AMINO-SUBSTITUTED HETEROCYCLES FOR TREATING CANCERS WITH EGFR MUTATIONS

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application Nos. 63/174,177, filed April 13, 2021; 63/239,089, filed August 31, 2021; 63/242,837, filed September 10, 2021; and 63/292,605, filed December 22, 2021, the content of which are incorporated by reference herein.

BACKGROUND

Receptor tyrosine kinases (RTKs) are cell surface proteins that transmit extracellular signals, such as growth signals, into the cell through kinase activity. RTKs regulate many crucial biological processes including development, proliferation, and cell homeostasis. Aberrations in RTK signaling may cause uncontrolled cell proliferation that ultimately leads to cancer.

The human epidermal growth factor receptor (HER)-family proteins are among the first RTKs to be identified and associated with cancer. HER is also known as ErbB, a name derived from the viral homolog erythroblastosis oncogene B. The HER family comprises 4 members: EGFR/HER1/ErbB1, HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4. They share highly related structures involving an extracellular domain that binds ligands, a single-pass transmembrane domain, and an intracellular kinase domain. Several ligands have been identified for EGFR (such as EGF and TGF-α) and HER3/HER4 (such as neuregulins), whereas no ligands are known for HER2. Upon activation, the HER receptors form homo- or heterodimers to catalyze downstream signal transduction through the mitogen-activated protein kinase (MAPK), the phosphoinositide 3-kinase (PI3K), and other pathways.

EGFR dysregulation is a hallmark of many cancers. Cancer cells overactivate EGFR through various mechanisms including overexpression, missense mutations, insertions, and deletions. EGFR is frequently overexpressed in many solid tumors such as non-small cell lung cancer (NSCLC), breast cancer, glioblastoma, prostate cancer, colorectal cancer, head-and-neck cancer, and many others. EGFR variant 3 (EGFR vIII), which bears a large deletion of exons 2-7, is found in about 30% of glioblastoma. A variety

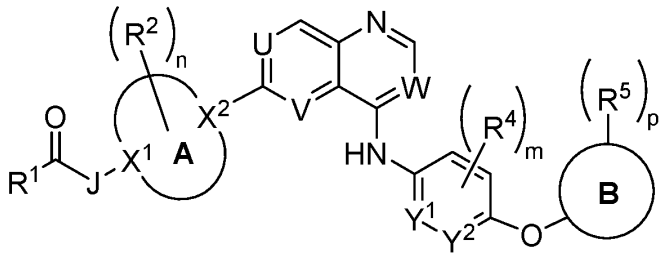
of activating mutations in EGFR drive around 30% of NSCLC, with higher prevalence associated with adenocarcinoma histology, non-smokers, Asians, and women. These activating mutations are further divided into point mutations (predominantly L858R in exon 21), short deletions in exon 19 (predominantly E746_A750del), short insertions in exon 20, and other rarer mutations not specified here. L858R, E746_A750del, and exon 20 insertions account for about 35-40%, 40-45%, and 5-10% of all EGFR-mutant NSCLC cases, respectively.

HER2 dysregulation is also a well-documented cause of cancer. HER2 overexpression is found in 15-25% of breast cancer cases, representing one of the major molecular subtypes of breast cancer, as well as in ovarian cancer, gastric cancer, esophageal cancer, endometrial cancer, and lung cancer. HER2 mutations are found in about 2% of NSCLC patients but, unlike EGFR, are largely restricted to exon 20 insertions (predominantly A775_G776insYVMA).

Known agents used to treat oncogenic EGFR or HER2 have significant deficiencies including one or more of the following: toxicity arising from wild-type EGFR inhibition, limited activity in the central nervous system (CNS), and inadequate activity against exon 20 insertions and drug resistance mutations. EGFR has important epithelial functions in the gastrointestinal lining and on the skin of adult humans, so inhibition of non-mutated EGFR is believed to cause adverse reactions such as diarrhea and rash, which are common safety signals for many existing EGFR inhibitors. Up to 60% of EGFR-mutant and 45% of HER2-mutant NSCLC patients will develop brain metastases over the course of the disease; therefore, CNS activity is an important consideration for future therapeutic development. Among the major forms of EGFR and HER2 mutations, exon 20 insertions represent an unmet need as no targeted therapies have been FDA-approved for these indications. For these reasons, there is a need for development of a new generation of inhibitors that spare wild-type EGFR, penetrate the blood-brain barrier, and show specific activity against exon 20 insertions and/or drug-resistance mutations.

SUMMARY

In certain aspects, the present disclosure provides compounds of Formula (I), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(I)

wherein:

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge; or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 8-membered heterocyclic ring;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

U is CR^c or N;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

V is CR^d or N;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

W is N or CR^e;

R^e is hydrogen, halo (e.g., fluoro), or cyano;

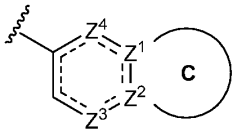
Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

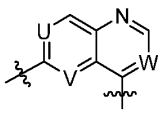
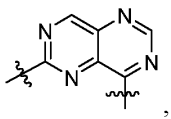
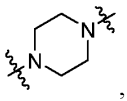
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

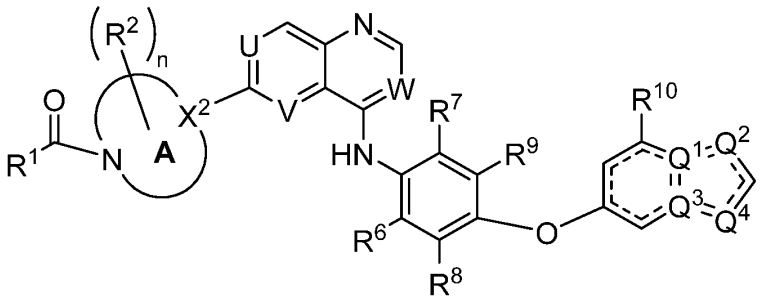
p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

In some embodiments of Formula (I) (or a subformula thereof), it's provided that V is N; or ring B is , wherein C is 5- or 6-membered heteroaryl; Z^1, Z^2, Z^3, and Z^4 are each independently C or N; and any atom of ring B may be substituted by R^5 as permitted by valence.

In one embodiment of Formula (I) (or a sub-formula thereof), it is provided that when  is , ring A is , Y^1 and Y^2 are each independently CR^4, then R^4 in Y^2 is C_{1-5} alkyl and R^4 in Y^1 is halo. In one embodiment, R^4 in Y^2 is methyl. In one embodiment, R^4 in Y^1 is fluoro. In one embodiment, R^4 in Y^2 is methyl, and R^4 in Y^1 is fluoro.

In one embodiment of Formula (I) (or a sub-formula thereof), ring A is 6- to 10-membered bicyclic heterocyclyl or 3- to 5- or 7- to 8-membered monocyclic heterocyclyl.

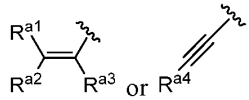
In certain aspects, the present disclosure provides compounds of Formula (II), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(II)

wherein:

ring  is 4- to 7-membered heterocyclyl;

R^1 is ;

each of R^{a1}, R^{a2}, R^{a3}, and R^{a4} is independently hydrogen, halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, optionally substituted $-CH_2O-C_{1-5}$ alkyl, optionally substituted $-CH_2O-(CH_2)_{1-2}-O-C_{1-5}$ alkyl, optionally substituted $-CO_2-C_{1-5}$ alkyl, or optionally substituted 3- to 6-membered heterocyclyl; or R^{a1} and R^{a2} are joined together to form an alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

or R^{a1} and R^{a2} are joined together to form an alkenyl group;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge; or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 8-membered heterocyclic ring;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

U is CR^c or N;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

V is CR^d or N;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

W is N or CR^e;

R^e is hydrogen, halo (e.g., fluoro), or cyano;

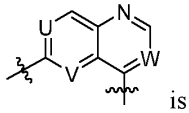
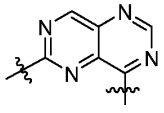
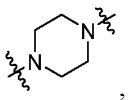
R^6, R^7, R^8, and R^9 are each independently hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

R^{10} is hydrogen, halo, or optionally substituted C_{1-5} alkyl;

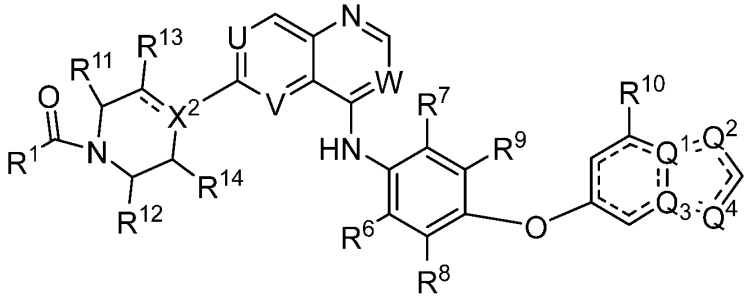
Q^1, Q^2, Q^3, and Q^4 are each independently NR^f or CR^g, provided that at least one of Q^1, Q^2, Q^3, and Q^4 is CR^g;

R^f, independently for each occurrence, is hydrogen, optionally substituted C_{1-5} alkyl, or absent; and

R^g, independently for each occurrence, is hydrogen, optionally substituted C_{1-5} alkyl, or absent.

In one embodiment of Formula (II) (or a sub-formula thereof), it is provided that when  is , ring A is , then R^8 is C_{1-5} alkyl and R^6 is halo. In one embodiment, R^8 is methyl. In one embodiment, R^6 is fluoro. In one embodiment, R^8 is methyl, and R^6 is fluoro.

In certain embodiments, the compounds of Formula (II) are compounds of Formula (III), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:

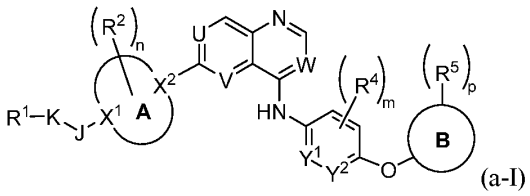


(III)

wherein:

R^{11}, R^{12}, R^{13}, and R^{14} are each independently hydrogen or optionally substituted C_{1-5} alkyl; or two non-geminal occurrences of R^{11}, R^{12}, R^{13}, and R^{14} taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge.

In certain aspects, the present disclosure provides compounds of Formula (a-I), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(a-I)

wherein:

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-4} alkyl;

K is a bond, C=O, or SO_2;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge; or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 8-membered heterocyclic ring;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

U is CR^c or N;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

V is CR^d or N;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

W is N or CR^e;

R^e is hydrogen, halo (e.g., fluoro), or cyano;

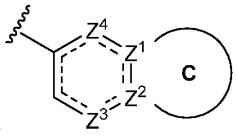
Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

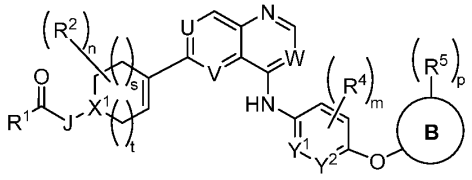
R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

In some embodiments of Formula (a-I) (a subformula thereof), it is provided that when K is C=O; V is N or ring B is , wherein C is 5- or 6-membered heteroaryl; Z^1, Z^2, Z^3, and Z^4 are each independently C or N; and any atom of ring B may be substituted by R^5 as permitted by valence.

In one embodiment of Formula (a-I) (or a sub-formula thereof), K is a bond. In one embodiment of Formula (a-I) (or a sub-formula thereof), K is a C=O. In one embodiment of Formula (a-I) (or a sub-formula thereof), K is a SO_2.

In certain aspects, the present disclosure provides compounds of Formula (I-i), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(I-i)

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

wherein:

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, optionally substituted -O-C_{1-5} alkyl, optionally substituted -O-C_{1-5} alkylene-O-C_{1-5} alkyl, optionally substituted -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

s is 0, 1, or 2;

t is 1 or 2;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_{1-4} alkylene bridge;

n is 0 an integer from 1 to 3, inclusive, as permitted by valence;

U is CR^c or N;

V is CR^d or N; provided that at least one of U and V is N;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 6-membered heterocyclic ring;

W is N or CR^e;

R^e is hydrogen, halo, or cyano;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

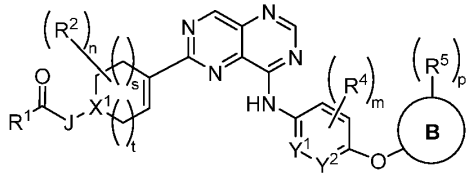
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

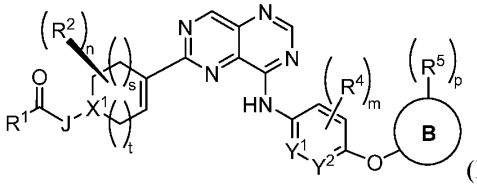
p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

In certain embodiments, the compounds of Formua (I-i) are of Formula (I-i-a), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



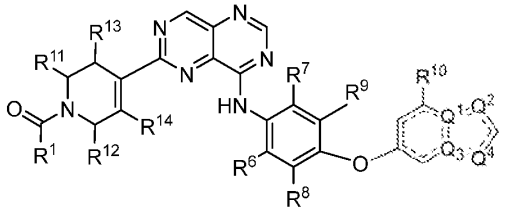
(I-i-a).

In certain embodiments, the compounds of Formua (I-i) are of Formula (I-i-a0), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(I-i-a0).

In certain embodiments, the compounds of Formua (I-i) are of Formula (I-i-a1):



(I-i-a1)

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

wherein:

R^6, R^7, R^8, and R^9 are each independently hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

R^{10} is hydrogen, halo, or optionally substituted C_{1-5} alkyl;

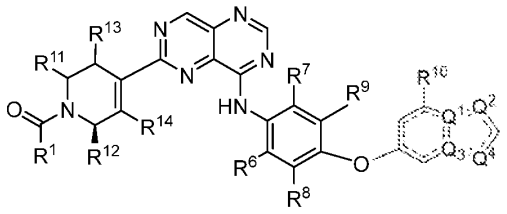
Q^1, Q^2, Q^3, and Q^4 are each independently NR^f or CR^g as valency permits, provided that at least one of Q^1, Q^2, Q^3, and Q^4 is CR^g;

R^f, independently for each occurrence, is hydrogen, optionally substituted C_{1-5} alkyl, or absent;

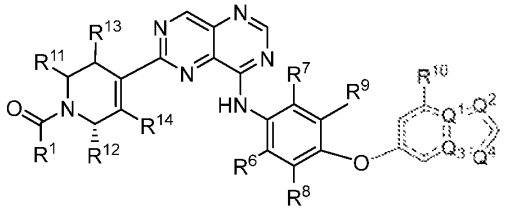
R^g, independently for each occurrence, is hydrogen, optionally substituted C_{1-5} alkyl, or absent; and

R^{11}, R^{12}, R^{13}, and R^{14} are each independently hydrogen or optionally substituted C_{1-5} alkyl, or two of R^{11}, R^{12}, R^{13}, and R^{14} taken together form a C_{1-4} alkylene bridge.

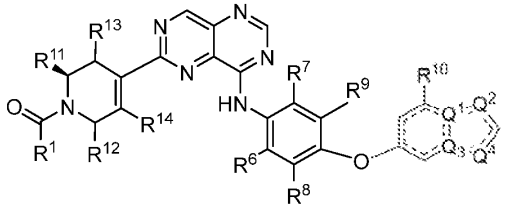
In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



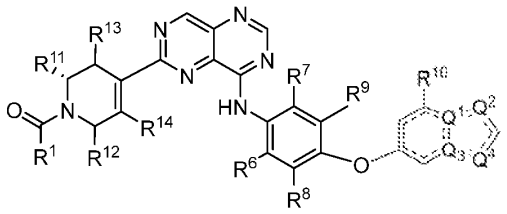
In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



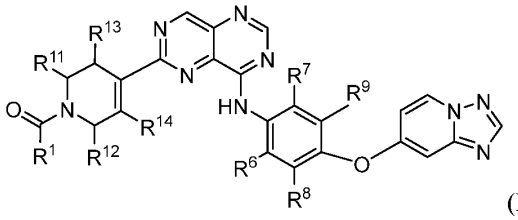
In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



In certain embodiments, the compounds of Formula (I-i-a1) are of Formula (I-i-a2):



(I-i-a2)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

In certain embodiments, the present disclosure provides a pharmaceutical composition suitable for use in a subject in the treatment or prevention of cancer comprising an effective amount of any of the compounds described herein (such as a compound of any of Formula (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (a-I), (II), or (III), or subformulae thereof) or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the pharmaceutical preparations may be for use in treating or preventing a condition or disease as described herein.

An aspect of the disclosure is methods of treating cancer, comprising administering to a mammal (e.g. a human subject) in need thereof an effective amount of a compound as disclosed herein (e.g., a compound of Formula (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (a-I), (II), or (III), or any of the embodiments thereof disclosed herein) or a pharmaceutical composition as provided herein. In certain embodiments, provided herein are methods of treating HER2-associated cancer, comprising administering to a mammal (e.g. a human subject) in need thereof an effective amount of a compound as disclosed herein (e.g., a compound of Formula (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (a-I), (II), or (III), or any of the embodiments thereof disclosed herein) or a pharmaceutical composition as provided herein. In certain embodiments, the human subject is in need of such treatment. In certain embodiments, the human subject is identified or diagnosed as having a HER2-associated cancer. In certain embodiments, HER2-associated cancer is associated with a dysregulation of a HER2 gene, a HER2 kinase, or expression or activity or level of any of the same. In certain embodiments, HER2-associated cancer is associated with HER2 overexpression, and/or HER2 amplification, and/or HER2 mutation(s). In certain embodiments, the cancer is solid tumor. In certain embodiments, the HER2-associated cancers include, but are not limited to, non-small cell lung cancer, breast cancer, ovarian cancer, brain cancer, biliary cancer, cervical cancer, gastric cancer, esophageal cancer, endometrial cancer, glioblastoma, prostate cancer, skin cancer, esophagus tumor,

colorectal cancer, bladder cancer, gastrointestinal cancer, gallbladder tumor, kidney cancer, liver cancer, prostate cancer, and head-and-neck cancer. In some embodiments, the HER2-associated cancer is non-small cell lung cancer. In some embodiments, the HER2-associated cancer is breast cancer. In certain embodiments, HER2-associated cancer is brain cancer. In certain embodiments, the HER2 exon 20 mutation is one or more selected from YVMA insertion, VC insertion, and GSP insertion. In certain embodiments, the HER2 exon 20 mutation is one or more selected from A775_G776insYVMA, P780_Y781insGSP, G776 > VC, G776 > IC, G776 > LC, G778_S779insCPG, G780_P781dupGSP, Y772_A775dup, G778_P780dup, E770_A771insGIRD, G778_S779insLPS, M774_A775insAYVM, G778_S779insLPG, G778dup, G776delinsVC, M774delinsWLV, A775_G776insSVMA, and A775_G776insI. In certain embodiments, the HER2 exon 20 mutation is one or more selected from A775_G776insYVMA, P780_Y781insGSP, G776 > VC, G776 > IC, G776 > LC, G778_S779insCPG, and G780_P781dupGSP. In certain embodiments, the HER2 exon 20 mutation is one or more selected from A775_G776insYVMA, P780_Y781insGSP, G776 > VC, G776 > IC, G776 > LC, and G778_S779insCPG.

In some embodiments, the method of treating or preventing cancer may comprise administering a compound of Formula (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (a-I), (II), (III), or and subformulae thereof by administering with a second therapeutic agent (e.g. immunomodulator or platinum analog).

DESCRIPTION OF FIGURES

Figures 1-17 show certain exemplified compounds encompassed by the present invention.

DETAILED DESCRIPTION

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art of the present disclosure. The following references provide one of skill with a general definition of many of the terms used in this disclosure: Singleton et al., Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988);

The Glossary of Genetics, 5th Ed., R. Rieger et al. (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them below, unless specified otherwise.

In some embodiments, chemical structures are disclosed with a corresponding chemical name. In case of conflict, the chemical structure controls the meaning, rather than the name.

In this disclosure, "comprises," "comprising," "containing" and "having" and the like can have the meaning ascribed to them in U.S. Patent law and can mean " includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited are not substantially changed by the presence of more than that which is recited, but excludes prior art embodiments.

Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. Unless specifically stated or obvious from context otherwise, as used herein, the terms "a", "an", and "the" are understood to be singular or plural.

The term "acyl" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term "acylamino" is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH-.

The term "acyloxy" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O-, preferably alkylC(O)O-.

The term "alkoxy" refers to an alkyl group, preferably a lower alkyl group, having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

The term "alkenyl", as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds.

Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

An "alkyl" group or "alkane" is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10 unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C_1-C_6 straight chained or branched alkyl group is also referred to as a "lower alkyl" group.

Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), $-CF_3$, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, $-CF_3$, -CN, and the like.

The term "C_{x-y}" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term "C_{x-y}alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-tirfluoroethyl, etc. C_0 alkyl indicates a hydrogen where

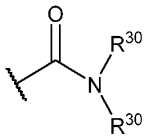
the group is in a terminal position, a bond if internal. The terms "C_{2-y}alkenyl" and "C_{2-y}alkynyl" refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term "alkylamino", as used herein, refers to an amino group substituted with at least one alkyl group.

The term "alkylthio", as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS-.

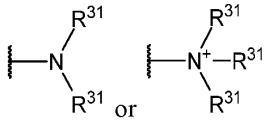
The term "alkynyl", as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

The term "amide", as used herein, refers to a group



wherein each R^{30} independently represents a hydrogen or hydrocarbyl group, or two R^{30} are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by

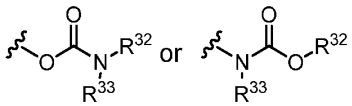


wherein each R^{31} independently represents a hydrogen or a hydrocarbyl group, or two R^{31} are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure. The term "aminoalkyl", as used herein, refers to an alkyl group substituted with an amino group.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group.

The term "aryl" as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably, the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

The term "carbamate" is art-recognized and refers to a group



wherein R^{32} and R^{33} independently represent hydrogen or a hydrocarbyl group, such as an alkyl group, or R^{32} and R^{33} taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms "carbocycle", and "carbocyclic", as used herein, refers to a saturated or unsaturated ring in which each atom of the ring is carbon. The term carbocycle includes both aromatic carbocycles and non-aromatic carbocycles. Non-aromatic carbocycles include both cycloalkane rings, in which all carbon atoms are saturated, and cycloalkene rings, which contain at least one double bond.

The term "carbocycle" includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused carbocycle" refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary "carbocycles" include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles

include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. "Carbocycles" may be substituted at any one or more positions capable of bearing a hydrogen atom.

A "cycloalkyl" group is a cyclic hydrocarbon which is completely saturated. "Cycloalkyl" includes monocyclic and bicyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms unless otherwise defined. The second ring of a bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. Cycloalkyl includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused cycloalkyl" refers to a bicyclic cycloalkyl in which each of the rings shares two adjacent atoms with the other ring. The second ring of a fused bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. A "cycloalkenyl" group is a cyclic hydrocarbon containing one or more double bonds.

The term "carbocyclylalkyl", as used herein, refers to an alkyl group substituted with a carbocycle group.

The term "carbonate" is art-recognized and refers to a group $-OCO_2-R^{34}$, wherein R^{34} represents a hydrocarbyl group.

The term "carboxy", as used herein, refers to a group represented by the formula $-CO_2H$.

The term "ester", as used herein, refers to a group $-C(O)OR^{35}$ wherein R^{35} represents a hydrocarbyl group.

The term "ether", as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include "alkoxyalkyl" groups, which may be represented by the general formula alkyl-O-alkyl.

The terms "halo" and "halogen" as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

The terms "hetaralkyl" and "heteroaralkyl", as used herein, refers to an alkyl group substituted with a hetaryl group.

The term "heteroalkyl", as used herein, refers to a saturated or unsaturated chain of carbon atoms and at least one heteroatom, wherein no two heteroatoms are adjacent.

The terms "heteroaryl" and "hetaryl" include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heteroaryl" and "hetaryl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

The terms "heterocyclyl", "heterocycle", and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polycyclic ring systems, such as bicyclic ring systems (e.g., fused or spiro bicyclic heterocyclyl), having two or more cyclic rings in which one or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. The terms "heterocyclyl" and "heterocyclic" also include substituted or unsubstituted partially unsaturated non-aromatic ring structures. In some embodiments, the heterocyclyl is a 3- to 10-membered monocyclic or bicyclic ring system with at least one double bond. In some embodiments, the heterocyclyl is a 3- to 10-membered monocyclic or bicyclic ring system with only one double bond. In some embodiments, the heterocyclyl is a 6-membered heterocyclyl ring having at least one double bond. In some embodiments, the heterocyclyl is a 6-membered heterocyclyl ring having only one double bond. the Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, tetrahydrofurans, 1,4-diazabicyclo[2.2.2]octane (DABCO), tetrahydroquinoline, and the like.

The term "heterocyclylalkyl", as used herein, refers to an alkyl group substituted with a heterocycle group.

The term "hydrocarbyl", as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocyclyl, alkyl, alkenyl, alkynyl, and combinations thereof.

The term "hydroxyalkyl", as used herein, refers to an alkyl group substituted with a hydroxy group.

The term "lower" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer non-hydrogen atoms in the substituent, preferably six or fewer. A "lower alkyl", for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

The terms "polycyclyl", "polycycle", and "polycyclic" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more atoms are common to two adjoining rings, e.g., the rings are "fused rings". Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

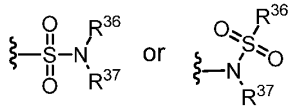
The term "silyl" refers to a silicon moiety with three hydrocarbyl moieties attached thereto.

The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation

such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as "unsubstituted," references to chemical moieties herein are understood to include substituted variants. For example, reference to an "aryl" group or moiety implicitly includes both substituted and unsubstituted variants.

The term "sulfate" is art-recognized and refers to the group $-OSO_3H$, or a pharmaceutically acceptable salt thereof.

The term "sulfonamide" is art-recognized and refers to the group represented by the general formulae



wherein R^{36} and R^{37} independently represent hydrogen or hydrocarbyl, such as alkyl, or R^{36} and R^{37} taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term "sulfoxide" is art-recognized and refers to the group $-S(O)-R^{38}$, wherein R^{38} represents a hydrocarbyl.

The term "sulfonate" is art-recognized and refers to the group SO_3H, or a pharmaceutically acceptable salt thereof.

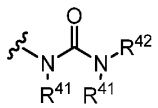
The term "sulfone" is art-recognized and refers to the group $-S(O)_2-R^{39}$, wherein R^{39} represents a hydrocarbyl.

The term "thioalkyl", as used herein, refers to an alkyl group substituted with a thiol group.

The term "thioester", as used herein, refers to a group $-C(O)SR^{40}$ or $-SC(O)R^{40}$ wherein R^{40} represents a hydrocarbyl.

The term "thioether", as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

The term "urea" is art-recognized and may be represented by the general formula



wherein R^{41} and R^{42} independently represent hydrogen or a hydrocarbyl, such as alkyl, or either occurrence of R^{41} taken together with R^{42} and the intervening atom(s)complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term "protecting group" refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry,* 3rd Ed., 1999, John Wiley & Sons, NY and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative nitrogen protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxyl protecting groups include, but are not limited to, those where the hydroxyl group is either acylated (esterified) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPS groups), glycol ethers, such as ethylene glycol and propylene glycol derivatives and allyl ethers.

In certain embodiments, compounds of the disclosure may be racemic. In certain embodiments, compounds of the disclosure may be enriched in one enantiomer. For example, a compound of the disclosure may have greater than about 30% ee, about 40% ee, about 50% ee, about 60% ee, about 70% ee, about 80% ee, about 90% ee, or even about

95% or greater ee. In certain embodiments, compounds of the disclosure may have more than one stereocenter. In certain such embodiments, compounds of the disclosure may be enriched in one or more diastereomer. For example, a compound of the disclosure may have greater than about 30% de, about 40% de, about 50% de, about 60% de, about 70% de, about 80% de, about 90% de, or even about 95% or greater de.

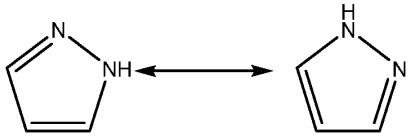
In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one enantiomer of a compound (e.g., of Formula (I) or (II) or (III)). An enantiomerically enriched mixture may comprise, for example, at least about 60 mol percent of one enantiomer, or more preferably at least about 75, about 90, about 95, or even about 99 mol percent. In certain embodiments, the compound enriched in one enantiomer is substantially free of the other enantiomer, wherein substantially free means that the substance in question makes up less than about 10%, or less than about 5%, or less than about 4%, or less than about 3%, or less than about 2%, or less than about 1% as compared to the amount of the other enantiomer, e.g., in the composition or compound mixture. For example, if a composition or compound mixture contains about 98 grams of a first enantiomer and about 2 grams of a second enantiomer, it would be said to contain about 98 mol percent of the first enantiomer and only about 2% of the second enantiomer.

