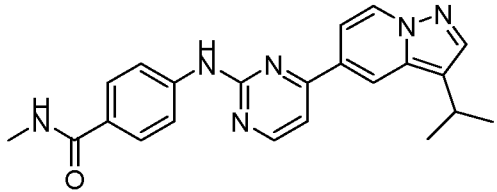
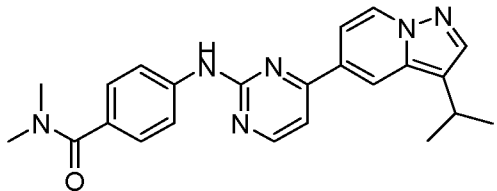
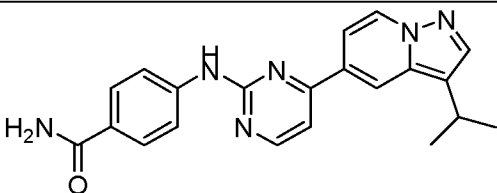
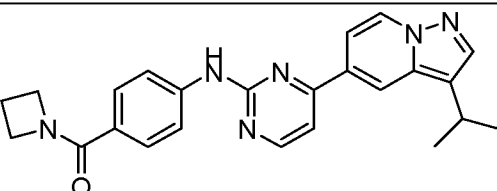
3		489.3	A	B	B
4		448.2	B		C
5		489.3	B	C	
6		426.1	C		B
7		465.2	A	B	A
8		487.2	B	C	D
9		475.3	A	B	C

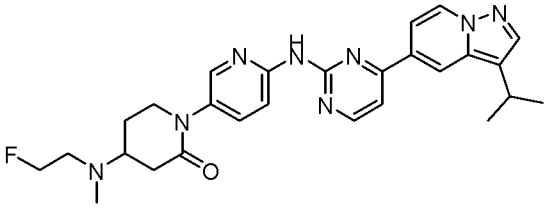
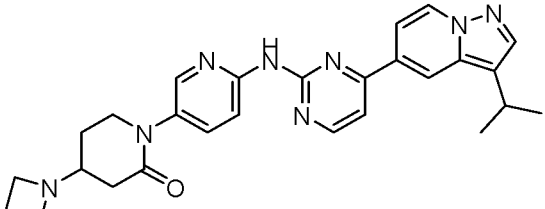
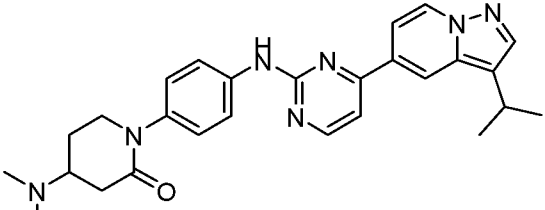
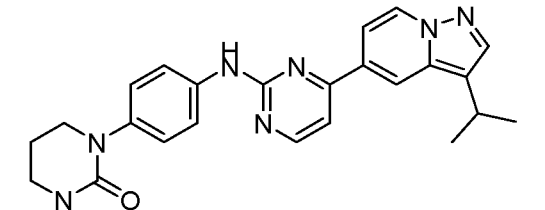
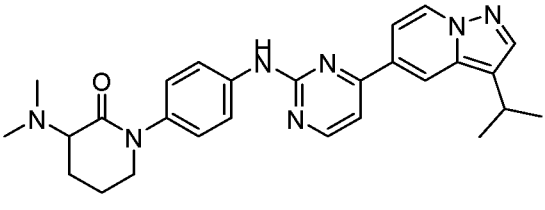
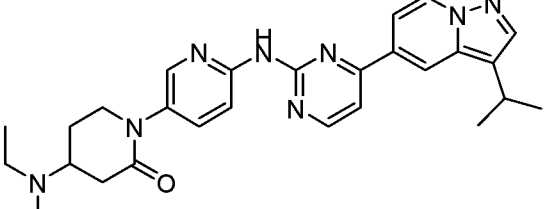
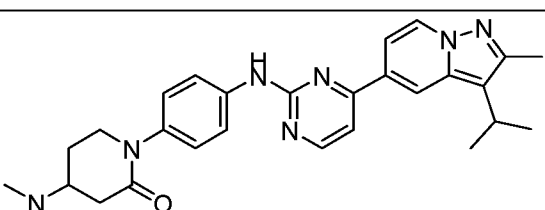
11		529.3	B	B	C
12		474.1	B		C
13		434.2	B	B	
14		489.2	B		B
15		462.1	B	C	C
17		488.1	B	C	
18		490.2	B	C	
19		473.3	B	C	

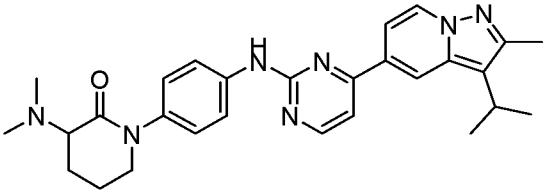
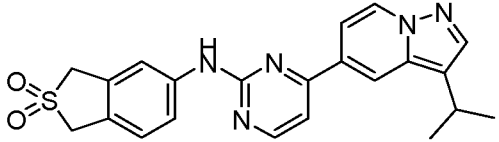
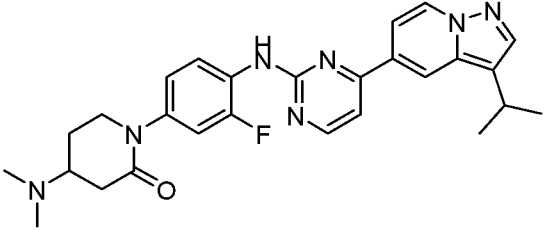
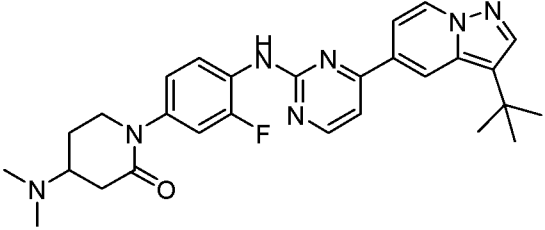
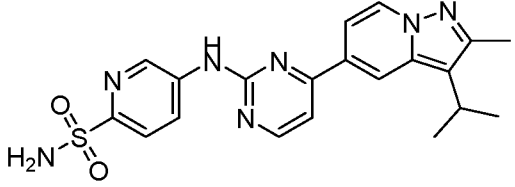
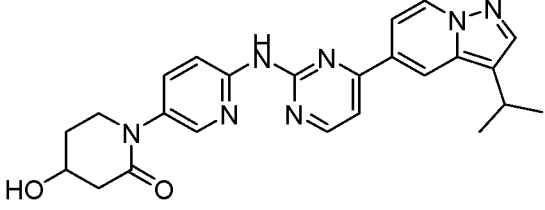
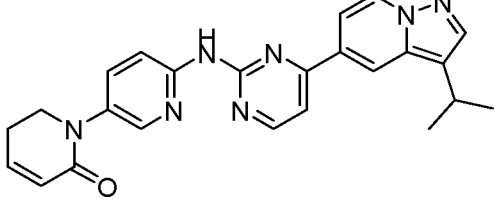
20		511.2	C	D	
21		482.3	A		A
22		475.3	A	B	
23		515.2	B	B	
24		475.2	C	D	
25		447.2	A	B	A
26		465.7	A	B	A

27		427.1	B	C	A
28		430.2	A	B	A
144		456.2	A		A
148		484.2	A		A
149		457.2	B		A
150		443.2	A		A
151		470.3	A		A
152		488.3	B		B

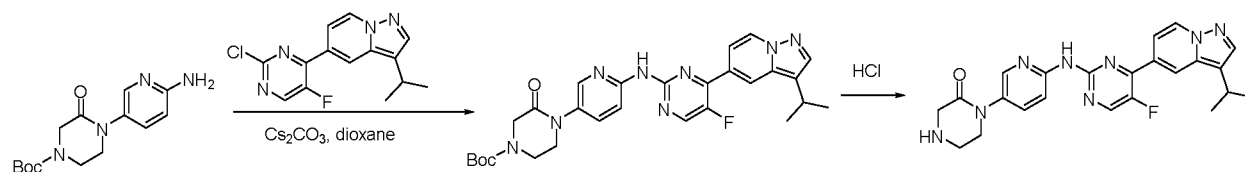
153		429.2	A		A
154		456.2	A		A
156		471.3	B	C	B
157		471.3	A	B	C
158		537.2	A	B	B
159		551.2	A	B	B
162		501.2	A	B	B

163		415.1	A	B	B
164		447.2	A	B	A
165		409.1	B	C	A
166		387.1	A	B	A
167		401.2	A	B	A
168		373.2	A	B	A
169		413.2	A	B	A

170		503.6	A		B
171		483.5	A	B	A
172		470.3	A	A	A
173		428.2	A	A	B
174		470.3	A		C
176		499.3	A	B	B
177		484.2	A	A	A

178		484.2	A		C
179		420.1	A	A	A
180		488.4	A		A
181		502.2	A		A
182		424.5	B		A
183		444.5	B	B	B
184		426.2	A	B	B

Synthetic Example 29



Step 1

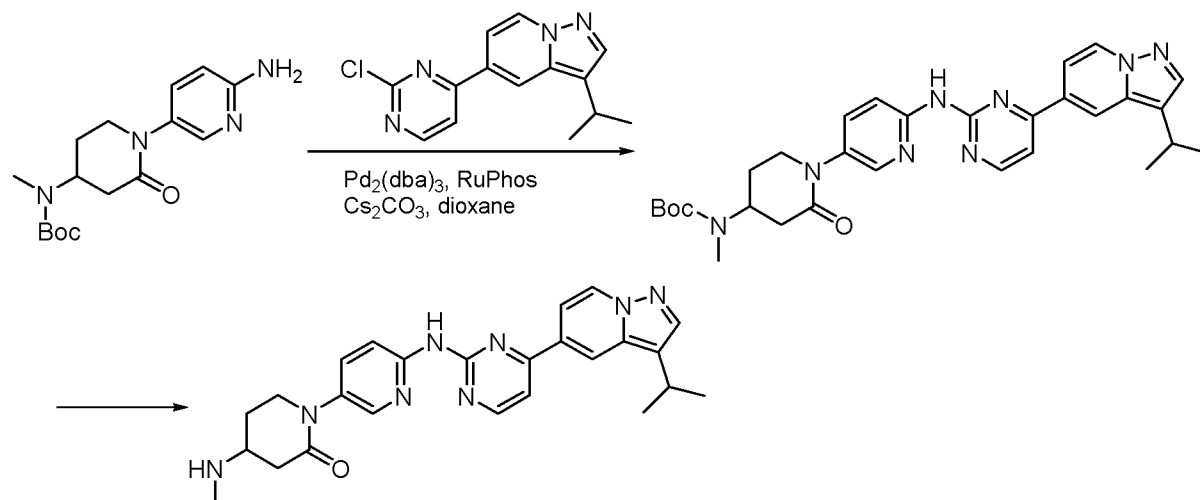
To a solution of 5-(2-chloro-5-fluoro-pyrimidin-4-yl)-3-isopropyl-pyrazolo[1,5-a]pyridine (150 mg, 515 μmol) and tert-butyl 4-(6-amino-3-pyridyl)-3-oxo-piperazine-1-carboxylate (196 mg, 670 μmol) in dioxane (20 mL) was added tris(dibenzylideneacetone)dipalladium(0) (47.2 mg, 51.6 μmol), RuPhos (24.0 mg) and cesium carbonate (336 mg, 1.0 mmol) at 25 °C. Then the mixture was stirred at 110 °C for 2 hours. The solvent was removed under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH in DCM 0-15% in 20 minutes to give desired product (240 mg, 85% yield) as light-yellow solid. LC-MS: m/z 547.2 $[\text{M}+\text{H}]^+$.

Step 2

To a solution of tert-butyl 4-[6-[[5-fluoro-4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-yl]amino]-3-pyridyl]-3-oxo-piperazine-1-carboxylate (240 mg, 439 μmol) in DCM (2 mL) was added HCl (2 mL, 2 N in EA) at 25 °C. Then the mixture was stirred for 2 hours. The mixture was filtered, and the residue was washed by Et₂O (10 mL) to obtain desired product (190 mg, 96% yield) as a yellow solid. LC-MS: m/z 447.2 $[\text{M}+\text{H}]^+$.

CDK4 IC₅₀: A; CDK6 IC₅₀: B; CDK2 IC₅₀: B.

Synthetic Example 204



Step 1

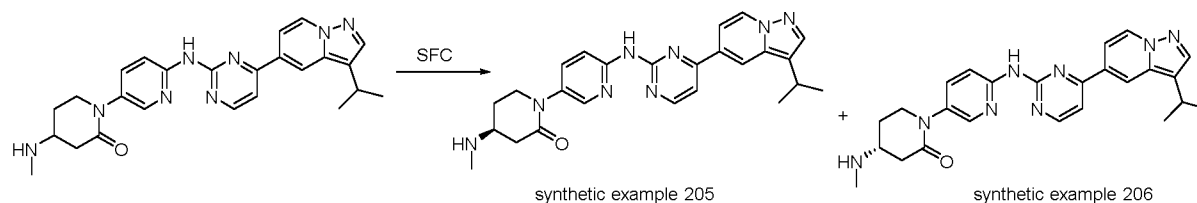
To a solution of tert-butyl N-[1-(6-amino-3-pyridyl)-2-oxo-4-piperidyl]-N-methyl-carbamate (399.4 mg, 1.2 mmol) in dioxane (30 mL) was added 5-(2-chloropyrimidin-4-yl)-3-isopropylpyrazolo[1,5-a]pyridine (340 mg, 1.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (114.1 mg, 124.6 μ mol), RuPhos (116.3 mg, 249.3 μ mol) and cesium carbonate (812.3 mg, 2.4 mmol). The reaction mixture was stirred at 110 °C for 16 hours in a 15 mL sealed tube. The mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography (12 g silica gel, MeOH in DCM 0-10%) to afford desired product (544 mg, 78% yield) as yellow oil. LC-MS: m/z 557.3 [M+H]⁺.

Step 2

To a solution of tert-butyl N-[1-[6-[[4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-yl]amino]-3-pyridyl]-2-oxo-4-piperidyl]-N-methyl-carbamate (544 mg, 977.2 μ mol) in DCM (10 mL) was added hydrogen chloride solution (2.0 M in ethyl acetate) (5 mL) at 25 °C. The mixture was stirred at 25 °C for 2 hours. The mixture was filtered and concentrated in vacuo to afford desired product (430 mg, 96% yield) as yellow solid. LC-MS: m/z 457.3 [M+H]⁺.

CDK4 IC₅₀: A; CDK6 IC₅₀: A; CDK2 IC₅₀: A.

Synthetic Examples 205 and 206

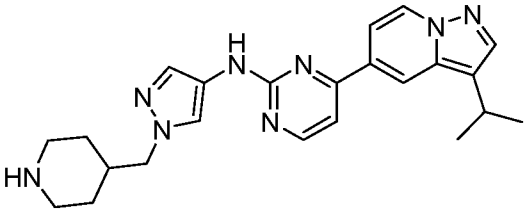
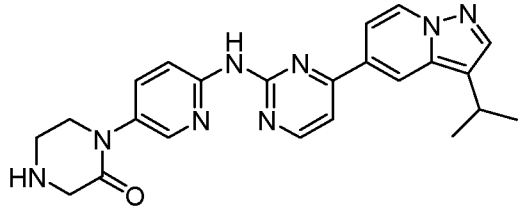
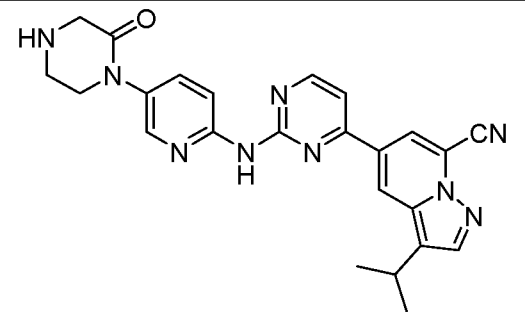
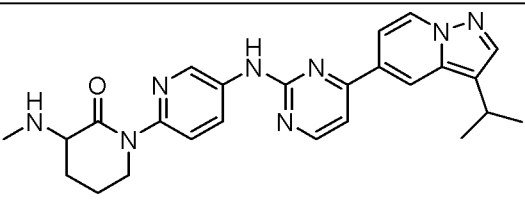
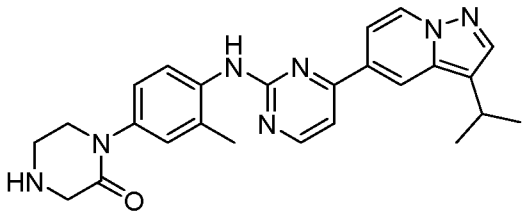
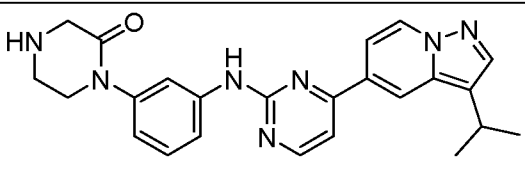
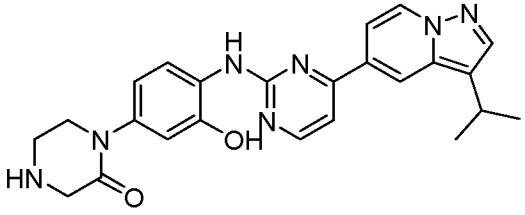


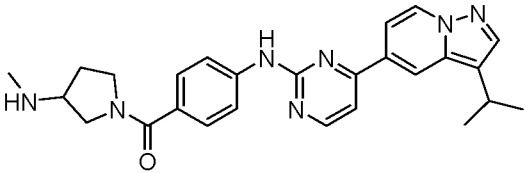
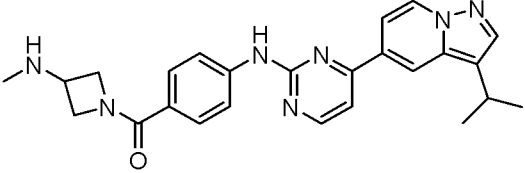
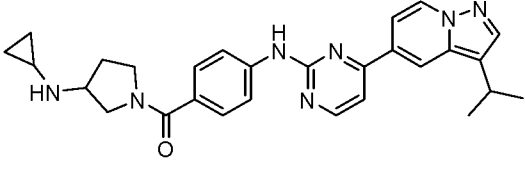
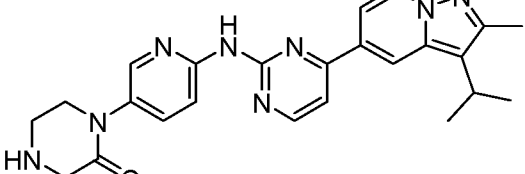
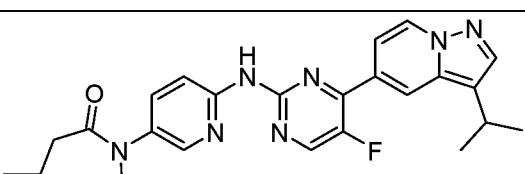
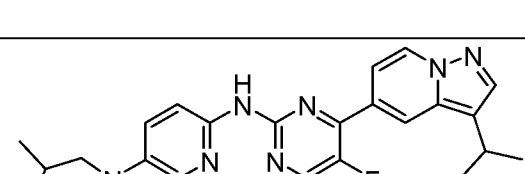
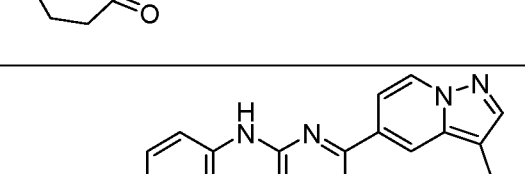
1-[6-[[4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-yl]amino]-3-pyridyl]-4-(methylamino)piperidin-2-one (380 mg, 832 μ mol) was chiral separated by ID column with mobile phase (MeOH/ACN/DEA=50/50/0.1) (wave length: UV 214 nm, Column: CHIRALPAK ID-H 25 cm L 5.0 cm I.D., 10 μ m, Flow rate: 60 g/min) to give synthetic example 205 (132 mg, 34% yield) as a white solid (LC-MS: m/z 457.3 [M+H]⁺, ee value: >98%) and synthetic example 206 (120 mg, 31% yield) as a white solid (LC-MS: m/z 457.3 [M+H]⁺, ee value: >98%).

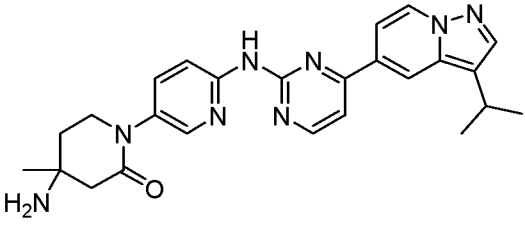
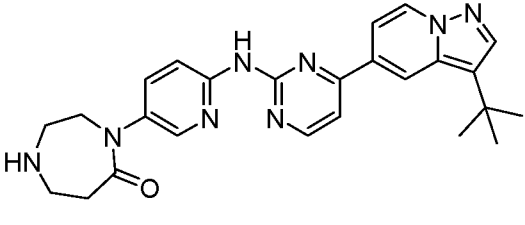
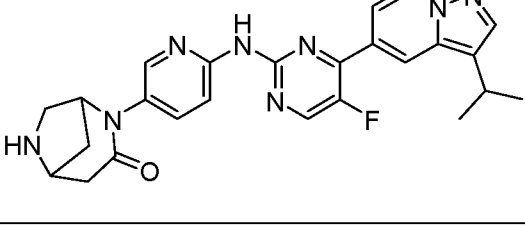
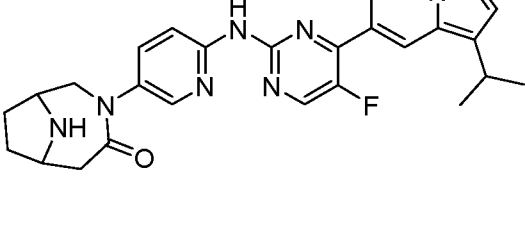
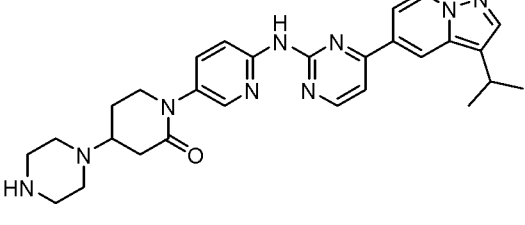
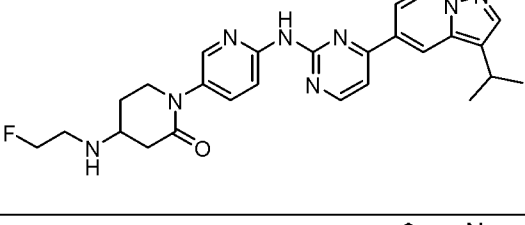
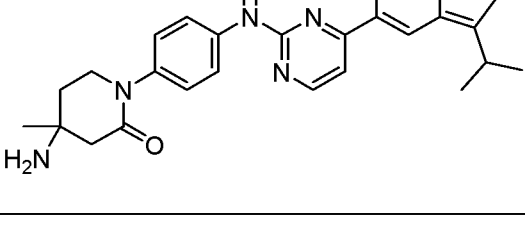
Synthetic Example 205, CDK4 IC₅₀: A; CDK6 IC₅₀: A; CDK2 IC₅₀: A.

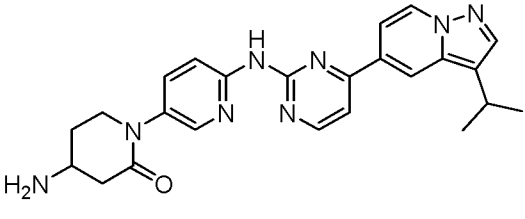
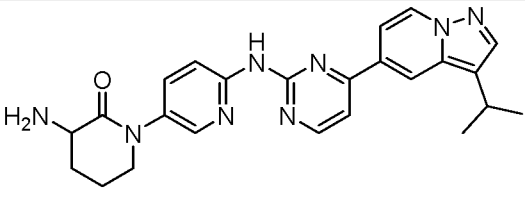
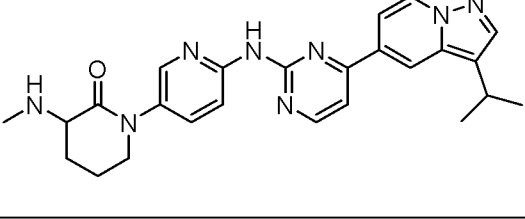
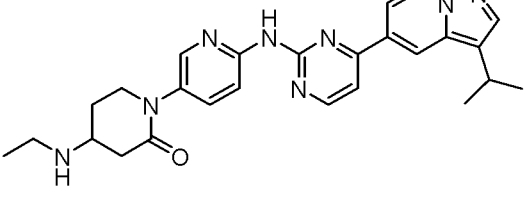
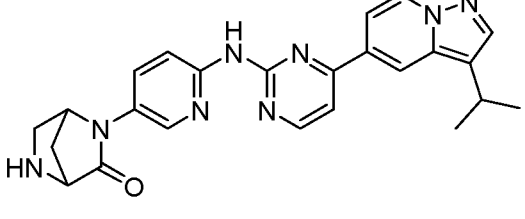
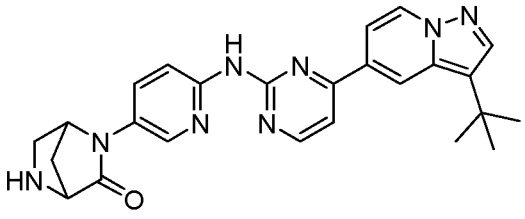
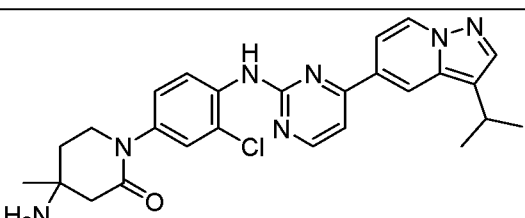
Synthetic Example 206, CDK4 IC₅₀: A; CDK2 IC₅₀: A.