In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one diastereomer of a compound (e.g., of Formula (I) or (II) or (III)). A diastereomerically enriched mixture may comprise, for example, at least about 60 mol percent of one diastereomer, or more preferably at least about 75, about 90, about 95, or even about 99 mol percent.

As used herein, the term “stereoisomers” refer to isomeric molecules that have the same molecular constitution and connectivity, but a different three-dimensional spatial arrangement of the atoms. Stereoisomers are isomers that differ in spatial arrangement of atoms, rather than order of atomic connectivity. In some embodiments, “stereoisomers” refer to the various stereoisomeric forms of a compound that comprises one or more asymmetric centers or stereohindrance in the structure. In some embodiments, a stereoisomer is an enantiomer, a mixture of enantiomers, an atropisomer, or a tautomer thereof. In some embodiments, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer (e.g. an atropisomer), or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. In some embodiments, a steroiosmer includes

diastereoisomer(s), enantiomer(s), a mixtutre of diastereoisomers, and a mixture of enantiomers. In some embodiments, compounds provided herein may be atropisomers. In certain embodiments, atropisomers are stereoisomers arising because of hindered rotation about a single bond, where energy differences due to steric strain or other contributors create a barrier to rotation that is high enough to allow for isolation of individual conformers. Stereoisomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. 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).

In some embodiments, a moiety in a compound exists as a mixture of tautomers. A "tautomer" is a structural isomer of a moiety or a compound that readily interconverts with another structural isomer. For example, a pyrazole ring has two tautomers:



,

which differ in the positions of the pi-bonds and a hydrogen atom. Unless explicitly stated otherwise, a drawing of one tautomer of a moiety or a compound encompasses all of the possible tautomers.

The term "mammal" includes human subjects, primates, and commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, quail, and/or turkeys. The term "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or other primates (e.g., cynomolgus monkeys, rhesus monkeys). In certain embodiments, the mammal is a human subject.

As used herein, a therapeutic that "prevents" a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces

the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

The term "treating" includes prophylactic and/or therapeutic treatments. The term "prophylactic or therapeutic" treatment is art-recognized and includes administration to the subject of one or more of the disclosed compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the subject) then the treatment is prophylactic (i.e., it protects the subject against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The term "prodrug" is intended to encompass compounds which, under physiologic conditions, are converted into the therapeutically active agents of the present disclosure. A common method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the subject. For example, esters or carbonates (e.g., esters or carbonates of alcohols or carboxylic acids) are preferred prodrugs of the present disclosure. In certain embodiments, some or all of the compounds as disclosed herein in a formulation represented above can be replaced with the corresponding suitable prodrug, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate or carboxylic acid.

An "effective amount", as used herein, refers to an amount that is sufficient to achieve a desired biological effect. A "therapeutically effective amount", as used herein, refers to an amount that is sufficient to achieve a desired therapeutic effect. For example, a therapeutically effective amount can refer to an amount that is sufficient to improve at least one sign or symptom of cancer.

A "response" to a method of treatment can include a decrease in or amelioration of negative symptoms, a decrease in the progression of a disease or symptoms thereof, an increase in beneficial symptoms or clinical outcomes, a lessening of side effects, stabilization of disease, partial or complete remedy of disease, among others.

In certain embodiments, the pharmaceutically acceptable salt of the compound is selected from the group consisting of alkyl ammonium salts, dialkyl ammonium salts, trialkyl ammonium salts, tetra-alkyl ammonium salts, L-arginine salts, benenthamine salts, benzathine salts, betaine salts, calcium hydroxide salts, choline salts, deanol salts,

diethanolamine salts, diethylamine salts, 2-(diethylamino)ethanol salts, ethanolamine salts, ethylenediamine salts, N-methylglucamine salts, hydrabamine salts, 1H-imidazole salts, lithium salts, L-lysine salts, magnesium salts, 4-(2-hydroxyethyl)morpholine salts, piperazine salts, potassium salts, 1-(2-hydroxyethyl)pyrrolidine salts, sodium salts, triethanolamine salts, tromethamine salts, Na salts, Ca salts, K salts, Mg salts, and Zn salts.

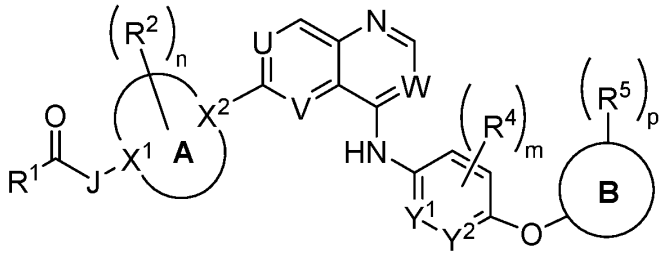
In specific embodiments, the pharmaceutically acceptable salt is a solvate selected from the group consisting of water, methanol, ethanol, and dimethylformamide.

In certain embodiments the compound is a pharmaceutical composition including a pharmaceutically acceptable carrier or excipient.

In specific embodiments, the composition is in a form selected from the group consisting of a tablet, a capsule, a granule, a lyophile for reconstitution, a powder, a solution, a syrup, a suppository, an injection, a suspension, an infusion, a transdermal delivery system (such as cream, gel, ointment), and a solution suitable for topical administration.

Compounds

The present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(I)

wherein:

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or

optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge; or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 8-membered heterocyclic ring;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

U is CR^c or N;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

V is CR^d or N;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

W is N or CR^e;

R^e is hydrogen, halo (e.g., fluoro), or cyano;

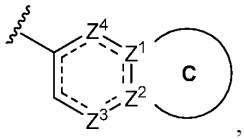
Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

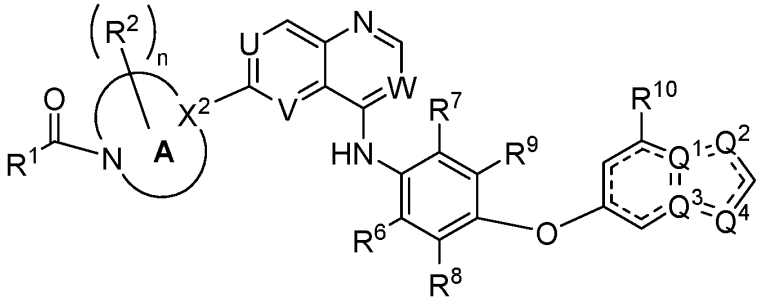
p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

In some embodiments of Formula (I), it's provided when V is N; or ring B is 

, wherein C is 5- or 6-membered heteroaryl; Z^1, Z^2, Z^3, and Z^4

are each independently C or N; and any atom of ring (B) may be substituted by R^5 as permitted by valence.

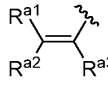
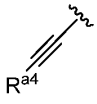
In some aspects, the present disclosure provides a compound of Formula (II), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(II)

wherein:

ring (A) is 4- to 7-membered heterocyclyl;

R^1 is  or ;

R^{a1}, R^{a2}, R^{a3}, and R^{a4} are each independently hydrogen, halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, optionally substituted $-CH_2O-C_{1-5}$ alkyl, optionally substituted $-CH_2O-(CH_2)_{1-2}-O-C_{1-5}$ alkyl, optionally substituted $-CO_2-C_{1-5}$ alkyl, or optionally substituted 3- to 6-membered heterocyclyl;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 are an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

U is CR^c or N;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

V is CR^d or N;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a heterocyclic ring;

W is N or CR^e;

R^e is hydrogen, halo (e.g., fluoro), or cyano;

R^6, R^7, R^8, and R^9 are each independently hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

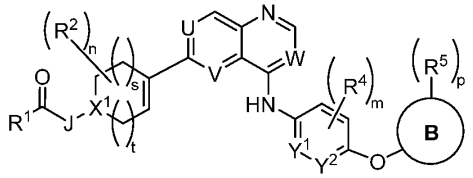
R^{10} is hydrogen, halo, or optionally substituted C_{1-5} alkyl;

Q^1, Q^2, Q^3, and Q^4 are each independently NR^f or CR^g, provided that at least one of Q^1, Q^2, Q^3, and Q^4 is CR^g;

R^f, independently for each occurrence, is hydrogen, optionally substituted C_{1-5} alkyl, or absent; and

R^g, independently for each occurrence, is hydrogen, optionally substituted C_{1-5} alkyl, or absent.

In some aspects, the present disclosure provides a compound of Formula (I-i), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(I-i)

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

wherein:

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, optionally substituted -O-C_{1-5} alkyl, optionally substituted -O-C_{1-5} alkylene-O-C_{1-5} alkyl, optionally substituted -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

s is 0, 1, or 2;

t is 1 or 2;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_{1-4} alkylene bridge;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

U is CR^c or N;

V is CR^d or N; provided that at least one of U and V is N;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 6-membered heterocyclic ring;

W is N or CR^e;

R^e is hydrogen, halo, or cyano;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

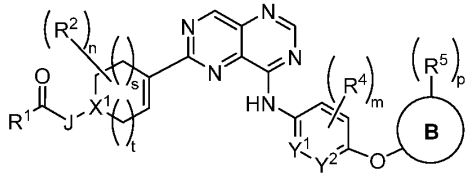
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

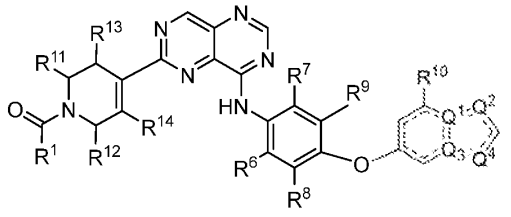
In certain aspects, the compound of Formula (I-i) is a compound of Formula (I-i-a):



(I-i-a)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

In certain aspects, the compound of Formula (I-i-a) is a compound of Formula (I-i-a1):



(I-i-a1)

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

wherein:

R^6, R^7, R^8, and R^9 are each independently hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

R^{10} is hydrogen, halo, or optionally substituted C_{1-5} alkyl;

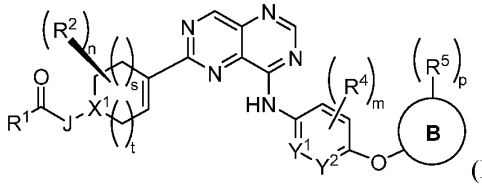
Q^1, Q^2, Q^3, and Q^4 are each independently NR^f or CR^g as valency permits, provided that at least one of Q^1, Q^2, Q^3, and Q^4 is CR^g;

R^f, independently for each occurrence, is hydrogen, optionally substituted C_{1-5} alkyl, or absent;

R^g, independently for each occurrence, is hydrogen, optionally substituted C_{1-5} alkyl, or absent; and

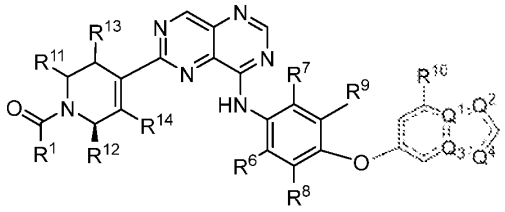
R^{11}, R^{12}, R^{13}, and R^{14} are each independently hydrogen or optionally substituted C_{1-5} alkyl, or two of R^{11}, R^{12}, R^{13}, and R^{14} taken together form a C_{1-4} alkylene bridge.

In certain aspects, the compound of Formula (I-i) is a compound of Formula (I-i-a0), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(I-i-a0).

In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



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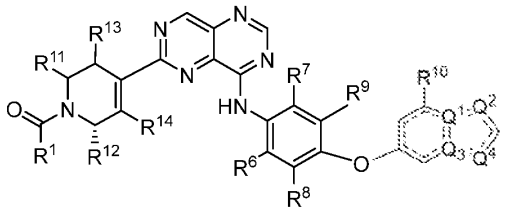
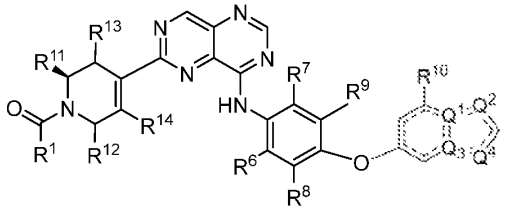
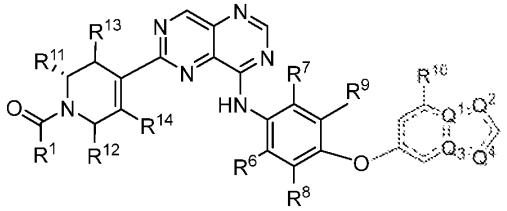
In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



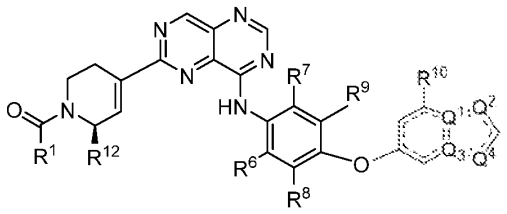
In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



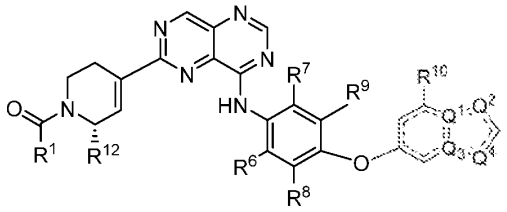
In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



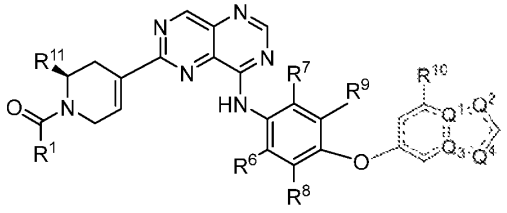
In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



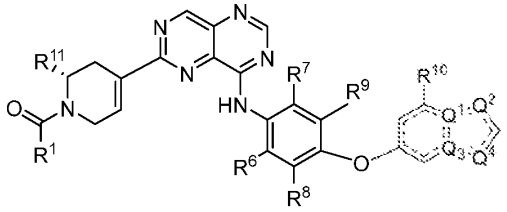
In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



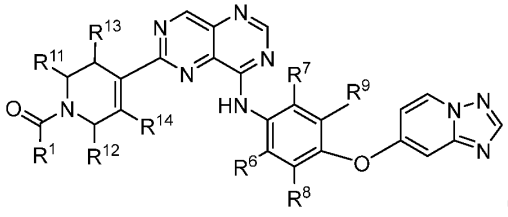
In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



In certain embodiments, the compounds of Formua (I-i-a1) are of the following formula, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



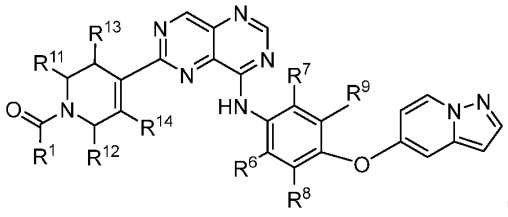
In certain aspects, the compound of Formula (I-i-a1) is a compound of Formula (I-i-a2):



(I-i-a2)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

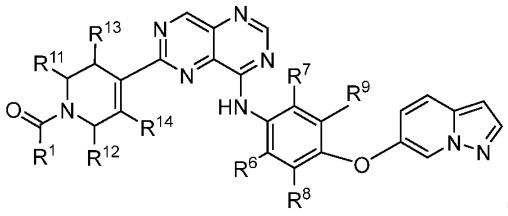
In certain aspects, the compound of Formula (I-i-a1) is a compound of Formula (I-i-a3):



(I-i-a3)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

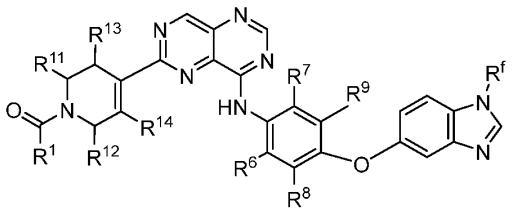
In certain aspects, the compound of Formula (I-i-a1) is a compound of Formula (I-i-a4):



(I-i-a4)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

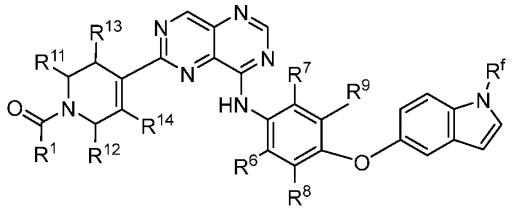
In certain aspects, the compound of Formula (I-i-a1) is a compound of Formula (I-i-a5):



(I-i-a5)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

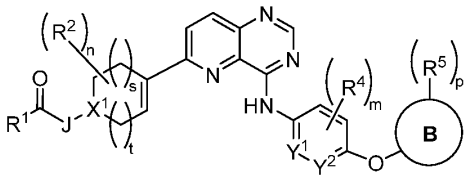
In certain aspects, the compounds of Formula (I-i-a1) is a compound of Formula (I-i-a6):



(I-i-a6)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

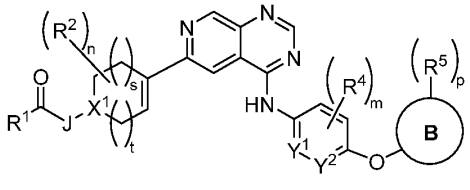
In certain aspects, the compounds of Formula (I-i) is a compound of Formula (I-i-b):



(I-i-b)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

In certain aspects, the compounds of Formula (I-i) is a compound of Formula (I-i-c):



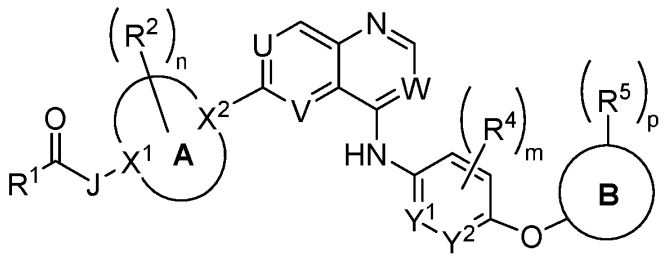
(I-i-c)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

In one embodiment of any one of Formula (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), wherein s is 0 and t is 1 or 2. In one embodiment of any one of Formula (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), wherein s is 1 and t is 1 or 2. In one embodiment of any one of Formula (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), wherein s is 2 and t is 1 or 2. In one embodiment of any one of Formula (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), wherein s is 1 and t is 1. In one embodiment of any one of Formula (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), wherein s is 1 and t is 2.

In one embodiment of any one of Formula (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), R^{11} is optionally substituted C_{1-5} alkyl. In one embodiment of any one of Formula (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), R^{11} is methyl. In one embodiment of any one of Formula (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), R^{12} is optionally substituted C_{1-5} alkyl. In one embodiment of any one of Formula (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), R^{12} is methyl.

In certain aspects, the present disclosure provides compounds of Formula (I):



(I)

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

ring A is 6- to 10-membered bicyclic heterocyclyl or 3- to 5- or 7- to 8-membered monocyclic heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_{1-4} alkylene bridge; or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 8-membered heterocyclic ring;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

U is CR^c or N;

V is CR^d or N;

W is N or CR^e;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

R^e is hydrogen, halo (e.g., fluoro), or cyano;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

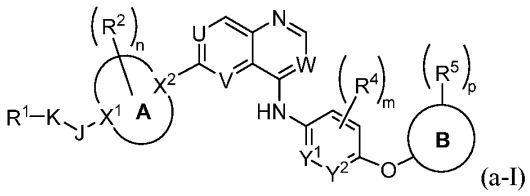
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

In certain aspects, the present disclosure provides compounds of Formula (a-I), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(a-I)

wherein:

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-4} alkyl;

K is a bond, C=O, or SO_2;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge; or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 8-membered heterocyclic ring;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

U is CR^c or N;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

V is CR^d or N;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

W is N or CR^e;

R^e is hydrogen, halo (e.g., fluoro), or cyano;

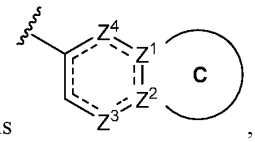
Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

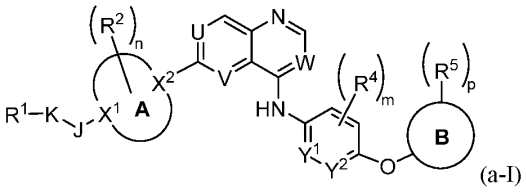
R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

provided that when K is C=O; V is N or ring (B) is 

, wherein (C) is 5- or 6-membered heteroaryl; Z^1, Z^2, Z^3, and Z^4 are each independently C or N; and any atom of ring (B) may be substituted by R^5 as permitted by valence.

In certain aspects, the present disclosure provides compounds of Formula (a-I), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(a-I)

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

wherein:

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

K is a bond or SO_2;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge; or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 8-membered heterocyclic ring;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

U is CR^c or N;

V is CR^d or N;

W is N or CR^e;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

R^e is hydrogen, halo (e.g., fluoro), or cyano;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

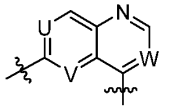
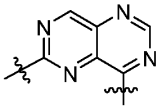
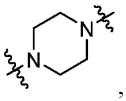
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

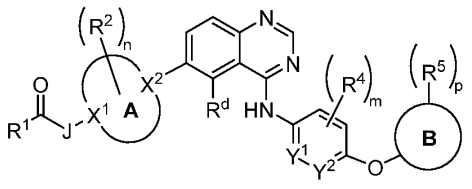
R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

In one embodiment of Formula (a-I) (or a sub-formula thereof), K is a bond. In one embodiment of Formula (a-I) (or a sub-formula thereof), K is C=O. In one embodiment of Formula (a-I) (or a sub-formula thereof), K is SO_2. In one embodiment of Formula (a-I) (or a sub-formula thereof), J is a bond; X^1 is N; and K is C=O. In other embodiments of Formula (a-I) (or a sub-formula thereof), J is a bond; X^1 is N; and K is SO_2. In other embodiments of Formula (a-I) (or a sub-formula thereof), J is a bond; X^1 is N; and K is a bond. In other embodiments of Formula (a-I) (or a sub-formula thereof), J is a bond; X^1 is N; K is a bond; and R^1 is CN.

In one embodiment of Formula (I), (II), (I-i), or (a-I) (or a sub-formula thereof), it is provided that when  is , ring is , Y^1 and Y^2 are each independently CR^4, then R^4 in Y^2 is alkyl and R^4 in Y^1 is halo. In one embodiment, R^4 in Y^2 is methyl. In one embodiment, R^4 in Y^1 is fluoro. In one embodiment, R^4 in Y^2 is methyl, and R^4 in Y^1 is fluoro.

In certain aspects, the present disclosure provides compounds of Formula (B):



(B)

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

wherein:

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge; or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 8-membered heterocyclic ring;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

R^d is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and

Y^2 is CH or CR^4;

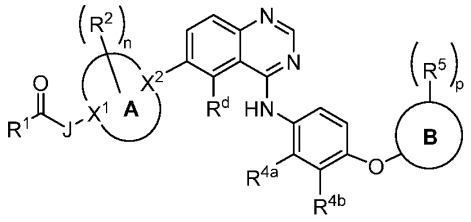
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

In certain aspects, the compounds of Formula (B) is a compound of Formula (B-i):



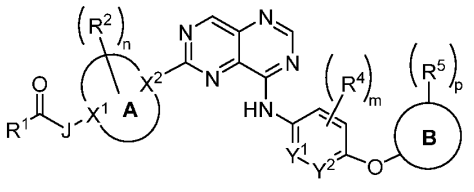
(B-i)

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

wherein each of R^{4a} and R^{4b} is independently halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy.

In certain embodiments of Formula (B-i) (or a sub-formula thereof), R^{4a} is halo and R^{4b} is optionally substituted C_{1-5} alkyl. In certain embodiments of Formula (B-i) (or a sub-formula thereof), R^{4a} is F or Cl and R^{4b} is methyl. In certain embodiments of Formula (B-i) (or a sub-formula thereof), R^{4b} is halo and R^{4a} is optionally substituted C_{1-5} alkyl. In certain embodiments of Formula (B-i) (or a sub-formula thereof), R^{4b} is F or Cl and R^{4a} is methyl. In certain embodiments of Formula (B-i) (or a sub-formula thereof), each of R^{4a} and R^{4b} is independently halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and R^d is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring. In certain embodiments, each of R^{4a} and R^{4b} is independently halo (e.g., F or Cl), optionally substituted C_{1-5} alkyl (e.g., methyl), R^d is halo (e.g., F). In certain embodiments, each of R^{4a} and R^{4b} is independently halo (e.g., F or Cl), optionally substituted C_{1-5} alkyl (e.g., methyl), R^d is optionally substituted C_{1-5} alkoxy. In certain embodiments, each of R^{4a} and R^{4b} is independently halo (e.g., F or Cl), optionally substituted C_{1-5} alkyl (e.g., methyl), R^d is optionally substituted C_{1-5} alkyl or optionally substituted C_{1-5} alkoxy, and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring.

In certain aspects, the present disclosure provides compounds of Formula (C):



(C)

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

wherein:

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_{1-4} alkylene bridge;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence, provided that when ring A is 6-membered monocyclic heterocyclyl with one or two N ring atoms, n is 2 or 3;

X^2 is –C=, –CH–, or N;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and

Y^2 is CH or CR^4;

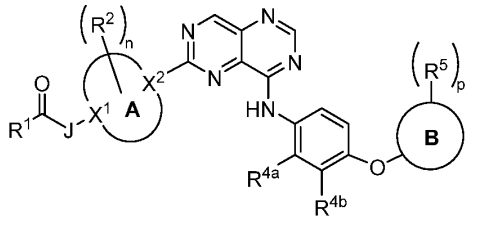
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

In certain aspects, the present disclosure provides compounds of Formula (D):



(D)

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

wherein:

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted alkyl;

R^2, independently for each occurrence, is optionally substituted alkyl; or taken together two geminal occurrences of R^2 are an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

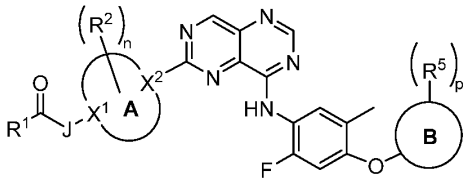
X^2 is –C=, –CH–, or N;

each of R^{4a} and R^{4b} is independently halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

R^5, independently for each occurrence, is halo, optionally substituted alkyl, or optionally substituted alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

In certain aspects, the present disclosure provides compounds of Formula (E):



(E)

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

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_{1-4} alkylene bridge;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

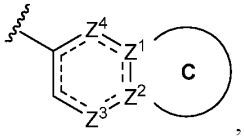
R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

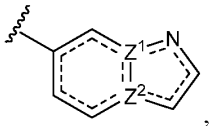
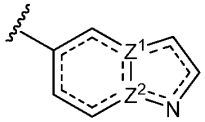
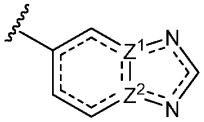
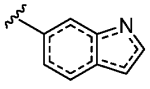
p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

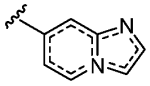
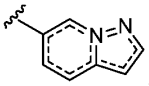
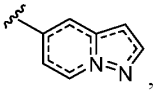
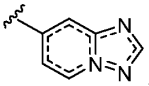
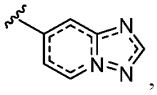
In certain embodiments of any of Formulae (I), (a-I), (B), (B-i), (C), (D), and (E), and subformulea thereof, ring  is a heterocyclyl comprising at least one nitrogen atom. In some embodiments, ring  is a 3- to 10-membered heterocyclyl. In some embodiments, ring  is 6- to 10-membered bicyclic heterocyclyl or 3- to 5- or 7- to 8-membered monocyclic heterocyclyl. In some embodiments, ring  is a 4- to 7-membered monocyclic heterocyclyl containing at least one nitrogen (e.g., one or two nitrogen) ring atom. In some embodiments, ring  is 6-membered monocyclic heterocyclyl. In some embodiments, ring  is 6-membered monocyclic heterocyclyl with one or two nitrogen. In some embodiments, ring  is 6- to 10-membered spiro bicyclic heterocyclyl. In some embodiments, ring  is 6- to 10-membered fused bicyclic heterocyclyl. In some embodiments, ring  is partitially unsaturated heterocyclyl. In certain embodiments, ring  comprises one and only one double bond. In certain embodiments, ring  is azetidinyl, spirocyclic bis-azetidinyl, pyrrolidinyl, pyrrolinyl, piperidinyl, piperazinyl, tetrahydropyridinyl, azepanyl, or tetrahydroazepinyl. In certain such embodiments, ring  is piperazinyl or tetrahydropyridinyl. In some embodiments, ring  is tetrahydropyridinyl. In other embodiments, ring  is piperazinyl. In still other embodiments, ring  is spirocyclic bis-azetidinyl.