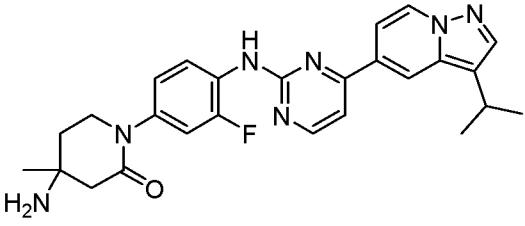
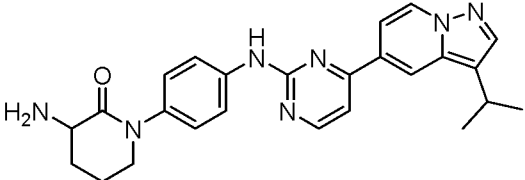
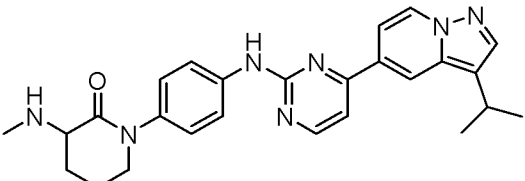
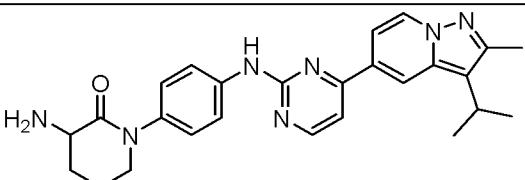
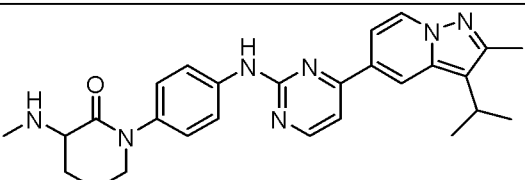
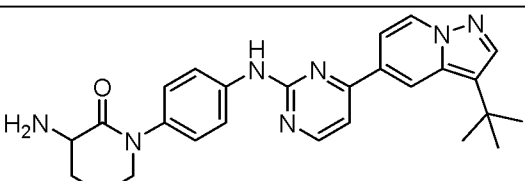
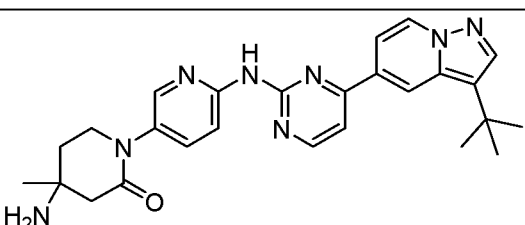
Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC ₅₀	CDK6 IC ₅₀	CDK2 IC ₅₀
30		443.7	A	B	B
31		443.2	A	B	B
32		417.2	B		D
33		461.2	A	B	B
34		461.2	A	B	B
35		451.3 [M+Na] +	A	B	A

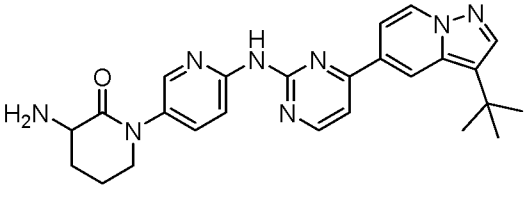
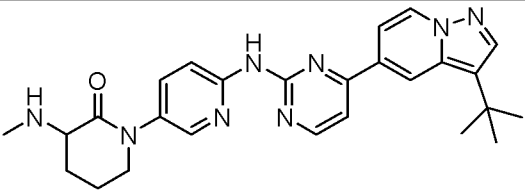
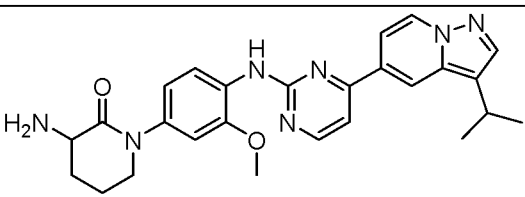
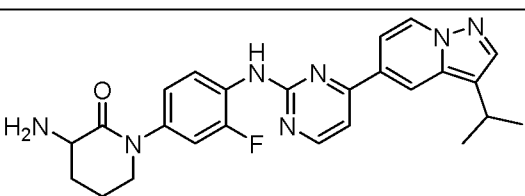
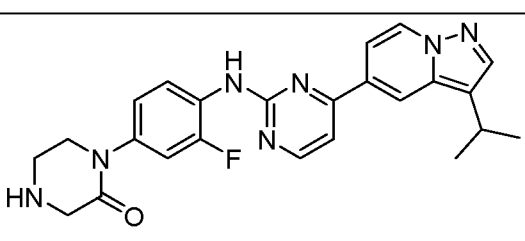
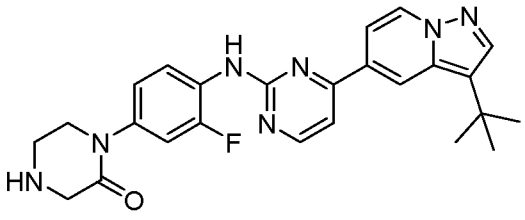
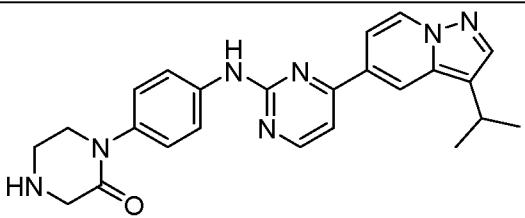
36		417.2	B		B
37		429.2	A	B	A
38		454.2	B		D
185		457.5	A		B
186		442.2	B		A
187		428.2	B		B
188		444.2	B		B

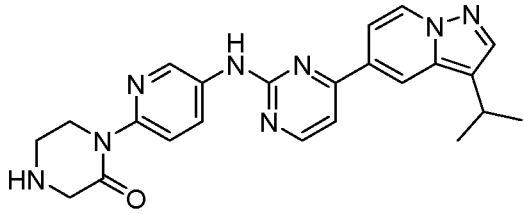
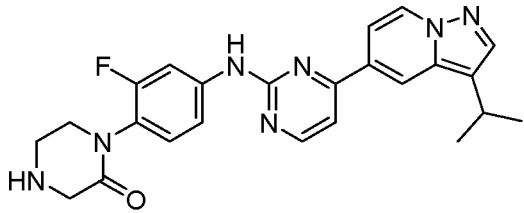
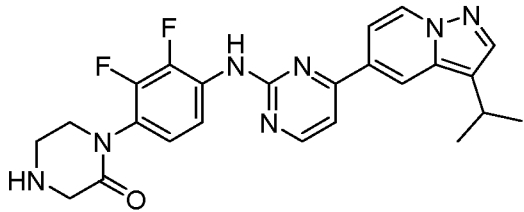
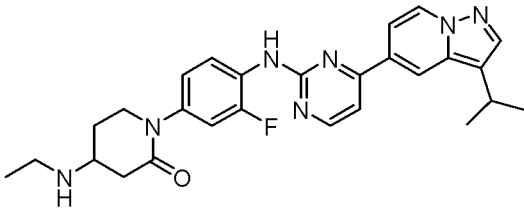
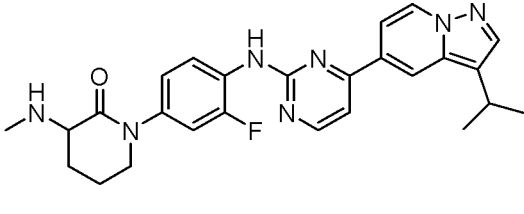
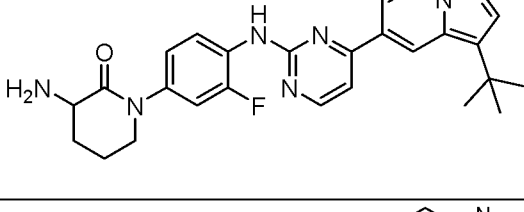
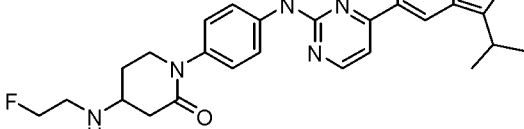
189		456.6	A	A	A
190		442.2	A		B
191		482.3	A	B	A
192		443.1	A	B	B
193		475.1	A	B	B
194		475.1	A	B	B
195		459.2	A	B	C

196		457.1	A	B	A
197		457.1	A	B	B
198		473.2	A	B	B
199		487.2	A	A	B
200		512.3	A	B	B
201		489.2	A		A
202		456.2	A	A	A

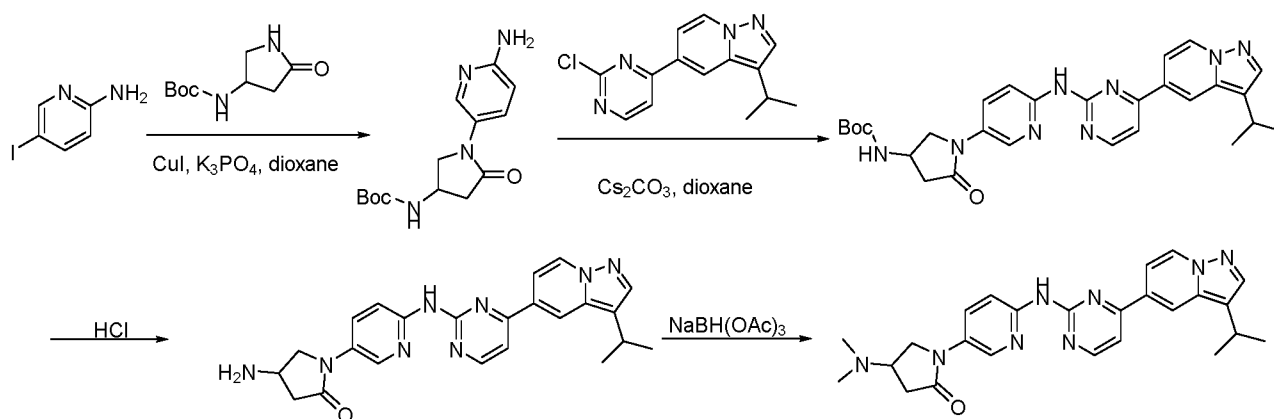
203		443.2	A	B	A
207		443.2	A	A	B
208		457.5	A		C
209		471.3	A		A
210		441.2	A		B
211		455.2	A		A
212		490.2	A		A

213		474.1	A	B	A
214		442.2	A	A	A
215		456.3	A	A	A
216		456.3	A		B
217		470.3	A	A	B
218		456.2	A	A	A
219		471.3	A		A

220		457.2	A		B
221		471.3	A		D
222		472.2	B		B
223		460.5	A		B
224		446.2	A	B	A
225		460.2	A	B	A
226		428.5	A	A	A

227		429.5	A	A
228		446.2	A	A
229		464.1	A	A
230		488.3	A	A
231		474.6	A	B
232		474.6	A	A
233		488.3	A	A

Synthetic Example 39



Step 1

To a solution of 5-iodopyridin-2-amine (100 mg, 454 μ mol) and tert-butyl N-(5-oxopyrrolidin-3-yl)carbamate (91.1 mg, 454 μ mol) in dioxane (5 mL) was added CuI (8.6 mg, 45.4 μ mol), tripotassium phosphate (289 mg, 1.3 mmol) and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (12.9 mg, 90.9 μ mol) under N₂ atmosphere. The reaction was stirred at 110 °C for 8 hr. The mixture was concentrated under reduced pressure. The residue was purified with flash column chromatography (eluting with MeOH in DCM 0-35%) to afford desired product (90.0 mg, 67% yield) as a yellow solid. LC-MS: *m/z* 292.2 [M+H]⁺.

Step 2

To a solution of tert-butyl N-[1-(6-amino-3-pyridyl)-5-oxo-pyrrolidin-3-yl]carbamate (90.0 mg, 307 μ mol) and 5-(2-chloropyrimidin-4-yl)-3-isopropylpyrazolo[1,5-a]pyridine (83.9 mg, 307 μ mol) in dioxane (2 mL) was added cesium carbonate (300 mg, 923 μ mol), dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane (28.7 mg, 61.5 μ mol) and tris(dibenzylideneacetone)dipalladium(0) (28.1 mg, 30.7 μ mol) under N₂ atmosphere. The reaction was stirred at 110 °C for 8 hr. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with MeOH in DCM 0-10% to afford desired product (90.0 mg, 55% yield) as a yellow solid. LC-MS: *m/z* 529.3 [M+H]⁺.

Step 3

To a solution of tert-butyl N-[1-[6-[[4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-yl]amino]-3-pyridyl]-5-oxo-pyrrolidin-3-yl]carbamate (90.0 mg, 170 μ mol) in DCM (10 mL) was added HCl (4 N, 0.1 mL) in EA. The reaction was stirred at 25 °C for 2 hr. The mixture

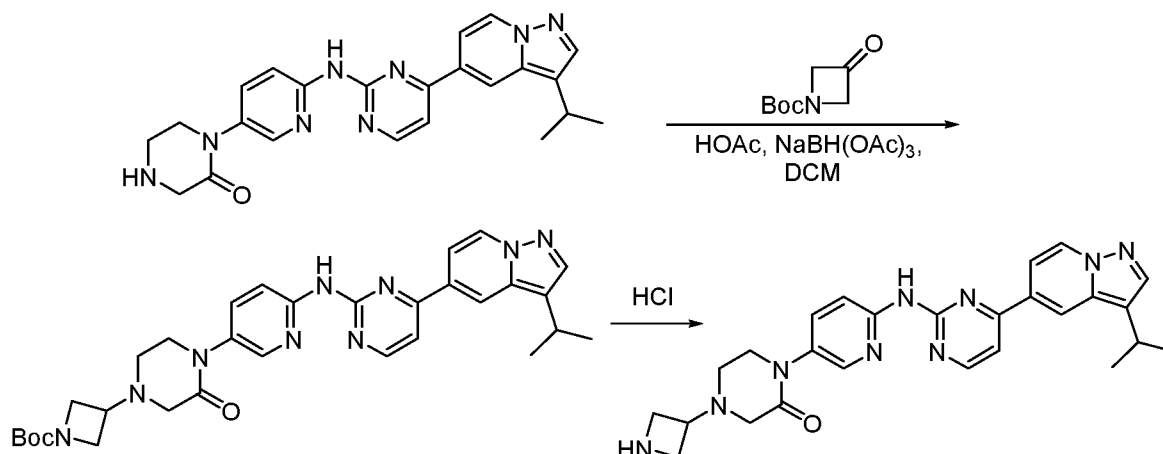
was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with MeOH in DCM 0-10% to afford desired product (70.0 mg, 95% yield) as a yellow solid. LC-MS: m/z 429.2 $[M+H]^+$.

Step 4

The solution of 4-amino-1-[6-[[4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-yl]amino]-3-pyridyl]pyrrolidin-2-one (50.0 mg, 116 μ mol) and formaldehyde (14.0 mg, 466 μ mol) in DCM (5 mL) was stirred at 25 °C for 0.5 hr. Then $\text{NaBH}(\text{OAc})_3$ (74.1 mg, 350 μ mol) was added to the above solution. The mixture was stirred at 25 °C for 8 hr. The reaction was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford desired product (15.9 mg, 29% yield) as a yellow solid. LC-MS: m/z 457.2 $[M+H]^+$.

CDK4 IC_{50} : A; CDK6 IC_{50} : B; CDK2 IC_{50} : B.

Synthetic Example 40



Step 1

To a solution of 1-[6-[[4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-yl]amino]-3-pyridyl]piperazin-2-one (80 mg, 186 μ mol) and tert-butyl 3-oxoazetidine-1-carboxylate (63.9 mg, 373 μ mol) in DCM (10 mL) were added sodium triacetoxyboranuide (118 mg, 560 μ mol) and acetic acid (16.8 mg, 280 μ mol). The reaction mixture was stirred at 15 °C for 12 h. The reaction mixture was washed with H_2O (5 mL) and brine (5 mL). The organic layer was concentrated, and the residue was purified by flash column chromatography (12 g silica gel column, MeOH in DCM 0-10%) to afford desired product (72.0 mg, 66% yield) as yellow solid. LC-MS: m/z 584.3 $[M+H]^+$.

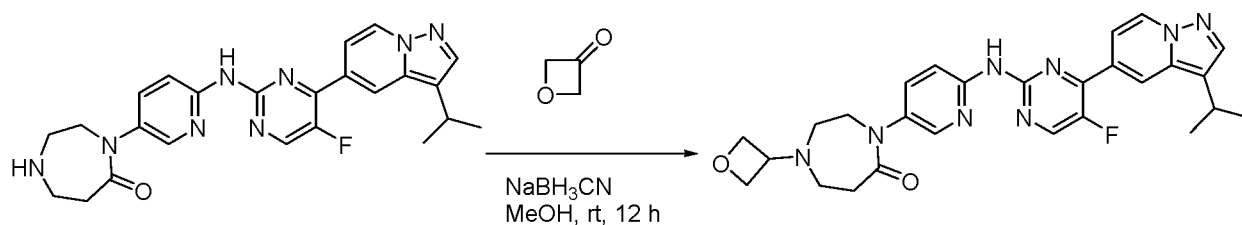
Step 2

A solution of tert-butyl 3-[4-[6-[[4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-yl]amino]-3-pyridyl]-3-oxo-piperazin-1-yl]azetidine-1-carboxylate (70.0 mg, 119 μ mol) in HCl / 1,4-dioxane (1 N, 10 mL) was stirred at 25 °C for 2 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (20 g silica gel column, MeOH in DCM 0-10%) to afford desired product (12.5 mg, 21% yield) as yellow solid. LC-MS: m/z 484.2 [M+H]⁺.

CDK4 IC₅₀: A; CDK6 IC₅₀: B; CDK2 IC₅₀: B.

Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC ₅₀	CDK6 IC ₅₀	CDK2 IC ₅₀
41		512.3	A	B	B
42		516.3	A	B	B

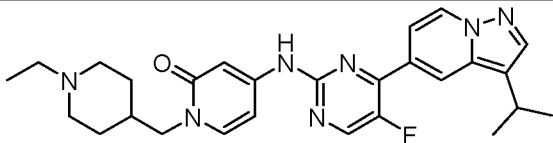
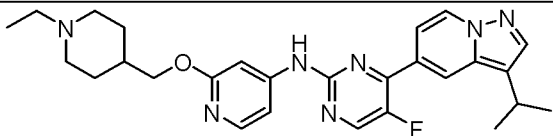
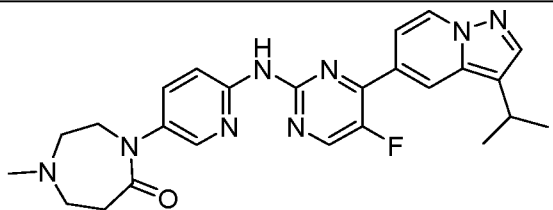
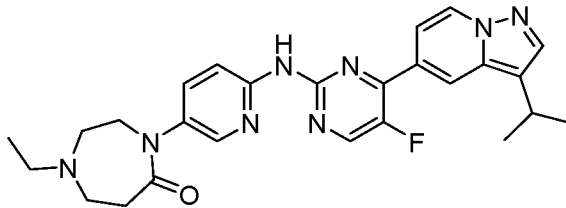
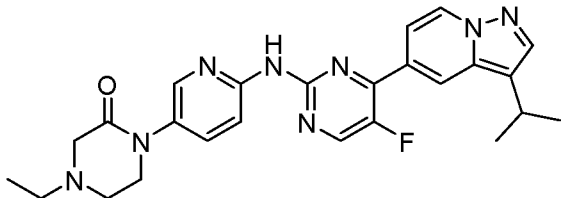
Synthetic Example 43

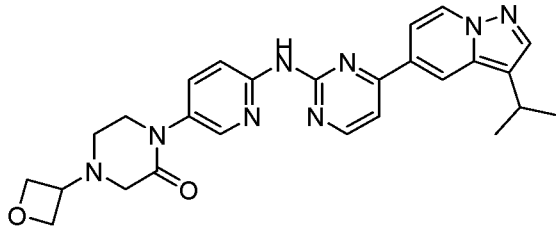
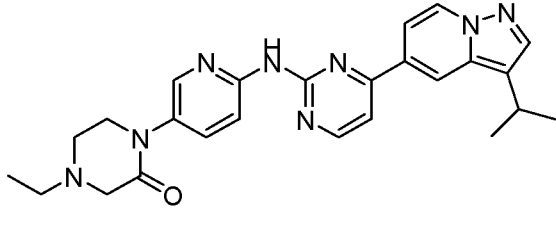


A solution of 4-[6-[[5-fluoro-4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-yl]amino]-3-pyridyl]-1,4-diazepan-5-one (40.0 mg, 86.8 μ mol), oxetan-3-one (9.0 mg, 124 μ mol) and NaBH₃CN (20.0 mg, 300 μ mol) in methanol (8 mL) was stirred at 25 °C for 16

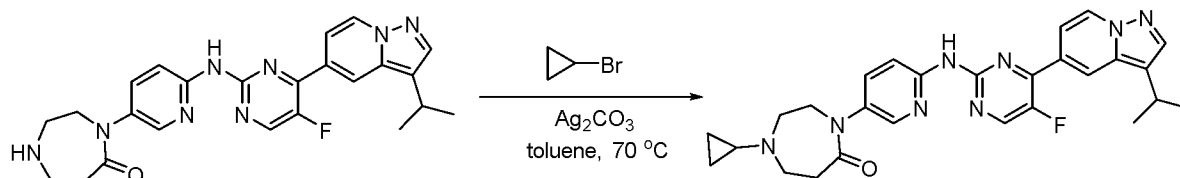
hours. The mixture was filtered, and the filtrate was concentrated. The residue was purified by prep-HPLC to afford desired product (12.3 mg, 27% yield) as a yellow solid. LC-MS: m/z 517.3 $[M+H]^+$.

CDK4 IC_{50} : A; CDK6 IC_{50} : B; CDK2 IC_{50} : B.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$	CDK4 IC_{50}	CDK6 IC_{50}	CDK2 IC_{50}
44		490.3	A	B	C
45		490.3	A	B	A
46		475.2	A	B	B
47		489.2	A	B	B
48		475.2	A	B	B

234		485.2	A	B	B
235		457.3	A	B	B

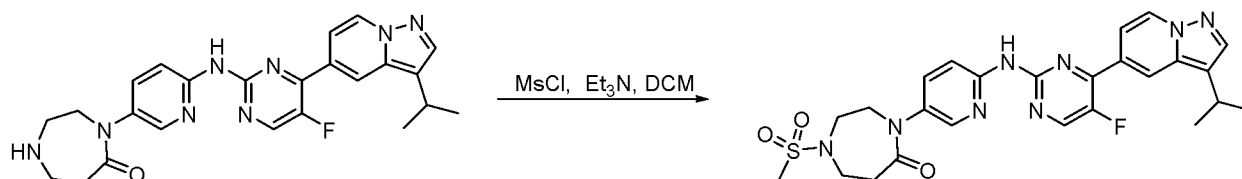
Synthetic Example 49



A solution of 1-[6-[[5-fluoro-4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-yl]amino]-3-pyridyl]-1,4-diazepan-5-one (20 mg, 43.4 μ mol), bromocyclopropane (4.7 mg, 39.0 μ mol) and silver carbonate (7.2 mg, 43.4 μ mol) in methylbenzene (5 mL) was stirred at 70 °C for 5 hours. The mixture was diluted with water (15 mL), extracted with DCM (2 $\times$ 20 mL). The combined organic phase was concentrated under reduced pressure. The residue was purified by prep-HPLC to give desired product (2 mg, 9% yield) as a yellow solid. LC-MS: m/z 501.2 $[M+H]^+$.

CDK4 IC_{50} : A; CDK2 IC_{50} : C.

Synthetic Example 50



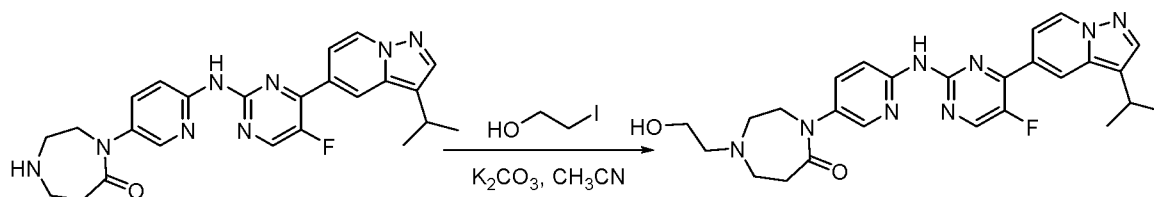
To a stirred solution of 1-[6-[[5-fluoro-4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-yl]amino]-3-pyridyl]-1,4-diazepan-2-one (22.0 mg, 47.7 μ mol) and TEA (10 mg, 100

μmol) in DCM (5 mL) solution was added methyl sulfonyl chloride (7.3 mg, 64.2 μmol). The reaction mixture was stirred at 20 °C for 16 hours. The reaction mixture was quenched with water (3 mL) and then extracted with ethyl acetate (2×5 mL). The combined organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to give desired product (5.0 mg, 17% yield) as a yellow solid. LC-MS: m/z 539.2 $[\text{M}+\text{H}]^+$.

CDK4 IC_{50} : A; CDK6 IC_{50} : B; CDK2 IC_{50} : B.

Synthetic Example	Structure	LC-MS: m/z $[\text{M}+\text{H}]^+$	CDK4 IC_{50}	CDK6 IC_{50}	CDK2 IC_{50}
51		525.2	A	B	B
236		521.2	A	A	B

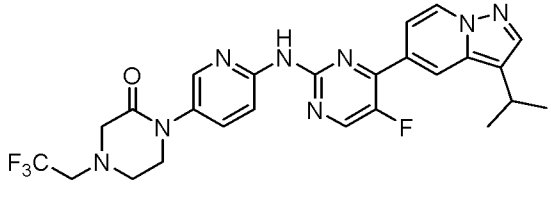
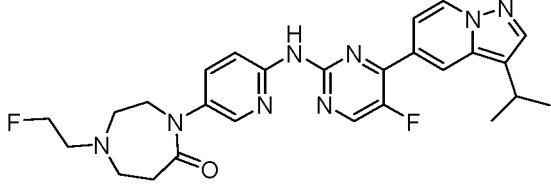
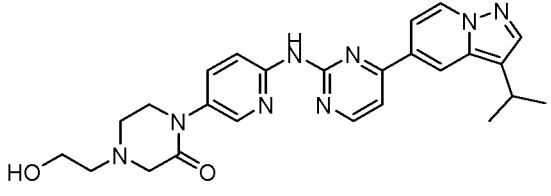
Synthetic Example 52



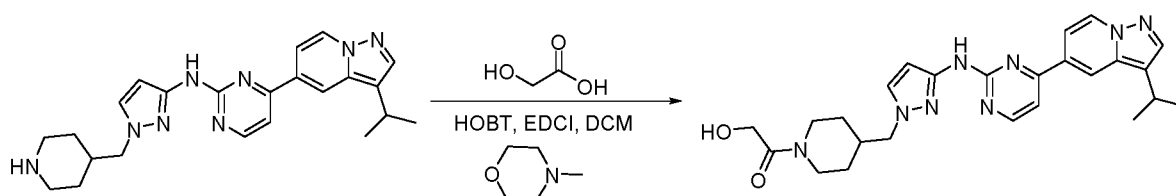
To a solution of 5-[6-[[5-fluoro-4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)pyrimidin-2-yl]amino]-3-pyridyl]azepan-4-one (30.0 mg, 65.2 μmol) and dipotassium carbonate (27.0 mg, 195 μmol) in acetonitrile (5 mL) was added 2-iodoethanol (13.4 mg, 78.3 μmol) at 25 °C. The reaction mixture was stirred at 50 °C for 16 hours. The mixture was quenched with water (20 mL) and then extracted with ethyl acetate (2×10 mL). The combined organic phase was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure.

The residue was purified by prep-HPLC to give desired product (5.0 mg, 15% yield) as a yellow solid. LC-MS: m/z 505.3 $[M+H]^+$.

CDK4 IC_{50} : A; CDK6 IC_{50} : B; CDK2 IC_{50} : B.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$	CDK4 IC_{50}	CDK6 IC_{50}	CDK2 IC_{50}
53		529.1	A	B	B
54		507.2	A		B
237		473.2	A	B	B

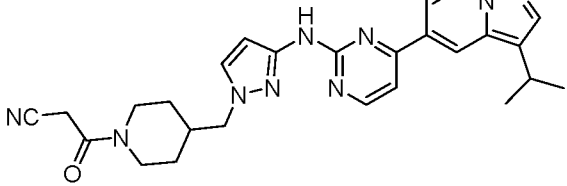
Synthetic Example 55



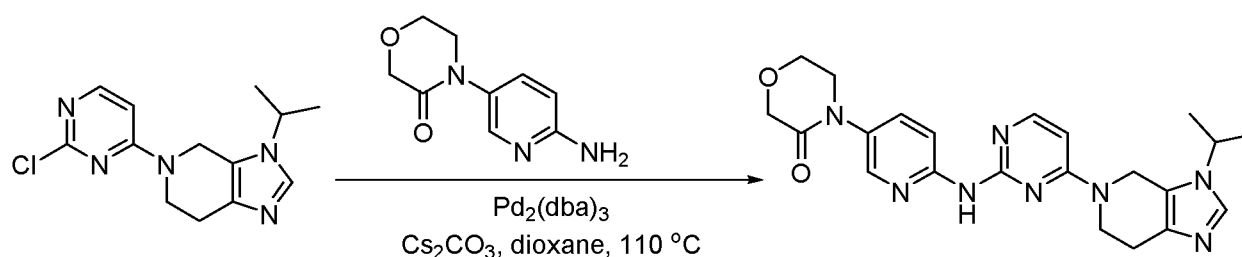
A solution of 4-(3-isopropylpyrazolo[1,5-a]pyridin-5-yl)-N-[1-(4-piperidylmethyl)pyrazol-3-yl]pyrimidin-2-amine (20.0 mg, 48.0 μ mol), 2-hydroxyacetic acid (5.4 mg, 72.0 μ mol), 4-methylmorpholine (4.8 mg, 48.0 μ mol), EDCI (13.8 mg, 71.9 μ mol) and HOBT (9.7 mg, 72.0 μ mol) in DCM (4 mL) was stirred at 20 °C for 5 hours. The mixture was diluted with water (15 mL), extracted with DCM (2 $\times$ 20 mL). The combined organic phases were

concentrated under reduced pressure. The residue was purified to give desired product (3.7 mg, 16% yield) as a yellow solid. LC-MS: (ESI) m/z 475.3 $[M+H]^+$.

CDK4 IC_{50} : B; CDK2 IC_{50} : D.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$	CDK4 IC_{50}	CDK6 IC_{50}	CDK2 IC_{50}
56		484.3	B		D

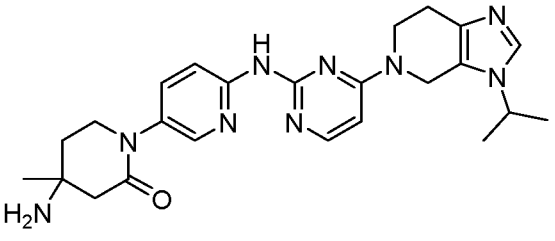
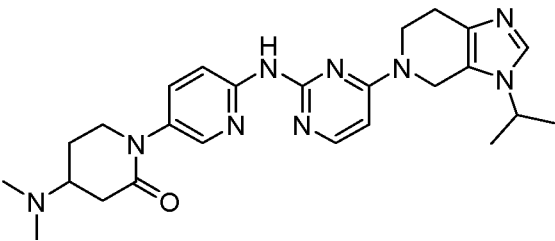
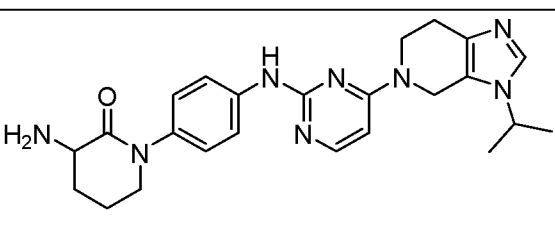
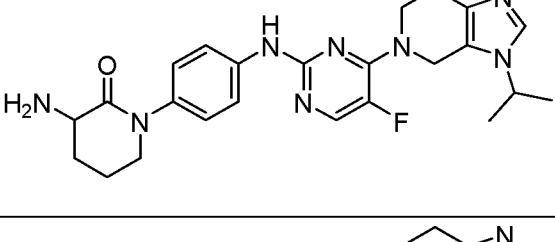
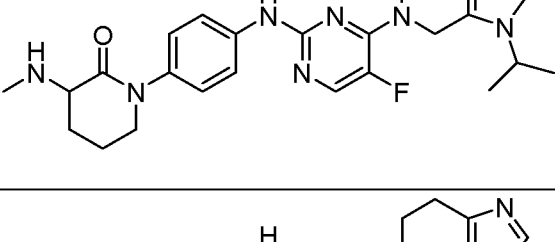
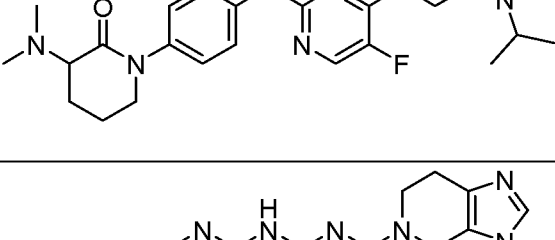
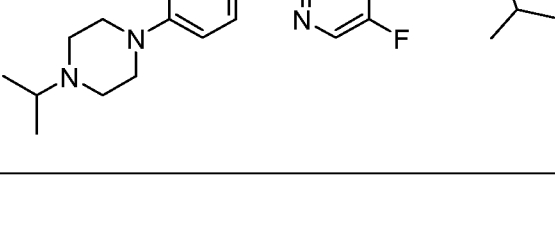
Synthetic Example 57

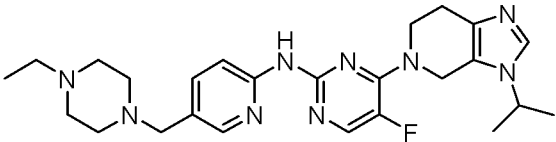
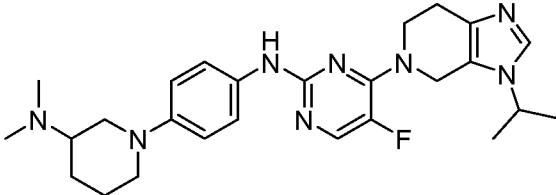
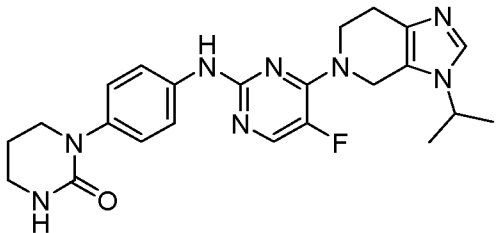
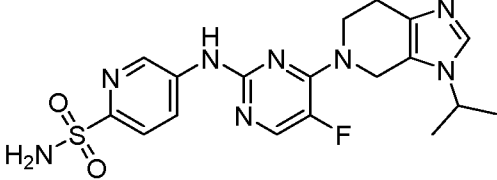
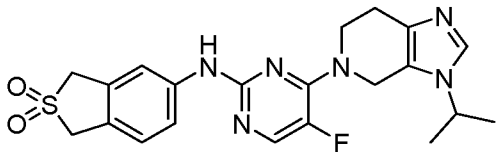
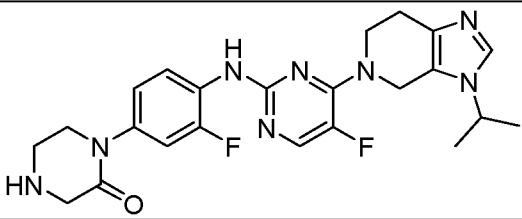
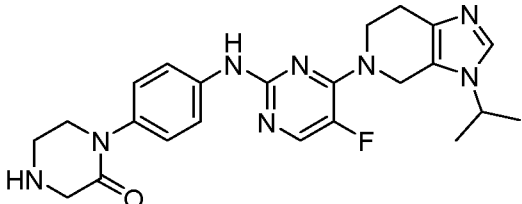


A mixture of 5-(2-chloropyrimidin-4-yl)-3-isopropyl-6,7-dihydro-4H-imidazo[4,5-c]pyridine (66.0 mg, 237 μ mol) 4-(6-amino-3-pyridyl)tetrahydropyran-3-one (54.8 mg, 285 μ mol) tris(dibenzylideneacetone)dipalladium(0) (21.7 mg, 23.7 μ mol), dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane (22.1 mg, 47.5 μ mol) and cesium carbonate (232 mg, 712 μ mol) in dioxane (6.5 mL) was stirred under N_2 atmosphere at 110 °C for 6 hours. The reaction mixture was quenched with water (50 mL) and then extracted with EtOAc (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then was filtered. The filtrate was concentrated. The residue was purified by prep-HPLC to desired product (9.9 mg, 19% yield) as a white solid. LC-MS: (ESI) m/z 435.3 $[M+H]^+$.

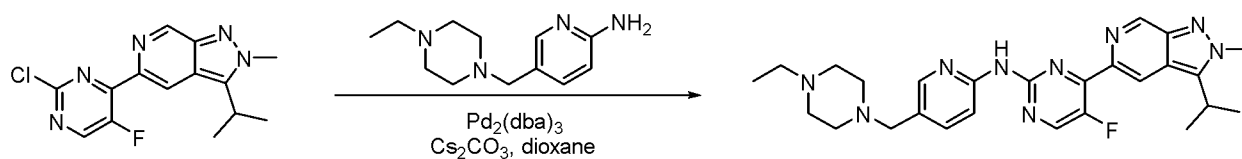
CDK4 IC_{50} : A; CDK6 IC_{50} : C; CDK2 IC_{50} : B.

Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC ₅₀	CDK6 IC ₅₀	CDK2 IC ₅₀
238		452.5	A		B
239		453.4	A		B
240		512.2	B		B
241		462.3	B		C
242		433.5	A	B	C
243		506.3	B		B

244		462.3	A	C	B
245		476.3	A	C	B
246		447.3	A		C
247		465.2	A		B
248		479.3	A		B
249		493.3	A		B
250		480.3	A		C

251		480.3	B		D
252		479.3	A		A
253		451.2	A		B
254		433.1	B		A
255		443.1	A		A
256		469.2	A		A
257		451.2	A		A

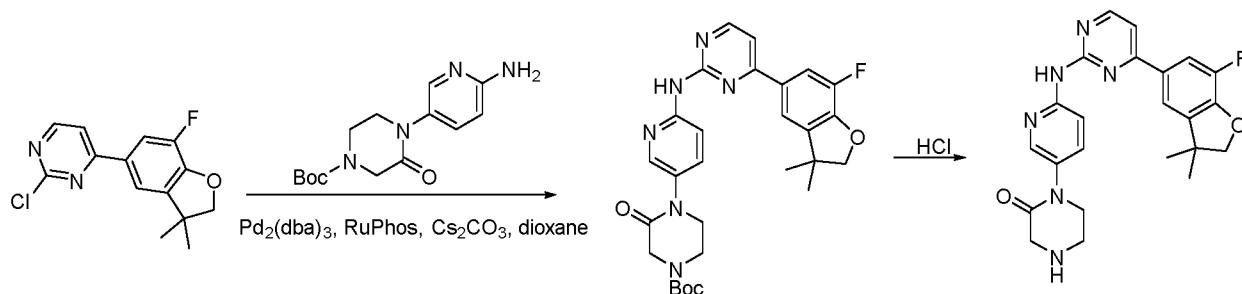
Synthetic Example 58



A mixture of 5-(6-chloro-3-fluoro-2-pyridyl)-3-isopropyl-2-methyl-pyrazolo[3,4-c]pyridine (30.0 mg, 98.4 μ mol), 5-[(4-ethylpiperazin-1-yl)methyl]pyridin-2-amine (26.0 mg, 118 μ mol), $\text{Pd}_2(\text{dba})_3$ (4.5 mg, 4.9 μ mol), RuPhos (4.5 mg, 9.8 μ mol) and Cs_2CO_3 (64.1 mg, 196 μ mol) in dioxane (4 mL) was stirred under N_2 atmosphere at 100 $^\circ\text{C}$ for 1 hour. The reaction mixture was quenched with water (50 mL) and extracted with EA (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to give desired product (3.0 mg, 6% yield) as a yellow solid. LC-MS: (ESI) m/z 490.1 $[\text{M}+\text{H}]^+$.

CDK4 IC_{50} : C; CDK6 IC_{50} : D.

Synthetic Example 59



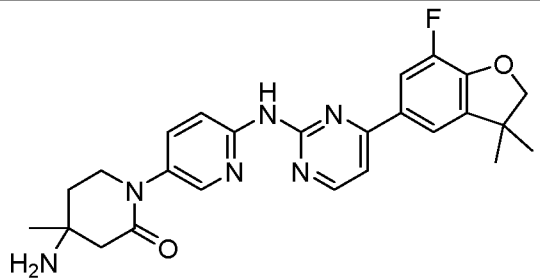
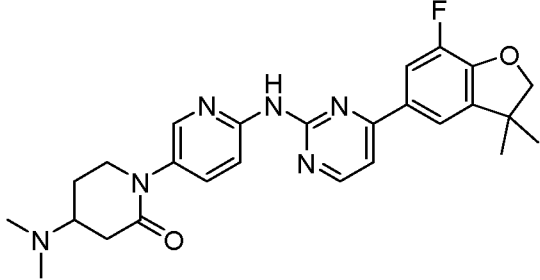
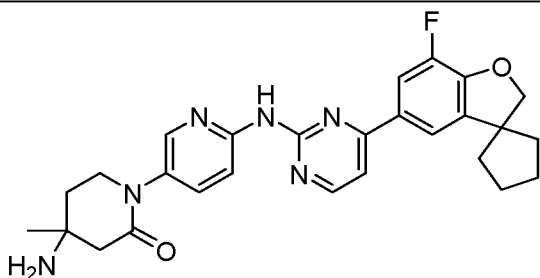
Step 1

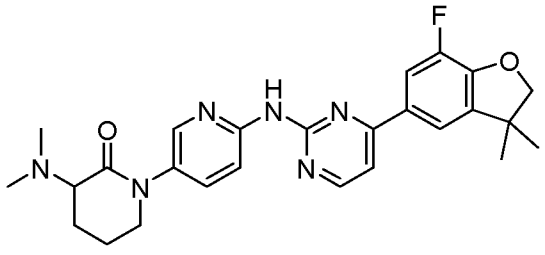
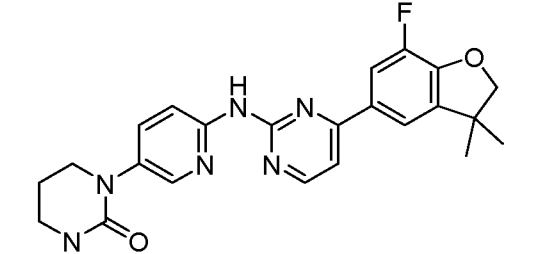
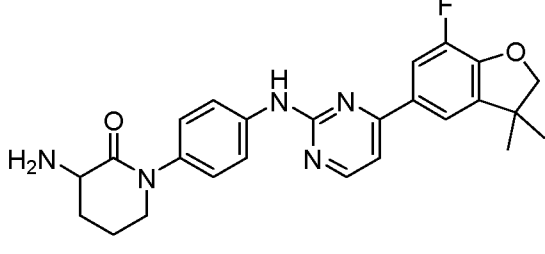
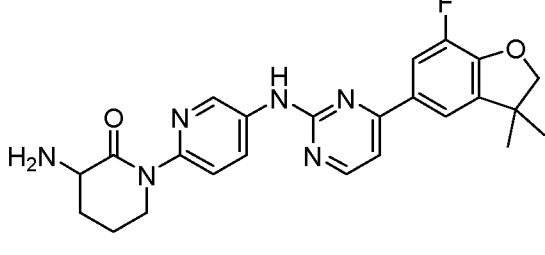
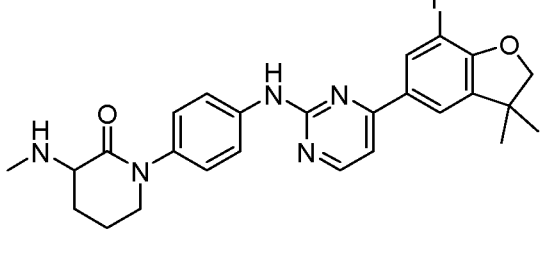
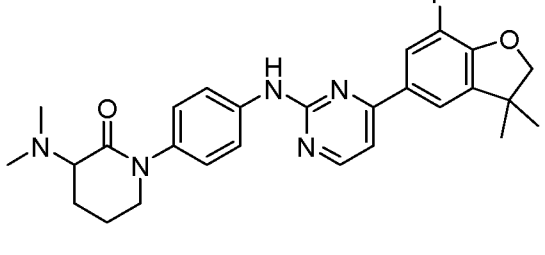
A mixture of 2-chloro-4-(7-fluoro-3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)pyrimidine (50.0 mg, 180 μ mol), tert-butyl 4-(6-aminopyridin-3-yl)-3-oxopiperazine-1-carboxylate (26.0 mg, 216 μ mol), $\text{Pd}_2(\text{dba})_3$ (10.0 mg, 10.0 μ mol), RuPhos (10.0 mg, 19.0 μ mol) and Cs_2CO_3 (130 mg, 400 μ mol) in dioxane (8 mL) was stirred under N_2 atmosphere at 100 $^\circ\text{C}$ for 1 hour. The reaction mixture was quenched with water (50 mL) and extracted with EA (2×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to give desired product (60 mg, 50%). LC-MS: (ESI) m/z 535.2 $[\text{M}+\text{H}]^+$.

Step 2

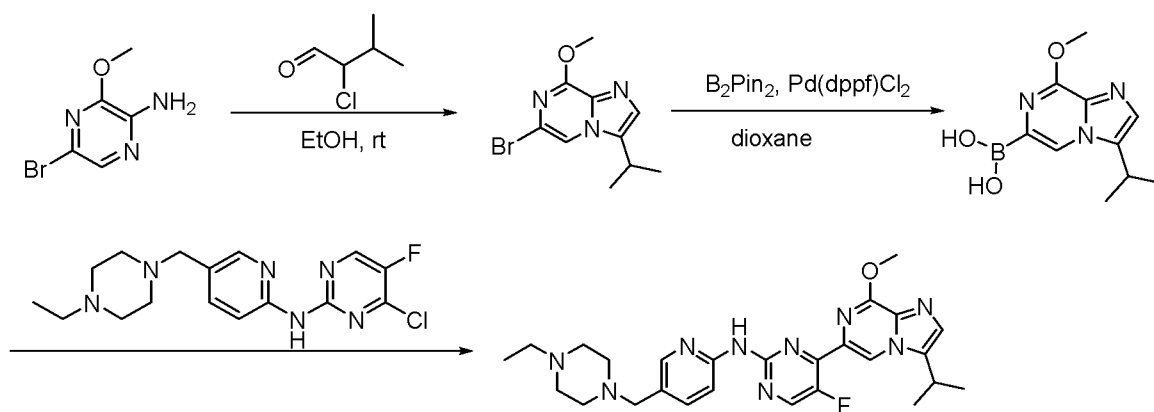
A solution of tert-butyl 4-(6-((4-(7-fluoro-3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)pyrimidin-2-yl)amino)pyridin-3-yl)-3-oxopiperazine-1-carboxylate (60.0 mg, 112 μ mol) in HCl / 1,4-dioxane (1 N, 10 mL) was stirred at 25 °C for 2 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (20 g silica gel column, MeOH in DCM 0-10%) to afford desired product (38.0 mg, 78% yield) as yellow solid. LC-MS: m/z 435.2 [M+H]⁺.

CDK4 IC₅₀: A; CDK6 IC₅₀: B; CDK2 IC₅₀: B.

Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC ₅₀	CDK6 IC ₅₀	CDK2 IC ₅₀
258		463.2	A	B	B
259		477.2	A	B	B
260		489.2	A		B

261		477.2	A	B	D
262		435.1	A		C
263		448.5	A		B
264		449.2	A		B
265		462.2	A		B
266		476.2	A		C

Synthetic Example 60



Step 1

To a solution of 5-bromo-3-methoxypyrazin-2-amine (500 mg, 2.5 mmol) in EtOH (10 mL) was added 2-chloro-3-methylbutanal (443 mg, 3.68 mmol) dropwise at 25 °C. The mixture was stirred at 80 °C for 2 h. The mixture was concentrated to get a residue. The residue was purified by silica gel column chromatography (PE:EtOAc=10:1-5:1) to get desired product (25.0 mg, 4% yield) as a yellow solid. LC-MS: (ESI) m/z 270.0 $[M+H]^+$.

Step 2

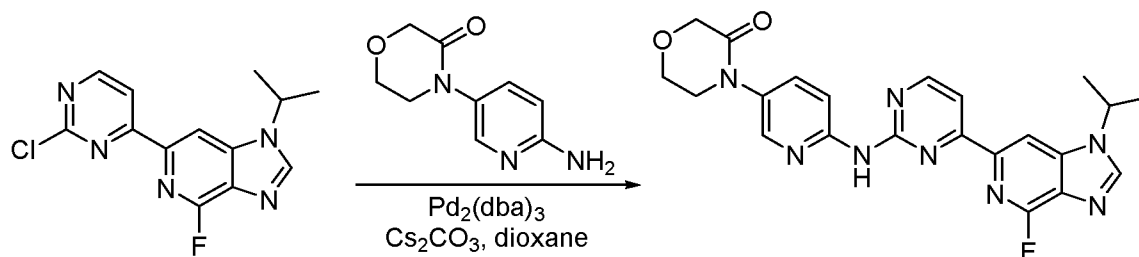
To a solution of 6-bromo-3-isopropyl-8-methoxyimidazo[1,2-a]pyrazine (25.0 mg, 0.09 mmol) in dioxane (5 mL) was added B_2Pin_2 (150 mg, 0.6 mmol), KOAc (27.0 mg, 0.3 mmol) and $Pd(dppf)Cl_2$ (15.0 mg, 0.02 mmol) at 25 °C in a N_2 atmosphere. The mixture was stirred at 110 °C for 3 h. The mixture was filtered with diatomite, concentrated to get desired product (30 mg) as a yellow solid, which was used in next step without purification. LC-MS: (ESI) m/z 236.1 $[M+H]^+$.

Step 3

To a solution of (3-isopropyl-8-methoxyimidazo[1,2-a]pyrazin-6-yl)boronic acid (25.0 mg, 0.1 mmol) and 4-chloro-N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoropyrimidin-2-amine (37.0 mg, 0.2 mmol) in dioxane (4 mL) and water (1 mL) was added K_2CO_3 (30.0 mg, 0.2 mmol) and $Pd(dppf)Cl_2$ (15.0 mg, 0.02 mmol) at 25 °C in N_2 atmosphere. The mixture was stirred at 100 °C for 3 h. The mixture was filtered through Celite and concentrated. The residue was purified by prep-HPLC to get desired product (5.1 mg, 9% yield) as a yellow solid. LC-MS: (ESI) m/z 506.3 $[M+H]^+$.

CDK4 IC_{50} : B; CDK6 IC_{50} : C.

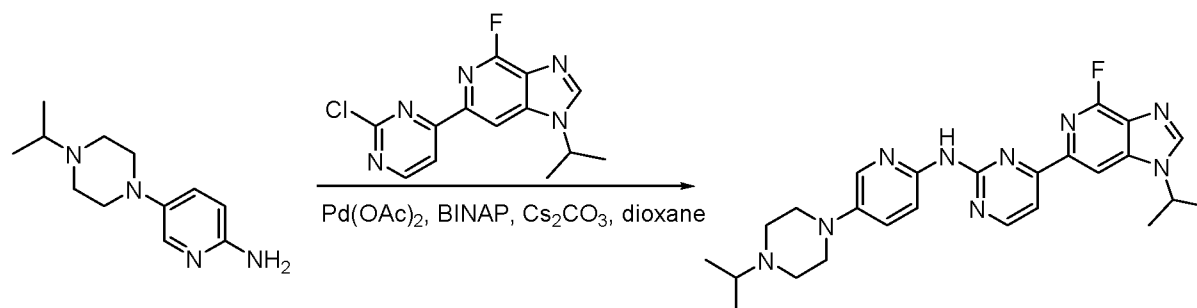
Synthetic Example 61



To a mixture of 6-(2-chloropyrimidin-4-yl)-4-fluoro-1-isopropyl-imidazo[4,5-c]pyridine (22.0 mg, 75.4 μmol) in 1,4-dioxane (5 mL) were added 4-(6-amino-3-pyridyl)morpholin-3-one (16.0 mg, 82.8 μmol), dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl] phosphane (12.0 mg, 25.7 μmol), tris(dibenzylideneacetone) dipalladium (11.0 mg, 12.0 μmol) and cesium carbonate (80.0 mg, 245 μmol), the mixture was degassed by N_2 . The resulting mixture was stirred at 100 $^\circ\text{C}$ for 12 hours. The mixture was concentrated and purified by column (DCM/MeOH=20/1-8/1) to afford desired product (1 mg, 3% yield). LC-MS: m/z 449.1 $[\text{M}+\text{H}]^+$.

CDK4 IC_{50} : A; CDK6 IC_{50} : B; CDK2 IC_{50} : B.

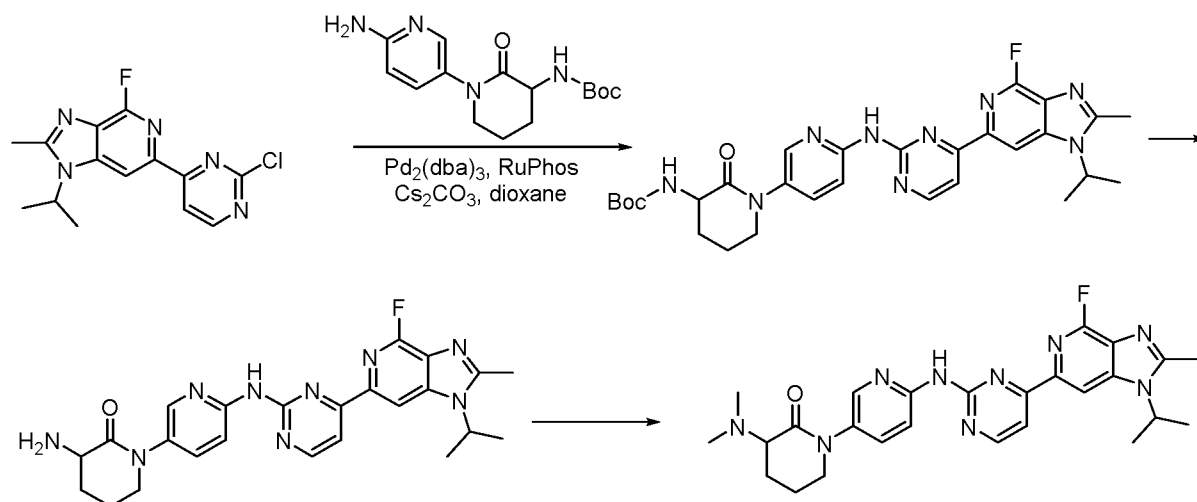
Synthetic Example 287



To a solution of 5-(4-isopropylpiperazin-1-yl)pyridin-2-amine (124.6 mg, 565 μmol) and 6-(2-chloropyrimidin-4-yl)-4-fluoro-1-isopropyl-imidazo[4,5-c]pyridine (150 mg, 514 μmol) in dioxane (15 mL) was added $\text{Pd}_2(\text{dba})_3$ (47.1 mg, 51 μmol), RuPhos (47.9 mg, 102 μmol) and Cs_2CO_3 (502.6 mg, 1.5 mmol). The mixture was stirred at 110 $^\circ\text{C}$ under N_2 for 3 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH in DCM 0-10% to afford desired product (107.2 mg, 43% yield) as a yellow solid. LC-MS: m/z 476.2 $[\text{M}+\text{H}]^+$.

CDK4 IC_{50} : A; CDK6 IC_{50} : B; CDK2 IC_{50} : C.

Synthetic Example 301



Step 1

To a solution of 6-(2-chloropyrimidin-4-yl)-4-fluoro-1-isopropyl-2-methyl-imidazo[4,5-c]pyridine (150 mg, 490.6 μmol) and tert-butyl N-[1-(6-amino-3-pyridyl)-2-oxo-3-piperidyl]carbamate (150.3 mg, 490.6 μmol in dioxane (5 mL) was added cesium carbonate (479.5 mg, 1.4 mmol), RuPhos (45.7 mg, 98.1 μmol) and tris(dibenzylideneacetone)dipalladium(0) (44.9 mg, 49.0 μmol). The reaction was stirred at 110 $^{\circ}\text{C}$ and 8 hr. The reaction was purified by column chromatography eluting with MeOH in DCM 0-4% in 15 min to give desired product (170 mg, 60% yield) as a yellow solid.

Step2

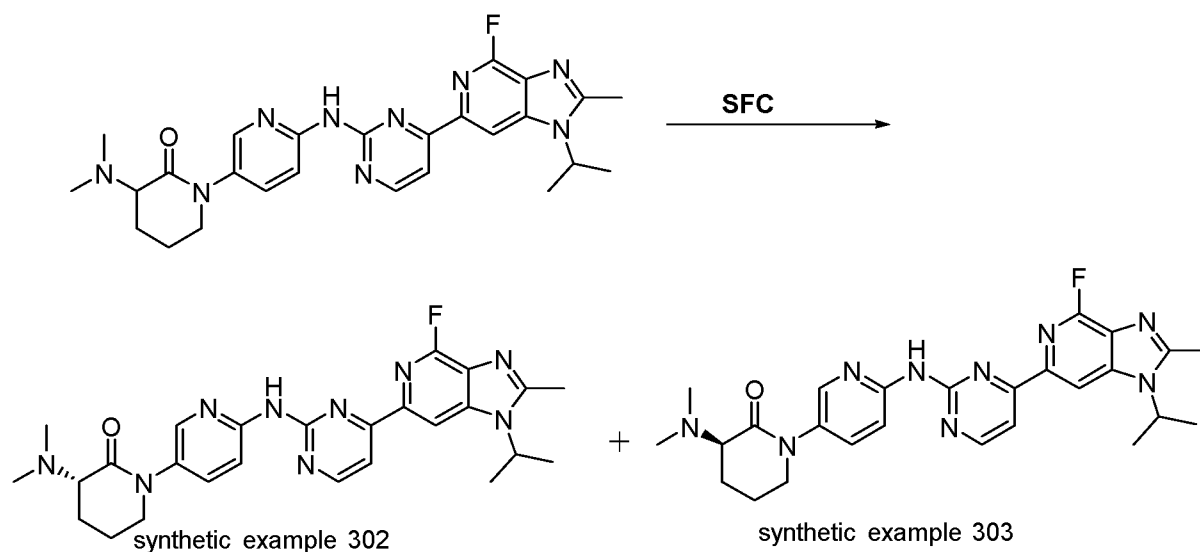
To a solution of tert-butyl N-[1-[6-[[4-(4-fluoro-1-isopropyl-2-methyl-imidazo[4,5-c]pyridin-6-yl)pyrimidin-2-yl]amino]-3-pyridyl]-2-oxo-3-piperidyl]carbamate (170 mg, 295.3 μmol) in DCM (5 mL) was added HCl (2 M, 738 μL). The reaction was stirred at 25 $^{\circ}\text{C}$ for 3 hr. The reaction was concentrated under reduced pressure to give desired product (140 mg, 99% yield) as a yellow solid.

Step 3

To a solution of 3-amino-1-[6-[[4-(4-fluoro-1-isopropyl-2-methyl-imidazo[4,5-c]pyridin-6-yl)pyrimidin-2-yl]amino]-3-pyridyl]piperidin-2-one (80 mg, 168.2 μmol) in THF (5 mL) was added formaldehyde (50.5 mg, 1.6 mmol). After 1 hour, sodium cyanoborane (31.7 mg, 504.7 μmol) was added to the above solution. The reaction was stirred at 25 $^{\circ}\text{C}$ for 2 hr. The reaction was concentrated under reduced pressure. The residue was purified by pre-HPLC to afford desired product (5.7 mg, 6% yield) as a yellow solid. LC-MS: m/z 504.3 $[\text{M}+\text{H}]^{+}$.

CDK4 IC₅₀: A; CDK6 IC₅₀: A; CDK2 IC₅₀: D.

Synthetic Example 302 and 303

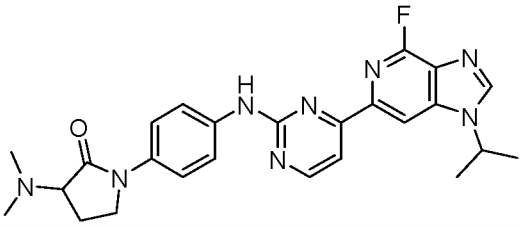
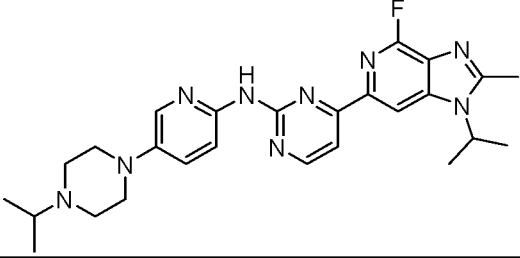
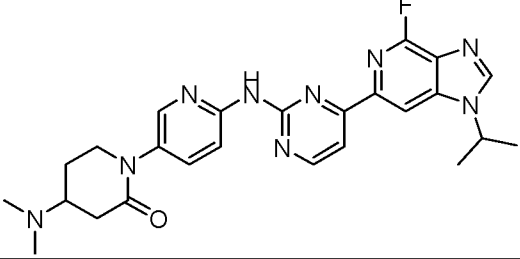
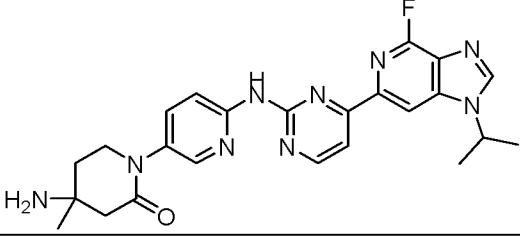
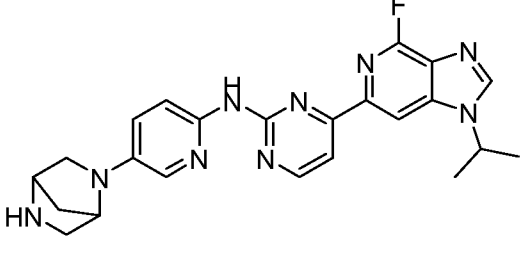
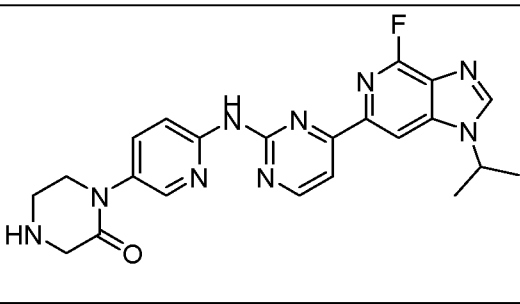
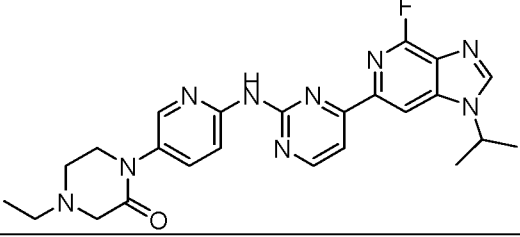


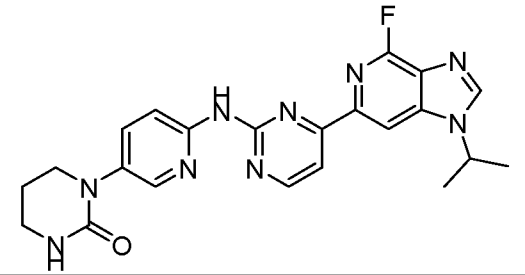
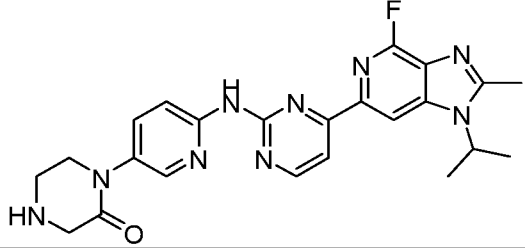
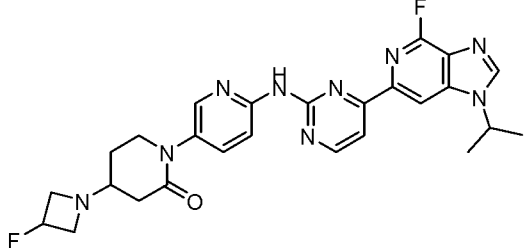
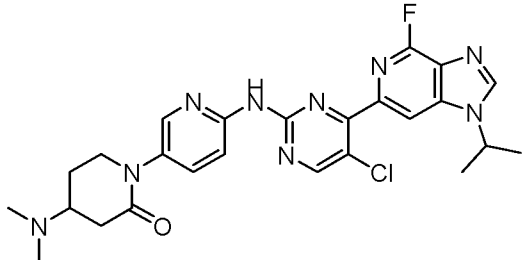
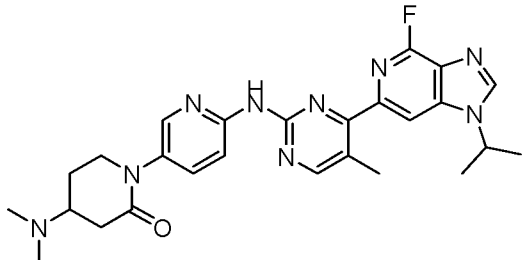
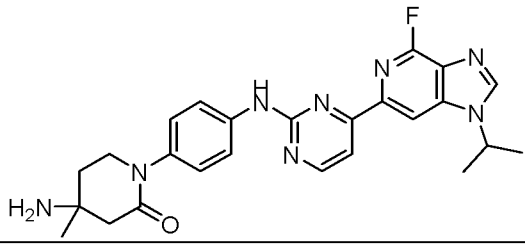
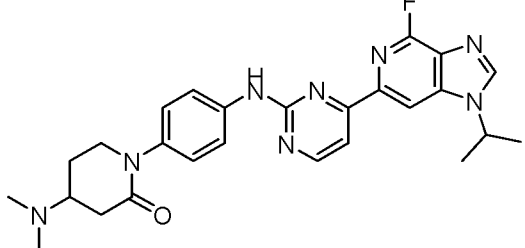
3-(dimethylamino)-1-[6-[[4-(4-fluoro-1-isopropyl-2-methyl-imidazo[4,5-c]pyridin-6-yl)pyrimidin-2-yl]amino]-3-pyridyl]piperidin-2-one (170 mg, 337.6 μ mol) was separated by SFC (Column: Daicel CHIRALPAK OD₃, 3 $\times$ 150 mm, 3 μ m; Mobile phase: A/B: CO₂/MeOH (0.1% DEA)=70/30; Flow rate: 2.0 mL/min) to give synthetic example 302 (50 mg, 29% yield) (LC-MS: m/z 504.3 [M+H]⁺, ee value: 94%) and synthetic example 303 (50 mg, 29% yield) as a white solid (LC-MS: m/z 504.3 [M+H]⁺, ee value: 94%).

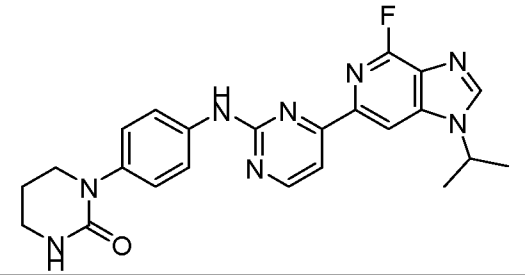
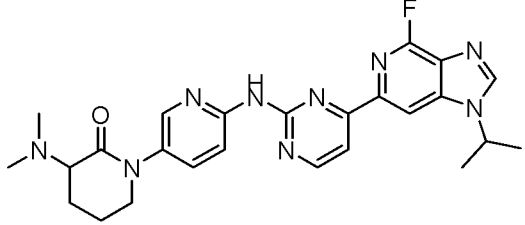
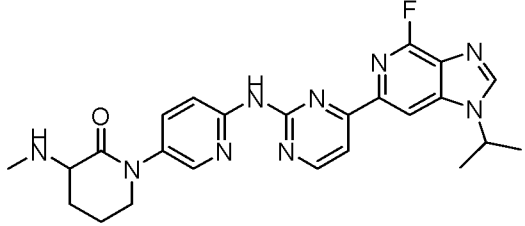
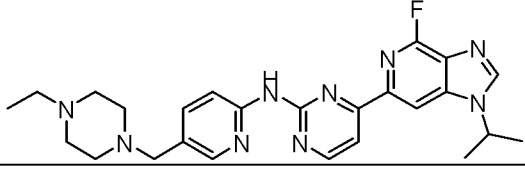
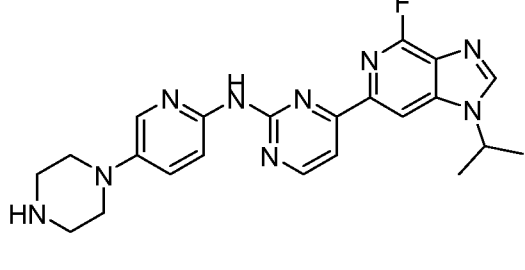
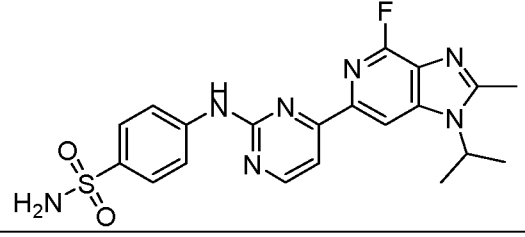
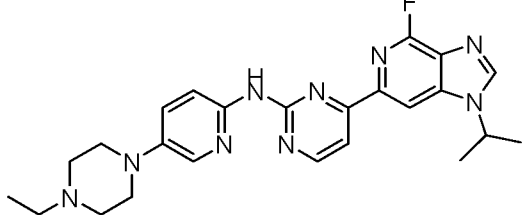
Synthetic Example 302, CDK4 IC₅₀: A; CDK2 IC₅₀: D.

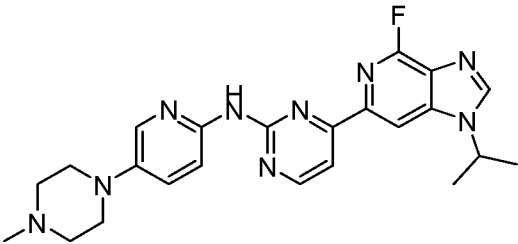
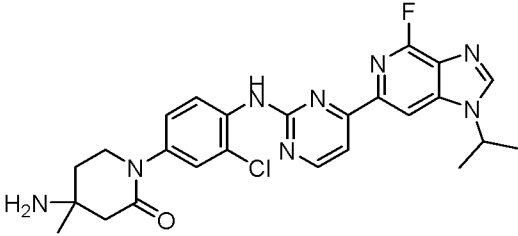
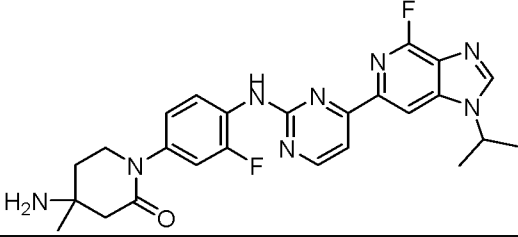
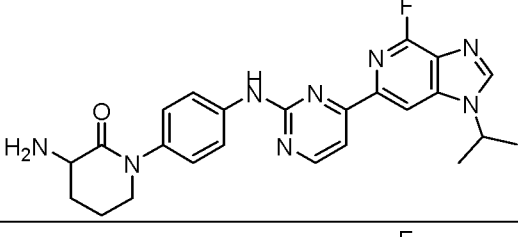
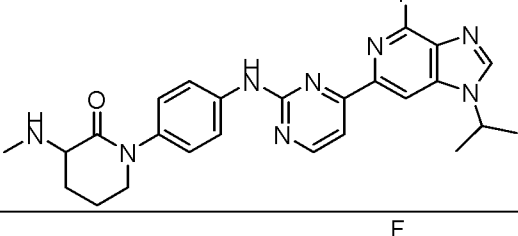
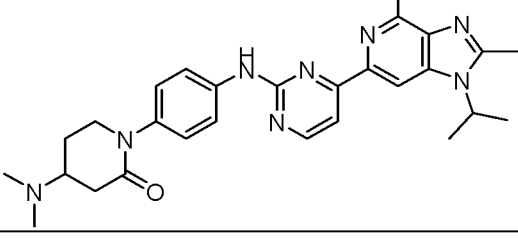
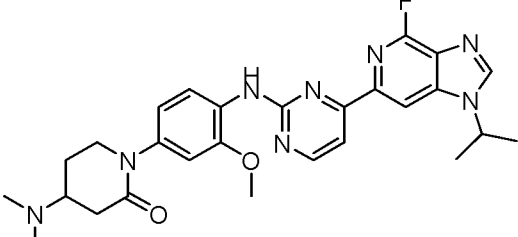
Synthetic Example 303, CDK4 IC₅₀: A; CDK2 IC₅₀: D.