In certain embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) and subformulae thereof, ring  is 6- to 10-membered

aryl. In some embodiments, ring B is 5-membered to 10-membered heteroaryl. In certain embodiments, ring B comprises 1 to 3 nitrogen atoms. In certain such embodiments, ring B comprises three and only three nitrogen atoms. In some embodiments, ring B is a bicyclic heteroaryl. In certain embodiments, ring B is a 9- or 10-membered bicyclic heteroaryl. In certain such embodiments, ring B is a 9-membered bicyclic heteroaryl.

In certain embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) and subformulae thereof, ring B is , C is 5- or 6-membered heteroaryl; Z^1, Z^2, Z^3, and Z^4 are each independently C or N; and any atom of ring B may be substituted by R^5 as permitted by valence. In some embodiments, at least one of Z^1, Z^2, Z^3, and Z^4 is N. In some embodiments, one and only one of Z^1, Z^2, Z^3, and Z^4 is N. In certain embodiments, Z^1 or Z^2 is N. In some embodiments, Z^1 is C and Z^2 is N. In certain embodiments, ring C, inclusive of Z^1 and Z^2, comprises 1 to 3 nitrogen atoms. In certain such embodiments, ring C, inclusive of Z^1 and Z^2, comprises three and only three nitrogen atoms.

In certain embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) and subformulae thereof, ring B is , , or , and any atom of ring B may be substituted by R^5 as permitted by valence. In some embodiments, ring B is ,

, , , or , and any atom of ring B may be substituted by R^5 as permitted by valence. In certain embodiments, ring B is , and any atom of ring B may be substituted by R^5 as permitted by valence.

In some membodiments, R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy. In some membodiments, R^5, independently for each occurrence, is optionally substituted C_{1-5} alkyl.

In some membodiments, p is 0. In some membodiments, p is 1. In some membodiments, p is 2. In some membodiments, p is 3.

In some embodiments, R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^1 is C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a. In some embodiments, R^1 is C_{2-5} alkenyl or C_{2-5} alkynyl, wherein the alkenyl or alkynyl is optionally substituted by one or more occurrences of R^a.

In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^1 is C_{1-5} alkyl optionally substituted by one or more occurrences of R^a. In some embodiments, R^1 is C_{1-5} alkyl. In some embodiments, R^1 is C_{1-5} haloalkyl. In some embodiments, R^1 is C_{2-5} alkenyl optionally substituted by one or more occurrences of R^a. In some embodiments, R^1 is C_{2-5} alkynyl optionally substituted by one or more occurrences of R^a. In some embodiments, R^1 is ethenyl, ethynyl, methyl, ethyl, or oxiranyl. In some embodiments, R^1 is ethenyl. In some embodiments, R^1 is ethenyl. In some embodiments, R^1 is ethynyl.

In some embodiments, R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, optionally substituted -O-C_{1-5} alkyl, optionally

substituted -O-C_{1-5} alkylene-O-C_{1-5} alkyl, optionally substituted -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl; and each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^a is C_{1-5} alkyl (e.g., methyl or ethyl). In certain embodiments, R^a is C_{1-5} haloalkyl. In certain embodiments, R^a is -O-C_{1-5} alkyl (e.g., methoxy). In certain embodiments, R^a is halogen (e.g., F or Cl). In certain embodiments, R^a is CN. In certain embodiments, R^a is $N(R^{n1})_2$. In certain embodiments, R^a is $N(CH_3)_2$.

In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^1 is substituted by at least one R^a that is optionally substituted C_{1-5} alkyl. In certain such embodiments, R^a is optionally substituted by an amine or a heterocyclic ring, and the amine or the heterocyclic ring is optionally substituted by an alkyl. In some embodiments, R^1 is substituted by at least one R^a that is dialkylaminomethyl. In certain embodiments, R^1 is substituted by one and only one R^a that is dialkylaminomethyl. In certain such embodiments, the dialkylaminomethyl is dimethylaminomethyl. In other embodiments, R^1 is substituted by at least one R^a that is fluoro, methyl, morpholinomethyl, or pyrrolidinyl. In further embodiments, R^1 is not substituted by R^a. In one embodiment, R^1 is unsubstituted.

In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^1 is alkynyl. In certain embodiments, R^a is optionally substituted alkyl. In certain such embodiments, R^a is methyl.

In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (I-i-a3), (I-i-a4), (I-i-a5), (I-i-a6), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^1 is ethenyl, ethynyl, methyl, ethyl, or oxiranyl and is substituted by at least one R^a that is CN, F, Cl, -CH_3, -CH_2OCH_3, -$CH_2O(CH_2)_2OCH_3$, -CO_2CH_3, -$N(CH_3)_2$, -$CH_2N(CH_3)_2$, -$(CH_2)_2N(CH_3)_2$, morpholinomethyl, or pyrrolidinyl. In some embodiments, R^1 is ethenyl or ethynyl and is substituted by at least one R^a that is CN, F, Cl, -CH_3, -CH_2OCH_3, -$CH_2O(CH_2)_2OCH_3$, -CO_2CH_3, -$N(CH_3)_2$, -$CH_2N(CH_3)_2$, -$(CH_2)_2N(CH_3)_2$, morpholinomethyl, or pyrrolidinyl. In some embodiments, R^1 is methyl, ethyl, or oxiranyl and is substituted by at least one R^a that is CN, F, Cl, -CH_3, -CH_2OCH_3,

- $CH_2O(CH_2)_2OCH_3$, $-CO_2CH_3$, $-N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-(CH_2)_2N(CH_3)_2$, morpholinomethyl, or pyrrolidinyl.

In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), J is NR^b; and X^1 is CH. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^b is hydrogen or methyl. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^b is hydrogen. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), J is a bond and X^1 is N.

In some embodiments, R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_{1-4} alkylene bridge. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^2, independently for each occurrence, is C_{1-5} alkyl. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^2, independently for each occurrence, is methyl. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^2, independently for each occurrence, is C_{1-5} haloalkyl. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^2, independently for each occurrence, is CH_2F. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^2, independently for each occurrence, is CHF_2. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), taken together two geminal occurrences of R^2 are an oxo moiety. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), R^2, independently for each occurrence, is methyl or CH_2F or taken together two geminal occurrences of R^2 are an oxo moiety. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), two non-geminal occurrences of R^2 taken together form a methylene or ethylene bridge. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae

thereof), R^d and an occurrence of R^2 taken together with the intervening atoms form a heterocyclic ring.

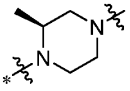
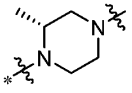
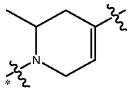
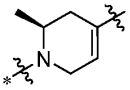
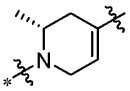
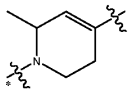
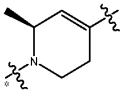
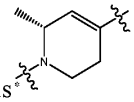
In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), n is 0 or an integer from 1 to 2, inclusive, as permitted by valence. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), n is 0. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), n is 1. In other embodiments, n is 2.

In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), n is 1, and R^2 is attached to an atom adjacent to X^1 (*e.g.*, R^2 is at ortho-position to X^1 in a 6-membered ring A). In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), n is 1, and R^2 is attached to an atom adjacent to X^2 (*e.g.*, R^2 is at ortho-position to X^2 in a 6-membered ring A). The presence of R^2 may result in a chiral center at the atom to which R^2 is attached. In one embodiment, the compound has a R-configuration at the atom to which R^2 is attached. In one embodiment, the compound has a S-configuration at the atom to which R^2 is attached. In one embodiment, the compound is a racemic mixture at the atom to which R^2 is attached.

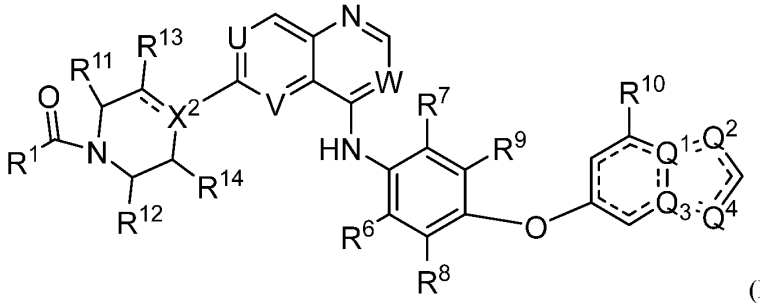
In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), n is 1, and R^2 is attached to an atom adjacent to N-C(=O)-R^1 (*e.g.*, R^2 is at ortho-position to N-C(=O)-R^1 in a 6-membered ring A). In one embodiment, n is 1, and R^2 is attached to an atom adjacent to X^2 (*e.g.*, R^2 is at ortho-position to X^2 in a 6-membered ring A). The presence of R^2 may result in a chiral center at the atom to which R^2 is attached. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), the compound has a R-configuration at the atom to which R^2 is attached. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), the compound has a S-configuration at the atom to which R^2 is attached. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), the compound is a racemic mixture at the atom to which R^2 is attached.

In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), m is 0 or an integer from 1 to 2,

inclusive, as permitted by valence. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), m is 0. In some embodiments of any of Formulae (I), (I-i), (I-i-a), (I-i-b), (I-i-c), (a-I), (B), (B-i), (C), (D), and (E) (and subformulae thereof), m is 1. In other embodiments, m is 2.

In one embodiment, ring A (including any substituent R^2) is . In one embodiment, ring A (including any substituent R^2) is . In one embodiment, ring A (including any substituent R^2) is . In one embodiment, ring A (including any substituent R^2) is . In one embodiment, ring A (including any substituent R^2) is . In one embodiment, ring A (including any substituent R^2) is . In one embodiment, ring A (including any substituent R^2) is . In one embodiment, ring A (including any substituent R^2) is . As used herein, * refers to the attachment point to -C(=O)-R^1, and J is a bond.

In certain aspects, the compounds of Formula (II) are compounds of Formula (III), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof:



(III)

wherein:

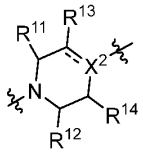
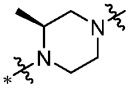
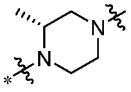
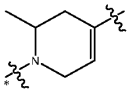
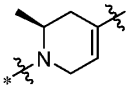
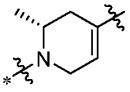
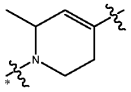
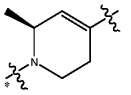
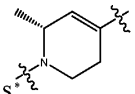
R^{11}, R^{12}, R^{13}, and R^{14} are each independently hydrogen or optionally substituted C_{1-5} alkyl; or two non-geminal occurrences of R^{11}, R^{12}, R^{13}, and R^{14} taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge.

In some embodiments, at least one of R^{11} and R^{12} is optionally substituted C_{1-5} alkyl. In certain such embodiments, at least one of R^{11} and R^{12} is methyl. In some embodiments, at least one of R^{13} and R^{14} is optionally substituted C_{1-5} alkyl. In certain embodiments, at least one of R^{13} and R^{14} is methyl. In some embodiments, R^d and one of R^{13} and R^{14}, taken together with the intervening atoms, form a heterocyclic ring. In further embodiments, R^{11}, R^{12}, R^{13}, and R^{14} are hydrogen.

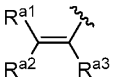
In one embodiment, none of R^{11}, R^{12}, R^{13}, and R^{14} is hydrogen. In one embodiment, one of R^{11}, R^{12}, R^{13}, and R^{14} is hydrogen, and the other three of R^{11}, R^{12}, R^{13}, and R^{14} are not hydrogen. In one embodiment, two of R^{11}, R^{12}, R^{13}, and R^{14} are hydrogen, and the other two of R^{11}, R^{12}, R^{13}, and R^{14} are not hydrogen.

In one embodiment, three of R^{11}, R^{12}, R^{13}, and R^{14} are hydrogen, and the other one of R^{11}, R^{12}, R^{13}, and R^{14} is not hydrogen. In one embodiment, R^{12}, R^{13}, and R^{14} are hydrogen, and R^{11} is not hydrogen. In one embodiment, R^{11}, R^{13}, and R^{14} are hydrogen, and R^{12} is not hydrogen. In one embodiment, R^{11}, R^{12}, and R^{14} are hydrogen, and R^{13} is not hydrogen. In one embodiment, R^{11}, R^{12}, and R^{13} are hydrogen, and R^{14} is not hydrogen. In one embodiment, the non-hydrogen group is optionally substituted alkyl. In one embodiment, the non-hydrogen group is methyl.

The presence of non-hydrogen R^{11}, R^{12}, R^{13}, or R^{14} may result in a chiral center at the atom to which the non-hydrogen R^{11}, R^{12}, R^{13}, or R^{14} is attached. In one embodiment, the compound has a R-configuration at the atom to which the non-hydrogen R^{11}, R^{12}, R^{13}, or R^{14} is attached. In one embodiment, the compound has a S-configuration at the atom to which the non-hydrogen R^{11}, R^{12}, R^{13}, or R^{14} is attached. In one embodiment, the compound is a racemic mixture at the atom to which the non-hydrogen R^{11}, R^{12}, R^{13}, or R^{14} is attached.

In one embodiment, the ring  is . In one embodiment, the ring is . In one embodiment, the ring is . In one embodiment, the ring is . In one embodiment, the ring is . In one embodiment, the ring is . In one embodiment, the ring is . In one embodiment, the ring is . As used herein, * refers to the attachment point to -C(=O)-R^1.

In certain embodiments, the bond between X^2 and the carbon attached to R^{13} is a double bond. In other embodiments, the bond between X^2 and the carbon attached to R^{13} is a single bond.

In some embodiments, R^1 is . In further embodiments, R^1 is .

As used herein, R^{a1} is independently hydrogen, halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, optionally substituted -CH_2O-C_{1-5} alkyl, optionally substituted -CH_2O-$(CH_2)_{1-2}$-O-C_{1-5} alkyl, optionally substituted -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl; each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl. In certain such embodiments, R^{a1} is hydrogen. In certain embodiments, R^{a1} is CN. In certain embodiments, R^{a1} is CN. In certain embodiments, R^{a1} is -CH_2O-C_{1-5} alkyl. In certain embodiments, R^{a1} is -CH_2OCH_3. In certain embodiments, R^{a1} is optionally substituted -CH_2O-$(CH_2)_{1-2}$-O-C_{1-5} alkyl. In certain embodiments, R^{a1} is -CH_2O-$(CH_2)_{1-2}$-O-C_{1-5} alkyl. In certain embodiments, R^{a1} is -CH_2O-$(CH_2)_2$-O-CH_3. In certain embodiments, R^{a1} is optionally substituted -CO_2-C_{1-5} alkyl. In certain embodiments, R^{a1} is -CO_2CH_3.

As used herein, R^{a2} is independently hydrogen, halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, optionally substituted -CH_2O-C_{1-5} alkyl, optionally substituted -

CH_2O-$(CH_2)_{1-2}$-O-C_{1-5} alkyl, optionally substituted -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl; each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl. In certain such embodiments, R^{a2} is hydrogen. In some embodiments, R^{a2} is optionally substituted C_{1-5} alkyl or optionally substituted 3- to 6-membered heterocyclyl. In some embodiments, R^{a2} is methyl, -CH_2-$N(CH_3)_2$, -CO_2CH_3, -CH_2OCH_3, -$CH_2O(CH_2)_2CH_3$, morpholinomethyl, or pyrrolidinyl. In some embodiments, R^{a2} is optionally substituted C_{1-5} alkyl. In certain embodiments, R^{a2} is optionally substituted by an amine or a 3- to 6-membered heterocyclic ring, and the amine or the heterocyclic ring is optionally substituted by C_{1-5} alkyl. In some embodiments, R^{a2} is dialkylaminomethyl. In certain embodiments, R^{a2} is dimethylaminomethyl. In other embodiments, R^{a2} is hydrogen. In certain embodiments, R^{a2} is CN. In certain embodiments, R^{a2} is CN. In certain embodiments, R^{a2} is -CH_2O-C_{1-5} alkyl. In certain embodiments, R^{a2} is -CH_2OCH_3. In certain embodiments, R^{a2} is optionally substituted -CH_2O-$(CH_2)_{1-2}$-O-C_{1-5} alkyl. In certain embodiments, R^{a2} is -CH_2O-$(CH_2)_{1-2}$-O-C_{1-5} alkyl. In certain embodiments, R^{a2} is -CH_2O-$(CH_2)_2$-O-CH_3. In certain embodiments, R^{a2} is optionally substituted -CO_2-C_{1-5} alkyl. In certain embodiments, R^{a2} is -CO_2CH_3.

As used herein, R^{a3} is independently hydrogen, halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, optionally substituted -CH_2O-C_{1-5} alkyl, optionally substituted -CH_2O-$(CH_2)_{1-2}$-O-C_{1-5} alkyl, optionally substituted -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl; each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl. In certain such embodiments, R^{a3} is hydrogen. In some embodiments, R^{a4} is optionally substituted C_{1-5} alkyl. In certain such embodiments, R^{a3} is methyl. In certain such embodiments, R^{a3} is CN. In certain such embodiments, R^{a3} is F.

In some embodiments, R^{a1} is independently hydrogen or C_{1-5} alkyl; R^{a2} is independently hydrogen, halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, optionally substituted -CH_2O-C_{1-5} alkyl, optionally substituted -CH_2O-$(CH_2)_{1-2}$-O-C_{1-5} alkyl, optionally substituted -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl; each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl; and R^{a3} is independently hydrogen, halo, CN, optionally substituted C_{1-5} alkyl.

In some embodiments, R^{a1} and R^{a2} are joined together to form an alkenyl group.

In some embodiments, R^{a1} and R^{a2} are hydrogen. In some embodiments, R^{a1}, R^{a3}, and R^{a3} are hydrogen.

In certain embodiments, X^2 is –C=. In other embodiments, X^2 is N. In other embodiments, X^2 is –CH–.

In some embodiments, wherein U is CR^c. In certain such embodiments, R^c is fluoro. In some embodiments, R^c is hydrogen. In other embodiments, U is N.

In certain embodiments, V is CR^d. In some embodiments, R^d is hydrogen, fluoro, methyl, or methoxy. In certain embodiments, R^d is methoxy. In certain embodiments, R^d is fluoro. In other embodiments, V is N.

In some embodiments, W is N. In some embodiments, W is CR^e. In some embodiments, W is CH or CF.

In some embodiments, Y^1 and Y^2 are CR^4. In some embodiments, Y^1 is CR^4; and Y^2 is N.

In some embodiments, R^4, independently for each occurrence, is fluoro, chloro, methyl, methoxy, or difluoromethyl.

In certain embodiments, R^6 and R^7 are each independently hydrogen, halo, optionally substituted alkoxy, or optionally substituted alkyl. In some embodiments, R^6 and R^7 are each independently hydrogen, fluoro, methoxy, or difluoromethyl. In certain embodiments, R^6 and R^7 are hydrogen. In some embodiments, R^8 and R^9 are each independently hydrogen, halo, or optionally substituted alkyl. In certain embodiments, R^8 and R^9 are each independently hydrogen, chloro, or methyl. In some embodiments, R^8 is methyl. In other embodiments, R^9 is hydrogen. In some embodiments, R^{10} is hydrogen, fluoro, chloro, methyl, ethyl, or methoxy. In some embodiments, R^{10} is hydrogen.

In one embodiment, none of R^6, R^7, R^8, and R^9 is hydrogen.

In one embodiment, one of R^6, R^7, R^8, and R^9 is hydrogen, and the other three of R^6, R^7, R^8, and R^9 are not hydrogen. In one embodiment, R^7 is hydrogen, and R^6, R^8, and R^9 are not hydrogen. In one embodiment, R^9 is hydrogen, and R^6, R^7, and R^8 are not hydrogen.

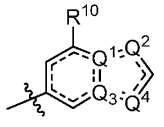
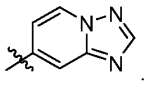
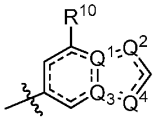
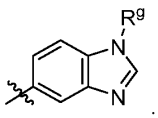
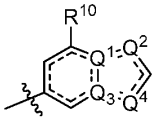
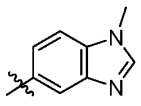
In one embodiment, two of R^6, R^7, R^8, and R^9 are hydrogen, and the other two of R^6, R^7, R^8, and R^9 are not hydrogen. In one embodiment, R^7 and R^9 are hydrogen, and R^6 and R^8 are not hydrogen. In one embodiment, R^6 and R^9 are hydrogen, and R^7 and R^8 are not hydrogen.

In one embodiment, three of R^6, R^7, R^8, and R^9 are hydrogen, and the other one of R^6, R^7, R^8, and R^9 is not hydrogen. In one embodiment, R^6, R^7, and R^9 are hydrogen, and

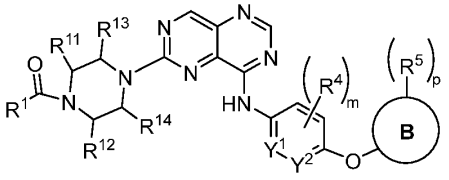
R^8 is not hydrogen. In one embodiment, R^7, R^8, and R^9 are hydrogen, and R^6 is not hydrogen.

In one embodiment, R^7 and R^9 are hydrogen, one of R^6 and R^8 is optionally substituted alkyl, and the other one of R^6 and R^8 is halo. In one embodiment, R^7 and R^9 are hydrogen, R^6 is optionally substituted alkyl, and R^8 is halo. In one embodiment, R^7 and R^9 are hydrogen, R^8 is optionally substituted alkyl, and R^6 is halo. In one embodiment, the optionally substituted alkyl is methyl. In one embodiment, the halo is fluoro. In one embodiment, R^7 and R^9 are hydrogen, R^8 is methyl, and R^6 is fluoro.

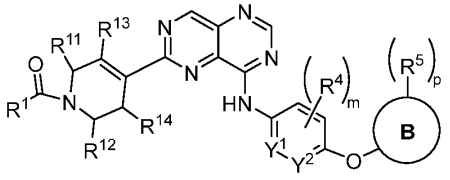
In some embodiments, Q^1 is CR^g, Q^2 is CR^g, Q^3 is CR^g, and Q^4 is NR^f. In other embodiments, Q^1 is NR^f, Q^2 is CR^g, Q^3 is CR^g, and Q^4 is NR^f. In further embodiments, Q^1 is CR^g, Q^2 is CR^g, Q^3 is NR^f, and Q^4 is NR^f. In some embodiments, Q^1 is NR^f, Q^2 is NR^f, Q^3 is CR^g, and Q^4 is NR^f. In still other embodiments, Q^1 is NR^f, Q^2 is NR^f, Q^3 is NR^f, and Q^4 is CR^g. In still other embodiments, Q^1 is CR^g, Q^2 is NR^f, Q^3 is CR^g, and Q^4 is NR^f. In still other embodiments, Q^1 is CR^g, Q^2 is NR^f, Q^3 is NR^f, and Q^4 is CR^g. In some embodiments, R^f is hydrogen, methyl, or absent. In certain embodiments, R^f is hydrogen or absent. In some embodiments, R^g is hydrogen. In some embodiments, R^g is absent.

In one embodiment,  is . In one embodiment,  is . In one embodiment,  is .

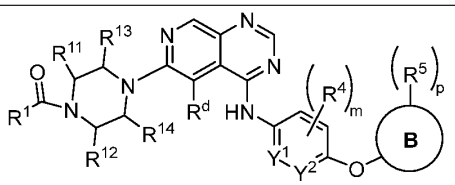
In one embodiment, the compound is a compound of any one of following formulas:



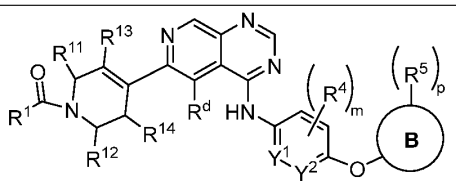
(I-A),



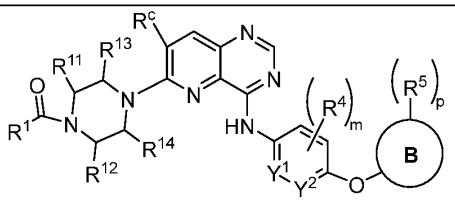
(I-B),



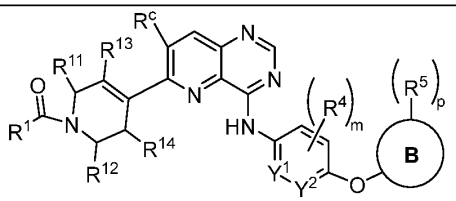
(I-C),



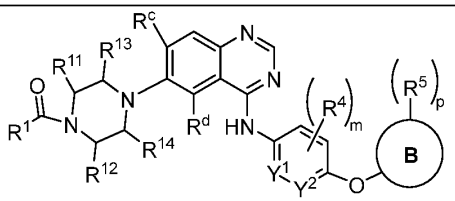
(I-D),



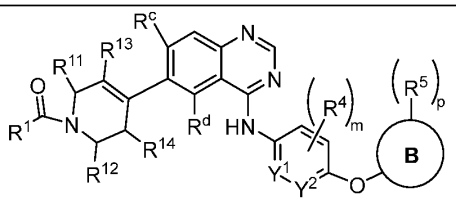
(I-E),



(I-F),



(I-G), or

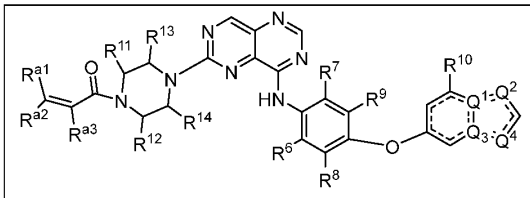


(I-H),

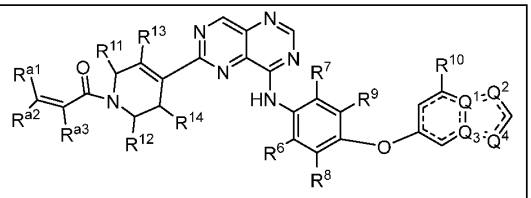
or an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt thereof,

wherein R^1, R^4, R^5, R^{11}, R^{12}, R^{13}, R^{14}, R^c, R^d, Y^1, Y^2, ring B, m, and p are as defined herein or elsewhere.

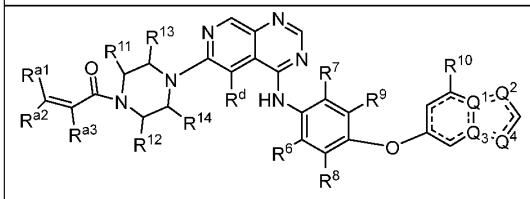
In one embodiment, the compound is a compound of any one of following formulas:



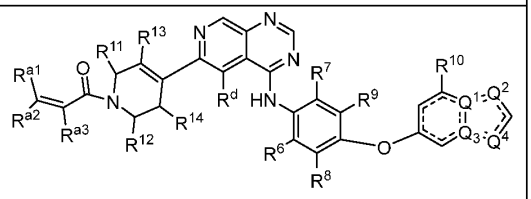
(III-A),



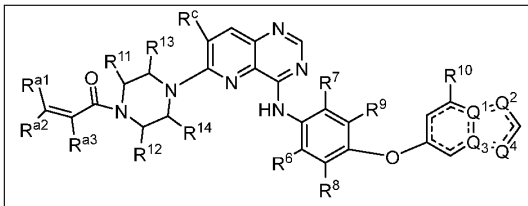
(III-B),



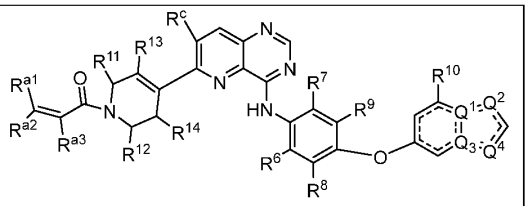
(III-C),



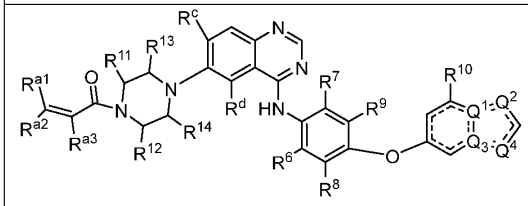
(III-D),



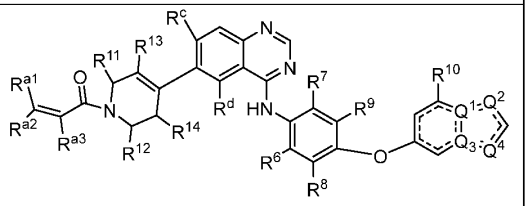
(III-E),



(III-F),



(III-G), or

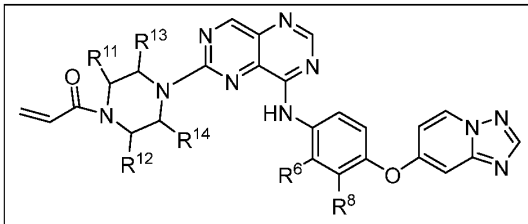


(III-H),

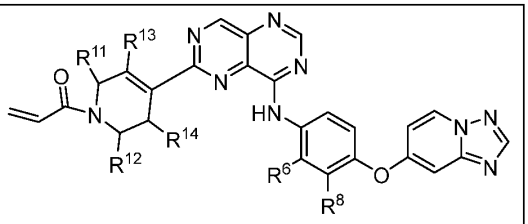
or an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt thereof,

wherein R^{a1}, R^{a2}, R^{a3}, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^c, R^d, Q^1, Q^2, Q^3, and Q^4 are as defined herein or elsewhere.