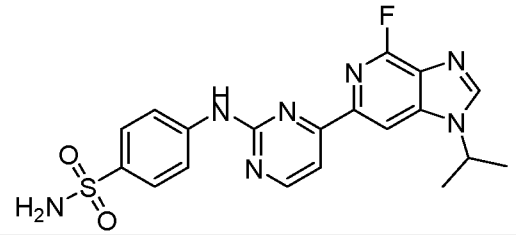
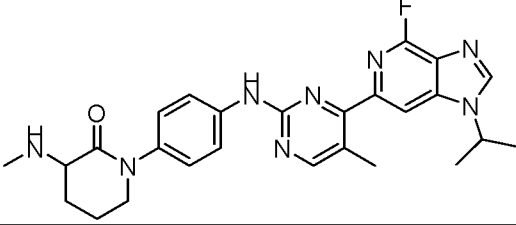
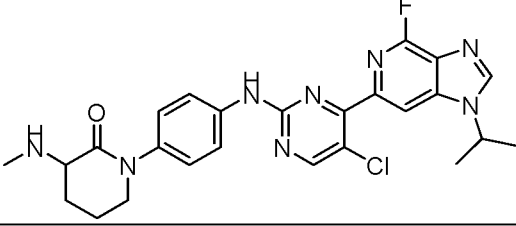
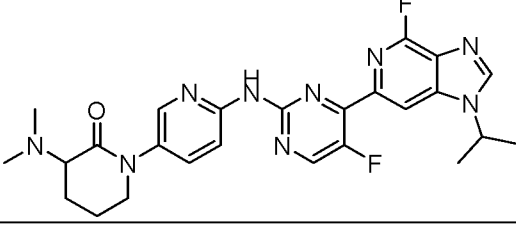
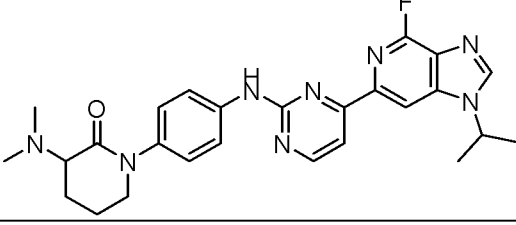
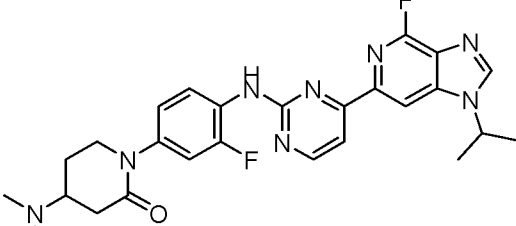
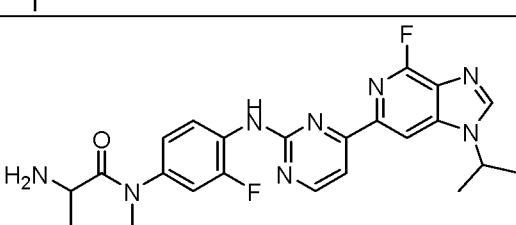
Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC ₅₀	CDK6 IC ₅₀	CDK2 IC ₅₀
267		474.2	A		C

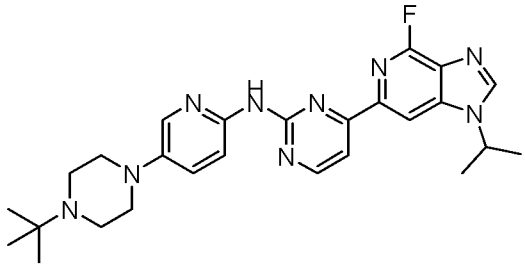
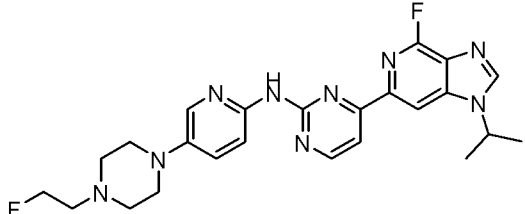
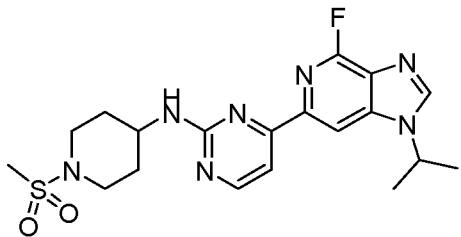
268		475.5	A		B
269		490.3	A		D
270		490.2	A	A	B
271		476.2	A	A	B
272		446.5	A	B	C
273		448.1	A	B	B
274		476.2	A		C

275		448.1	A	A	C
276		462.2	A	A	B
277		520.1	A	B	B
278		524.2	A	B	C
279		504.3	A	B	C
280		475.2	A	A	A
281		489.2	A	A	A

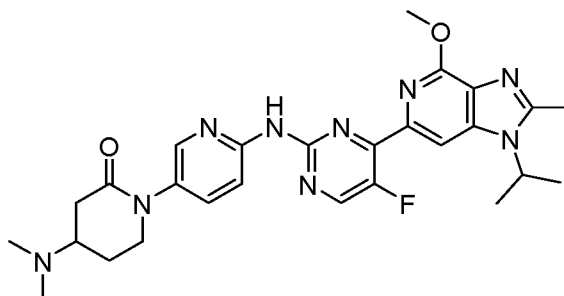
282		447.2	A	A	A
283		490.5	A	A	D
284		476.2	A		D
285		476.2	A	B	D
286		434.5	A	B	C
288		442.1	B	B	A
289		462.3	A	A	C

290		448.2	A		C
291		509.1	A		A
292		493.2	A	A	A
293		461.2	A	A	B
294		475.2	A		B
295		503.3	A		A
296		519.3	A		A

297		428.1	A	B	A
298		489.2	A		C
299		509.1	A		C
300		508.5	A		D
304		489.2	A		B
305		507.2	A		A
306		479.2	A		B

308		490.3	A		C
309		480.2	A		C
310		434.1	B		B

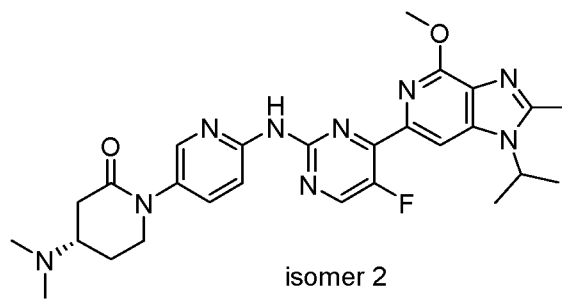
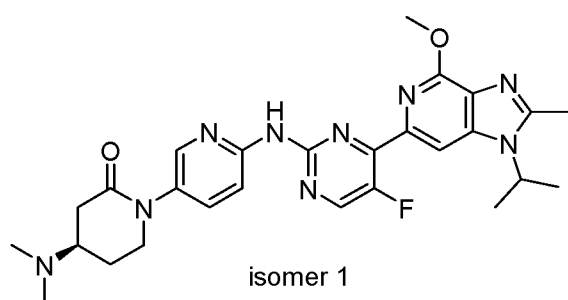
Synthetic Example 62



To a mixture of 1-(6-amino-3-pyridyl)-4-(dimethylamino) piperidin-2-one (85.0 mg, 363 μmol), 6-(2-chloro-5-fluoro-pyrimidin-4-yl)-1-isopropyl-4-methoxy-2-methyl-imidazo[4,5-c]pyridine (122 mg, 363 μmol) and 2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl (33.0 mg, 72.6 μmol) in dioxane (10 mL) was added Cs_2CO_3 (355 mg, 1.1 mmol) and tris(dibenzylideneacetone)dipalladium (33.0 mg, 36.3 μmol), the resulting mixture was stirred under nitrogen atmosphere at 110 °C for 4 h. The reaction was filtered. The filtrate was concentrated in vacuo to give the residue. The residue was purified by reverse phase column (C18, 20 g) eluting with (ACN:water (0.1% formic acid)=1:10) to give desired product (9.8 mg, 5% yield) as white solid. LC-MS: m/z 534.3 $[\text{M}+\text{H}]^+$.

CDK4 IC_{50} : A; CDK6 IC_{50} : B; CDK2 IC_{50} : D.

Synthetic Examples 62-1 and 62-2

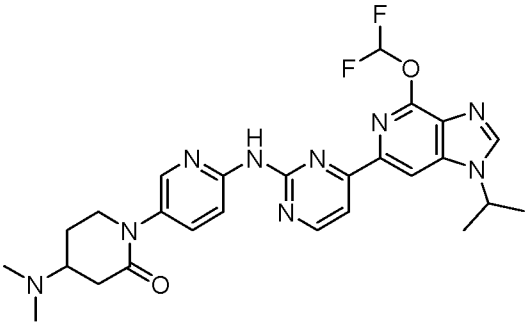
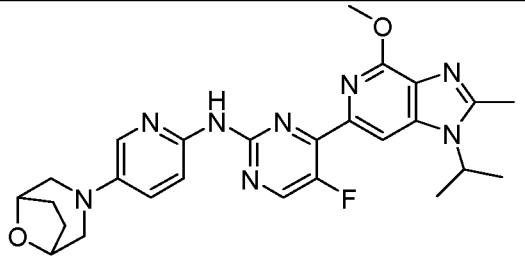
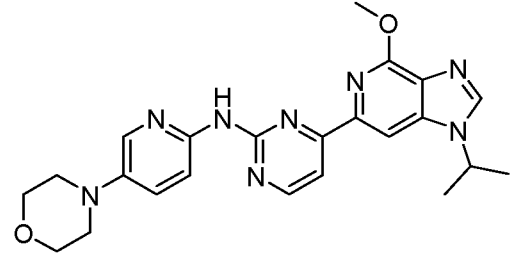
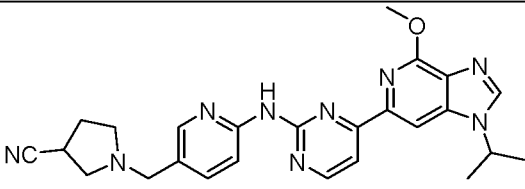
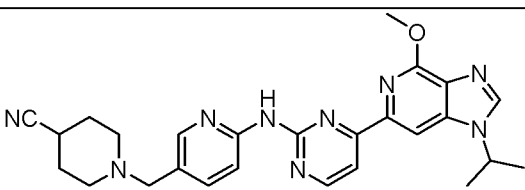
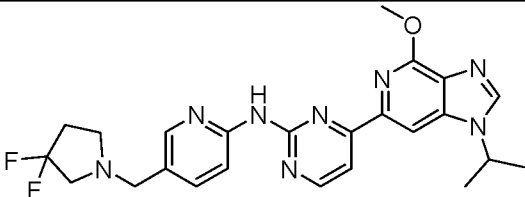


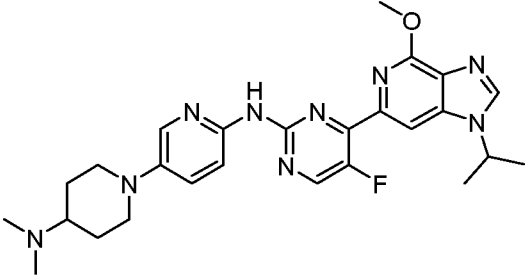
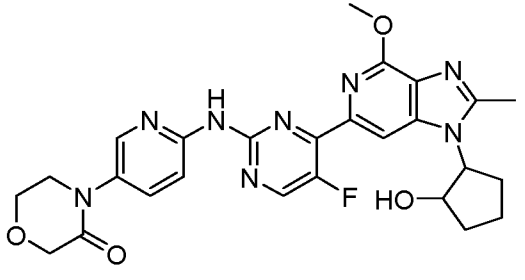
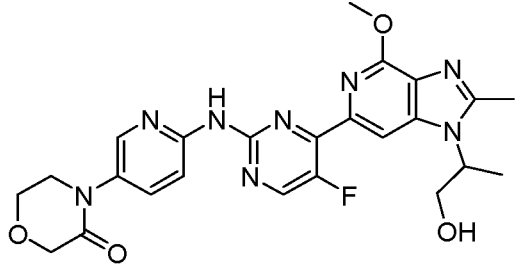
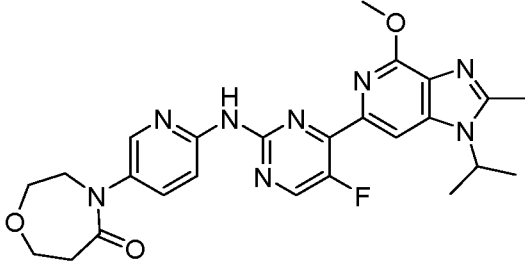
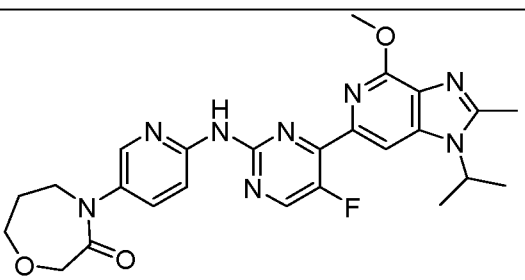
4-(dimethylamino)-1-[6-[[5-fluoro-4-(1-isopropyl-4-methoxy-2-methyl-imidazo[4,5-c]pyridin-6-yl)pyrimidin-2-yl]amino]-3-pyridyl]piperidin-2-one (7.9 mg, 14.8 μ mol) was purified by chiral-HPLC (Apparatus: SFC 80, Column: Daicel CHIRALPAK OJ-H250mm 20 mm I.D., 5 μ m, Mobile phase: CO₂/MeOH(0.2%NH₄OH) = 50/50, Flow rate: 45 g/min, Wave length: UV214 nm, Temperature: 35 °C) to give isomer 2: (2.3 mg, 29% yield), LC-MS: m/z 534.3 [M+H]⁺, RT = 12.72 min, ee value >99%; isomer 1: (1.6 mg, 20% yield), LC-MS: m/z 534.3 [M+H]⁺, RT = 10.95 min, ee value >99%.

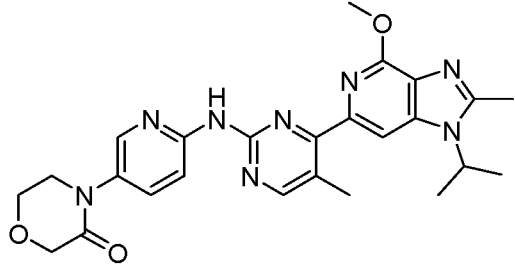
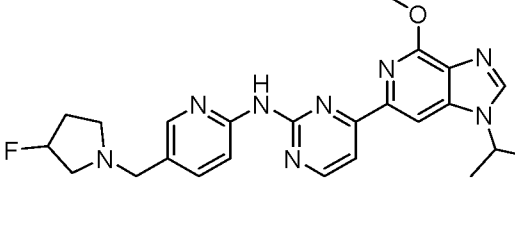
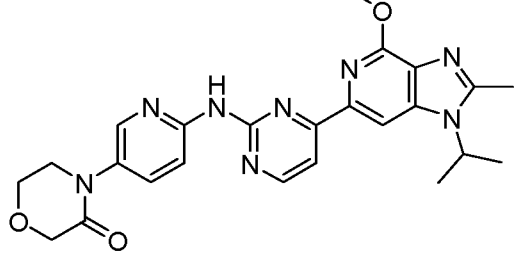
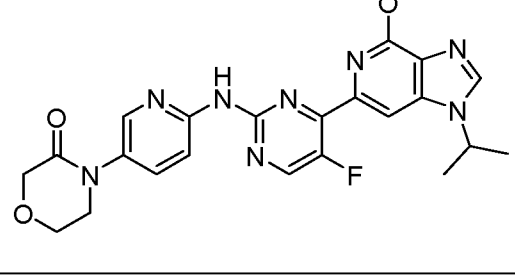
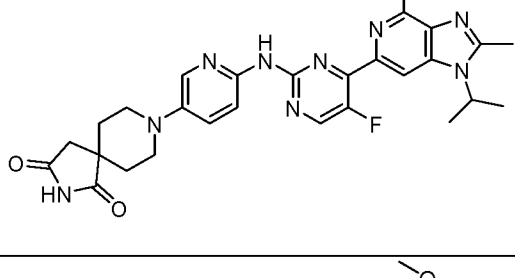
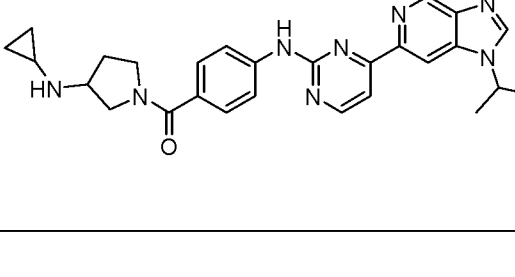
Example 62-1, CDK4 IC₅₀: A; CDK6 IC₅₀: B; CDK2 IC₅₀: D.

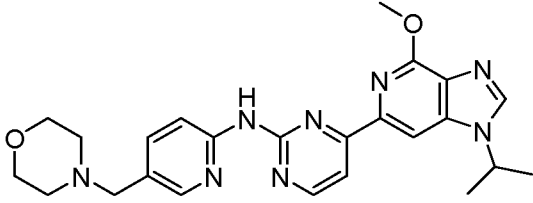
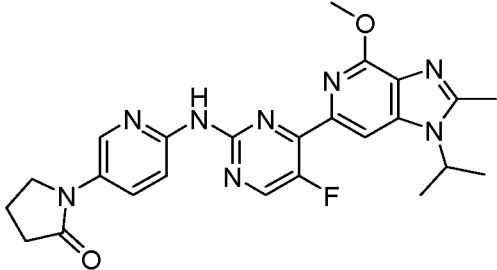
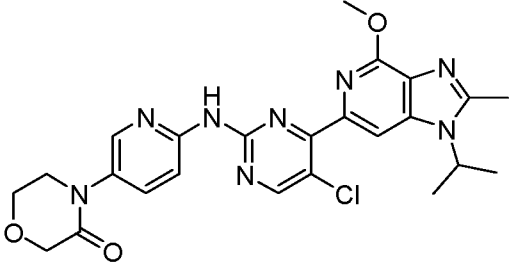
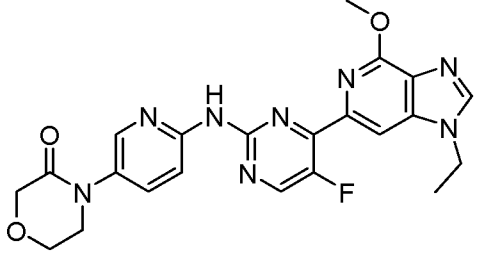
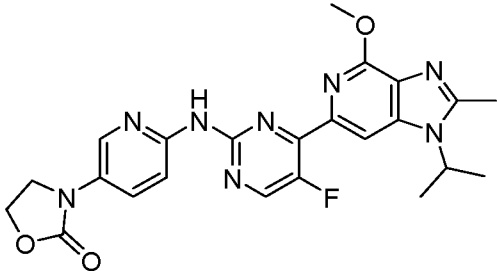
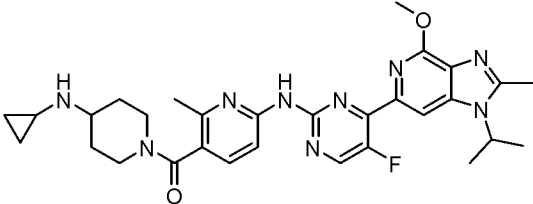
Example 62-2, CDK4 IC₅₀: A; CDK6 IC₅₀: B; CDK2 IC₅₀: D.

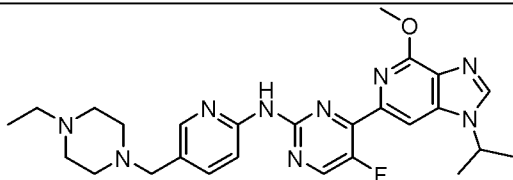
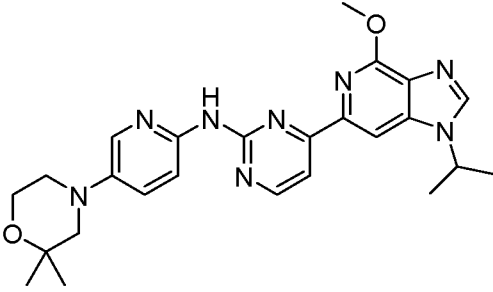
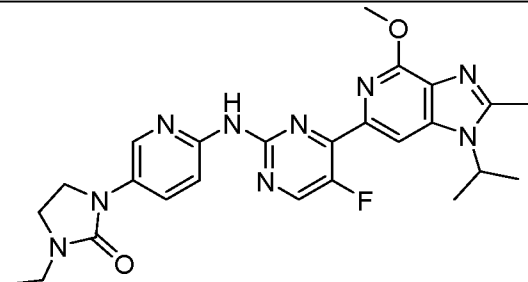
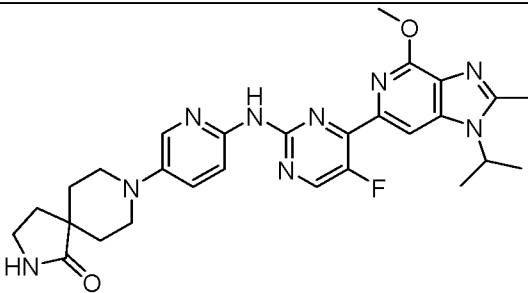
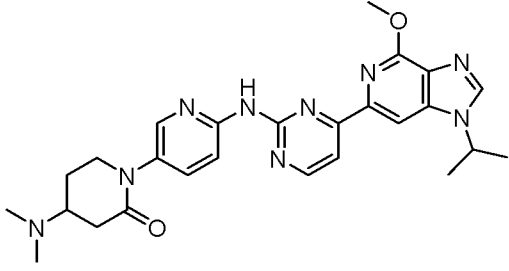
Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC ₅₀	CDK6 IC ₅₀	CDK2 IC ₅₀
63		497.2	A	B	C

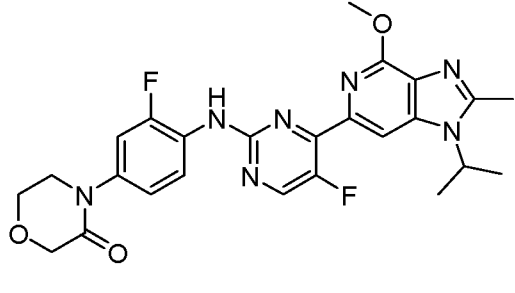
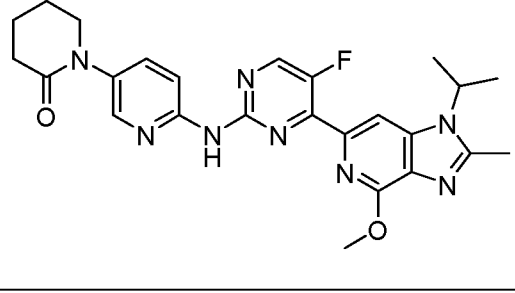
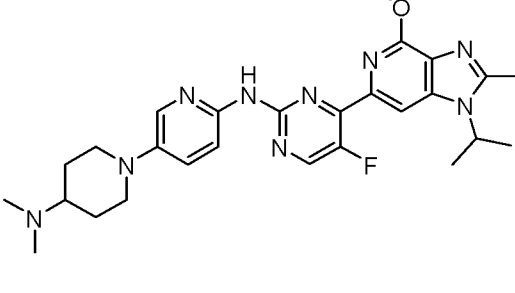
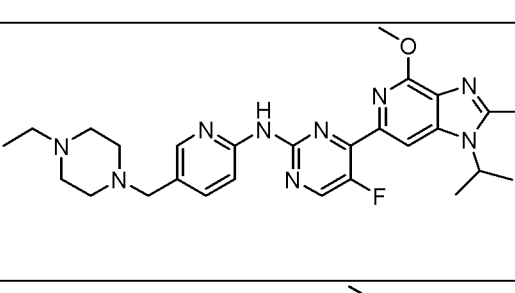
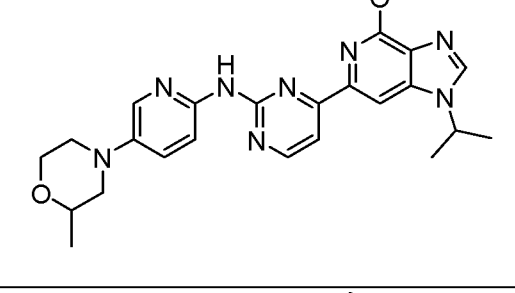
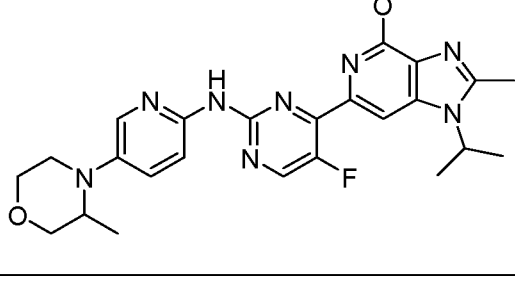
64		538.2	A		D
65		505.2	B		D
66		447.3	A		D
67		470.2	B		D
68		484.3	A	B	D
69		481.3	B		D