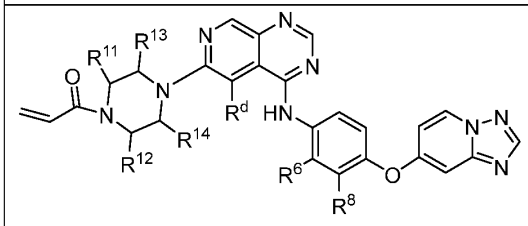
In one embodiment, the compound is a compound of any one of following formulas:



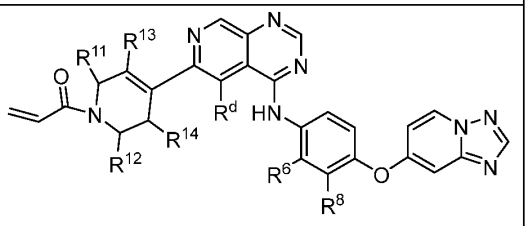
(III-A-1),



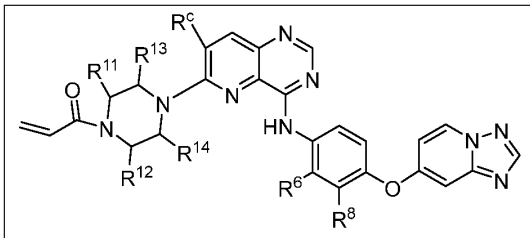
(III-B-1),



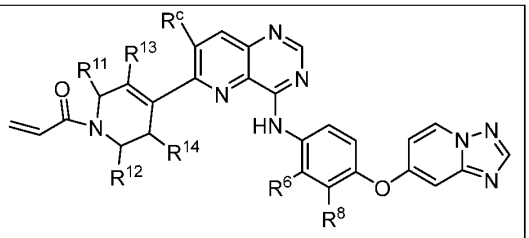
(III-C-1),



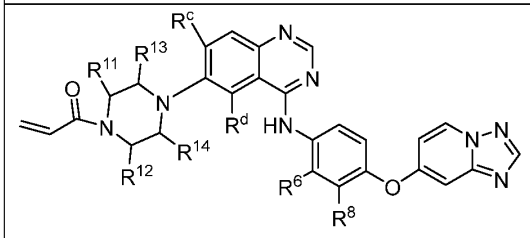
(III-D-1),



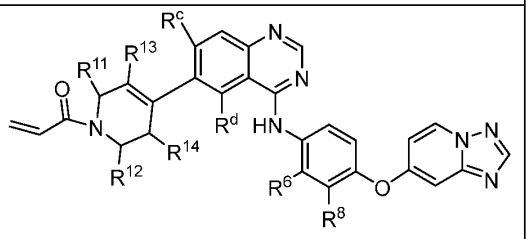
(III-E-1),



(III-F-1),



(III-G-1), or

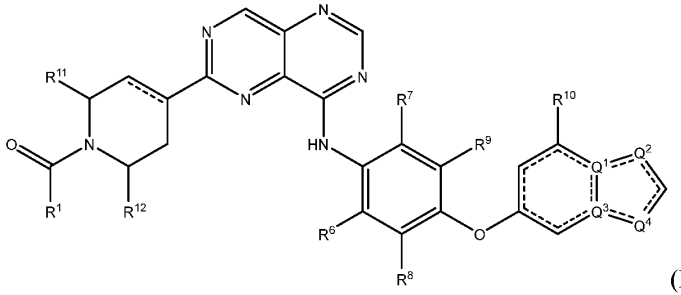


(III-H-1),

or an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt thereof,

wherein R^6, R^8, R^{11}, R^{12}, R^{13}, R^{14}, R^c, and R^d are as defined herein or elsewhere.

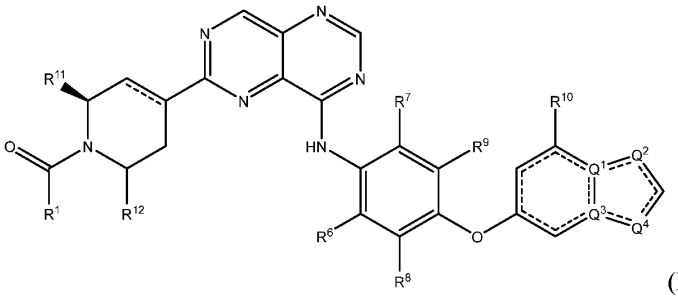
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-1) or a pharmaceutically acceptable salt thereof:



(III-I-1)

wherein Q^1-Q^4, R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

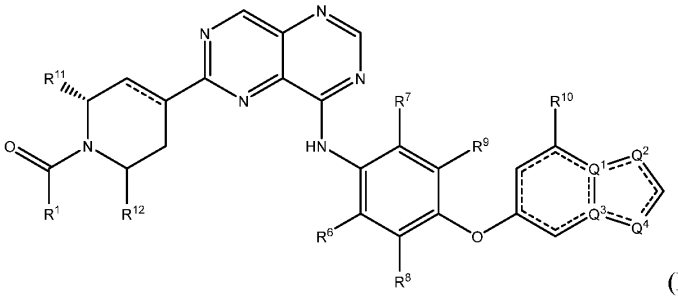
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-2) or a pharmaceutically acceptable salt thereof:



(III-I-2)

wherein Q^1-Q^4, R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

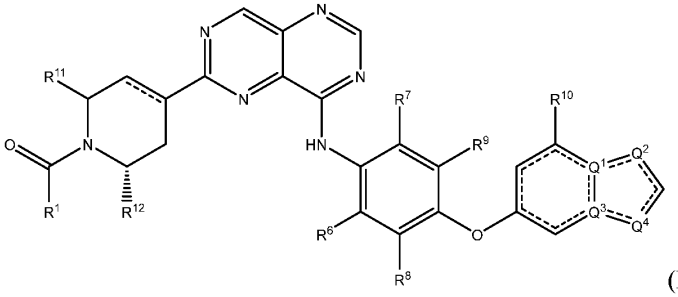
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-3) or a pharmaceutically acceptable salt thereof:



(III-I-3)

wherein Q^1-Q^4, R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

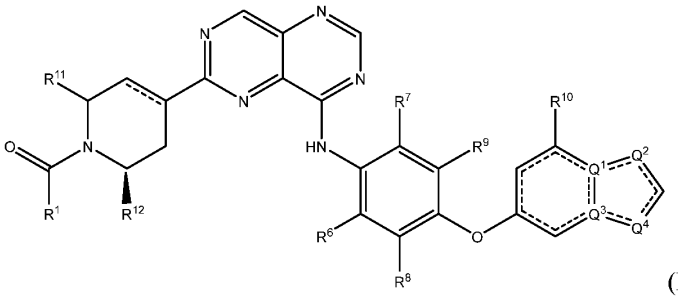
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-4) or a pharmaceutically acceptable salt thereof:



(III-I-4)

wherein Q^1-Q^4, R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

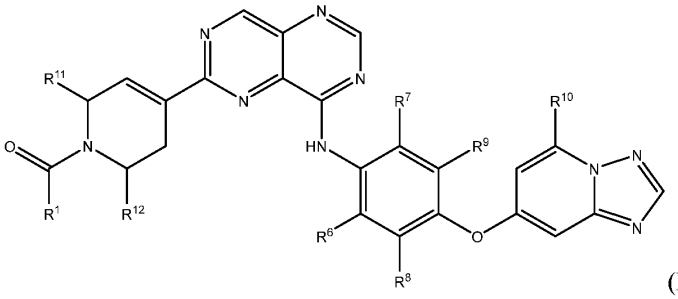
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-5) or a pharmaceutically acceptable salt thereof:



(III-I-5)

wherein Q^1-Q^4, R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

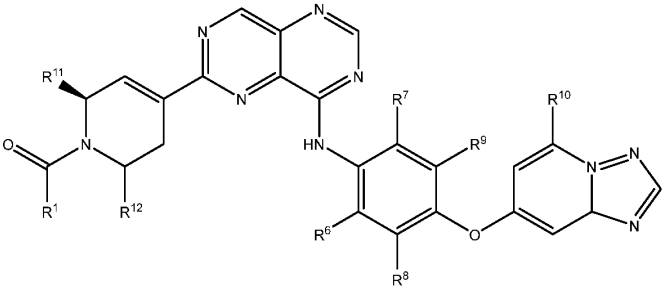
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-6) or a pharmaceutically acceptable salt thereof:



(III-I-6)

wherein R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

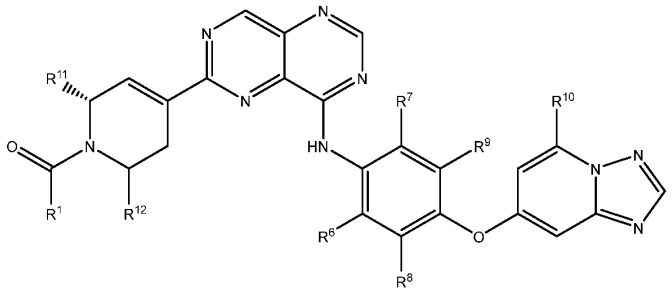
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-7) or a pharmaceutically acceptable salt thereof:



(III-I-7)

wherein R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

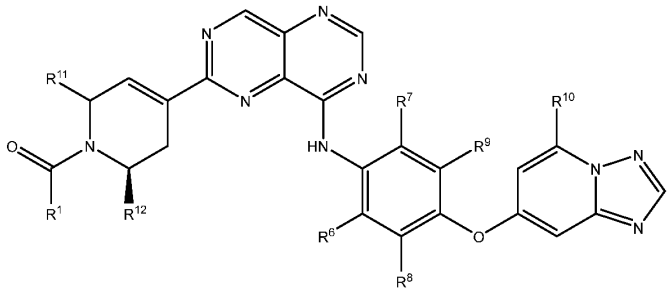
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-8) or a pharmaceutically acceptable salt thereof:



(III-I-8)

wherein R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

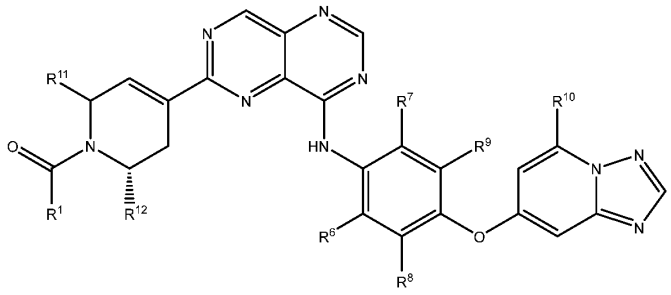
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-9) or a pharmaceutically acceptable salt thereof:



(III-I-9)

wherein R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

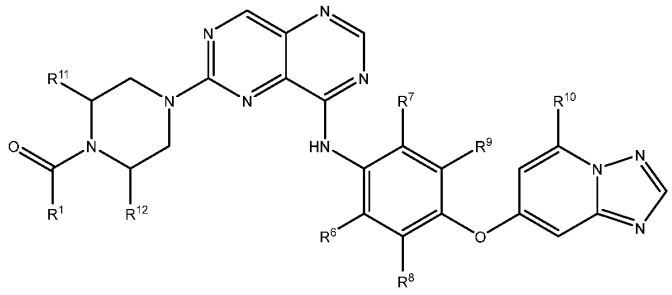
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-10) or a pharmaceutically acceptable salt thereof:



(III-I-10)

wherein R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

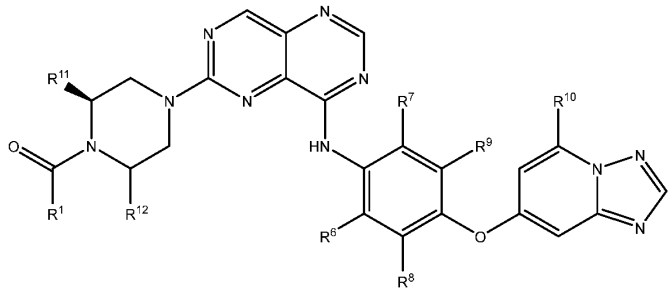
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-11) or a pharmaceutically acceptable salt thereof:



(III-I-11)

wherein R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

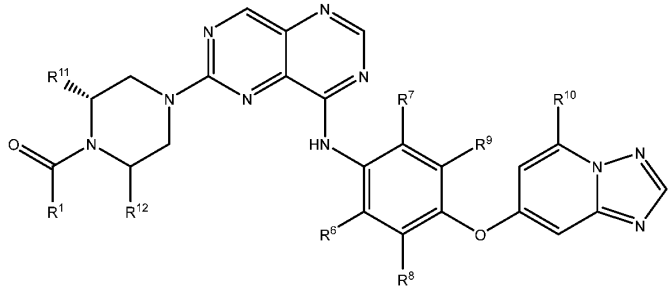
In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-12) or a pharmaceutically acceptable salt thereof:



(III-I-12)

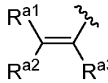
wherein R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

In certain aspects, the compounds of Formula (III) are compounds of Formula (III-I-13) or a pharmaceutically acceptable salt thereof:



(III-I-13)

wherein R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined herein.

In one embodiment of any one of Formulae (III-I-1) to (III-I-13), R^1 is , wherein R^{a1}, R^{a2}, and R^{a3} are as defined herein. In certain embodiments, R^{a1}, R^{a2}, and R^{a3} are H.

In one embodiment of any one of Formulae (III-I-1) to (III-I-13), each of R^6, R^7, R^8, and R^9 is independently H, halogen, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^7 and R^9 are H; and R^6 and R^8 are each independently halogen or C_{1-4} alkyl.

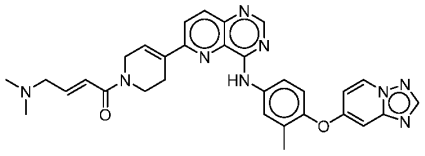
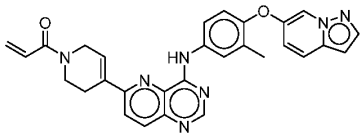
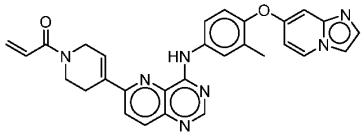
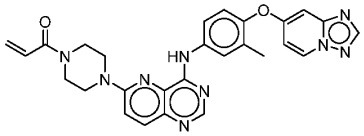
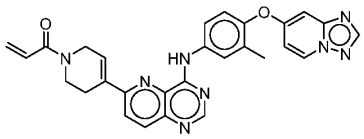
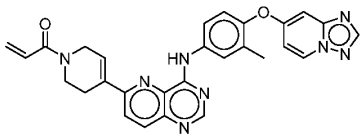
In one embodiment of any one of Formulae (III-I-1) to (III-I-13), each of R^{11} and R^{12} is independently H or C_{1-4} alkyl. In certain embodiments, R^{11} is H and R^{12} is C1-C4 alkyl. In certain embodiments, R^{12} is H and R^{11} is C_{1-4} alkyl.

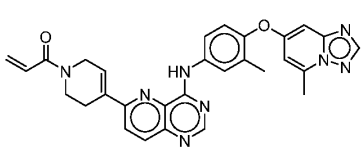
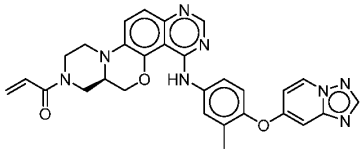
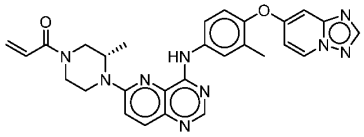
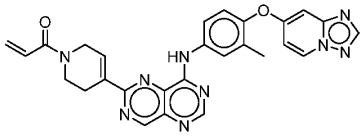
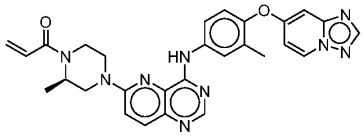
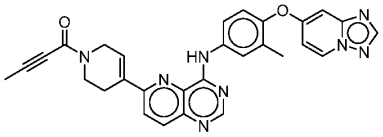
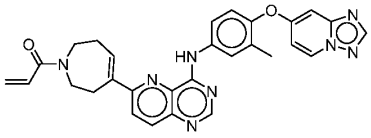
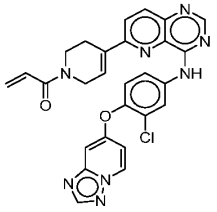
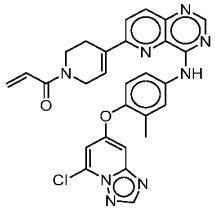
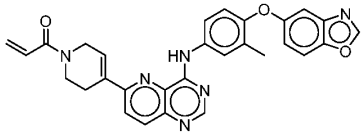
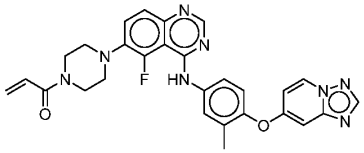
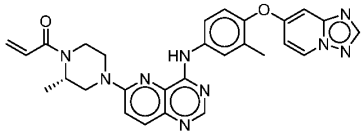
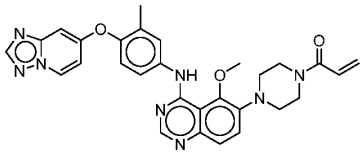
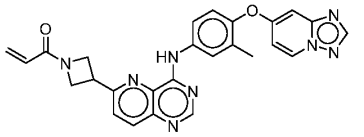
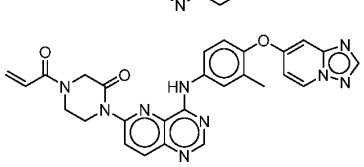
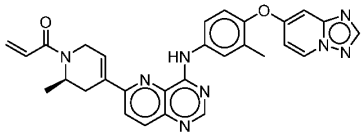
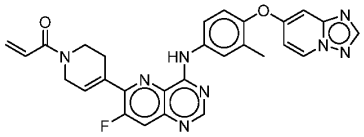
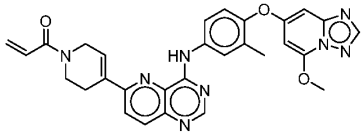
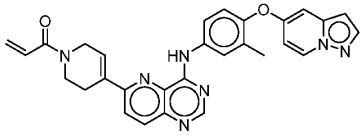
In one embodiment of any one of Formulae (III-I-1) to (III-I-13), R^{10} is H, halogen, or C1-C4 alkyl.

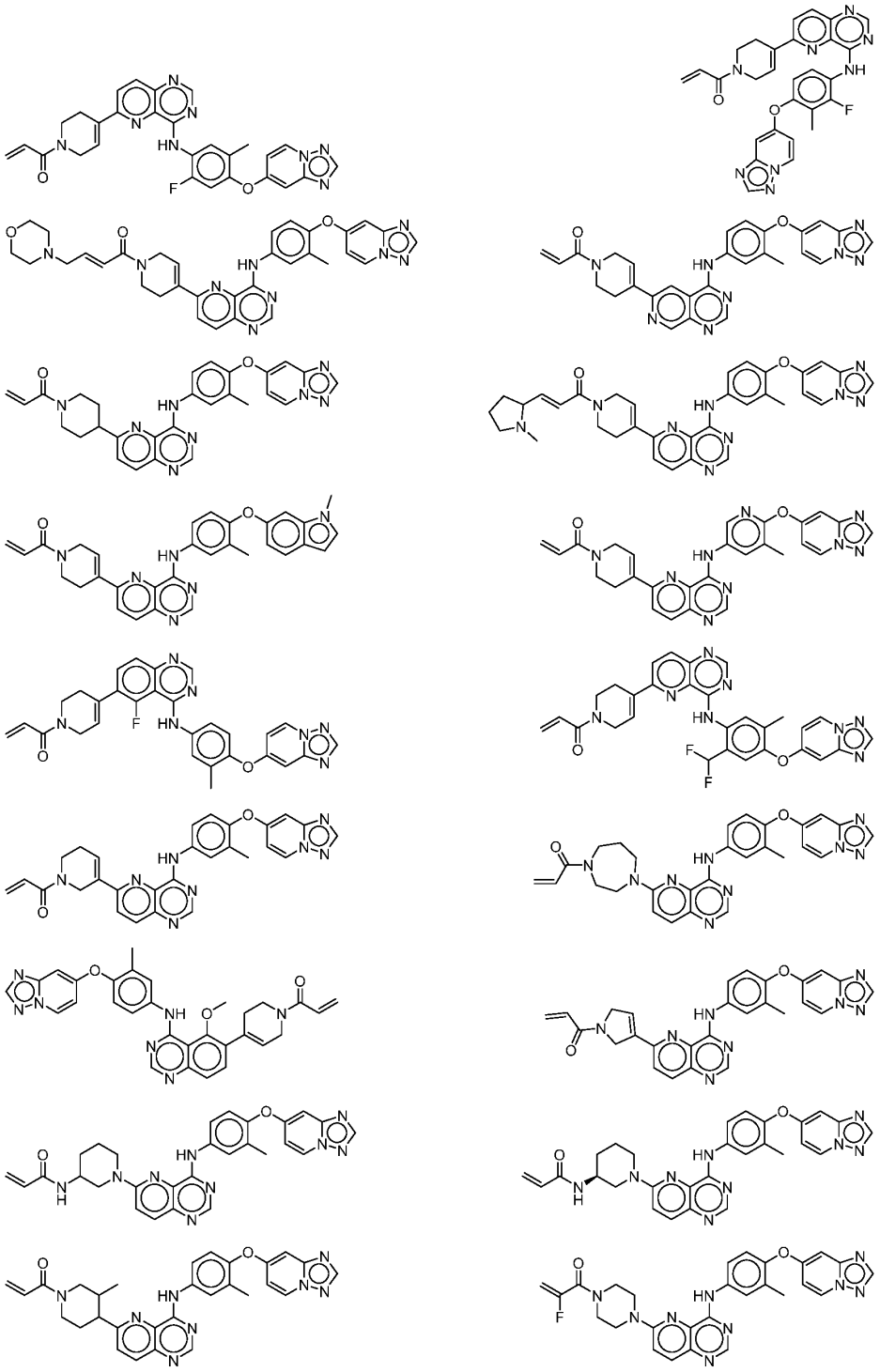
In one embodiment of any one of Formulae (III-I-1) to (III-I-13), R^1 is ; each of R^6, R^7, R^8, and R^9 is independently H, halogen, or C_{1-4} alkyl; each of R^{11} and R^{12} is independently H or C_{1-4} alkyl; and R^{10} is H, halogen, or C_{1-4} alkyl.

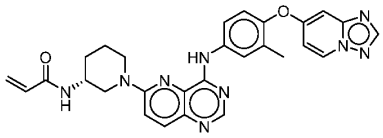
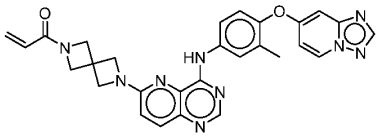
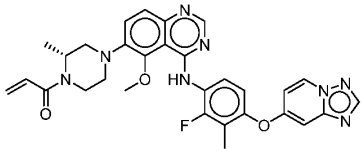
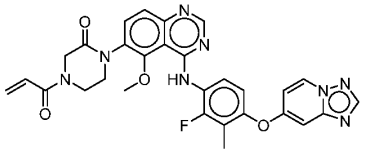
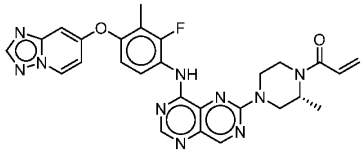
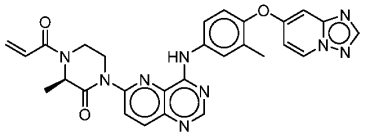
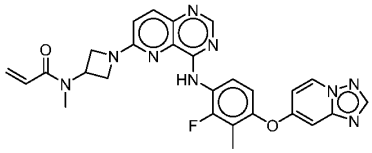
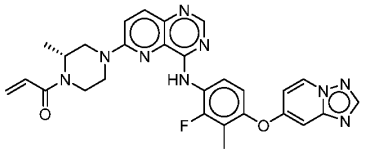
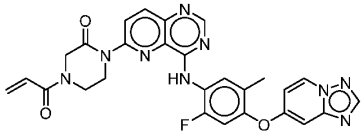
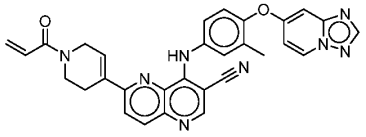
In one embodiment of any one of Formulae (III-A-1), (III-B-1), (III-C-1), (III-D-1), (III-E-1), (III-F-1), (III-G-1), (III-H-1), and (III-I-1) to (III-I-13), R^8 is optionally substituted C_{1-4} alkyl, and R^6 is halo. In one embodiment, the optionally substituted C_{1-4} alkyl is methyl. In one embodiment, the halo is fluoro. In one embodiment, R^8 is methyl, and R^6 is fluoro.

In some embodiments, disclosed herein are compounds of the following structures:

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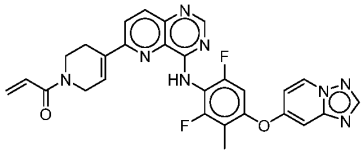
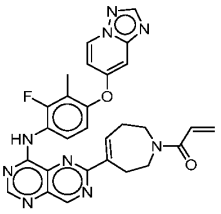
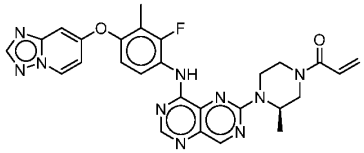
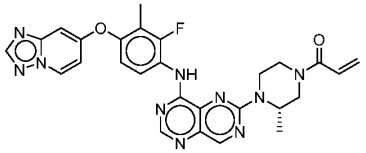
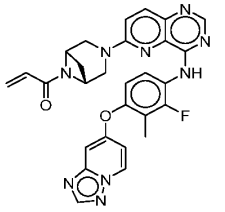
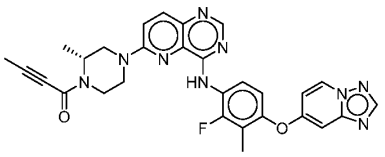
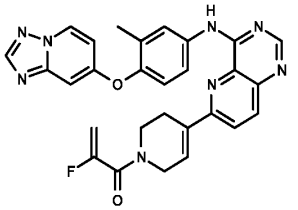

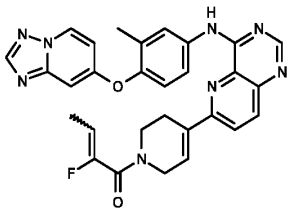
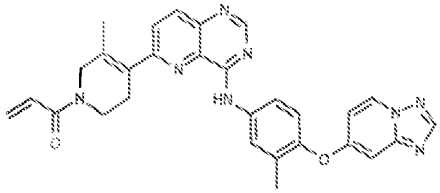
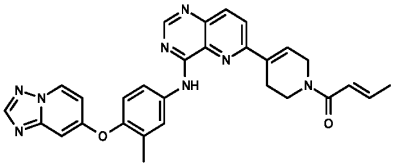
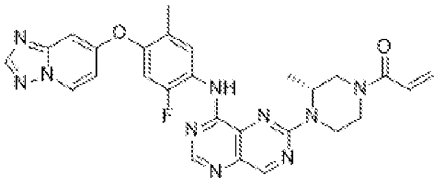
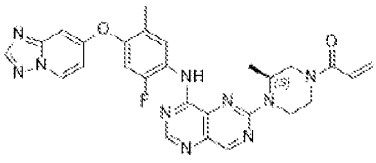
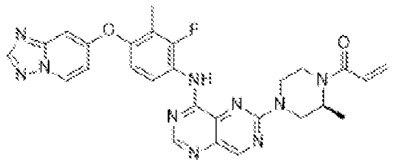
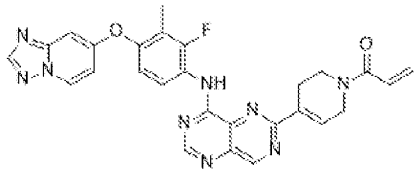
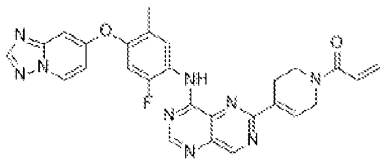
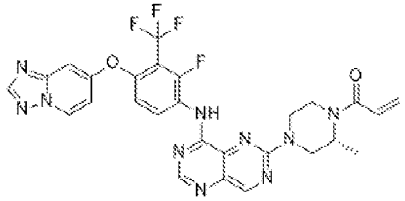
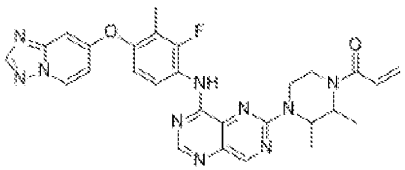

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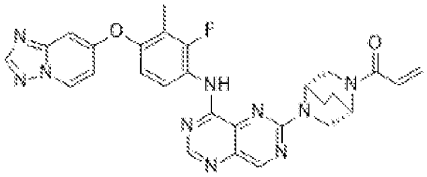
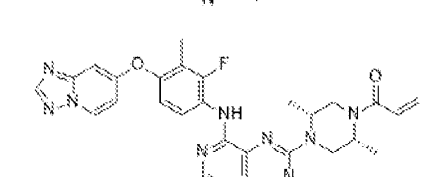
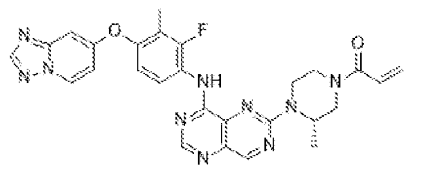

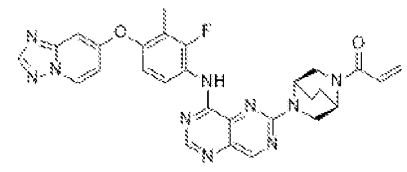
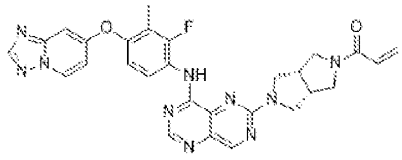
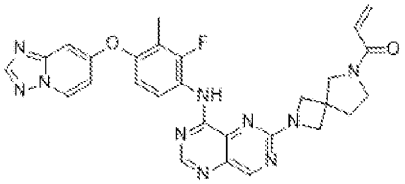

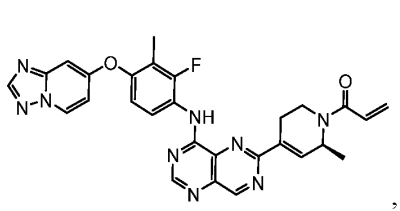
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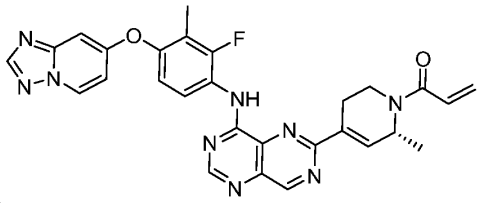
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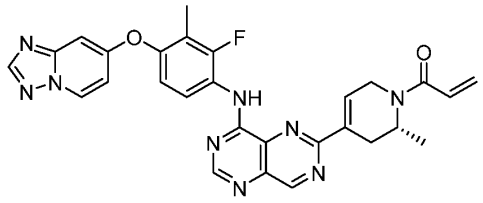
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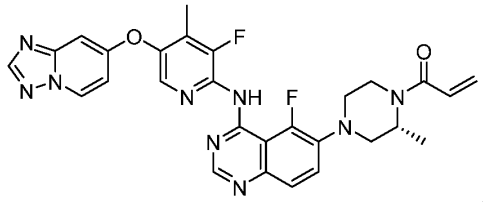
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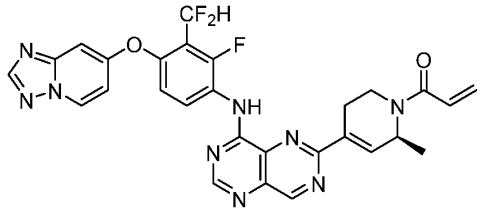
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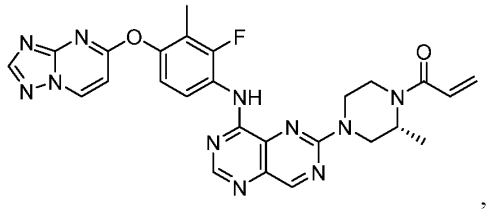
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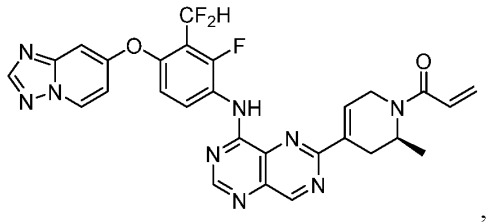
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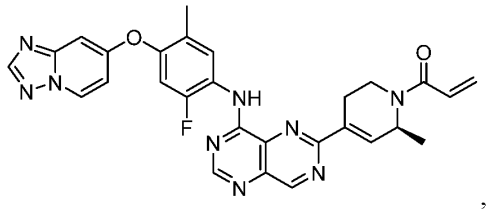
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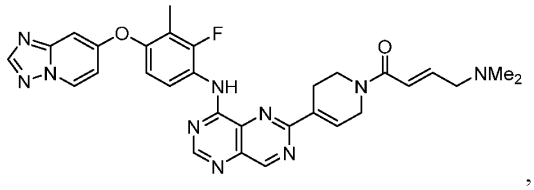
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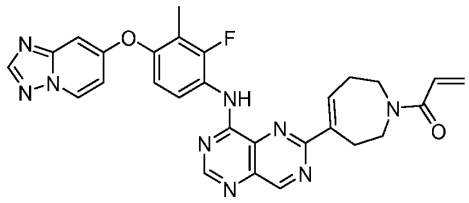
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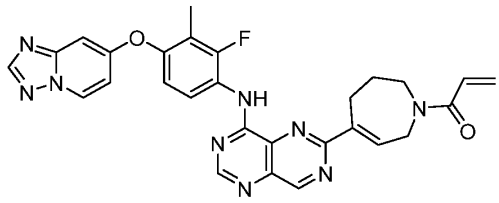
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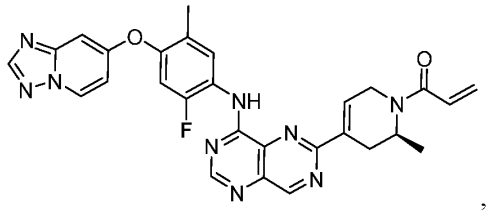
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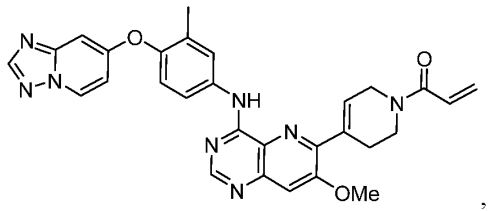
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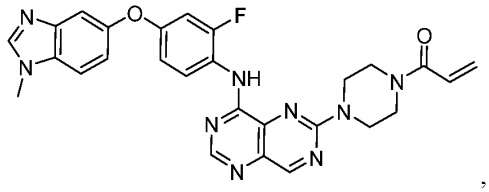
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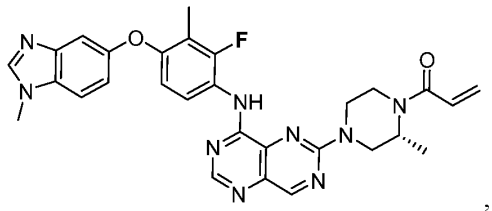
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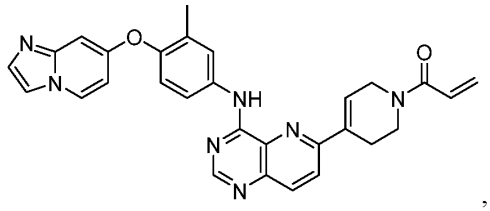
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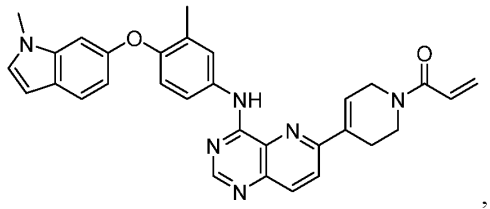
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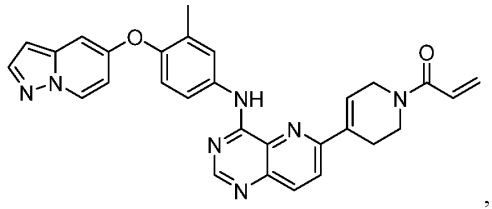
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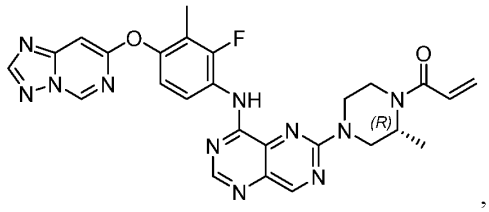
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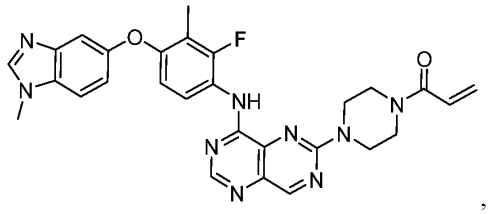
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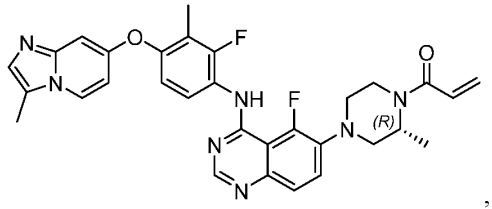
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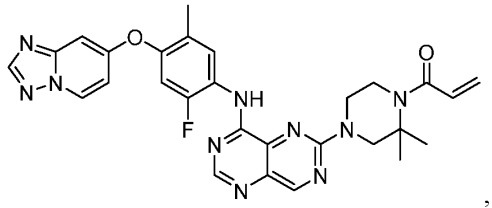
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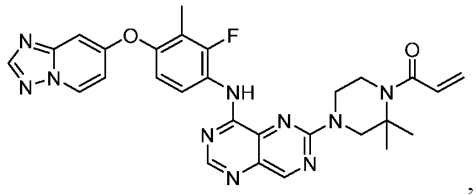
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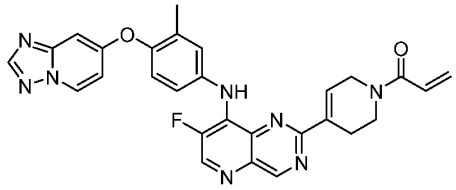
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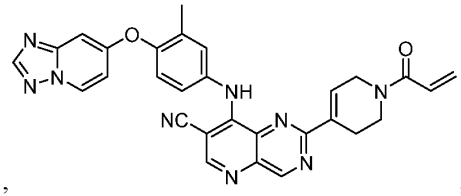
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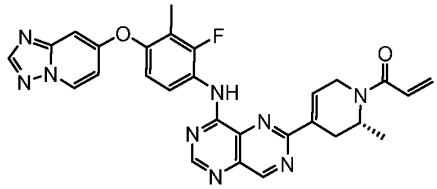
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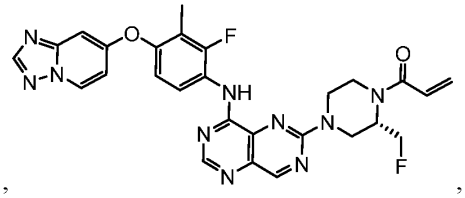
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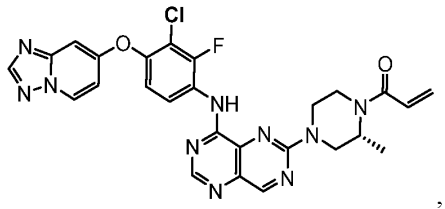
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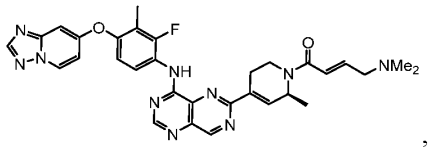
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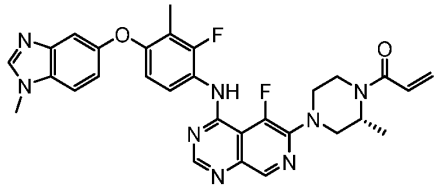
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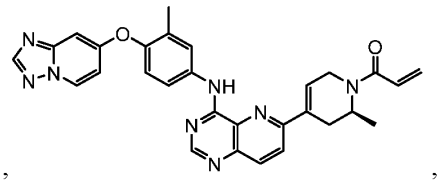
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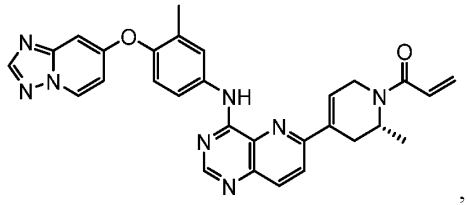
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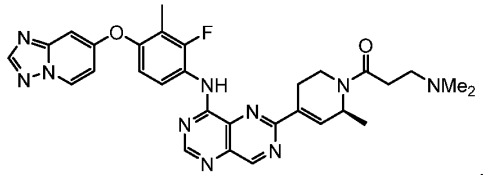
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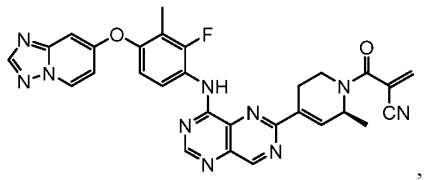
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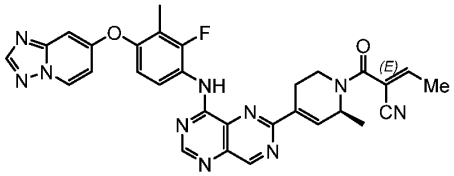
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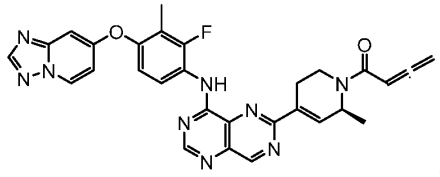
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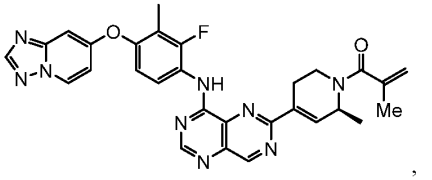
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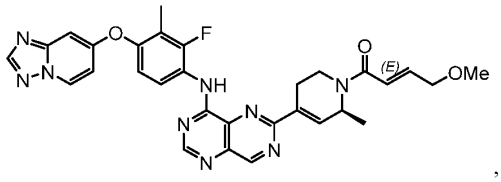
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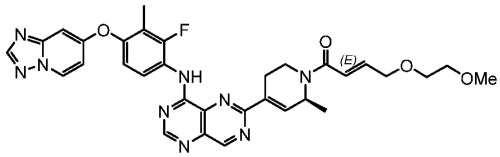
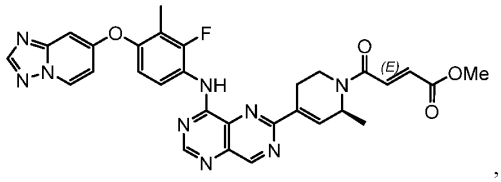
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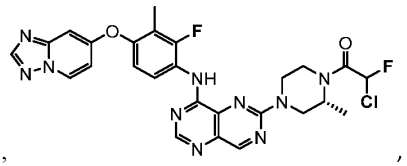
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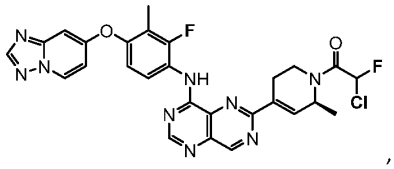
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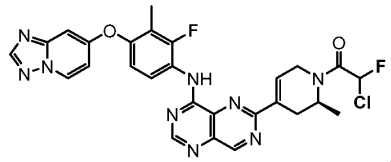
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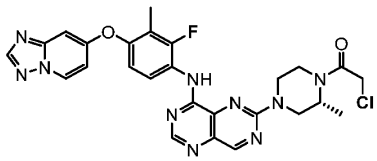
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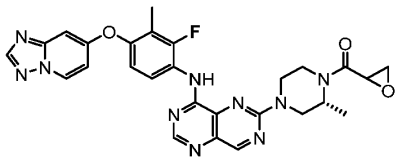
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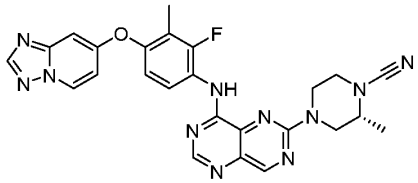
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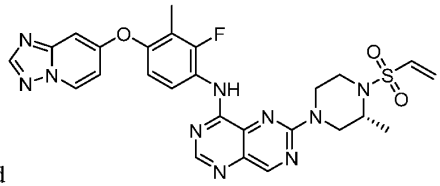
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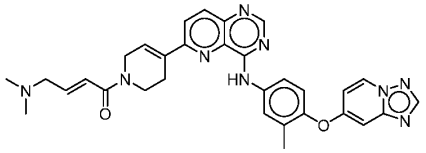
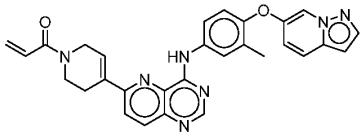
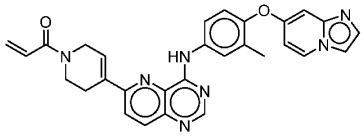
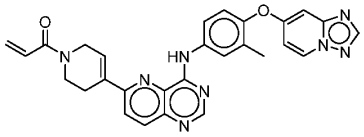
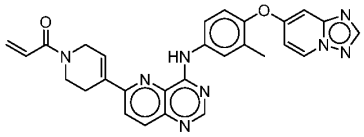
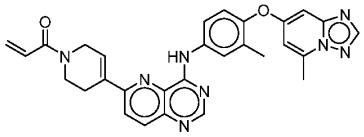
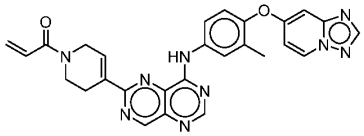
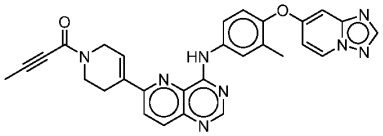
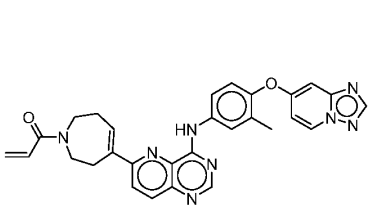
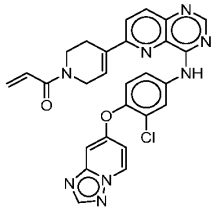
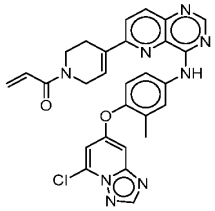
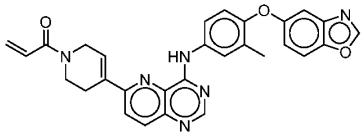
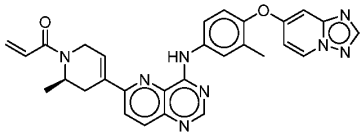
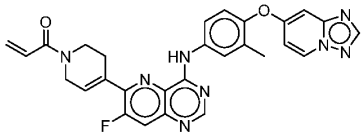
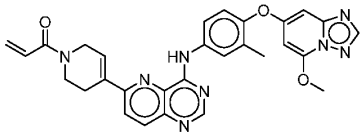
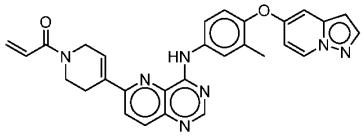
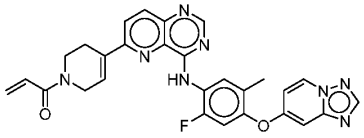
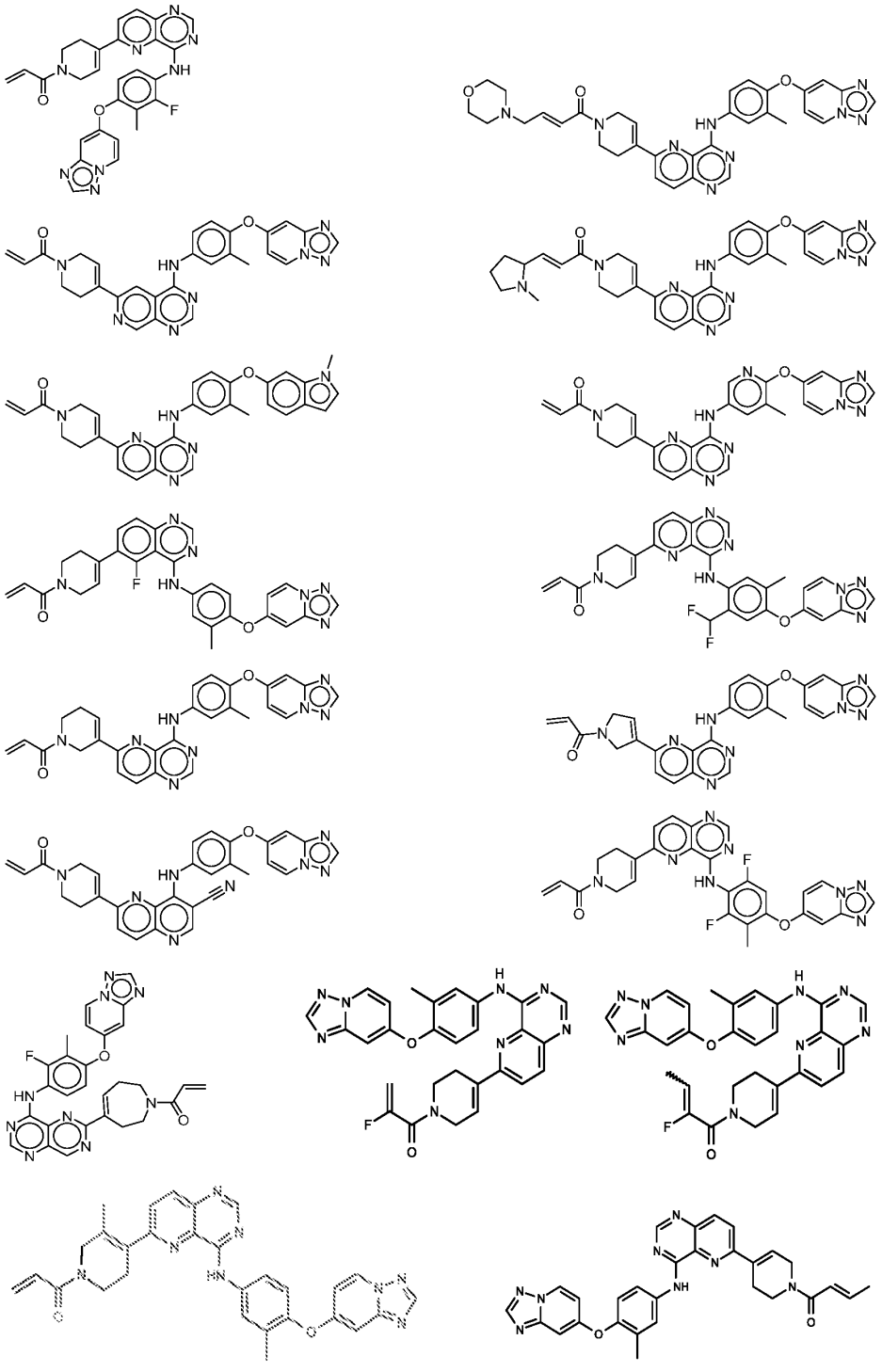
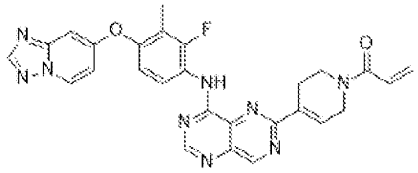
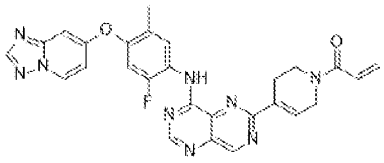
or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

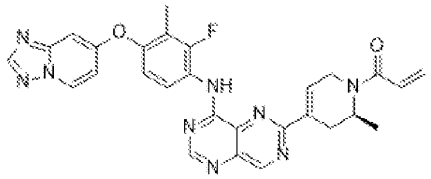
In some embodiments, disclosed herein are compounds of the following structures:

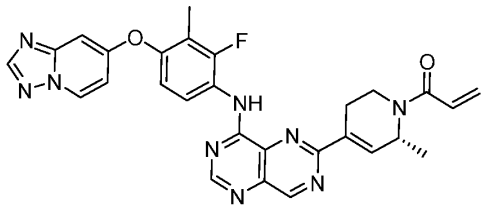


















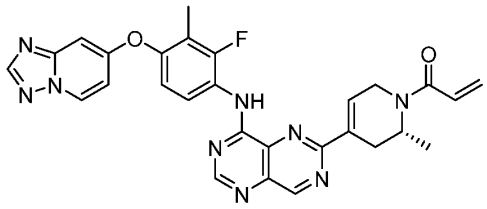


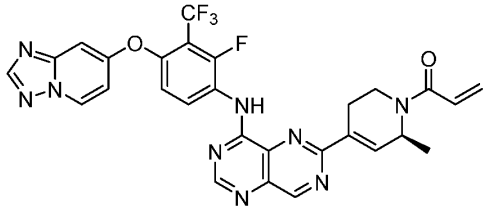












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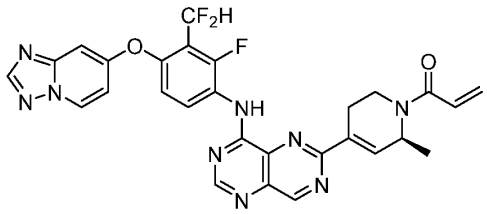

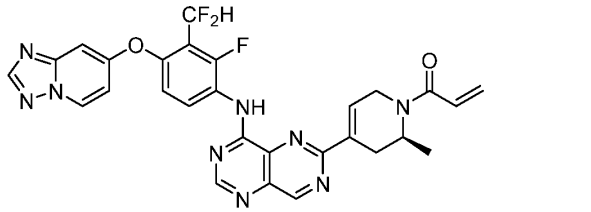

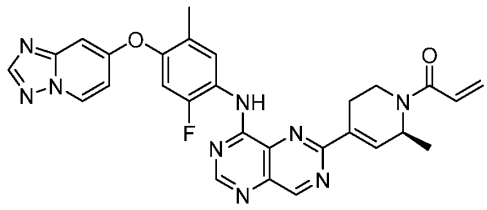

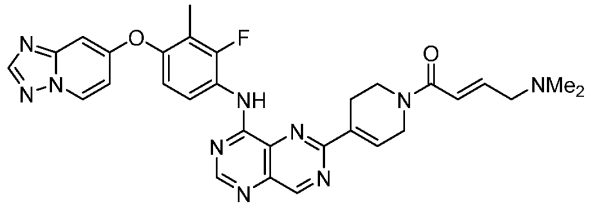

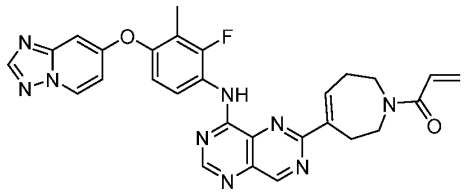

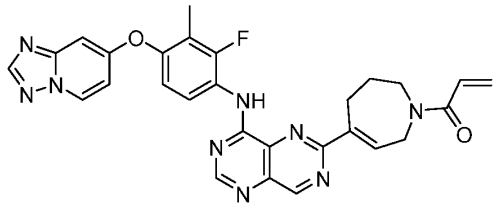

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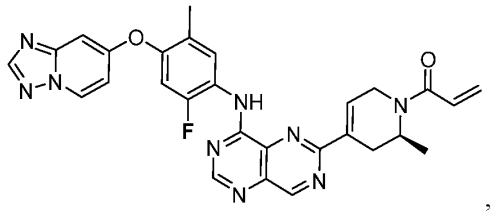
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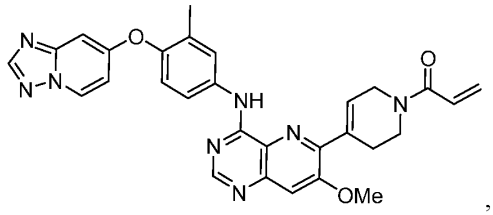
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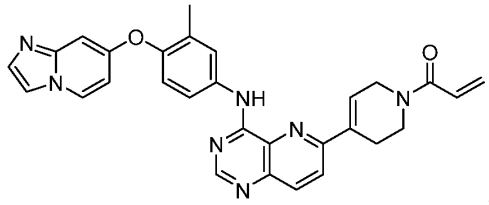
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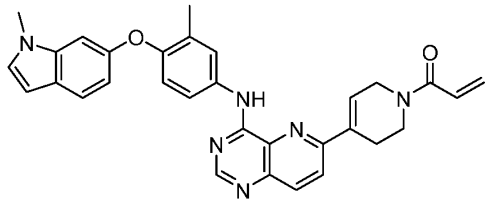