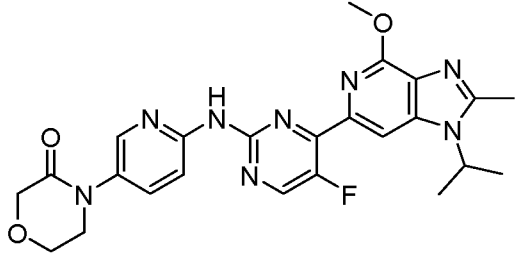
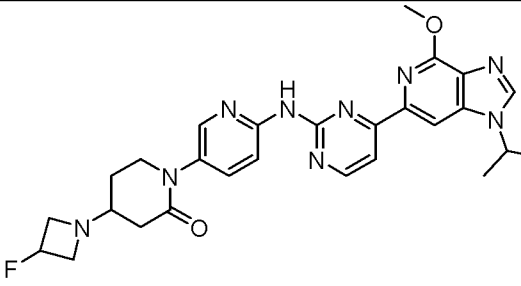
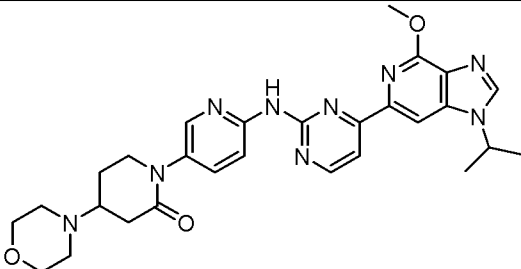
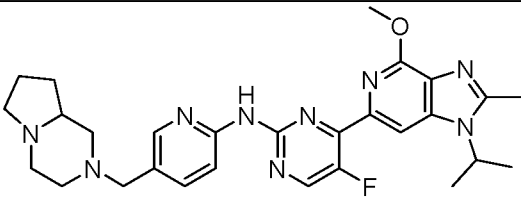
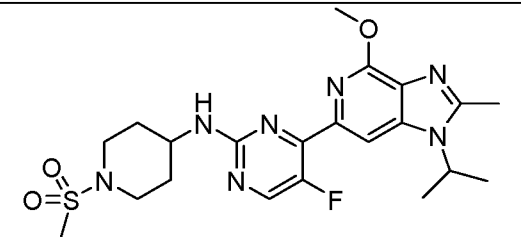
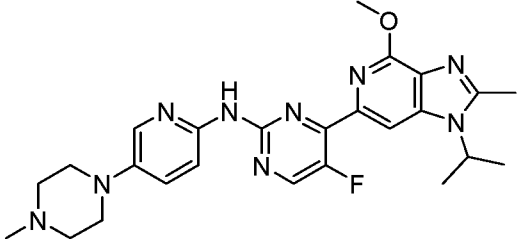
70		506.3	A	B	D
71		535.2	B		D
72		509.2	B		D
73		507.2	A	B	D
74		507.2	A	B	D

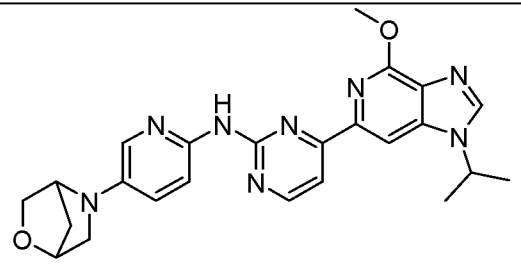
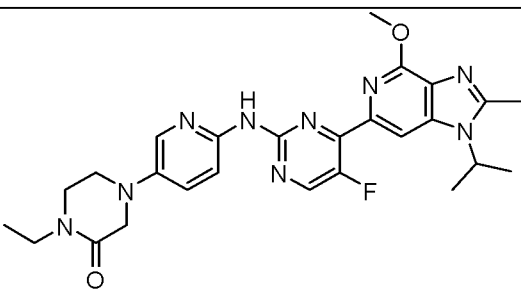
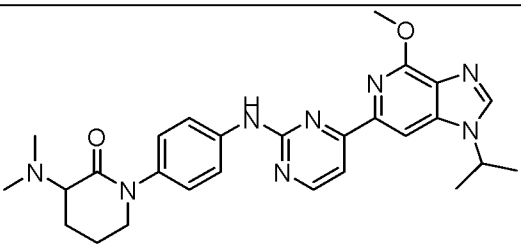
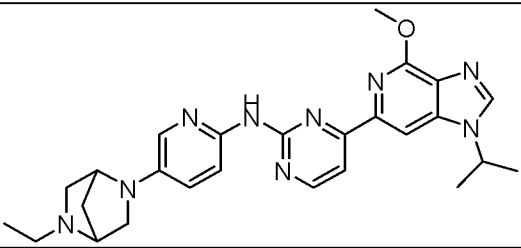
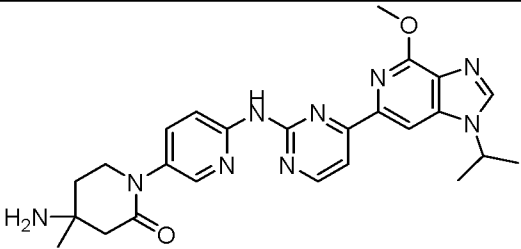
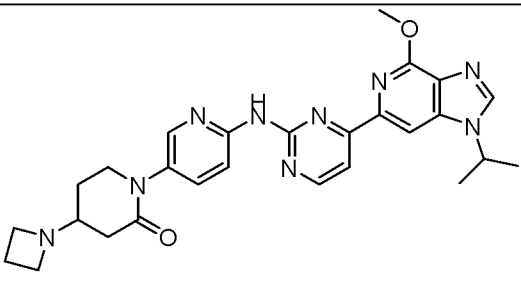
75		489.2	A	B	C
76		463.2	B		D
77		475.2	A	B	C
78		479.2	A	B	C
79		560.2	B		D
80		513.3	A	B	A

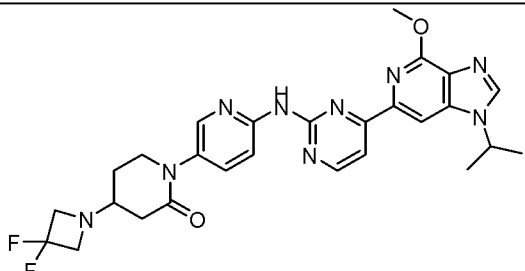
81		461.2	B		D
82		477.2	B		C
83		509.2	A	A	C
84		465.1	B	C	D
85		479.2	B		D
86		574.1	B	B	D

87		506.2	A	B	
88		475.3	B		D
89		506.2	B		D
90		546.3	B		D
91		502.3	A	A	C

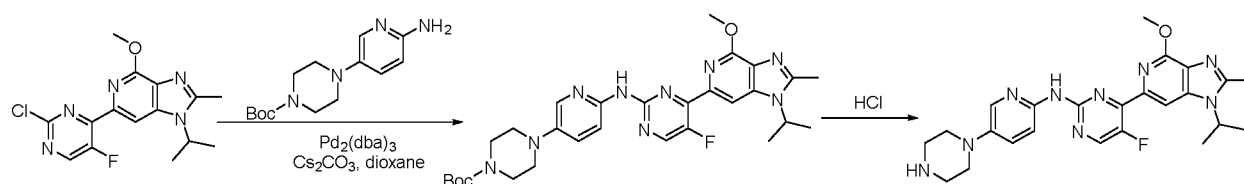
92		510.2	A	B	B
93		491.2	A	B	D
94		520.1	A	B	D
95		520.3	B	B	D
96		461.2	B		D
97		493.2	B		D

98		493.3	A	B	D
99		532.2	A	B	C
100		544.3	A	B	C
101		532.3	B	B	
102		478.1	B	C	C
103		492.2	B	B	D

104		459.2	B		D
105		520.2	B		D
311		501.3	A		C
312		486.3	A	B	D
313		488.2	B	A	C
314		514.3	A	B	B

315		550.2	A	B	C
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Synthetic Example 106



Step 1

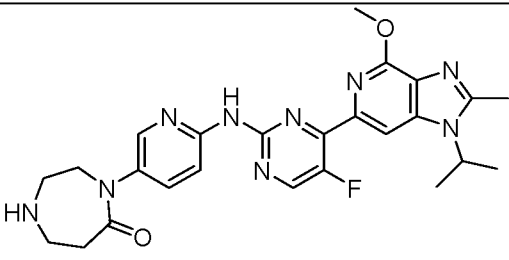
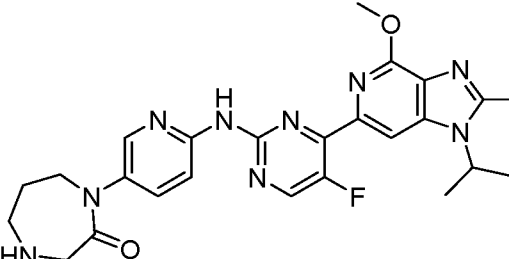
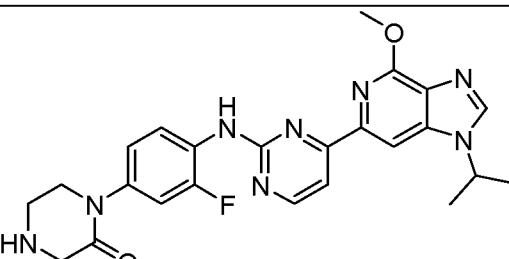
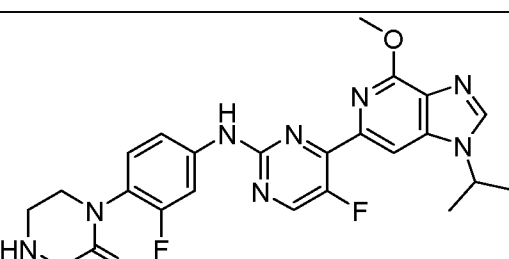
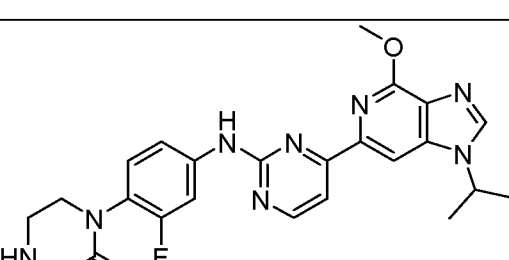
To a solution of 6-(2-chloro-5-fluoro-pyrimidin-4-yl)-1-isopropyl-4-methoxy-2-methylimidazo[4,5-c]pyridine (70.0 mg, 208 μ mol) in dry dioxane (10 mL) were added tert-butyl 4-(6-amino-3-pyridyl)piperazine-1-carboxylate (69.6 mg, 250 μ mol), tris(dibenzylideneacetone)dipalladium(0) (19.0 mg, 20.8 μ mol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (24.1 mg, 41.7 μ mol) and cesium carbonate (203 mg, 625 μ mol). The mixture was stirred at 110 °C for 16 hours. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (4 g silica gel, MeOH in DCM 0-15% in 20 minutes) to afford desired product (92.0 mg, yield: 76%) as a white solid. LC-MS: m/z 578.2 $[M+H]^+$.

Step 2

To a solution of tert-butyl 4-[6-[[5-fluoro-4-(1-isopropyl-4-methoxy-2-methylimidazo[4,5-c]pyridin-6-yl)pyrimidin-2-yl]amino]-3-pyridyl]piperazine-1-carboxylate (92.0 mg, 159 μ mol) in dry DCM (5 mL) was added hydrogen chloride (4 N in 1,4-dioxane) (5 mL). The reaction mixture was stirred at 25 °C for 2 hours. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC to give desired product (10.8 mg, 14% yield) as yellow solid. LC-MS: m/z 478.2 $[M+H]^+$.

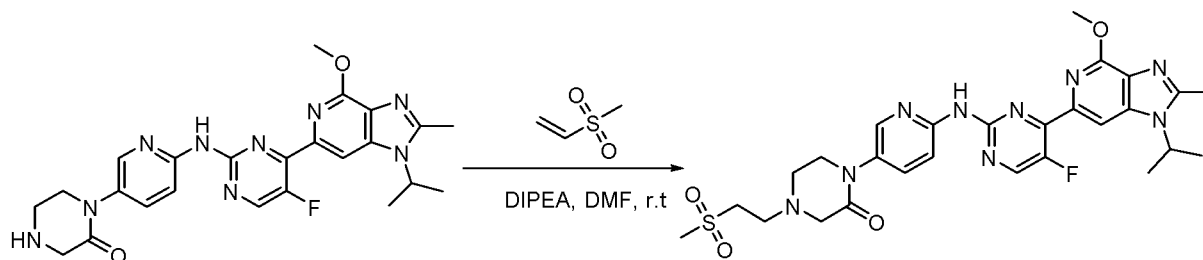
CDK4 IC_{50} : A; CDK6 IC_{50} : B; CDK2 IC_{50} : D.

Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC ₅₀	CDK6 IC ₅₀	CDK 2 IC ₅₀
107		492.2	A	B	D
108		448.3	B		D
109		458.2	A	B	D
110		504.3	B		D
111		495.2	A	B	B

112		506.3	A	B	D
113		506.2	A	B	C
114		477.2	A	B	B
115		495.2	A	B	B
116		477.2	A	B	B

117		460.3	B	B	D
118		474.3	A	B	D
119		460.2	A	B	B
120		534.3	B		D

Synthetic Example 121



To a solution of 1-[6-[[5-fluoro-4-(1-isopropyl-4-methoxy-2-methylimidazo[4,5-c]pyridin-6-yl)pyrimidin-2-yl]amino]-3-pyridyl] piperazin-2-one (50.0 mg, 101 μ mol) and 1-

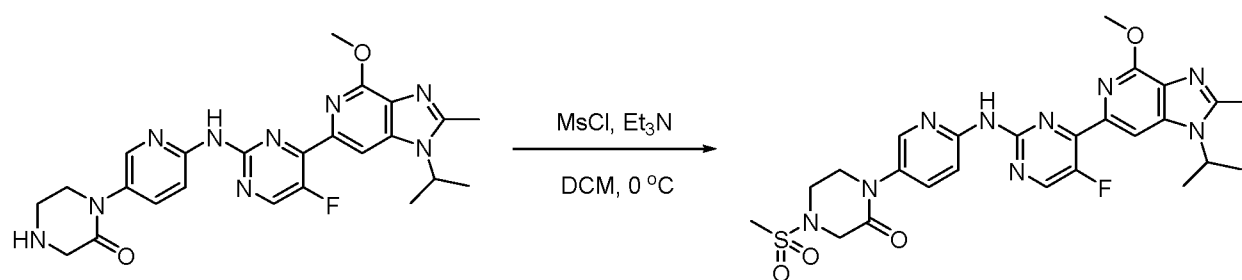
methylsulfonylethylene (21.6 mg, 203 μ mol) in DMF (5 mL) was added DIPEA (30.9 mg, 305 μ mol). The reaction mixture was stirred at 25 °C for 48 h. Then the reaction mixture was diluted with H₂O (30 ml) and extracted with EA (3 $\times$ 10 mL). The organic layer was concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with acetonitrile in water (0.1% FA) 22%-24% in 6.0 minutes to afford desired product (2.7 mg, 4% yield) as yellow solid. LC-MS: m/z 598.3 [M+H]⁺.

CDK4 IC₅₀: A; CDK6 IC₅₀: B; CDK2 IC₅₀: D.

Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC ₅₀	CDK6 IC ₅₀	CDK2 IC ₅₀
122		506.2	A	B	C
123		492.3	A	B	D
124		574.2	A	B	D
125		510.3	B		D

126		524.2	A	B	C
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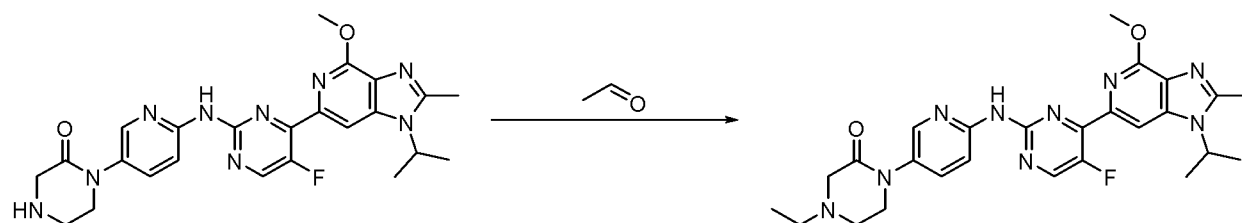
Synthetic Example 127



To a solution of 1-[6-[[5-fluoro-4-(1-isopropyl-4-methoxy-2-methyl-imidazo[4,5-c]pyridin-6-yl)pyrimidin-2-yl]amino]-3-pyridyl]piperazin-2-one (0.2 g, 305 μmol) and TEA (92.6 mg, 915 μmol) in DCM (5 mL) was added methyl sulfonyl chloride (52.4 mg, 457 μmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 0.5 h. The mixture was concentrated and purified by prep-HPLC to get desired product (7.8 mg, 4% yield) as a yellow solid. LC-MS: m/z 570.2 $[\text{M}+\text{H}]^+$.

CDK4 IC_{50} : A; CDK6 IC_{50} : B; CDK2 IC_{50} : C.

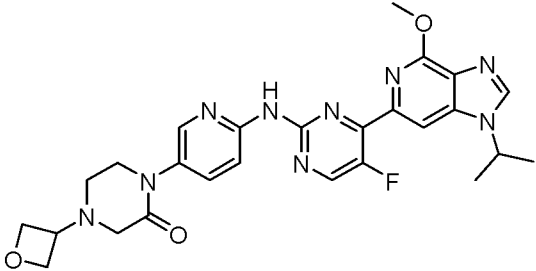
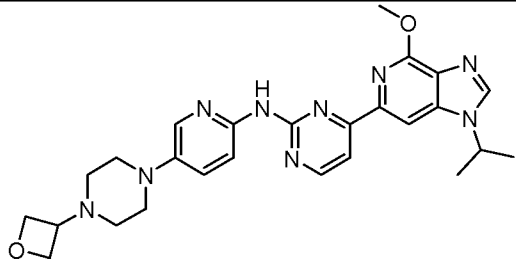
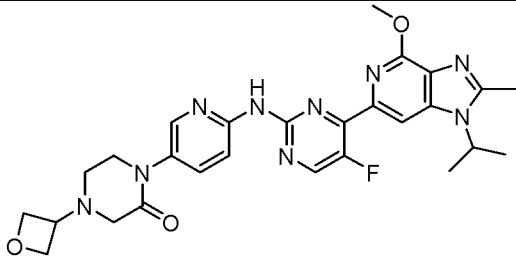
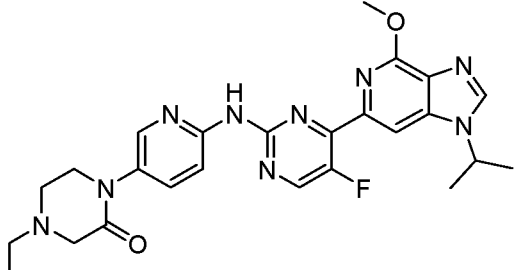
Synthetic Example 128

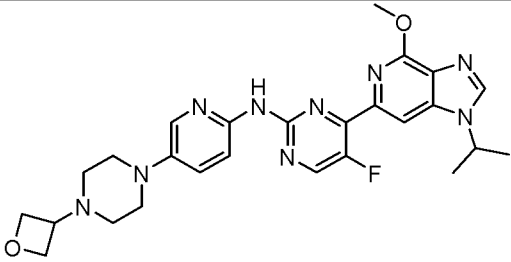
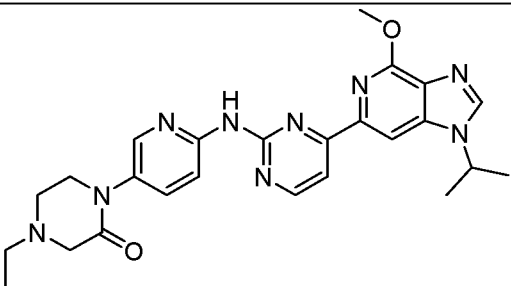
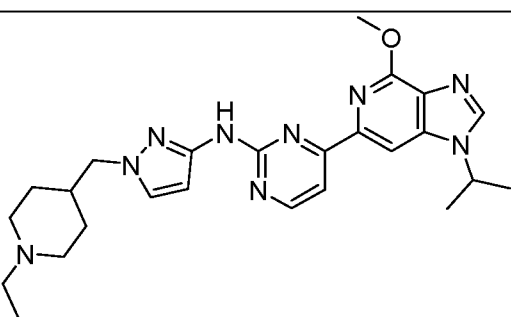
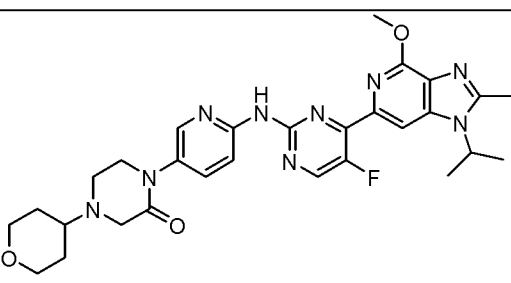
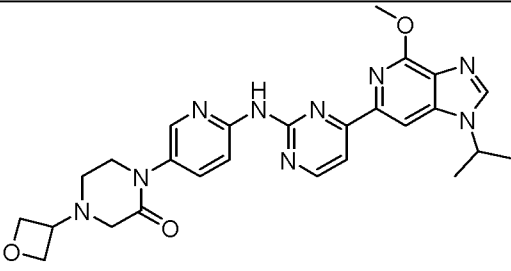


To a solution of 1-[6-[[5-fluoro-4-(1-isopropyl-4-methoxy-2-methyl-imidazo[4,5-c]pyridin-6-yl)pyrimidin-2-yl]amino]-3-pyridyl]piperazin-2-one (100 mg, 203 μmol) and acetaldehyde (17.9 mg, 406 μmol) in DCM (5 mL) was added $\text{NaB}(\text{OAc})_3\text{H}$ (129 mg, 610 μmol). The mixture was stirred at 25 °C for 1 h. The mixture was diluted with water (10 mL) and

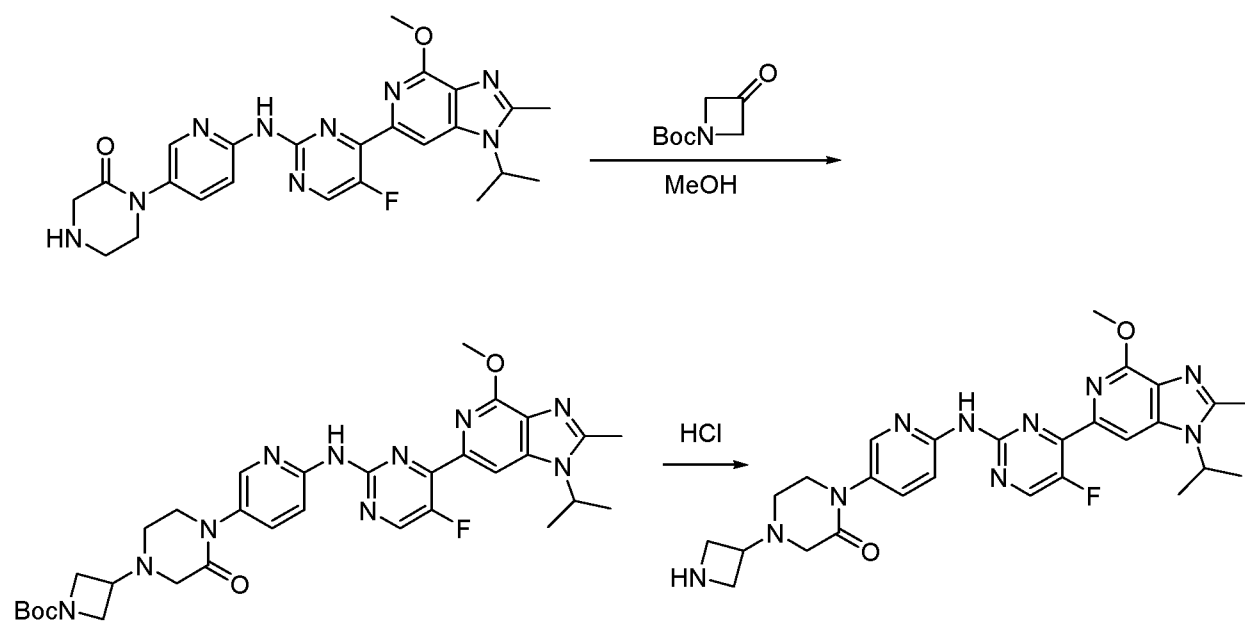
extracted with DCM (2×10 mL). The organic layers were combined, dried over Na_2SO_4 , filtered, concentrated and purified by prep-HPLC to get desired product (16.0 mg, 15% yield) as a yellow solid.