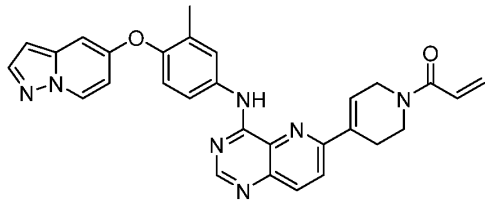

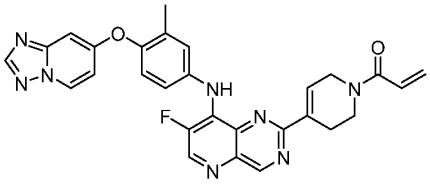
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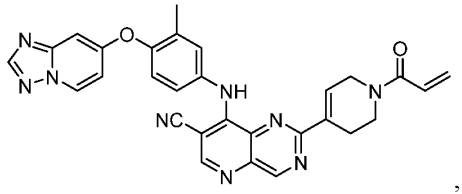
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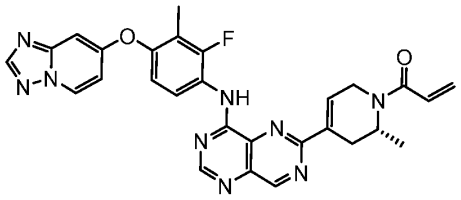
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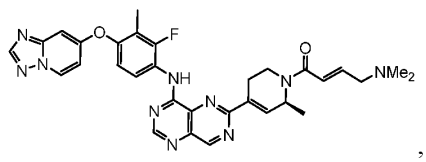
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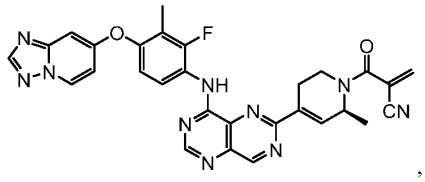
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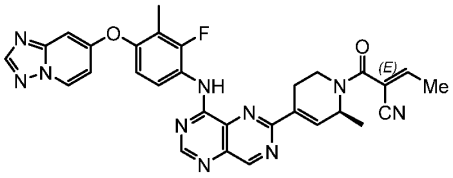
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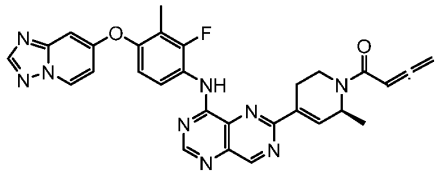
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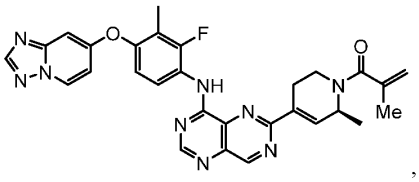
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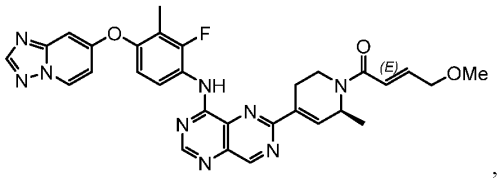
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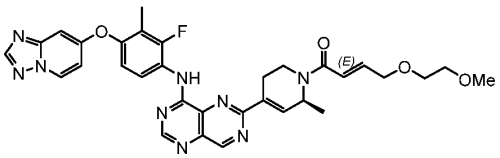
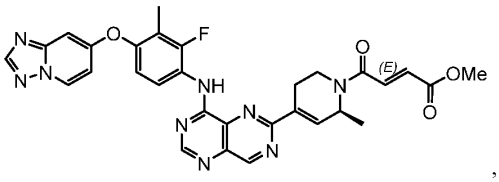
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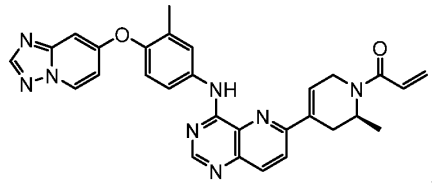
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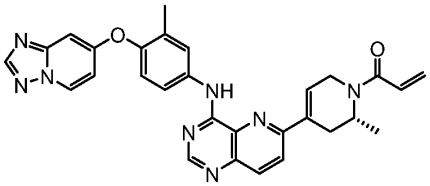
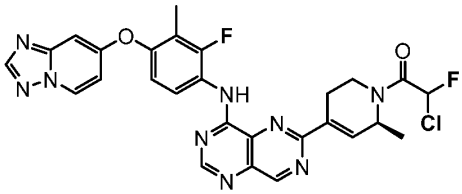
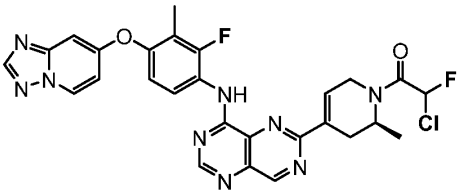
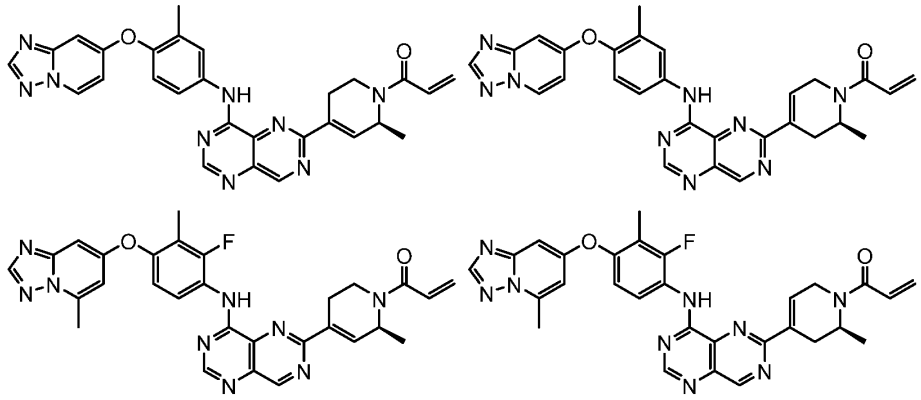
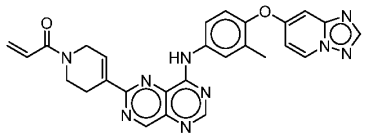
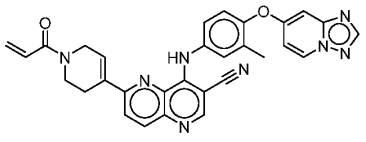




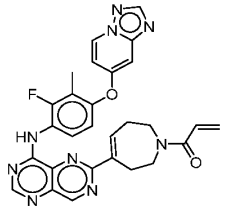


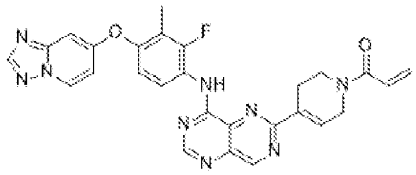
or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

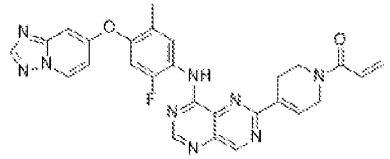
In some embodiments, disclosed herein are compounds of the following structures:

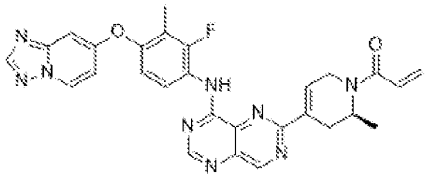


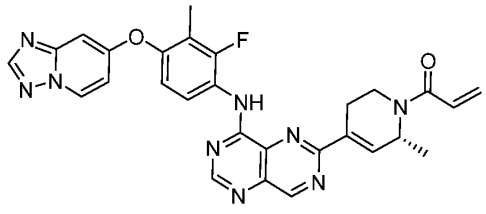


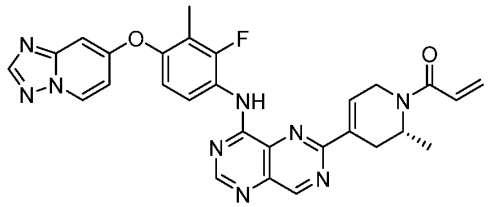


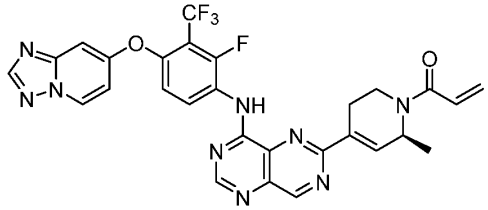


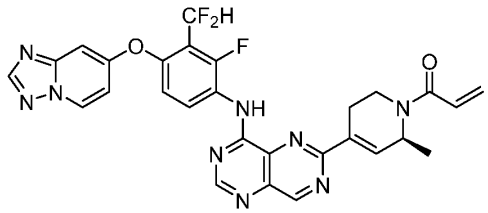


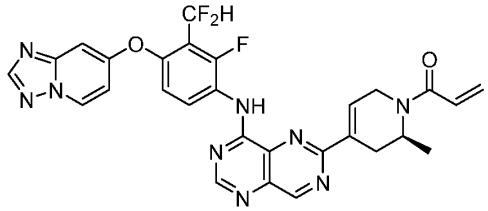


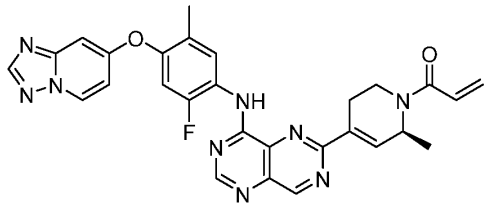












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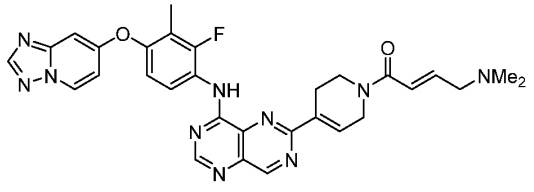

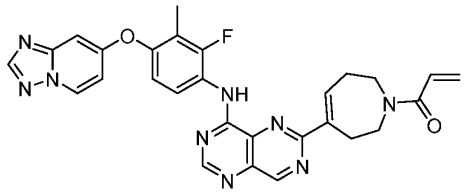

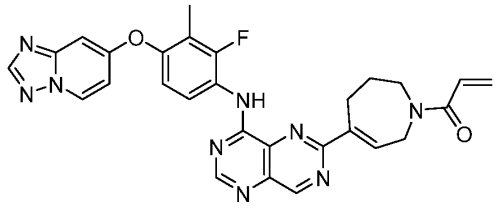

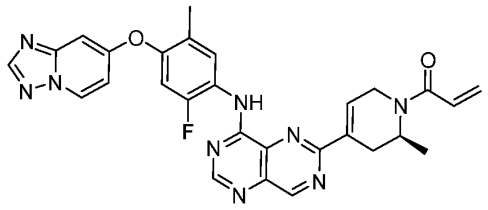

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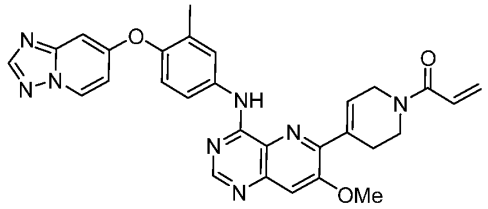

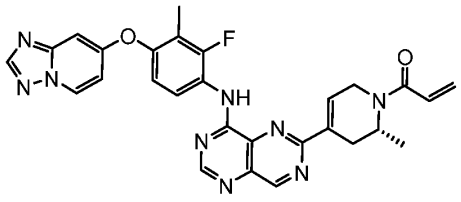

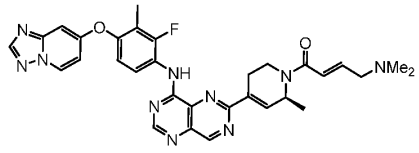

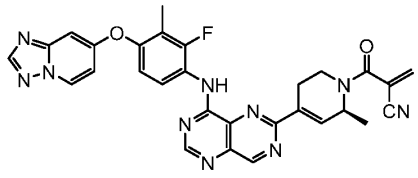

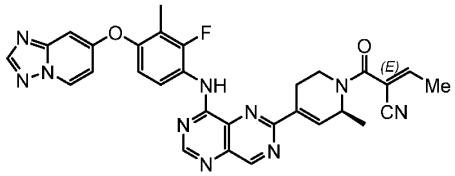

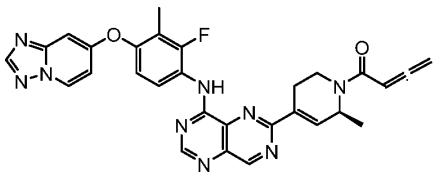

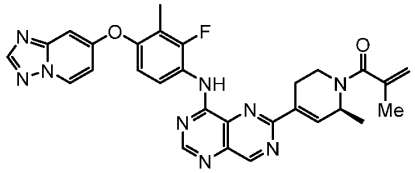

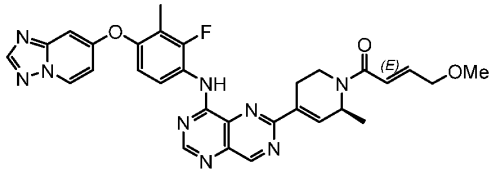

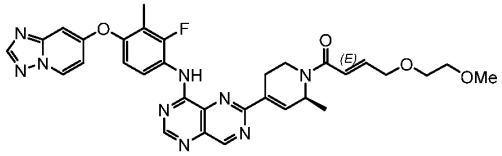

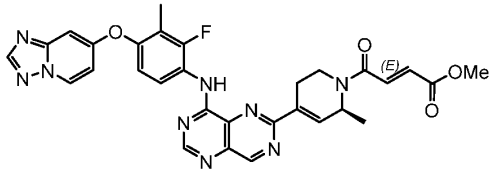

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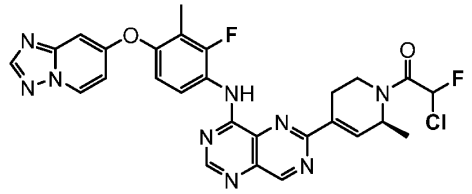
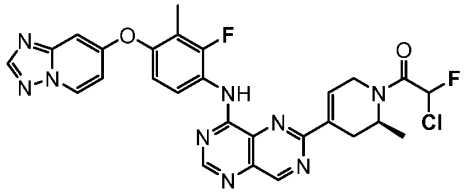
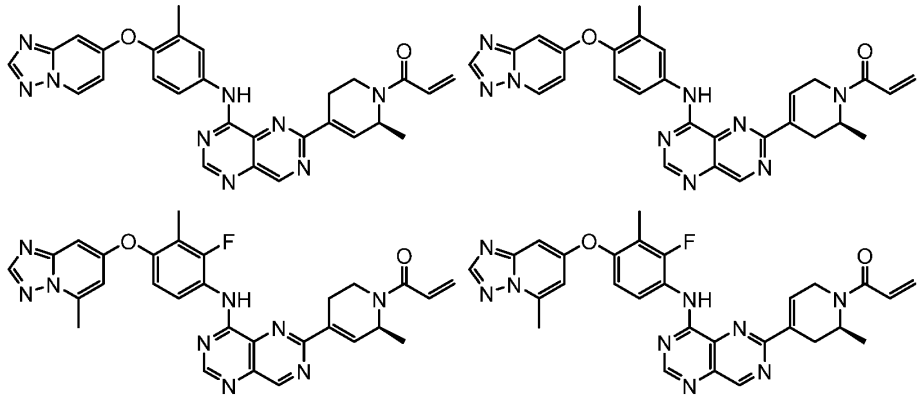






or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

Provided herein are methods of treating cancer, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound disclosed herein. In some embodiments, the cancer is non-small cell lung cancer. In other embodiments the cancer is squamous head and neck cancer. In certain embodiments, the non-small cell lung cancer has one or more ErbB family mutations. In other embodiments, the non-small cell lung cancer has one or more EGFR ex20 insertion mutations. In some embodiments, the non-small cell lung cancer has one or more HER2 ex20 insertion mutations. In certain embodiments, the mammal is a human. In some embodiments, the compound is administered orally or intravenously.

Methods of Use

In one aspect, provided herein are methods of preventing and/or treating a proliferative disease such as cancer in a subject (*e.g.*, a subject in need thereof). The methods comprise administering to the subject a compound of the present disclosure (*e.g.*, an effective amount, such as a therapeutically effective amount).

Cancer is a disease of uncontrolled cell proliferation that results from alterations in certain genes. Some of these alterations occur in genes that encode receptor tyrosine kinases (RTKs), a family of membrane-bound proteins that transmit signals from outside the cell to promote cell survival, growth, and proliferation. Aberrant RTK activation can lead to excessive cell proliferation and hence cancer. Generally, RTKs contain an N-terminal domain that binds extracellular ligands, a transmembrane domain, and a C-terminal kinase domain that catalyzes intracellular signal transduction.

The human EGFR, also known as ErbB1 or HER1, is an RTK encoded by the *EGFR* gene on chromosome 7. Multiple ligands of EGFR have been identified including epidermal growth factor (EGF), transforming growth factor α (TGF-α), amphiregulin (AREG), heparin-binding EGFR-like growth factor (HB-EGF), betacellulin (BTC), epiregulin (EPR), and epigen (EPGN). EGFR is believed to play essential roles in development, proliferation, differentiation, and migration of mammalian cells. EGFR-deficient mice do not survive the first few weeks of life and show improper development of various organs including, but not limited to, the skin, the gut, and the nervous system. In humans, EGFR overexpression and activating mutations are a well-documented cause of cancer. EGFR overexpression is found in many solid tumors at high frequency and can be targeted with FDA-approved monoclonal antibodies: cetuximab, panitumumab, and necitumumab.

In some embodiments, the compound of the present disclosure is a regulator of HER2. The human HER2, also known as ErbB2, is an RTK encoded by the *ERBB2* gene on chromosome 17. There are no known ligands for HER2, but it can modulate downstream signaling by heterodimerizing with other HER2-family RTKs, including EGFR. Mouse studies have demonstrated the essential roles of HER2 in mammalian development and cell differentiation, particularly in the cardiac and the nervous systems. HER2 deficiency is embryonically lethal in mice due to abnormal cardiac development, and conditional HER2 deletion causes defects in neuronal cell maturation, myelination, and migration. In humans, HER2 overexpression and activating mutations are known causes of cancer. HER2 overexpression is found in many solid tumors, most notably in 15-25% breast cancer. HER2 amplification is observed in cancers including esophagogastric cancer, breast cancer, peritoneal cancer, salivary gland cancer, bladder cancer, endometrial cancer, ampullary cancer, small bowel cancer, vaginal cancer, cervical cancer, hepatobillary cancer, ovarian cancer, colorectal cancer, NSCLC, head and neck cancer, pancreatic cancer, skin cancer, appendiceal cancer, B-lymphoblastic leukemia/lymphoma, melanoma, germ cell tumor, small cell lung cancer, mature B-cell neoplasms, prostate cancer, soft tissue sarcoma, and glioma. Many targeted therapies have been developed for the treatment of HER2-positive breast cancer including monoclonal antibodies (trastuzumab and pertuzumab), antibody-drug conjugates (ado-trastuzumab emtansine and fam-trastuzumab deruxtecan), and small-molecule kinase inhibitors (lapatinib, neratinib, and tucatinib). Tucatinib, the most recent FDA-approved HER2 inhibitor, extended the objective response rate from 23% to 41%, the

median progression free survival from 5.6 to 7.8 months, and the median overall survival from 17.4 to 21.9 months compared to placebo. In contrast, HER2 exon 20 insertions are found in about 2% of NSCLC, but no targeted therapies have been approved for these mutations.

Many existing HER2 therapies including erlotinib, gefitinib, afatinib, dacomitinib, lapatinib, and neratinib are also potent inhibitors of wild-type EGFR. This presents a substantial drawback because native EGFR plays important roles in epithelial biology, including the integrity of the skin and the gut lining. Inhibition of wild-type EGFR is associated with common adverse reactions including skin rash, diarrhea, and stomatitis. New therapies that spare wild-type EGFR while selectively targeting mutant HER2 are a need in the art.

In one aspect, provided herein are methods of treating and/or preventing a proliferative disease, wherein the inhibition of wild type HER2 and/or mutant HER2 provides therapeutic benefit. In certain embodiments, provided herein are methods of treating and/or preventing a proliferative disease, wherein the inhibition of HER2 exon 20 mutant protein provides therapeutic benefit.

In another aspect, provided herein are methods of inhibiting wild type and/or mutant HER2, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound as described herein, or a phamarceutically acceptable salt thereof. In another embodiments, provided herein are methods of inhibiting a HER2 exon 20 mutant, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound as described herein, or a phamarceutically acceptable salt thereof.

In another aspect, provided herein are methods of treating cancer comprising administering to a mammal (e.g., human subject) in need thereof a therapeutically effective amount of a compound as described herein, or a phamarceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein. In some embodiments, the cancer is HER2-associated cancer. In some embodiments, the HER2-associated cancer is associated with HER2 overexpression and/or HER2 amplification and/or HER2 mutation(s).

In some embodiments, “associated with” indicates the cause of the cancer. In some embodiments, “associated with” indicates the charasteristics of the cancer.

In another aspect, provided herein are methods of treating cancer comprising administering to a mammal (e.g., human subject) in need thereof a therapeutically effective

amount of a compound as described herein, or a phamarceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, wherein the cancer is associated with HER2 exon 20 mutation. In some embodiments, HER2 exon 20 mutation is one or more from the group consisting of YVMA insertion, VC insertion, and GSP insertion. In some embodiments, HER2 exon 20 mutation is one or more from the group consisting of YVMA insertion and VC insertion.

In certain embodiments, the HER2 exon 20 insertion mutation is one or more selected from A775_G776insYVMA, P780_Y781insGSP, G776 > VC, G776 > IC, G776 > LC, G778_S779insCPG, G780_P781dupGSP, Y772_A775dup, G778_P780dup, E770_A771insGIRD, G778_S779insLPS, M774_A775insAYVM, G778_S779insLPG, G778dup, G776delinsVC, M774delinsWLV, A775_G776insSVMA, and A775_G776insI. In certain embodiments, the HER2 exon 20 insertion mutation is one or more selected from A775_G776insYVMA, P780_Y781insGSP, G776 > VC, G776 > IC, G776 > LC, G778_S779insCPG, and G780_P781dupGSP. In certain embodiments, the HER2 exon 20 insertion mutation is one or more selected from A775_G776insYVMA, P780_Y781insGSP, G776 > VC, G776 > IC, G776 > LC, and G778_S779insCPG.

In another aspect, provided herein are methods of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a compound as described herein, or a phamarceutically acceptable salt thereof, wherein the cancer is characterized by HER2 overexpression, HER2 amplification, and/or HER2 exon 20 mutation(s).

In some embodiments, the cancer is a solid cancer. In some embodiments, the cancer is selected from brain cancer, breast cancer, biliary cancer, bladder cancer, cervical cancer, colorectal cancer, endometrial cancer, skin cancer, esophagus tumor, head and neck tumor, gastrointestinal cancer, gallbladder tumor, kidney cancer, liver cancer, lung cancer, and prostate cancer. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is NSCLC. In some embodiments, the cancer is small cell lung cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is a metastatic cancer.

In certain embodiment, a compound provided herein is a CNS-penetrating compound. In one embodiment, after the administration of a therapeutic effective amount of a compound provided herein, the compound is able to penetrate CNS (e.g., blood-brain barrier) and achieve a concentration in CNS (e.g., brain) that is still sufficient to inhibit

(e.g., selectively inhibit) HER2 overexpression and/or HER2 amplification and/or HER2 mutation(s).

In one embodiment, provided herein is a method for treating CNS metastases of a cancer, comprising administering to mammal (e.g., human subject) in need thereof a therapeutic effective amount of a compound provided herein, e.g., a compound of Formula (I), or an enantiomer, a mixture of enantiomers, or a tautomer thereof, or a pharmaceutically acceptable salt thereof. In one embodiment, the CNS metastases is brain metastases. In one embodiment, the cancer is a HER-associated cancer (e.g., associated with HER2 overexpression, and/or HER2 amplification, and/or HER2 exon 20 mutation(s)).

In another embodiments, provided herein are methods of inhibiting a HER2 exon 20 mutant(s) in a subject in need thereof, comprising administering to a mammal (e.g. human subject) a therapeutically effective amount of a compound as described herein (e.g., Formula (I) or any subformula), or a phamarceutically acceptable salt thereof.

In certain embodiments, the compounds of the present disclosure selectively inhibit wild type HER2 over EGFR wild type. In certain embodiments, the compounds of the present disclosure selectively inhibit wild type HER2 over EGFR wild type by about 10 to about 100 folds. In certain embodiments, the compounds of the present disclosure selectively inhibit wild type HER2 over EGFR wild type by about 20 to about 80 folds. In certain embodiments, the compounds of the present disclosure selectively inhibit wild type HER2 over EGFR wild type by about 30 to about 80 folds. In certain embodiments, the compounds of the present disclosure selectively inhibit wild type HER2 over EGFR mutant(s) (e.g., EGFR exon 20). In certain embodiments, the compounds of the present disclosure selectively inhibit wild type HER2 over EGFR mutant(s) (e.g., EGFR exon 20) by about 10 to about 100 folds. In certain embodiments, the compounds of the present disclosure selectively inhibit wild type HER2 over EGFR mutant(s) (e.g., EGFR exon 20) by about 20 to about 80 folds. In certain embodiments, the compounds of the present disclosure selectively inhibit HER2 mutant(s) over EGFR wild type. In certain embodiments, the compounds of the present disclosure selectively inhibit HER2 mutant(s) over EGFR wild type by about 10 to about 100 folds. In certain embodiments, the compounds of the present disclosure selectively inhibit HER2 mutant(s) over EGFR wild type by about 20 to about 100 folds. In certain embodiments, the compounds of the present disclosure selectively inhibit HER2 exon 20 mutant(s) over EGFR wild type. In certain

embodiments, the compounds of the present disclosure selectively inhibit HER2 exon 20 mutant(s) over EGFR wild type by about 10 to about 100 folds. In certain embodiments, the compounds of the present disclosure selectively inhibit HER2 exon 20 mutant(s) over EGFR wild type by about 20 to about 80 folds. In certain embodiments, the compounds of the present disclosure selectively inhibit HER2 exon 30 mutant(s) over EGFR wild type by about 20 to about 80 folds. In certain embodiments, the compounds of the present disclosure selectively inhibit HER2 mutant(s) (e.g., HER2 exon 20) over EGFR mutant(s) (e.g. EGFR exon 20). In certain embodiments, the compounds of the present disclosure selectively inhibit HER2 mutant(s) (e.g., HER2 exon 20) over EGFR mutant(s) (e.g. EGFR exon 20) by about 10 to about 100 folds. In certain embodiments, the compounds of the present disclosure selectively inhibit HER2 mutant(s) (e.g., HER2 exon 20) over EGFR mutant(s) (e.g. EGFR exon 20) by about 20 to about 80 folds. In some embodiments, the compounds of the present disclosure selectively inhibit HER2 exon 20 mutant(s) over EGFR wild type and/or EGFR exon 20 mutant(s). In some embodiments, the compounds of the present disclosure show an improved wild type EGFR sparing efficacy profile in addition to high selectivity over EGFR wild type, compared to the existing therapies. Furthermore, some compounds of the present invention show an improved pharmacokinetic and pharmacological profile. In some embodiments, the compounds as described herein have minimal activities against related kinase (e.g., wt EGFR). Inhibition of wt EGFR causes undersirable side effects (e.g., diarrhea and skin rashes) that can impact quality of life and compliance of treatments.

In some embodiments, the human subject has been identified or diagnosed as having a cancer associated with HER2 overexpression, and/or HER2 amplification, and/or HER2 exon 20 mutation(s) (a HER2-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for HER2 overexpression, and/or HER2 amplification, and/or HER2 exon 20 mutation(s) (e.g., as determined using a regulatory agency-approved assay or kit). The subject can be a subject whose tumors have HER2 overexpression, and/or HER2 amplification, and/or HER2 exon 20 mutation(s) (e.g., where the tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is suspected of having a HER2-associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has HER2 overexpression, and/or HER2 amplification, and/or HER2 exon 20 mutation(s).