CDK4 IC_{50} : A; CDK6 IC_{50} : B; CDK2 IC_{50} : D.

Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC_{50}	CDK6 IC_{50}	CDK2 IC_{50}
129		534.2	A	B	D
130		502.3	A		D
131		548.2	A	B	D
132		506.2	A	B	D

133		520.3	B		D
134		488.2	A	B	C
135		476.2	B		D
136		576.3	A	B	D
137		516.2	A	B	C

Synthetic Example 138



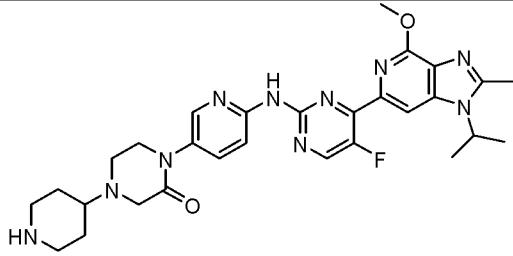
Step 1

To a stirred solution of tert-butyl 3-oxoazetidine-1-carboxylate (26.1 mg, 152 μmol) in methanol (5 mL) was added 1-[6-[[5-fluoro-4-(1-isopropyl-4-methoxy-2-methyl-imidazo[4,5-c]pyridin-6-yl) pyrimidin-2-yl]amino]-3-pyridyl]piperazin-2-one (50.0 mg, 101 μmol). The reaction mixture was stirred at 25 °C under N_2 atmosphere for 1 hour. To the above mixture was added sodium cyanoborohydride (12.8 mg, 203 μmol). The reaction mixture was stirred at 25 °C under N_2 atmosphere for 11 hours. The mixture was concentrated and purified by flash column chromatography (4 g silica gel column), eluting with DCM / MeOH with MeOH 0-6%, to obtain desired product (25.0 mg, 38% yield) as yellow solid. LC-MS: m/z 647.3 $[\text{M}+\text{H}]^+$.

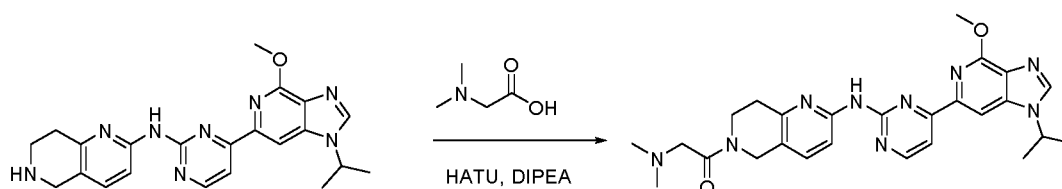
Step 2

To a stirred solution of tert-butyl 3-[4-[6-[[5-fluoro-4-(1-isopropyl-4-methoxy-2-methyl-imidazo[4,5-c]pyridin-6-yl) pyrimidin-2-yl]amino]-3-pyridyl]-3-oxo-piperazin-1-yl]azetidine-1-carboxylate (20.0 mg, 30.9 μmol) in DCM (3 mL) was added HCl (1 N in dioxane, 3 mL). The reaction mixture was stirred at 25 °C under N_2 atmosphere for 1 hour. The mixture was concentrated and purified by prep-HPLC to give desired product (1.8 mg, 11% yield) as a yellow solid. LC-MS: m/z 547.2 $[\text{M}+\text{H}]^+$.

CDK4 IC_{50} : A; CDK6 IC_{50} : B; CDK2 IC_{50} : C.

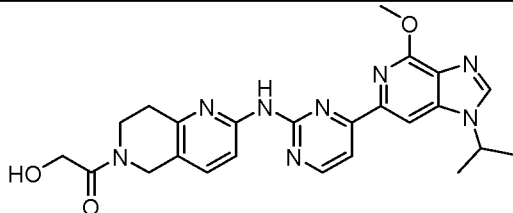
Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC ₅₀	CDK6 IC ₅₀	CDK2 IC ₅₀
139		575.3	A	A	D

Synthetic Example 140



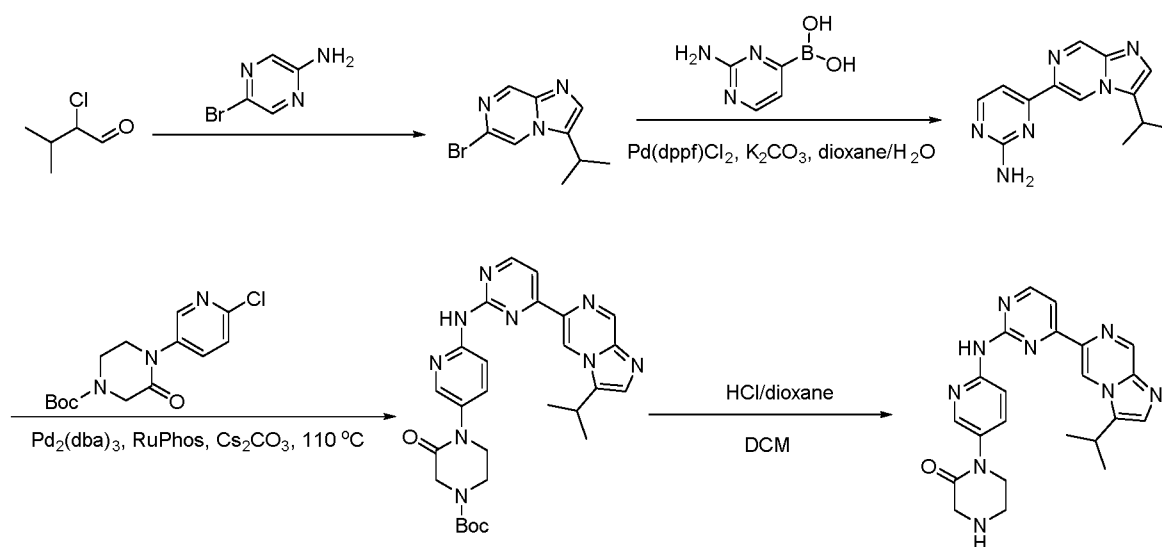
To a mixture of 2-(dimethylamino) acetic acid (6.9 mg, 67.2 μ mol) in DCM (6 mL) was added DIPEA (82.3 mg, 636 μ mol). The mixture was stirred at 20 °C for 10 min. To the above mixture was added N-[4-(1-isopropyl-4-methoxy-imidazo[4,5-c]pyridin-6-yl)pyrimidin-2-yl]-5,6,7,8-tetrahydro-1,6-naphthyridin-2-amine (28.0 mg, 67.2 μ mol) and HATU (25.7 mg, 67.3 μ mol). The mixture was stirred at 20 °C for 12 hours. The mixture was quenched with water (1 mL) and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford desired product (14.5 mg, 43% yield) as a yellow solid. LC-MS: (ESI) m/z 502.2 [M+H]⁺.

CDK4 IC₅₀: A; CDK6 IC₅₀: B; CDK2 IC₅₀: D.

Synthetic Example	Structure	LC-MS: m/z [M+H] ⁺	CDK4 IC ₅₀	CDK6 IC ₅₀	CDK2 IC ₅₀
141		475.2	B		D

142		484.2	B		D
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Synthetic Example 143



Step 1

A solution of 2-chloro-3-methylbutanal (1.1 g, 9.1 mmol) and 5-bromopyrazin-2-amine (1.6 g, 9.1 mmol) in ethylene glycol (10 mL) was stirred at 120 °C for 16 hours. The mixture was diluted with water (25 mL), extracted with EtOAc (2×25 mL). The combined organic phases were concentrated under reduced pressure. The residue was purified by FCC (20 g silica gel, 0-50% EtOAc in PE) to give desired product (200 mg, 9% yield) as a yellow solid. LC-MS: (ESI) m/z 240.2 $[M+H]^+$.

Step 2

A solution of 6-bromo-3-isopropylimidazo[1,2-a]pyrazine (480 mg, 999 μ mol), (2-aminopyrimidin-4-yl)boronic acid (138 mg, 999.5 μ mol), K_2CO_3 (276 mg, 2.0 mmol) and $Pd(dppf)Cl_2$ (73.1 mg, 99.9 μ mol) in dioxane (10 mL) and H_2O (0.5 mL) was stirred at 110 °C under N_2 for 16 hours. The mixture was concentrated under reduced pressure. The residue was purified by FCC (20 g silica gel, 0-10% MeOH in DCM) to give desired product (77.0 mg, 30% yield) as a dark solid. LC-MS: (ESI) m/z 255.1 $[M+H]^+$.

Step 3

A solution of 4-(3-isopropylimidazo[1,2-a]pyrazin-6-yl)pyrimidin-2-amine (77.0 mg, 302 μ mol), tert-butyl 4-(6-chloro-3-pyridyl)-3-oxo-piperazine-1-carboxylate (94.4 mg, 302 μ mol), Cs_2CO_3 (197 mg, 605 μ mol), RuPhos (28.2 mg, 60.5 μ mol) and $\text{Pd}_2(\text{dba})_3$ (27.7 mg, 30.2 μ mol) in dioxane (8 mL) was stirred at 110 °C under N_2 for 16 hours. The mixture was concentrated under reduced pressure. The residue was purified by FCC (12 g silica gel, 0-10% MeOH in DCM) to give desired product (95.0 mg, 59% yield) as a yellow solid. LC-MS: (ESI) m/z 530.2 $[\text{M}+\text{H}]^+$.

Step 4

To a solution of tert-butyl 4-[6-[[4-(3-isopropylimidazo[1,2-a]pyrazin-6-yl)pyrimidin-2-yl]amino]-3-pyridyl]-3-oxo-piperazine-1-carboxylate (95.0 mg, 179 μ mol) in DCM (8 mL) was added HCl (4 N, 180 μ L) at 25 °C. The reaction was stirred at 25 °C for 4 hours. The mixture was concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC to give desired product (19.4 mg, 25% yield) as a yellow solid. LC-MS: (ESI) m/z 430.2 $[\text{M}+\text{H}]^+$.

CDK4 IC_{50} : B; CDK2 IC_{50} : D.

Comparative Synthetic Example 1

Compound 10 disclosed in CN109503573A was prepared. As shown in the table below, this compound has very weak activity in the CDK4 and CDK6 assay.

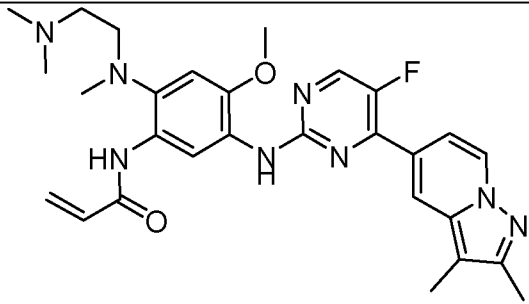
	Structure	CDK4 IC_{50}	CDK6 IC_{50}
Compound 10 in CN109503573A		>10000 nM	>10000 nM

Table A

Synthetic Example	T47D IC ₅₀	Phospho T47D Ser807 IC ₅₀	Synthetic Example	T47D IC ₅₀	Phospho T47D Ser807 IC ₅₀
1	++++	++++	64	+++	
2	++++		65		+++
3	++++	++++	66	+++	+++
4	+	+	67		+++
5	+	+	68	+++	++++
6	++		69	+++	+++
7	+++	+++	70	+++	++++
8	+		73	++	++++
9	+++		74	+++	+++
10	+++		75	++++	
11	+++		76		+++
12	++		77	+++	++++
13	+++		78	++++	++++
14	++++		79		+++
15	++		80	+++	++++
16	++++	++++	81	+++	+++
18	++		82	+++	+++
21	++++	++++	83	++++	++++
23	++		86	+++	
25	++++	++++	87	+++	
26	+++	++++	88	+++	+++
27	++++	+++	91	++++	++++

28	++++	++++	93	+++	+++
29	++++	++++	94	++++	+++
30	+++	++++	96	+++	+++
31	++++	++++	98	++++	++++
32	+++	+++	99	++++	++++
33	++++	++++	100		+++
34	++++	++++	103	+++	++++
35	++++	++++	104	+++	+++
36	+++	+++	106	+++	++++
37	++++	++++	107	+++	
38	+	++	109	++++	++++
39	++++	++++	111	+++	+++
40	++++	++++	112	++++	+++
41	++++	++++	113	+++	+++
42	++++	++++	114		+++
43	++++	++++	115	+++	+++
44	+	++	116	+++	++++
45	+++	++	117	+++	+++
46	++++	++++	118	+++	++++
47	++++	++++	119		+++
48	++++	++++	122	++++	++++
49	+++		123	+++	+++
50	++++	++++	124	+++	
51	++++	++++	125		+++
52		++++	126	+++	+++

53	+++	++++	127	+++	+++
54	+++		128	+++	++++
55	++	+++	129	+++	++++
56		+++	130	+++	+++
57	+++	++++	131	+++	+++
58	+		132	+++	++++
59	++++	++++	133		+++
61	++++	++++	134		++++
62	++++	++++	135	+++	
62-1	+++	+++	136		+++
62-2	++++	++++	137		++++
63	+++	++++	140		++++
144	++++		240	+	+
156	+++	++++	241	+++	++++
157	++++	++++	242	++	++++
158	++++	++++	243	++	+++
159	++++	++++	244	++	++
160	++++	++++	245	++	+++
161	++++	++++	246	++	
162	++++	++++	247	++++	
163	++++	++++	248	++++	
164	++++	++++	249	++++	
165	++++	+++	250	++++	
166	++++	++++	252	++++	
167	++++	++++	253	++++	

168	++++	++++	257	++++	
169		++++	258	++++	++++
170	++++		259	++++	++++
171	++++	++++	260	++++	
172	++++	++++	261		++++
173	++++	++++	262	++++	++++
174	+++		263	++++	
175	++++	++++	265	++++	
176	++++	++++	266	++++	
178	++++		267	++++	
184	++++	++++	268	++++	
185	++++		269	++++	
191	++++	++++	270	++++	++++
192	++++	++++	271		++++
193	++++	++++	272	++++	++++
194	+++	++++	273	++++	++++
195	++++	++++	275		++++
196	++++	++++	276	++++	++++
197	++++	++++	277	++++	++++
198	++++	++++	278	++++	++++
199	++++	++++	279	++++	++++
200	++++	++++	280	++++	++++
201	++++		281	++++	++++
202	++++	++++	282	++++	++++
203	++++	++++	283	++++	++++

204	++++	++++	284	++++	
205	++++	++++	285	++++	++++
206	++++	++++	286	++++	++++
207	++++	++++	287	++++	++++
208	++++		289		++++
209	++++	++++	290		++++
210	+		293	++++	++++
211	++		294	++++	
214	++++	++++	295	++++	
215	++++		298	++++	
216	++++		299	++++	
217	++++		300	++++	
218		++++	301	++++	++++
219	++++		302	++++	
220	++++		303	++++	
221	++++		304	++++	
226	++++		306	++++	
227	++++	++++	308	++++	
234	++++	++++	309	++++	
235	++++	++++	311	++++	
236	++++	++++	312	+++	++++
237	++++	++++	313		++++
238	+++		314	++++	++++
239	+++		315	+++	++++

$IC_{50} \leq 100 \text{ nM}$: “++++”

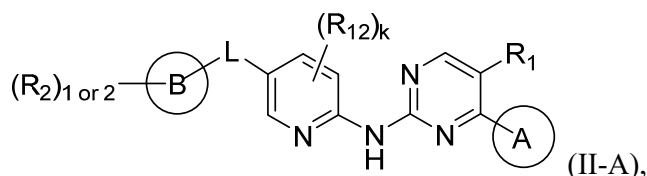
$100 \text{ nM} < IC_{50} \leq 500 \text{ nM}$: “+++”

$500 \text{ nM} < IC_{50} \leq 1 \text{ }\mu\text{M}$: “++”

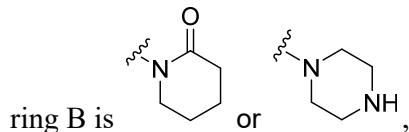
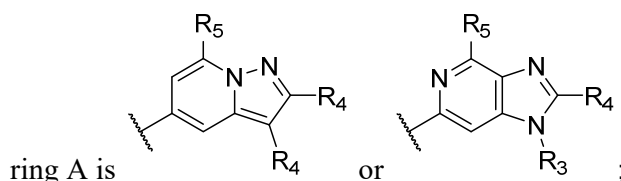
$1 \text{ }\mu\text{M} < IC_{50}$: “+”

CLAIMS

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



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



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;

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 thereof, wherein

each instance of R₂ is H, halogen, CN, -OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, -(CH₂)_nOR₆, -(CH₂)_nC(O)R₆, -(CH₂)_nC(O)OR₆, -(CH₂)_nS(O)₂R₆, -(CH₂)_nNR₇R₈, -(CH₂)_nC(O)NR₇R₈, -(CH₂)_nC(O)NHR₇, -(CH₂)_nNR₇C(O)R₆, -(CH₂)_nNR₇S(O)₂R₆, C₃₋₈ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl;

each instance of R₆ is independently H, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, 3-7 membered heterocyclyl, phenyl, 5-6 membered heteroaryl, wherein the C₁₋₄ alkyl, C₃₋₆ cycloalkyl, 3-7 membered heterocyclyl, phenyl, 5-6 membered heteroaryl represented by R₆ is each optionally substituted with halogen, CN, -OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, or NR₇R₈; and

n is 0, 1, or 2.

3. The compound of 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.

4. The compound of any one of claims 1-3 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.

5. The compound of any one of claims 1-4 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, and

n is 0, 1, or 2.

6. The compound of any one of claims 1-5 or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

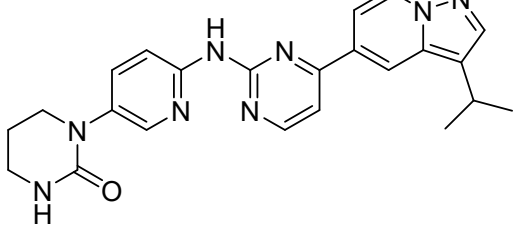
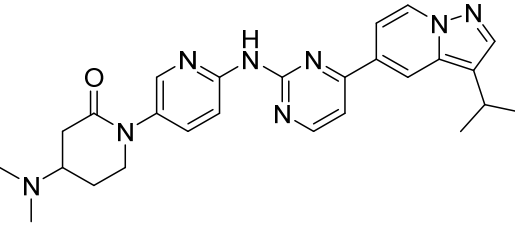
each instance of R₃ is H or C₁₋₃ alkyl;

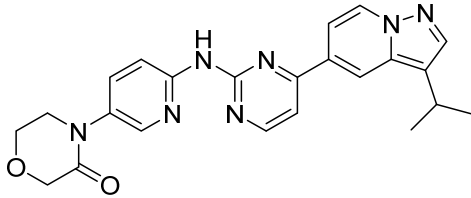
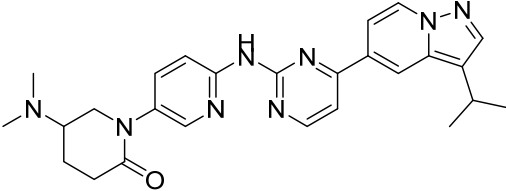
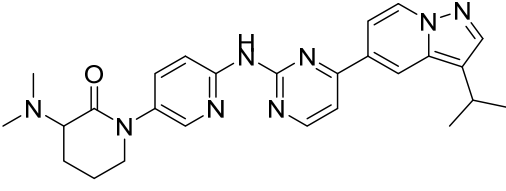
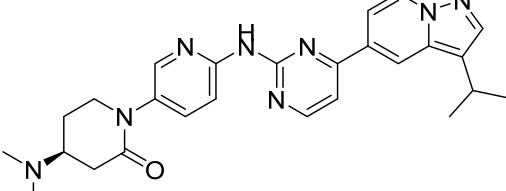
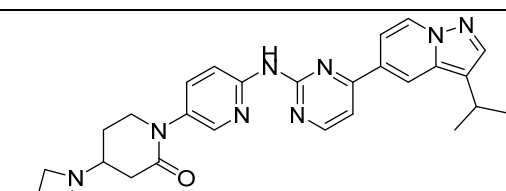
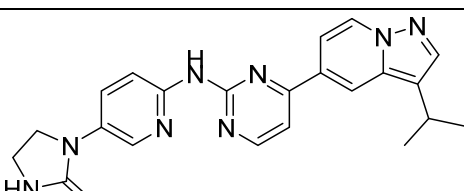
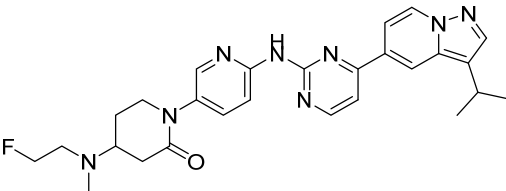
each instance of R₄ is H or C₁₋₃ alkyl; and

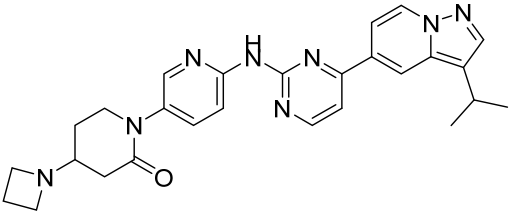
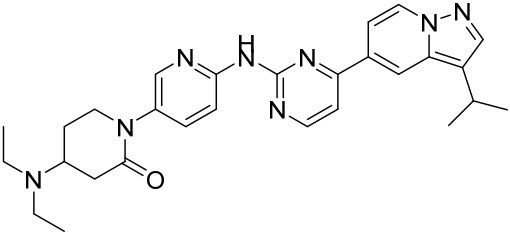
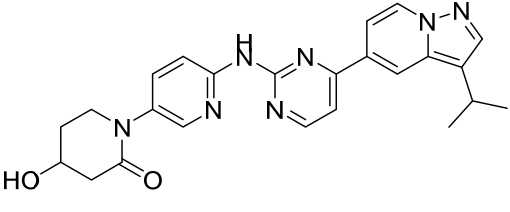
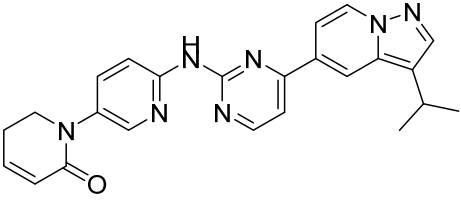
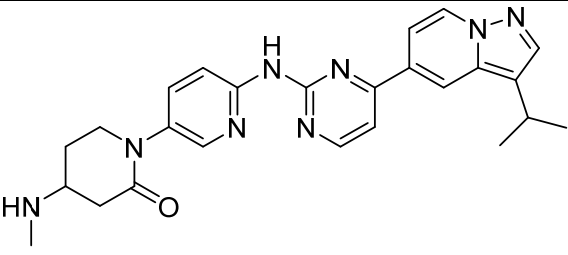
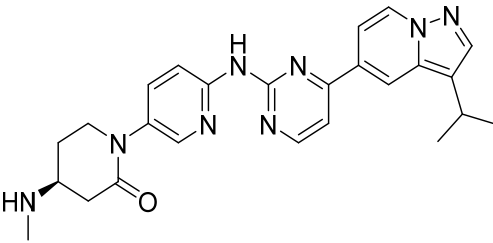
each instance of R₅ is H, F, or OMe.