In some embodiments of any of the methods or uses described herein, an assay used to determine whether the subject has HER2 overexpression, and/or HER2 amplification, and/or HER2 exon 20 mutation(s), using a sample from a subject can include, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quantitative real-time RT-PCR). As is well-known in the art, the assays are typically performed, e.g., with at least one labelled nucleic acid probe or at least one labelled antibody or antigen-binding fragment thereof. Assays can utilize other detection methods known in the art for detecting HER2 overexpression, and/or HER2 amplification, and/or HER2 exon 20 mutation(s) (see, e.g., the references cited herein). In some embodiments, the sample is a biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from the subject. In some embodiments, the subject is a subject suspected of having a HER2-associated cancer, a subject having one or more symptoms of a HER2-associated cancer, and/or a subject that has an increased risk of developing a HER2-associated cancer.

In some embodiments, HER2 overexpression, and/or HER2 amplification, and/or HER2 exon 20 mutation(s) can be identified using a liquid biopsy (variously referred to as a fluid biopsy or fluid phase biopsy). See, e.g., Karachialiou et al., "Real-time liquid biopsies become a reality in cancer treatment", Ann. Transl. Med., 3(3):36, 2016. Liquid biopsy methods can be used to detect total tumor burden and/or the dysregulation of a HER2 gene, a HER2 kinasev, or the expression or activity or level of any of the same. Liquid biopsies can be performed on biological samples obtained relatively easily from a subject (e.g., via a simple blood draw) and are generally less invasive than traditional methods used to detect tumor burden and/or dysregulation of a HER2 gene, a HER2 kinase, or the expression or activity or level of any of the same. In some embodiments, liquid biopsies can be used to detect the presence of HER2 overexpression, and/or HER2 amplification, and/or HER2 exon 20 mutation(s) at an earlier stage than traditional methods. In some embodiments, the biological sample to be used in a liquid biopsy can include, blood, plasma, urine, cerebrospinal fluid, saliva, sputum, broncho-alveolar lavage, bile, lymphatic fluid, cyst fluid, stool, ascites, and combinations thereof. In some embodiments, a liquid biopsy can be used to detect circulating tumor cells (CTCs). In some embodiments, a liquid biopsy can be used to detect cell-free DNA. In some embodiments, cell-free DNA detected using a liquid biopsy is circulating tumor DNA (ctDNA) that is

derived from tumor cells. Analysis of ctDNA (e.g., using sensitive detection techniques such as, without limitation, next-generation sequencing (NGS), traditional PCR, digital PCR, or microarray analysis) can be used to identify HER2 overexpression, and/or HER2 amplification, and/or HER2 exon 20 mutation(s).

In some embodiments, the compounds of the present disclosure inhibit a HER2 exon 20 mutant in a subject with NSCLC. In some embodiments, HER2 exon 20 mutant is one or more from the group consisting of YVMA insertion, VC insertion, and GSP insertion. In some embodiments, the compounds of the present disclosure inhibit a HER2 non-exon 20 mutant. In some embodiments, the compounds of the present disclosure selectively inhibit HER2 non-exon 20 mutant(s) over EGFR wild type and/or mutants (e.g., exon 20). In some embodiments, the HER2 non-exon 20 mutant is one or more from the group consisting of S310X (e.g., S310F and S310Y), R678Q, V842I, L755S, G776V, and V777X. In some embodiments, the non-exon 20 mutation is one or more selected from L755S, S310F, R678Q, V842I, and V777X.

In some embodiments, provided herein are methods of inhibiting wild type HER2 and/or mutant HER2 in a cell, comprising contacting the cell with a compound of the present disclosure. In some embodiments, the mutant HER2 carries one or more exon 20 mutations.

In some embodiments, provided herein are methods of increasing the level of HER2 (wild type HER2 and/or mutant(s)) in a cell, comprising contacting the cell with the compound of the present disclosure, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

In some embodiments, provided herein are methods of decreasing phosphorylation of HER2 (wild type HER2 and/or mutant(s)) in a cell, comprising contacting the cell with the compound of the present disclosure, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof. In another embodiment, provided herein are methods of inhibiting HER2 carrying exon 20 mutations in a cell, comprising contacting the cell with the compound of the present disclosure, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

In some embodiments, provided herein are methods of inhibiting phosphorylation of wild type HER2 and/or mutant HER2 in a cell, comprising contacting the cell with the compound of the present disclosure, or a pharmaceutically acceptable salt, a stereoisomer,

or a tautomer thereof. In some embodiments, the mutant HER2 carries one or more exon 20 mutations.

In some embodiments, provided herein are methods of treating and/or prevention of a disease and/or condition, wherein the inhibition of wild type and/or mutant HER2 is of therapeutic benefit. In another embodiment, provided herein are methods of treating or preventing a disease and/or condition, wherein the inhibition of HER2 exon 20 mutant protein is of therapeutic benefit.

In some embodiments, provided herein are methods of inhibiting wild type and/or mutant HER2, in a human subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

The compounds of the present disclosure are useful for inhibiting HER2 *in vitro* or *in vivo*. Accordingly, provided herein are methods of inhibiting HER2 in a cell (*e.g.*, a cell expressing HER2), comprising contacting the cell with a compound of the present disclosure (*e.g.*, a compound a compound of the disclosure, such as a compound of Formula (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (a-I), (II), or (III), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof). In some embodiments, the cell is in a subject, such as a human (*e.g.*, a subject having a disease, disorder or condition described herein). Also provided herein are methods of inhibiting HER2 in a subject in need thereof (*e.g.*, a subject having a disease, disorder or condition described herein), comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure (*e.g.*, a compound of the disclosure, such as a compound of Formula (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (a-I), (II), or (III), or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof).

In some embodiments, the cell is in a mammal. In some embodiments, the cell is in a human subject. In some embodiments, the cell is in a human subject having cancer. In some embodiments, the cell is in a human subject having cancer associated with HER2 overexpression and/or HER2 amplification and/or HER2 mutation(s). In some embodiments, the cell is isolated from a mammal (e.g., a human subject having cancer).

A "proliferative disease" refers to a disease that occurs due to abnormal growth or extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be

associated with: (1) the pathological proliferation of normally quiescent cells; (2) the pathological migration of cells from their normal location (*e.g.*, metastasis of neoplastic cells); (3) the pathological expression of proteolytic enzymes such as the matrix metalloproteinases (*e.g.*, collagenases, gelatinases, and elastases); and/or (4) pathological angiogenesis, as in proliferative retinopathy and tumor metastasis. Non-limiting examples of proliferative diseases include cancer (*i.e.*, "malignant neoplasms"), benign neoplasms, angiogenesis, inflammatory diseases and autoimmune diseases.

The terms "neoplasm" and "tumor" are used herein interchangeably and refer to an abnormal mass of tissue wherein the growth of the mass surpasses and is not coordinated with the growth of a normal tissue. A neoplasm or tumor may be "benign" or "malignant," depending, for example, on the following characteristics: degree of cellular differentiation (including morphology and functionality), rate of growth, local invasion, and metastasis.

A "benign neoplasm" is generally well differentiated, has characteristically slower growth than a malignant neoplasm, and remains localized to the site of origin. In addition, a benign neoplasm does not have the capacity to infiltrate, invade, or metastasize to distant sites. Non-limiting examples of benign neoplasms include, but are not limited to, lipomas, chondromas, adenomas, acrochordons, senile angiomas, seborrheic keratoses, lentigos, and sebaceous hyperplasias.

In some cases, benign tumors may later give rise to malignant neoplasms, which may result from additional genetic changes in a subpopulation of the tumor's neoplastic cells. Such tumors are referred to as "pre-malignant neoplasms." An exemplary pre-malignant neoplasm is a teratoma.

A "malignant neoplasm" is generally poorly differentiated (anaplasia) and has characteristically rapid growth accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue. Furthermore, a malignant neoplasm generally has the capacity to metastasize to distant sites. The term "metastasis," "metastatic," or "metastasize" refers to the spread or migration of cancerous cells from a primary or original tumor to another organ or tissue, and is typically identifiable by the presence of a "secondary tumor" or "secondary cell mass" of the tissue type of the primary or original tumor and not of that of the organ or tissue in which the secondary (metastatic) tumor is located.

In certain embodiments, the proliferative disease is cancer. Accordingly, provided herein are methods for treating a cancer in a subject (*e.g.*, a subject in need thereof), comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure.

The term "cancer" refers to a class of diseases characterized by the development of abnormal cells that proliferate uncontrollably and have the ability to infiltrate and destroy normal body tissues.

A wide variety of cancers, including solid tumors, leukemias, lymphomas, and myelomas are amenable to the methods disclosed herein. In some embodiments, the cancer is a solid tumor cancer. In some embodiments, the cancer comprises a solid tumor (*e.g.*, a colorectal, breast, prostate, lung, pancreatic, renal or ovarian tumor). Accordingly, in some embodiments, the cancer is a solid tumor cancer. In some embodiments, the cancer is selected from one or more of a cancer of the pulmonary system, a brain cancer (*e.g.*, neuroblastoma, glioblastoma, anaplastic astrocytoma), a cancer of the gastrointestinal tract, a skin cancer, a genitourinary cancer, head and neck cancer, a sarcoma, a carcinoma, and a neuroendocrine cancer. In various embodiments, the solid tumor cancer is breast cancer, bladder cancer, endometrial cancer, esophageal cancer, liver cancer, pancreatic cancer, lung cancer, cervical cancer, colon cancer, colorectal cancer, gastric cancer, kidney cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, a viral-induced cancer, melanoma or sarcoma. In some embodiments, the cancer is bladder cancer. In some embodiments, the cancer is lung cancer (*e.g.*, non-small cell lung cancer). In other embodiments, the cancer is liver cancer. In some embodiments, the cancer is a sarcoma, bladder cancer or renal cancer. In some embodiments, the cancer is prostate cancer (*e.g.,* castration-resistant prostate cancer, castration-sensitive prostate cancer). In other embodiments, the cancer is bladder cancer, pancreatic cancer, colorectal cancer, glioblastoma, kidney cancer, non-small cell lung carcinoma, prostate cancer, sarcoma, skin cancer, thyroid cancer (*e.g.*, anaplastic thyroid cancer), testicular cancer or vulvar cancer. In some embodiments, the cancer is endometrial cancer, pancreatic cancer, testicular cancer, renal cancer, melanoma, colorectal cancer, thyroid cancer, bladder cancer, pancreatic cancer, vulvar cancer, sarcoma, prostate cancer, lung cancer or anal cancer. In some embodiments, the cancer is a sarcoma. In some embodiments, the cancer is a renal cell carcinoma.

In some embodiments, the cancer is a non-solid tumor cancer. In some embodiments, the cancer is a hematologic cancer. Hematologic cancers that can be treated according to the methods described herein include leukemias (*e.g.*, acute leukemias, chronic leukemias), lymphomas (*e.g.*, B-cell lymphoma, T-cell lymphoma) and multiple myeloma. Non-limiting examples of hematologic cancers include leukemia (*e.g.*, acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, *T*-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, *T*-cell AML), early T-cell precursor (ETP)-acute lymphoblastic leukemia, chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, *T*-cell CML), chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, *T*-cell CLL)); lymphoma (*e.g.*, Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, *T*-cell HL)), non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B-cell lymphoma)), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomads, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.*, Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma, *T*-cell NHL such as precursor *T*-lymphoblastic lymphoma/leukemia, peripheral *T*-cell lymphoma (PTCL) (*e.g.*, cutaneous *T*-cell lymphoma (CTCL) (*e.g.*, mycosis fungoides, Sezary syndrome)), angioimmunoblastic *T*-cell lymphoma, extranodal natural killer *T*-cell lymphoma, enteropathy type *T*-cell lymphoma, subcutaneous panniculitis-like *T*-cell lymphoma, anaplastic large cell lymphoma); heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); a myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); multiple myeloma (MM); plasma cell neoplasia; familiar hypereosinophilia; inflammatory myofibroblastic tumors; and immunocytic amyloidosis. In some embodiments, the hematologic cancer is selected from multiple myeloma, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, lymphocytic lymphoma, mycosis

fungoides, chronic lymphogenous leukemia, chronic lymphocytic leukemia (CLL), mantle cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma or myelofibrosis.

Examples of cancer treatable according to the methods described herein include, but are not limited to, adenocarcinoma of the breast, prostate, and colon; all forms of bronchogenic carcinoma of the lung; myeloid; melanoma (*e.g.*, metastatic melanoma); astrocytoma (*e.g.*, anaplastic astrocytoma); hepatoma; neuroblastoma; papilloma; apudoma; choristoma; branchioma; malignant carcinoid syndrome; carcinoid heart disease; and carcinoma (*e.g.*, Walker, basal cell, basosquamous, Brown-Pearce, ductal, Ehrlich tumor, Krebs 2, merkel cell, mucinous, lung cancer (e.g., large cell lung cancer, such as squamous cell carcinoma, non-small cell lung cancer (NSCLC)), oat cell, papillary, scirrhous, bronchiolar, bronchogenic, squamous cell, and transitional cell). Additional examples of cancer treatable according to the methods described herein include, but are not limited to, histiocytic disorders; leukemia; histiocytosis malignant; Hodgkin's disease; hypereosinophilia, immunoproliferative small; non-Hodgkin's lymphoma; plasmacytoma; reticuloendotheliosis; melanoma (*e.g.*, metastatic melanoma); chondroblastoma; chondroma; chondrosarcoma; fibrotic cancer (*e.g.*, myelofibrosis, pancreatic cancer (*e.g.*, pancreatic ductal adenocarcinoma), kidney cancer, liver cancer, lung cancer (*e.g.*, large cell lung cancer, such as squamous cell carcinoma), breast cancer (*e.g.*, inflammatory breast cancer), ovarian cancer (*e.g.*, high grade serious ovarian carcinoma), endometrial cancer, uterine cancer, uterine sarcoma (*e.g.*, uterine leiomyosarcoma), renal cell cancer, sarcoma (*e.g.*, soft tissue sarcoma), malignant fibrous histiocytoma, fibrosarcoma (*e.g.*, dermatofibrosarcoma protuberans); hepatocellular carcinoma; fibroma; fibrosarcoma; giant cell tumors; histiocytoma; lipoma; liposarcoma; mesothelioma; myxoma; myxosarcoma; osteoma; osteosarcoma; pediatric malignancy, chordoma; craniopharyngioma; dysgerminoma; hamartoma; mesenchymoma; mesonephroma; myosarcoma; ameloblastoma; cementoma; odontoma; teratoma; thymoma; trophoblastic tumor. Further, the following types of cancers are also contemplated as amenable to treatment: adenoma; cholangioma; cholesteatoma; cyclindroma; cystadenocarcinoma; cystadenoma; granulosa cell tumor; gynandroblastoma; hepatocellular cancer, hepatoma; hidradenoma; islet cell tumor; Leydig cell tumor; papilloma; sertoli cell tumor; theca cell tumor; leiomyoma; leiomyosarcoma; myoblastoma; myomma; myosarcoma; rhabdomyoma;

rhabdomyosarcoma; ependymoma; ganglioneuroma; glioma; medulloblastoma; meningioma; neurilemmoma; neuroblastoma; neuroepithelioma; neurofibroma; neuroma; paraganglioma; paraganglioma nonchromaffin. Yet more examples of cancer treatable according to the methods described herein include, but are not limited to, angiokeratoma; angiolymphoid hyperplasia with eosinophilia; angioma sclerosing; angiomatosis; glomangioma; hemangioendothelioma; hemangioma; hemangiopericytoma; hemangiosarcoma; lymphangioma; lymphangiomyoma; lymphangiosarcoma; pinealoma; carcinosarcoma; chondrosarcoma; cystosarcoma phyllodes; fibrosarcoma; hemangiosarcoma; leiomyosarcoma; leukosarcoma; liposarcoma; lymphangiosarcoma; myosarcoma; myxosarcoma; ovarian carcinoma; rhabdomyosarcoma; sarcoma; neoplasms; nerofibromatosis; and cervical dysplasia.

In certain embodiments, provided herein are methods of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a compound as described herein. In certain embodiments, provided herein are methods of treating esophagogastric cancer, breast cancer, peritoneal cancer, salivary gland cancer, bladder cancer, endometrial cancer, ampullary cancer, small bowel cancer, vaginal cancer, cervical cancer, hepatobillary cancer, ovarian cancer, colorectal cancer, NSCLC, head and neck cancer, pancreatic cancer, skin cancer, appendiceal cancer, B-lymphoblastic leukemia/lymphoma, melanoma, germ cell tumor, small cell lung cancer, mature B-cell neoplasms, prostate cancer, soft tissue sarcoma, or glioma, comprising administering to a subject in need thereof a therapeutically effective amount of a compound as described herein. In certain embodiments, the cancer is breast cancer. In certain embodiments, the cancer is lung cancer. In certain embodiments, the cancer is NSCLC.

HPV-associated cancers are also treatable according to the methods described herein. Non-limiting examples of HPV-associated cancers include cervical cancer, oropharyngeal cancer, anal cancer, vulvar/vaginal cancer, and penile cancer.

Liver cancers, such as hepatocellular cancer (HCC) (*e.g.*, hepatocellular carcinoma, hepatoblastoma, hepatocellular adenoma), malignant hepatoma, hemangiomas and biliary cancer (*e.g.*, cholangiocarcinoma), are also treatable according to the methods described herein.

Musculoskeletal cancers are also treatable according to the methods described herein. Non-limiting examples of musculoskeletal cancers include bone cancer (*e.g.*,

osteosarcoma, osteoid osteoma, malignant fibrous histiocytoma, Ewing's sarcoma, chordoma, malignant giant cell tumor chordoma, chondrosarcoma osteochondroma, benign chondroma, chondroblastoma chondromyxofibroma, myelodysplastic syndrome (MDS)), muscle cancer (*e.g.*, rhabdomyosarcoma, rhabdomyoma), connective tissue cancer and synovioma.

Nervous system cancers are also treatable according to the methods described herein. Non-limiting examples of nervous system cancers include brain cancer (*e.g.*, astrocytoma, medulloblastoma, glioma (*e.g.*, astrocytoma, oligodendroglioma), glioblastomas, glioblastoma multiform, medulloblastoma, ependymoma, germinoma (*i.e.*, pinealoma), oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, craniopharyngioma), spinal cord cancer, neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis), neuroblastoma, primitive neuroectodermal tumors (PNT), meningeal cancer (*e.g.*, meningioma, meningiosarcoma, gliomatosis), skull cancer, acoustic neuroma, ependymoma, hemangioblastoma, ocular cancer (*e.g.*, intraocular melanoma, retinoblastoma), pleomorphic xenoanthrocytoma (PXA) and pediatric PXA.

Endocrine/exocrine cancers are also treatable according to the methods described herein. Non-limiting examples of endocrine/exocrine cancers include thyroid cancer (*e.g.*, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma), pancreatic cancer (*e.g.*, pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), islet cell tumors, ductal adenocarcinoma, insulinoma, glucagonoma, vipoma), adrenal gland cancer, neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor), sebaceous gland carcinoma and sweat gland cancer (*e.g.*, sweat gland carcinoma).

Head and neck cancers, such as squamous cell carcinoma of the head and neck (SCCHN) and adenoid cystic carcinoma, are also treatable according to the methods described herein.

Oral cancers, such as buccal cavity cancer, lip cancer, tongue cancer, mouth cancer, pharynx cancer, hypopharynx cancer (*e.g.*, hypopharyngeal carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer) and salivary gland cancer, are also treatable according to the methods described herein.

Esophageal cancers, such as esophageal squamous cell carcinoma, esophageal adenocarcinoma, Barrett's adenocarcinoma and esophageal leiomyosarcoma, are also treatable according to the methods described herein.

Gastrointestinal cancers are also treatable according to the methods described herein. Non-limiting examples of gastrointestinal cancers include anal cancer, colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma), gall bladder cancer, gastric cancer (*e.g.*, stomach cancer (*e.g.*, stomach adenocarcinoma)), gastrointestinal stromal tumor (GIST), small bowel cancer (*e.g.*, appendix cancer, small bowel carcinoma, *e.g.*, small bowel adenocarcinoma), small intestine cancer, large bowel cancer and large intestine cancer.

Cardiovascular cancers are also treatable according to the methods described herein. Non-limiting examples of cardiovascular cancers include primary cardiac tumors, angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma), endotheliosarcoma (*e.g.*, Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), cardiac myxoma and cardiac rhabdomyoma.

Lung cancers are also treatable according to the methods described herein. Non-limiting examples of lung cancers include bronchus cancer (*e.g.*, bronchogenic carcinoma, bronchial adenoma), alveolar carcinoma, mesothelioma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), lung adenocarcinoma, chondromatous hamartoma and papillary adenocarcinoma.

Genitourinary cancers are also treatable according to the methods described herein. Non-limiting examples of genitourinary cancers include bladder cancer (*e.g.*, urothelial carcinoma), urethral cancer, kidney cancer (*e.g.*, nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma), testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma), germ cell cancer, prostate cancer (*e.g.*, prostate adenocarcinoma) and penile cancer (*e.g.*, Paget's disease of the penis and scrotum).

Gynecological cancers are also treatable according to the methods described herein. Non-limiting examples of gynecological cancers include breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast, triple negative breast cancer, HER-2 positive breast cancer, HER2-negative breast cancer), endometrial cancer (*e.g.*, uterine cancer (*e.g.*, uterine sarcoma, choriocarcinoma), endometrial carcinoma), cervical cancer (*e.g.*, cervical adenocarcinoma), ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal

carcinoma, ovarian adenocarcinoma), germ cell cancer and vulvar cancer (*e.g.*, Paget's disease of the vulva), vaginal cancer and fallopian tube cancer.

Skin cancers are also treatable according to the methods described herein. Non-limiting examples of skin cancers include squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC) and dermatofibroma.

Soft tissue cancers, such as intraepithelial neoplasms, epithelial carcinomas, epithelial sarcomas, adenocarcinomas, adenomas, fibrosarcomas, fibromas, liposarcomas, lipomas, myxomas and teratomas, are also treatable according to the methods described herein.

Myeloproliferative neoplasms are also treatable according to the methods described herein. Non-limiting examples of myeloproliferative neoplasms include myelofibrosis, polycythemia vera and essential thrombocythemia.

Fibrotic cancers are also treatable according to the methods described herein. As used herein, a "fibrotic cancer" is a cancer associated with fibrosis. Fibrosis may precede (*e.g.*, be causative of) or follow (*e.g.*, be caused by) the cancer or treatment of the cancer in fibrotic cancers. Fibrosis may also or alternatively be present with the cancer in fibrotic cancers. Non-limiting examples of fibrotic cancers include myelofibrosis, pancreatic cancer (*e.g.*, pancreatic ductal adenocarcinoma), kidney cancer, liver cancer, lung cancer (*e.g.*, large cell lung cancer, such as squamous cell carcinoma), breast cancer (*e.g.*, inflammatory breast cancer), ovarian cancer (*e.g.*, high grade serious ovarian carcinoma), endometrial cancer, uterine cancer, uterine sarcoma (*e.g.*, uterine leiomyosarcoma), renal cell cancer, sarcoma (*e.g.*, soft tissue sarcoma), malignant fibrous histiocytoma, fibrosarcoma (*e.g.*, dermatofibrosarcoma protuberans), gastric cancer, esophageal cancer, head and neck cancer, cervical cancer, vulvar cancer and hepatocellular cancer (*e.g.*, hepatocellular carcinoma). In some embodiments, the fibrotic cancer is a solid tumor cancer (*e.g.*, kidney, liver, lung, breast, ovarian, endometrial, uterine, and/or pancreatic cancer). In some embodiments, the fibrotic cancer is carcinoma of an internal organ (*e.g.*, pancreas, lung, kidney, liver).

Further examples of cancers treatable according to the methods described herein include, but are not limited to, Acute Lymphoblastic Leukemia (ALL); Acute Myeloid Leukemia (AML); Adrenocortical Carcinoma; Adrenocortical Carcinoma, Childhood; AIDS-Related Cancer (*e.g.*, Kaposi Sarcoma, AIDS-Related Lymphoma, Primary CNS Lymphoma); Cancer of the anal region; Anal Cancer; Appendix Cancer; Astrocytomas,

Childhood; Atypical Teratoid/Rhabdoid Tumor, Childhood, Central Nervous System (CNS); Neoplasms of the CNS (*e.g.*, primary CNS lymphoma, spinal axis tumors, medulloblastoma, brain stem gliomas or pituitary adenomas), Barrett's esophagus (*e.g.*, pre-malignant syndrome), and mycoses fungoides, Basal Cell Carcinoma of the Skin; Bile Duct Cancer; Bladder Cancer; Bladder Cancer, Childhood; Bone Cancer (including Ewing Sarcoma, Osteosarcoma and Malignant Fibrous Histiocytoma); Brain Tumors/Cancer; Breast Cancer; Burkitt Lymphoma; Carcinoid Tumor (Gastrointestinal); Carcinoid Tumor, Childhood; Cardiac (Heart) Tumors, Childhood; Embryonal Tumors, Childhood; Germ Cell Tumor, Childhood; Primary CNS Lymphoma; Cervical Cancer; Childhood Cervical Cancer; Cholangiocarcinoma; Chordoma, Childhood; Chronic Lymphocytic Leukemia (CLL); Chronic Myelogenous Leukemia (CML); Chronic Myeloproliferative Neoplasms; Colorectal Cancer; Childhood Colorectal Cancer; Craniopharyngioma, Childhood; Cutaneous T-Cell Lymphoma (*e.g.*, Mycosis Fungoides and Sézary Syndrome); Ductal Carcinoma In Situ (DCIS); Embryonal Tumors, Central Nervous System, Childhood; Cancer of the Endocrine system (*e.g.*, cancer of the thyroid, pancreas, parathyroid or adrenal glands), Endometrial Cancer (Uterine Cancer); Ependymoma, Childhood; Esophageal Cancer; Childhood Esophageal Cancer; Esthesioneuroblastoma; Ewing Sarcoma; Extracranial Germ Cell Tumor, Childhood; Extragonadal Germ Cell Tumor; Eye Cancer; Childhood Intraocular Melanoma; Intraocular Melanoma; Retinoblastoma; Fallopian Tube Cancer; Fibrous Histiocytoma of Bone, Malignant, and Osteosarcoma; Gallbladder Cancer; Gastric (Stomach) Cancer; Childhood Gastric (Stomach) Cancer; Gastrointestinal Carcinoid Tumor; Gastrointestinal Stromal Tumors (GIST); Childhood Gastrointestinal Stromal Tumors; Germ Cell Tumors; Childhood Central Nervous System Germ Cell Tumors (*e.g.*, Childhood Extracranial Germ Cell Tumors, Extragonadal Germ Cell Tumors, Ovarian Germ Cell Tumors, Testicular Cancer); Gestational Trophoblastic Disease; Gynecologic Tumors ((*e.g.*, uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hairy Cell Leukemia; Head and Neck Cancer; Heart Tumors, Childhood; Hepatocellular (Liver) Cancer; Histiocytosis, Langerhans Cell; Hodgkin Lymphoma; Hypopharyngeal Cancer; Cutaneous or Intraocular Melanoma; Childhood Intraocular Melanoma; Islet Cell Tumors, Pancreatic Neuroendocrine Tumors; Kaposi Sarcoma; Kidney (Renal Cell) Cancer; Langerhans Cell Histiocytosis; Laryngeal Cancer; Leukemia; Lip and Oral

Cavity Cancer; Liver Cancer; Lung Cancer (Non-Small Cell and Small Cell); Childhood Lung Cancer; Lymphoma; Male Breast Cancer; Malignant Fibrous Histiocytoma of Bone and Osteosarcoma; Melanoma; Childhood Melanoma; Melanoma, Intraocular (Eye); Childhood Intraocular Melanoma; Merkel Cell Carcinoma; Mesothelioma, Malignant; Childhood Mesothelioma; Metastatic Cancer; Metastatic Squamous Neck Cancer with Occult Primary; Midline Tract Carcinoma With NUT Gene Changes; Mouth Cancer; Multiple Endocrine Neoplasia Syndromes; Multiple Myeloma/Plasma Cell Neoplasms; Mycosis Fungoides; Myelodysplastic Syndromes, Myelodysplastic/Myeloproliferative Neoplasms; Myelogenous Leukemia, Chronic (CML); Myeloid Leukemia, Acute (AML); Myeloproliferative Neoplasms, Chronic; Nasal Cavity and Paranasal Sinus Cancer; Nasopharyngeal Cancer; Neuroblastoma; Non-Hodgkin Lymphoma; Non-Small Cell Lung Cancer; Oral Cancer, Lip and Oral Cavity Cancer and Oropharyngeal Cancer; Osteosarcoma and Malignant Fibrous Histiocytoma of Bone; Ovarian Cancer; Childhood Ovarian Cancer; Pancreatic Cancer; Childhood Pancreatic Cancer; Pancreatic Neuroendocrine Tumors; Papillomatosis (Childhood Laryngeal); Paraganglioma; Childhood Paraganglioma; Paranasal Sinus and Nasal Cavity Cancer; Parathyroid Cancer; Penile Cancer; Pharyngeal Cancer; Pheochromocytoma; Childhood Pheochromocytoma; Pituitary Tumor; Plasma Cell Neoplasm/Multiple Myeloma; Pleuropulmonary Blastoma; Pregnancy and Breast Cancer; Primary Central Nervous System (CNS) Lymphoma; Primary Peritoneal Cancer; Prostate Cancer; Rectal Cancer; Recurrent Cancer; Renal Cell (Kidney) Cancer; Retinoblastoma; Rhabdomyosarcoma, Childhood; Salivary Gland Cancer; Sarcoma (*e.g.*, Childhood Rhabdomyosarcoma, Childhood Vascular Tumors, Ewing Sarcoma, Kaposi Sarcoma, Osteosarcoma (Bone Cancer), Soft Tissue Sarcoma, Uterine Sarcoma); Sézary Syndrome; Skin Cancer; Childhood Skin Cancer; Small Cell Lung Cancer; Small Intestine Cancer; Soft Tissue Sarcoma; Squamous Cell Carcinoma of the Skin; Squamous Neck Cancer with Occult Primary, Metastatic; Stomach (Gastric) Cancer; Childhood Stomach (Gastric) Cancer; T-Cell Lymphoma, Cutaneous (*e.g.*, Mycosis Fungoides and Sèzary Syndrome); Testicular Cancer; Childhood Testicular Cancer; Throat Cancer (*e.g.*, Nasopharyngeal Cancer, Oropharyngeal Cancer, Hypopharyngeal Cancer); Thymoma and Thymic Carcinoma; Thyroid Cancer; Transitional Cell Cancer of the Renal Pelvis and Ureter; Ureter and Renal Pelvis (e.g., renal cell carcinoma, carcinoma of the renal pelvis), benign prostatic hypertrophy, parathyroid cancer, Transitional Cell Cancer; Urethral Cancer; Uterine Cancer,

Endometrial; Uterine Sarcoma; Vaginal Cancer; Childhood Vaginal Cancer; Vascular Tumors; Vulvar Cancer; and Wilms Tumor and Other Childhood Kidney Tumors.