7. The compound of any one of claims 1-6 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, or NHcyclopropyl.

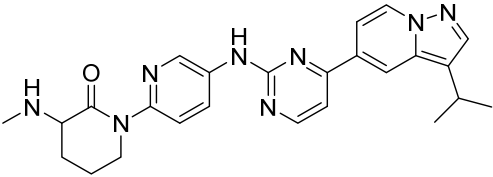
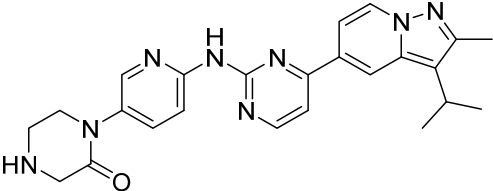
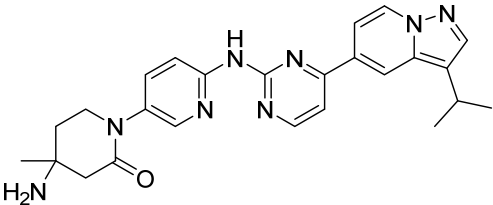
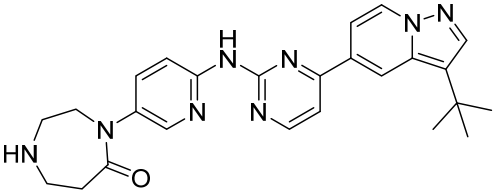
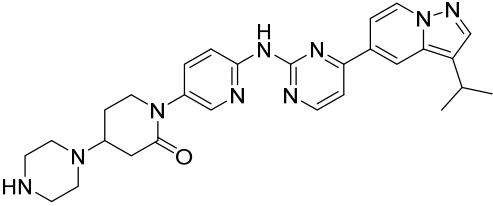
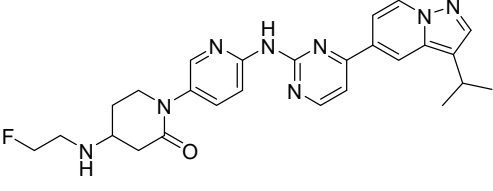
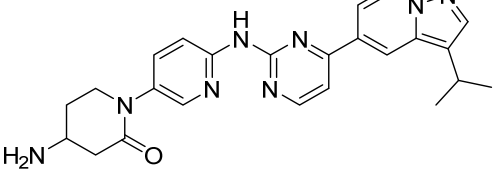
8. A compound, or a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein the compound is:

1	
16	

28	
156	
157	
161	
162	
163	
170	

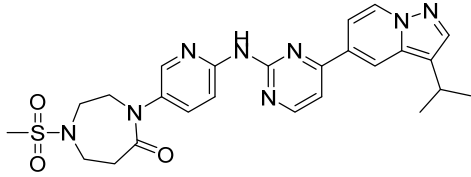
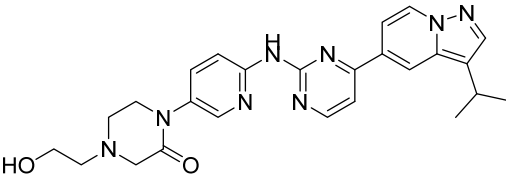
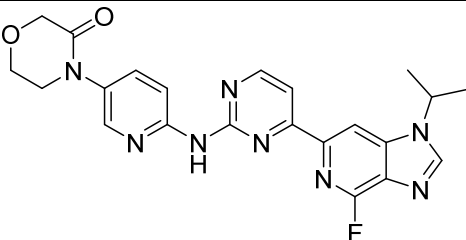
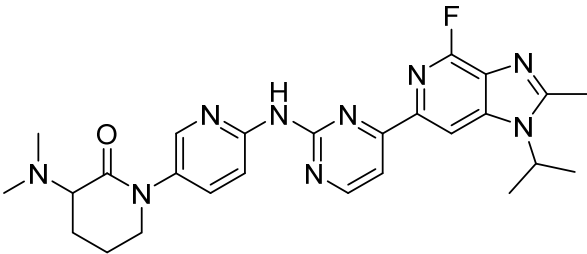
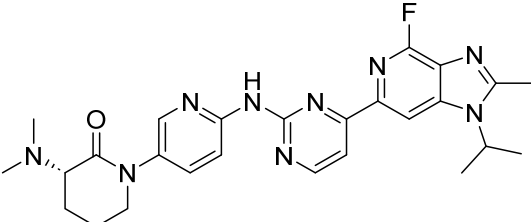
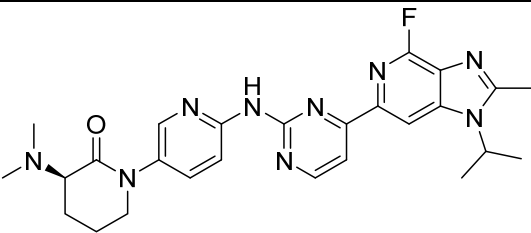
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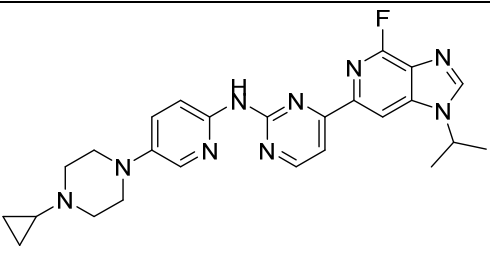
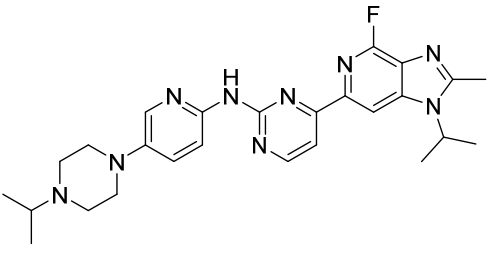
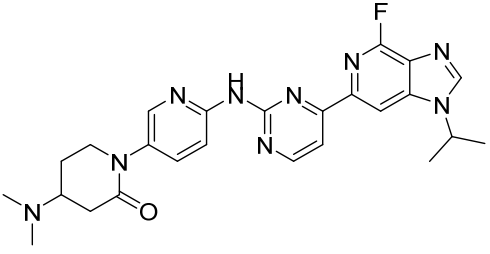
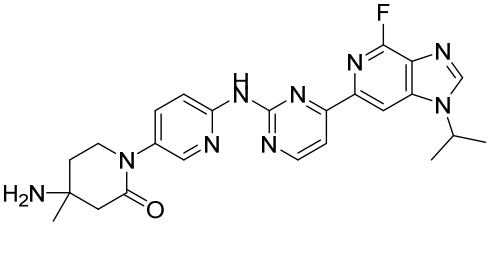
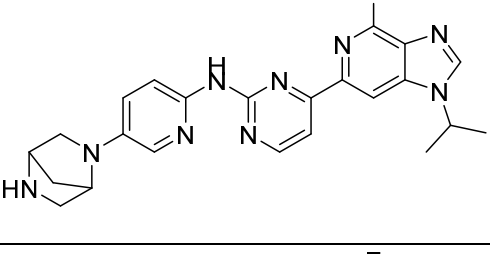
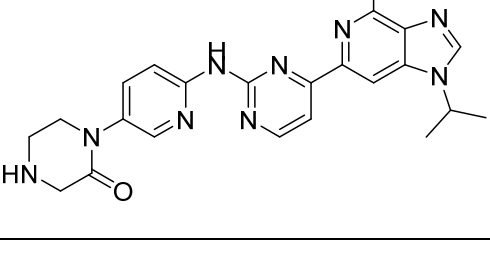
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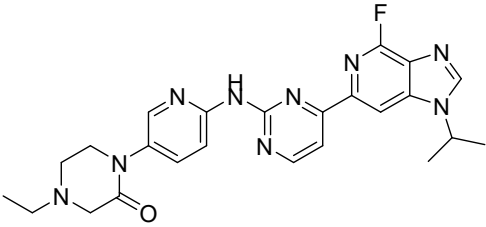
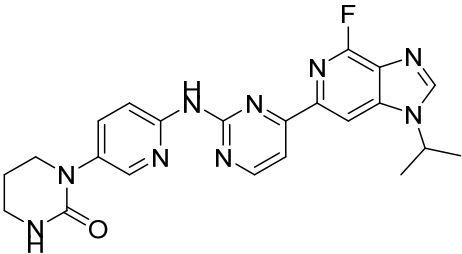
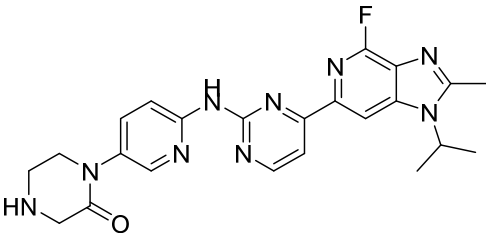
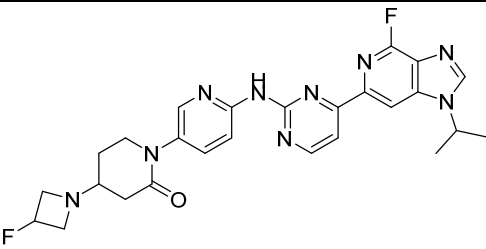
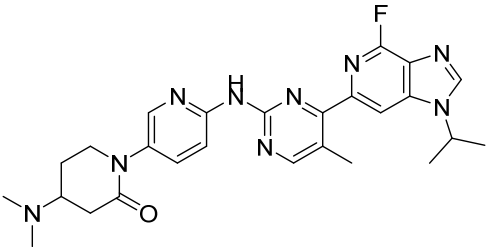
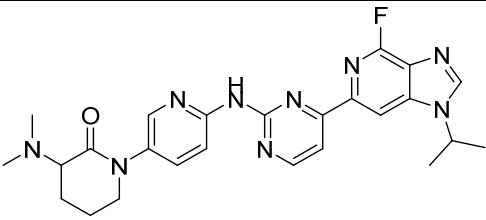
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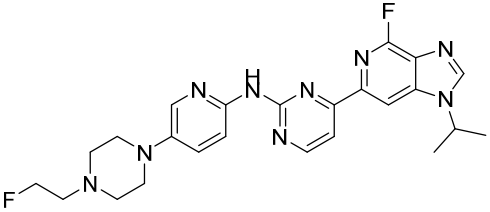
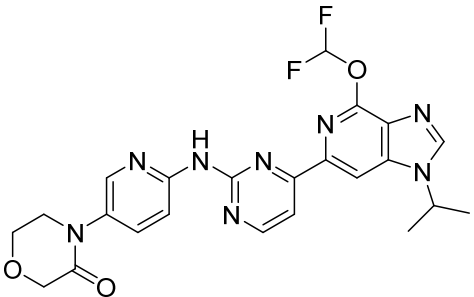
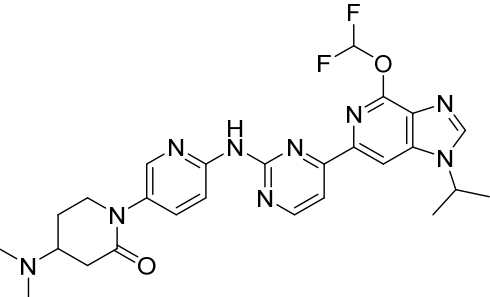
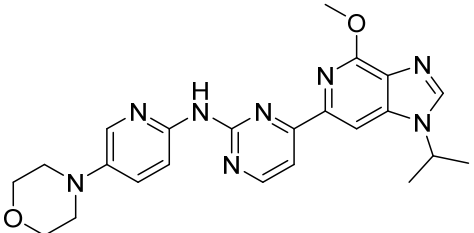
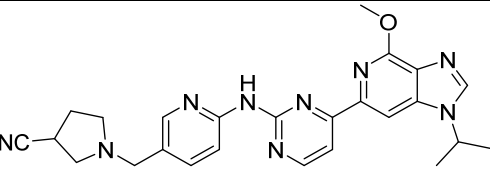
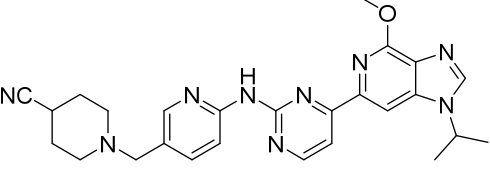
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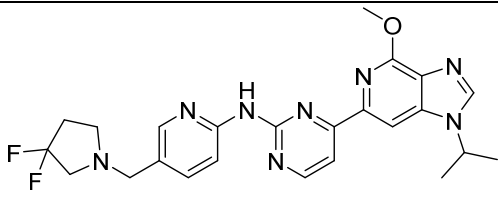
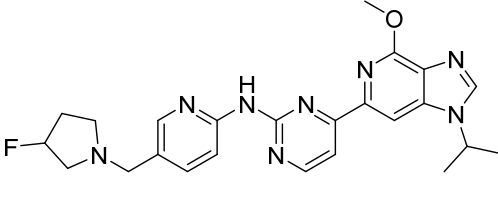
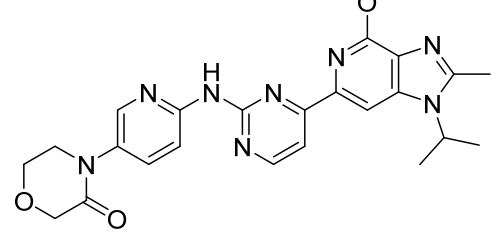
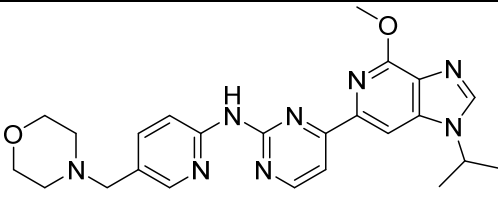
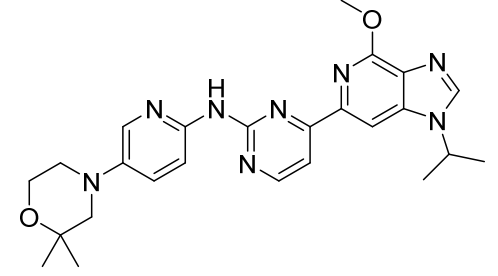
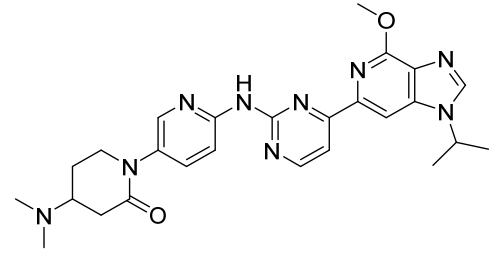
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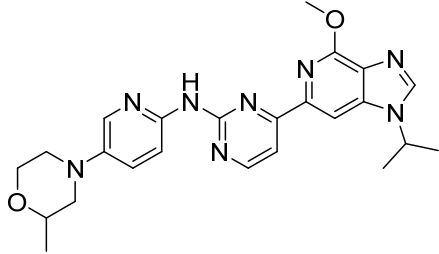
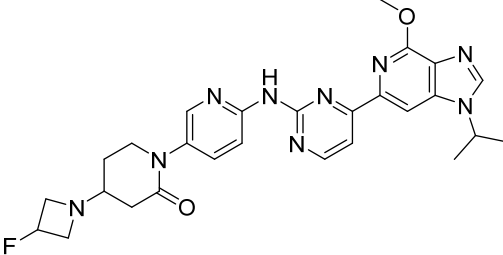
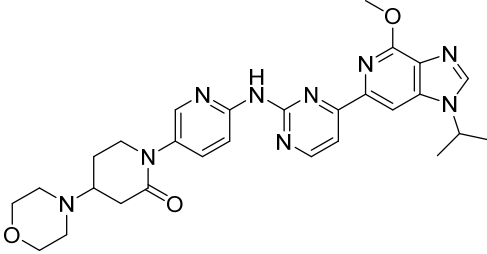
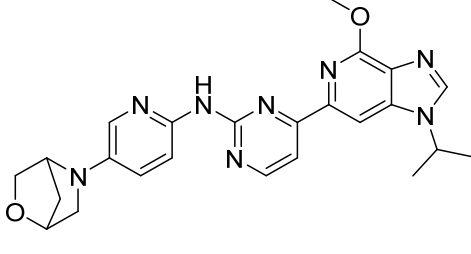
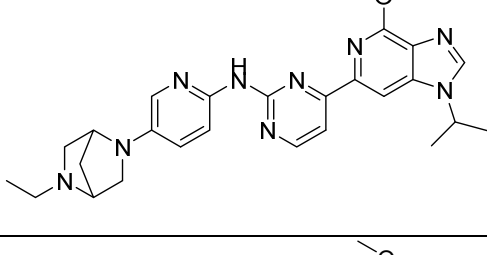
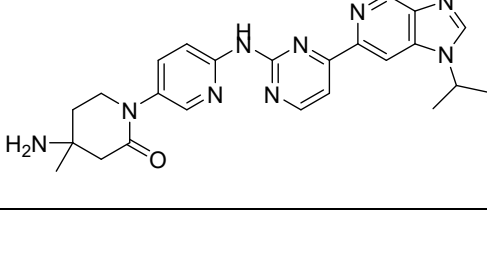
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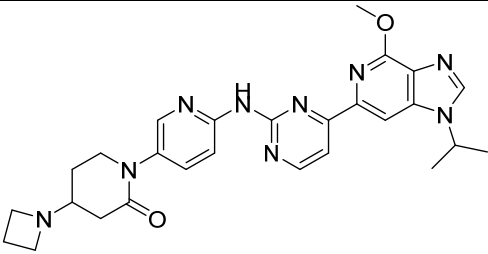
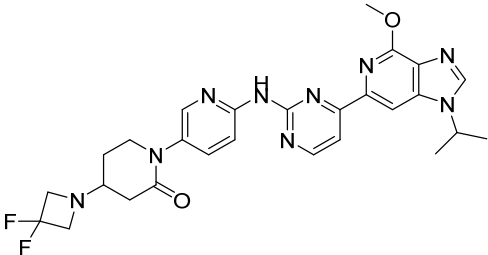
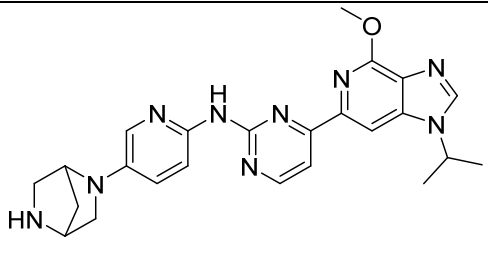
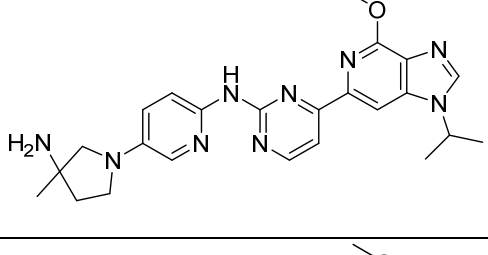
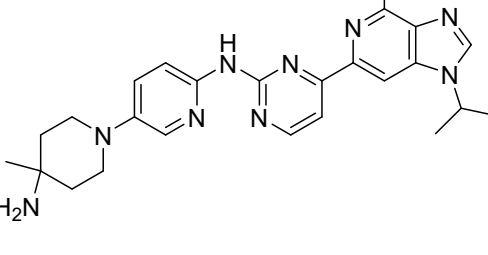
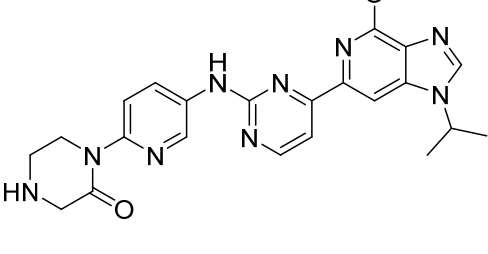
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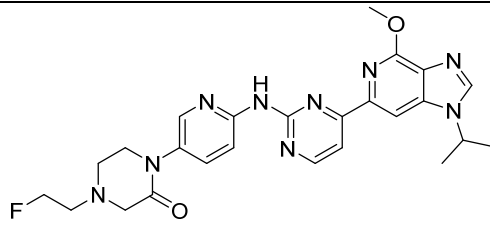
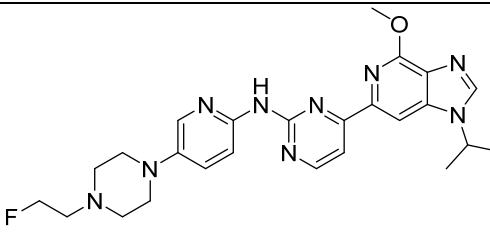
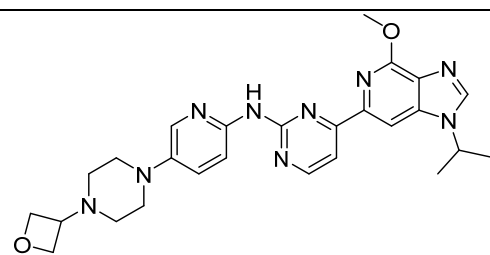
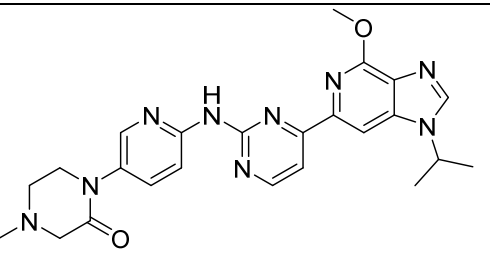
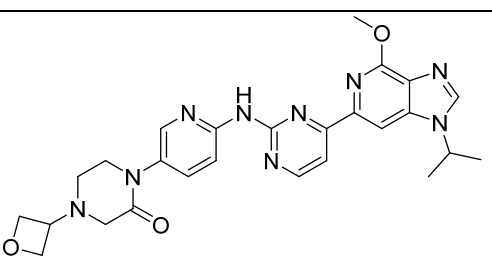
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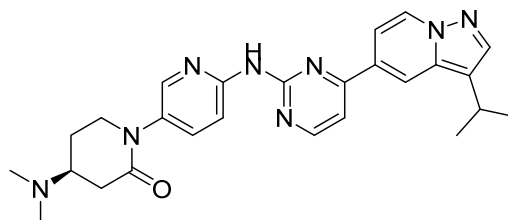
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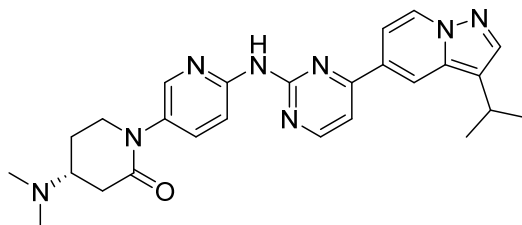
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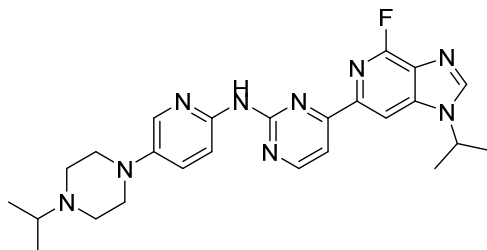
9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is



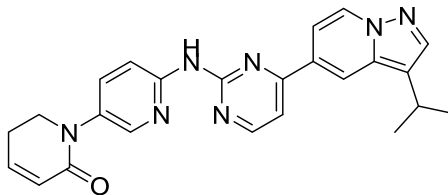
10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is



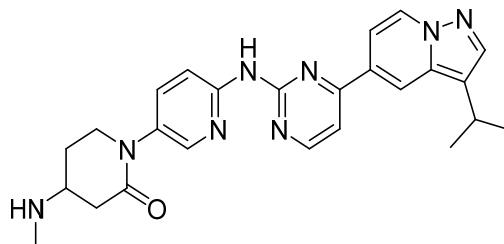
11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is



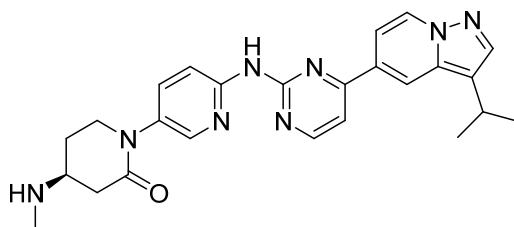
12. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein the compound is:



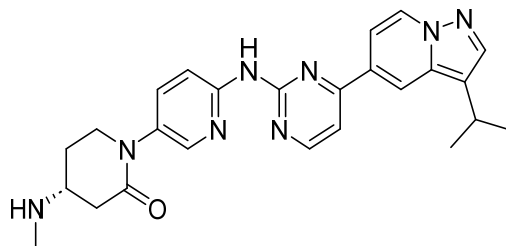
13. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein the compound is:



14. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein the compound is:



15. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein the compound is:



16. A pharmaceutical composition comprising an effective amount of the compound of any one of claims 1-15 or a pharmaceutically acceptable salt, or a stereoisomer thereof, and a pharmaceutically acceptable carrier.
17. Use of a compound of any one of claims 1-15, 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, mantle cell lymphoma, chronic myeloid leukemia and acute myeloid leukemia.
18. Use of a compound of any one of claims 1-15, in the manufacture of a medicament for treating a cancer by inhibiting a cyclin-dependent kinase (CDK), 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; keratoacanthoma; or Kaposi's sarcoma.
19. The use of claim 18, 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.

20. The use according to claim 18, 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.
21. The use of claim 20, wherein the cancer is advanced or metastatic or recurrent breast cancer.
22. The use of claim 21, wherein the breast cancer is in an adult woman, or a postmenopausal woman.
23. The use of any of claims 20-22, 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 CYP3A4, or a monoclonal antibody or an antigen-binding fragment thereof against IGF-1/IGF-2 is to be further administered.
24. The use of any of claims 17-23, 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 of hormone receptor (such as estrogen receptor) is to be further administered.
25. A compound of any one of claims 1-15, 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.