Metastases of the aforementioned cancers can also be treated in accordance with the methods described herein. Accordingly, in some embodiments, the cancer is a metastatic cancer. In other embodiments, the cancer is a pre-metastatic cancer.

In certain embodiments, the cancer is a rare cancer. The term "rare cancer" refers to cancers that occur in a relatively small number of patients.

In some embodiments, a proliferative disease, such as cancer (*e.g.*, a fibrotic cancer), is treated by targeting a tumor stromal cell (*e.g.*, in a tumor microenvironment), such as a cancer-associated fibroblast (CAF), stellate cell or myofibroblast, and/or an immune cell, such as a tumor-associated immune cell (*e.g.*, in the tumor-immune microenvironment), for example, to thereby modulate the tumor-stroma microenvironment and/or the tumor-immune microenvironment.

Also provided herein are methods for targeting a tumor stromal cell or immune cell (*e.g.*, tumor-associated immune cell), and/or (*e.g.*, and thereby) modulating (*e.g.*, normalizing) tumor microenvironment (*e.g.*, tumor-stroma microenvironment and/or tumor-immune microenvironment) *in vivo* or *in vitro*, the methods comprising contacting a tumor stromal cell or an immune cell (*e.g.*, a tumor-associated immune cell) with a compound of the present disclosure. In certain embodiments, the inhibition occurs *in vivo* in a subject. In certain embodiments, the inhibition occurs *in vitro* (*e.g.*, in a cell line, tissue or biological sample). In certain embodiments, the tumor stromal cell is a cancer-associated fibroblast (CAF), a stellate cell or a myofibroblast.

Without wishing to be bound by any particular theory, it is believed that certain compounds can normalize the tumor microenvironment and thereby improve blood vessel perfusion and drug delivery. Enhanced drug delivery is expected, in turn, to enhance the efficacy of a drug, such as an immunomodulator (*e.g.*, immunooncology agent), including any immunomodulator described herein. Accordingly, also provided herein are methods for modulating (*e.g.*, normalizing) tumor microenvironment (*e.g.*, tumor-stroma microenvironment and/or tumor-immune microenvironment) *in vivo* or *in vitro*, the methods comprising contacting a tumor with a compound of the present disclosure.

Also provided herein are methods of inhibiting viral infection and/or viral replication in a subject in need thereof, comprising administering to the subject an

effective amount (*e.g.*, a therapeutically effective amount, prophylactically effective amount) of a compound of the present disclosure.

The compounds of the present disclosure can be administered as a monotherapy, or can be administered as part of a combination therapy, as described herein, with other therapeutic agents and/or treatment modalities. Accordingly, in some embodiments, the methods described herein further comprise administering to the subject one or more additional therapies (*e.g.*, one or more additional therapeutic agents). The compound of the present disclosure and the additional therapy(ies) can be co-administered, *e.g.*, in a simultaneous or substantially simultaneous manner. The compound of the present disclosure and the additional therapy(ies) can also or alternatively be administered sequentially, either at approximately the same time or at different times. For example, the compound of the present disclosure can be administered before the additional therapy(ies). Or, the compound of the present disclosure can be administered after the additional therapy(ies). Suitable additional therapies for use in the methods disclosed herein include those discussed herein in the context of combinations.

Therapeutic agents (*e.g.*, compounds of the present disclosure) and pharmaceutical compositions thereof can be administered via a variety of routes of administration, including, for example, oral, dietary, topical, transdermal, rectal, parenteral (*e.g.*, intra-arterial, intravenous, intramuscular, subcutaneous injection, intradermal injection), intravenous infusion and inhalation (*e.g.*, intrabronchial, intranasal or oral inhalation, intranasal drops) routes of administration, depending on the compound and the particular disease to be treated. Administration can be local or systemic as indicated. The preferred mode of administration can vary depending on the particular compound chosen. In some embodiments, a therapeutic agent (*e.g.*, a compound of the present disclosure) is administered orally. In some embodiments, a therapeutic agent (*e.g.*, compound of the present disclosure) is administered intravenously.

Combination Therapies

The term "combination therapy" refers to the administration of two or more therapeutic agents to treat a disease, disorder or condition described herein. Such administration encompasses co-administration of the therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients. Alternatively, such administration encompasses co-administration in multiple, or in

separate containers (*e.g.*, capsules, powders, and liquids) for each active ingredient. Such administration also encompasses use of each type of therapeutic agent in a sequential manner, either at approximately the same time or at different times. The therapeutic agents in a combination therapy can be administered via the same administration route or via different administration routes. Powders and/or liquids may be reconstituted or diluted to a desired dose prior to administration. Typically, the treatment regimen will provide beneficial effects of the drug combination in treating the diseases, conditions or disorders described herein.

A therapy for use in combination with a compound of the present disclosure can comprise an agent known to modulate other pathway(s) than is(are) modulated by the compound of the present disclosure, other component(s) (*e.g.*, enzymes) of the same pathway(s) as is(are) modulated by the compound of the present disclosure or even one or more of the same targets (*e.g.*, target enzyme(s)) as is(are) modulated by the compound of the present disclosure. In one aspect, a combination therapy comprises a compound of the present disclosure and a chemotherapeutic agent, immunomodulator and/or radiation therapy, for example, to provide a synergistic or additive therapeutic effect.

Examples of therapies for use in combination with a compound of the present disclosure (*e.g.*, in combination therapy, in a pharmaceutical combination) include standard of care therapies and/or regimens (*e.g.*, standard of care agents), such as first-line standard of care therapies (*e.g.*, chemotherapies), intermediate-line standard of care therapies (*e.g.*, chemotherapies) or last-line standard of care therapies (*e.g.*, chemotherapies). Standard of care therapies are therapies that a clinician should use for a certain type of patient, illness and/or clinical circumstance. Often, organizations such as National Comprehensive Cancer Network (NCCN) publish guidelines and/or treatment algorithms setting forth best practices for treatment of certain patients, illnesses and/or clinical circumstances. *See* nccn.org. These guidelines often establish, set forth and/or summarize standard of care therapies.

In some embodiments, the method of treating or preventing cancer may comprise administering a compound of Formula (I), (I-i), (I-i-a), (I-i-a1), (I-i-a2), (a-I), (II), or (III), or any of the embodiments thereof disclosed herein with one or more other chemotherapeutic agent(s).

In some embodiments, one or more immunomodulators can be used in combination with compounds of the present disclosure. Non-limiting examples of

immunomodulators (*e.g.*, immunooncology agents) include afutuzumab (available from ROCHE®); pegfilgrastim (NEULASTA®); lenalidomide (CC-5013, REVLIMID®); thalidomide (THALOMID®); actimid (CC4047); and IRX-2 (mixture of human cytokines including interleukin 1, interleukin 2, and interferon γ, CAS 951209-71-5, available from IRX Therapeutics).

In certain embodiments, the immunomodulators are chimeric antigen receptor T-cell (CAR-T) therapies, such as tisagenlecleucel (Novartis), axicabtagene ciloleucel (Kite), and tocilizumab (atlizumab; Roche).

In certain embodiments, the immunomodulators are immune checkpoint inhibitors, such as PD-1 inhibitors, PD-L1 inhibitors, cytotoxic T-lymphocyte-associated modulators (*e.g.*, CTLA-4 inhibitors), LAG-3 inhibitors, TIM-3 inhibitors.

In certain embodiments, the immunomodulators are PD-1 inhibitors, such as pembrolizumab (also known as Lambrolizumab, MK-3475, MK03475, SCH-900475, or KEYTRUDA®) and other anti-PD-1 antibodies (as disclosed in Hamid, O. et al.(2013) New England Journal of Medicine 369 (2): 134–44, US 8,354,509, and WO 2009/114335, incorporated by reference in their entirety), nivolumab (also known as MDX-1106, MDX-1106-04, ONO-4538, BMS-936558, or OPDIVO®) and other anti-PD-1 antibodies (as disclosed in US 8,008,449 and WO 2006/121168, incorporated by reference in their entirety), cemiplimab (LIBTAYO®), sintilimab, spartalizumab (PDR001), pidilizumab (CureTech), MEDI0680 (Medimmune), dostarlimab (TSR-042), PF-06801591 (Pfizer), sintilimab, toripalimab, tislelizumab (BGB-A317), camrelizumab (INCSHR1210, SHR-1210), AMP-224 (Amplimmune), CBT-501 (CBT Pharmaceuticals), CBT-502 (CBT Pharmaceuticals), JS001 (Junshi Biosciences), IBI308 (Innovent Biologics), INCSHR1210 (Incyte), also known as SHR-1210 (Hengrui Medicine), BGBA317 (Beigene), BGB-108 (Beigene), BAT-I306 (Bio-Thera Solutions), GLS-010 (Gloria Pharmaceuticals; WuXi Biologics), AK103, AK104, AK105 (Akesio Biopharma; Hangzhou Hansi Biologics; Hanzhong Biologics), LZM009 (Livzon), HLX-10 (Henlius Biotech), MEDI0680 (Medimmune), PDF001 (Novartis), PF-06801591 (Pfizer), pidilizumab (CureTech) also known as CT-011 and other anti-PD-1 antibodies (as disclosed in Rosenblatt, J. et al. (2011) J Immunotherapy 34(5): 409-18, US 7,695,715, US 7,332,582, and US 8,686,119, incorporated by reference in their entirety), REGN2810 (Regeneron) and TSR-042 (Tesaro), also known as ANB011, or CS1003 (CStone Pharmaceuticals). MEDI0680 (Medimmune), is also known as AMP-514.

MEDI0680 and other anti-PD-1 antibodies are disclosed in US 9,205,148 and WO 2012/145493, incorporated by reference in their entireties. Further known anti-PD-1 antibody molecules include those described, *e.g.*, in WO 2015/112800, WO 2016/092419, WO 2015/085847, WO 2014/179664, WO 2014/194302, WO 2014/209804, WO 2015/200119, US 8,735,553, US 7,488,802, US 8,927,697, US 8,993,731, and US 9,102,727, incorporated by reference in their entireties. In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody molecule, as described in US 2015/0210769, published on July 30, 2015, entitled "Antibody Molecules to PD-1 and Uses Thereof," incorporated by reference in its entirety. In one embodiment, the anti-PD-1 antibody molecule comprises the CDRs, variable regions, heavy chains and/or light chains of BAP049-Clone-E or BAP049-Clone-B disclosed in US 2015/0210769. The antibody molecules described herein can be made by vectors, host cells, and methods described in US 2015/0210769, incorporated by reference in its entirety. In one embodiment, the PD-1 inhibitor is a peptide that inhibits the PD-1 signaling pathway, *e.g.*, as described in US 8,907,053, incorporated by reference in its entirety. In one embodiment, the PD-1 inhibitor is an immunoadhesin (*e.g.*, an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region (*e.g.*, an Fc region of an immunoglobulin sequence)). In one embodiment, the PD-1 inhibitor is AMP-224 (B7-DCIg (Amplimmune), *e.g.*, disclosed in WO 2010/027827 and WO 2011/066342, incorporated by reference in their entireties).

In certain embodiments, the immunomodulators are PD-L1 inhibitors, such as atezolizumab (also known as MPDL3280A, RG7446, RO5541267, YW243.55.S70, or TECENTRIQ®) and other anti-PD-L1 antibodies as disclosed in US 8,217,149, incorporated by reference in its entirety, avelumab (BAVENCIO® also known as MSB0010718C) and other anti-PD-L1 antibodies as disclosed in WO 2013/079174, incorporated by reference in its entirety, durvalumab (IMFINZI® or MEDI4736) and other anti-PD-L1 antibodies as disclosed in US 8,779,108, incorporated by reference in its entirety), FAZ053 (Novartis), and BMS-936559 (Bristol-Myers Squibb). In certain embodiments, the PD-L1 inhibitor is KN035 (Alphamab; 3DMed; Ascletis Pharma), Envafolimab (TRACON Pharmaceuticals), BMS 936559 (Bristol-Myers Squibb), CS1001 (CStone Pharmaceuticals, Ligand Pharmaceuticals), CX-072 (CytomX Therapeutics), FAZ053 (Novartis), SHR-1316 (Hengrui Medicine), TQB2450 (Chiatai Tianqing), STI-A1014 (Zhaoke Pharm; Lee's Pharm, Lonza, Sorrento Therapeutics,

NantWorks), LYN00102 (Lynkcell), A167 (Harbour BioMed, Kelun Group), BGB-A333 (Beigene), MSB2311 (Mabspace Biosciences), or HLX-20 (Henlius Biotech). In one embodiment, the anti-PD-L1 antibody molecule is BMS-936559 (Bristol-Myers Squibb), also known as MDX-1105 or 12A4. BMS-936559 and other anti-PD-L1 antibodies are disclosed in US 7,943,743 and WO 2015/081158, incorporated by reference in their entireties. In certain embodiments, the PD-L1 inhibitor is cosibelimab (Fortress Biotech), LY3300054 or iodapolimab (Eli Lilly), GS-4224 (Gilead Sciences), STI-A1015 (Yuhan, Sorrento Therapeutics), BCD-135 (BIOCAD), cosibelimab (Dana-Farber Cancer Institute, TG Therapeutics), APL-502 (Apollomics), AK106 (Akeso Biopharma), MSB2311 (Transcenta Holding), TG-1501 (TG Therapeutics) or FAZ053 (Novartis). In certain embodiments, the PD-L1 inhibitor is MT-6035 (Molecular Templates), icaritin or ZKAB001 (Lonza, Lee's Pharmaceutical Holdings, Sorrento Therapeutics, Shenogen Pharma Group), TRIDENT Antibody (MacroGenics, Zai Lab), YBL-007 (Anh-Gook Pharmaceutical, Y-Biologics), HTI-1316 (Hengrui Therapeutics), PD-L1 Oncology Project (Weizmann Institute of Sciences), JS003 (Shanghai Junshi Biosciences), ND021 (Numab Therapeutics, CStone Pharmaceuticals), Toca 521 (Tocagen) or STT01 (STCube). In certain embodiments, the PD-L1 inhibitor is DB004 (DotBio), MT-5050 (Molecular Templates), KD036 (Kadmon). In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule. In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule as disclosed in US 2016/0108123, published on April 21, 2016, entitled "Antibody Molecules to PD-L1 and Uses Thereof," incorporated by reference in its entirety. In one embodiment, the anti-PD-L1 antibody molecule comprises the CDRs, variable regions, heavy chains and/or light chains of BAP058-Clone O or BAP058-Clone N disclosed in US 2016/0108123, incorporated by reference in its entirety. Further known anti-PD-L1 antibodies include those described, *e.g.*, in WO 2015/181342, WO 2014/100079, WO 2016/000619, WO 2014/022758, WO 2014/055897, WO 2015/061668, WO 2013/079174, WO 2012/145493, WO 2015/112805, WO 2015/109124, WO 2015/195163, US 8,168,179, US 8,552,154, US 8,460,927, and US 9,175,082, incorporated by reference in their entireties.

In certain embodiments, the immunomodulators are CTLA-4 inhibitors, such as ipilimumab (YERVOY®), tremelimumab, ALPN-202 (Alpine Immune Sciences), RP2 (Replimune), BMS-986249 (Bristol-Myers Squibb), BMS-986218 (Bristol-Myers Squibb), zalifrelimab (Agenus, Ludwig Institute for Cancer Research, UroGen Pharma,

Recepta Biopharma), BCD-217 (BIOCAD), Onc-392 (Pfizer, OncoImmune), IBI310 (Innovent Biologics), KN046 (Alphamab), MK-1308 (Merck & Co), REGN4659 (Regeneron Pharmaceuticals), XmAb20717 (Xencor), XmAb22841 (Xencor), Anti-CTLA-4 NF (Bristol-Myers Squibb), MEDI5752 (AstraZeneca), AGEN1181 (Agenus), MGD019 (MacroGenics), ATOR-1015 (Alligator Bioscience), BCD-145 (BIOCAD), PSB205 (Sound Biologics), CS1002 (CStone Pharmaceuticals), ADU-1604 (Aduro Biotech), PF-06753512 (Pfizer), BioInvent-Transgene Research Program (Transgene), AGEN2041 (Agenus, Recepta Biopharam), ATOR-1144 (Alligator Bioscience), CTLA-4 Research Project (Sorrento Therapeutics), PD-L1/CTLA-4 Research Project (Sorrento Therapeutics), HLX13 (Shanghai Henlius Biotech), ISA203 (ISA Pharmaceuticals), PRS-300 Series A (Pieris Pharmaceuticals), BA3071 (BioAtla), CTLA4 Cancer Research Program (Biosortia Pharmaceuticals), RP3 (Replimune), CG0161 (Cold Genesys), APL-509 (Apollomics, JSR), AGEN2041 (Ludwig Institute for Cancer Research), APC 101 (Advanced Proteome), CTLA-4 Inhibitor (Advanced Proteome), BA3071 (BeiGene), BPI-002 (BeyondSpring Pharmaceuticals), CTLA-4 Antibody (Tikcro Technologies), Immuno-Oncology Research Program II (OliPass), PBP1701 (Prestige BioPharma), DB002 (DotBio), DB003 (DotBio), OR-2299 (OncoResponse) and NK044 (Alphamab).

In some embodiments, the immunodulators are LAG-3 inhibitors, such as LAG525 (Novartis), BMS-986016 (Bristol-Myers Squibb), and TSR-033 (Tesaro). In one embodiment, the LAG-3 inhibitor is an anti-LAG-3 antibody molecule. In one embodiment, the LAG-3 inhibitor is an anti-LAG-3 antibody molecule as disclosed in US 2015/0259420, published on September 17, 2015, entitled "Antibody Molecules to LAG-3 and Uses Thereof," incorporated by reference in its entirety. In one embodiment, the anti-LAG-3 antibody molecule comprises the CDRs, variable regions, heavy chains and/or light chains of BAP050-Clone I or BAP050-Clone J disclosed in US 2015/0259420. In one embodiment, the anti-LAG-3 antibody molecule is BMS-986016 (Bristol-Myers Squibb), also known as BMS986016. BMS-986016 and other anti-LAG-3 antibodies are disclosed in WO 2015/116539 and US 9,505,839, incorporated by reference in their entireties. In one embodiment, the anti-LAG-3 antibody molecule is TSR-033 (Tesaro). In one embodiment, the anti-LAG-3 antibody molecule is IMP731 or GSK2831781 (GSK and Prima BioMed). IMP731 and other anti-LAG-3 antibodies are disclosed in WO 2008/132601 and US 9,244,059, incorporated by reference in their entireties. In one embodiment, the anti-LAG-3 antibody molecule is IMP761 (Prima

BioMed). Further known anti-LAG-3 antibodies include those described, *e.g.*, in WO 2008/132601, WO 2010/019570, WO 2014/140180, WO 2015/116539, WO 2015/200119, WO 2016/028672, US 9,244,059, US 9,505,839, incorporated by reference in their entireties. In one embodiment, the anti-LAG-3 inhibitor is a soluble LAG-3 protein, *e.g.*, IMP321 (Prima BioMed), *e.g.*, as disclosed in WO 2009/044273, incorporated by reference in its entirety.

In some embodiments, the immunodulators are TIM-3 inhibitors, such as MGB453 (Novartis) and TSR-022 (Tesaro). In one embodiment, the TIM-3 inhibitor is an anti-TIM-3 antibody molecule. In one embodiment, the TIM-3 inhibitor is an anti-TIM-3 antibody molecule as disclosed in US 2015/0218274, published on August 6, 2015, entitled "Antibody Molecules to TIM-3 and Uses Thereof," incorporated by reference in its entirety. In one embodiment, the anti-TIM-3 antibody molecule comprises the CDRs, variable regions, heavy chains and/or light chains of ABTIM3-hum11 or ABTIM3-hum03 disclosed in US 2015/0218274, incorporated by reference in its entirety. In one embodiment, the anti-TIM-3 antibody molecule is TSR-022 (AnaptysBio/Tesaro). In one embodiment, the anti-TIM-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of APE5137 or APE5121. APE5137, APE5121, and other anti-TIM-3 antibodies are disclosed in WO 2016/161270, incorporated by reference in its entirety. In one embodiment, the anti-TIM-3 antibody molecule is the antibody clone F38-2E2. Further known anti-TIM-3 antibodies include those described, *e.g.*, in WO 2016/111947, WO 2016/071448, WO 2016/144803, US 8,552,156, US 8,841,418, and US 9,163,087, incorporated by reference in their entireties.

In some embodiments, a platinum analogue can be used in combination with compounds of the present disclosure. In certain embodiments, a platinum analogue (*e.g.*, cisplatin, paclitaxel, carboplatin) and combination therapy comprising a platinum analogue (*e.g.*, docetaxel and carboplatin; paclitaxel and carboplatin; carboplatin and liposomal doxorubicin (dox) can be used in combination with compounds of the present disclosure.

In some embodiments, exemplified chemotherapeutic agents that may be conjointly administered with compounds of the disclosure include: 1-amino-4-phenylamino-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate (acid blue 25), 1-amino-4-[4-hydroxyphenyl-amino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-

aminophenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[1-naphthylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-fluoro-2-carboxyphenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[2-anthracenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, ABT-263, ado-trastuzumab emtansine, afatinib dimaleate, axitinib, aminoglutethimide, amsacrine, anastrozole, APCP, asparaginase, AZD5363, Bacillus Calmette–Guérin vaccine (bcg), bicalutamide, bleomycin, bortezomib, β-methylene-ADP (AOPCP), buserelin, busulfan, cabazitaxel, cabozantinib, campothecin, capecitabine, carboplatin, carfilzomib, carmustine, ceritinib, chlorambucil, chloroquine, cisplatin, cladribine, clodronate, cobimetinib, colchicine, crizotinib, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, demethoxyviridin, dexamethasone, dichloroacetate, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, fam-trastuzumab deruxtecan, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gefitinib, gemcitabine, genistein, goserelin, GSK1120212, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ixabepilone, lenalidomide, letrozole, leucovorin, leuprolide, levamisole, lomustine, lonidamine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, metformin, methotrexate, miltefosine, mitomycin, mitotane, mitoxantrone, MK-2206, mutamycin, N-(4-sulfamoylphenylcarbamothioyl) pivalamide, NF279, NF449, nilutamide, nocodazole, octreotide, olaparib, oxaliplatin, paclitaxel, pamidronate, pazopanib, pemexetred, pentostatin, perifosine, PF-04691502, plicamycin, pomalidomide, porfimer, PPADS, procarbazine, quercetin, raltitrexed, ramucirumab, reactive blue 2, rituximab, rolofylline, romidepsin, rucaparib, selumetinib, sirolimus, sodium 2,4-dinitrobenzenesulfonate, sorafenib, streptozocin, sunitinib, suramin, talazoparib, tamoxifen, temozolomide, temsirolimus, teniposide, testosterone, thalidomide, thioguanine, thiotepa, titanocene dichloride, tonapofylline, topotecan, trametinib, trastuzumab, tretinoin, veliparib, vinblastine, vincristine, vindesine, vinorelbine, and vorinostat (SAHA). In other embodiments, chemotherapeutic agents that may be conjointly administered with compounds of the disclosure include: ABT-263, dexamethasone, 5-fluorouracil, PF-04691502, romidepsin, and vorinostat (SAHA). In other embodiments, chemotherapeutic agents that may be conjointly administered with compounds of the disclosure include: 1-amino-4-phenylamino-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate (acid blue 25), 1-

amino-4-[4-hydroxyphenyl-amino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-aminophenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[1-naphthylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-fluoro-2-carboxyphenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[2-anthracenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, APCP, β-methylene-ADP (AOPCP), capecitabine, cladribine, cytarabine, fludarabine, doxorubicin, gemcitabine, N-(4-sulfamoylphenylcarbamothioyl) pivalamide, NF279, NF449, PPADS, quercetin, reactive blue 2, rolofylline sodium 2,4-dinitrobenzenesulfonate, sumarin, and tonapofylline.

Many combination therapies have been developed for the treatment of cancer. In certain embodiments, compounds of the disclosure (e.g., compounds of Formula (I)) or (II) or (III) may be conjointly administered with one or more combination therapies. Examples of combination therapies with which compounds of the disclosure may be conjointly administered are included in

Table 1: Exemplary combinatorial therapies for the treatment of cancer

Name	**Therapeutic agents**
ABV	Doxorubicin, Bleomycin, Vinblastine
ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
AC (Breast)	Doxorubicin, Cyclophosphamide
AC (Sarcoma)	Doxorubicin, Cisplatin
AC (Neuroblastoma)	Cyclophosphamide, Doxorubicin
ACE	Cyclophosphamide, Doxorubicin, Etoposide
ACe	Cyclophosphamide, Doxorubicin
AD	Doxorubicin, Dacarbazine
AP	Doxorubicin, Cisplatin
ARAC-DNR	Cytarabine, Daunorubicin
B-CAVe	Bleomycin, Lomustine, Doxorubicin, Vinblastine
BCVPP	Carmustine, Cyclophosphamide, Vinblastine, Procarbazine, Prednisone
BEACOPP	Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone, Filgrastim
BEP	Bleomycin, Etoposide, Cisplatin
BIP	Bleomycin, Cisplatin, Ifosfamide, Mesna

Name	Therapeutic agents
BOMP	Bleomycin, Vincristine, Cisplatin, Mitomycin
CA	Cytarabine, Asparaginase
CABO	Cisplatin, Methotrexate, Bleomycin, Vincristine
CAF	Cyclophosphamide, Doxorubicin, Fluorouracil
CAL-G	Cyclophosphamide, Daunorubicin, Vincristine, Prednisone, Asparaginase
CAMP	Cyclophosphamide, Doxorubicin, Methotrexate, Procarbazine
CAP	Cyclophosphamide, Doxorubicin, Cisplatin
CAV	Cyclophosphamide, Doxorubicin, Vincristine
CAVE ADD	CAV and Etoposide
CA-VP16	Cyclophosphamide, Doxorubicin, Etoposide
CC	Cyclophosphamide, Carboplatin
CDDP/VP-16	Cisplatin, Etoposide
CEF	Cyclophosphamide, Epirubicin, Fluorouracil
CEPP(B)	Cyclophosphamide, Etoposide, Prednisone, with or without/ Bleomycin
CEV	Cyclophosphamide, Etoposide, Vincristine
CF	Cisplatin, Fluorouracil or Carboplatin Fluorouracil
CHAP	Cyclophosphamide or Cyclophosphamide, Altretamine, Doxorubicin, Cisplatin
ChlVPP	Chlorambucil, Vinblastine, Procarbazine, Prednisone
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CHOP-BLEO	Add Bleomycin to CHOP
CISCA	Cyclophosphamide, Doxorubicin, Cisplatin
CLD-BOMP	Bleomycin, Cisplatin, Vincristine, Mitomycin
CMF	Methotrexate, Fluorouracil, Cyclophosphamide
CMFP	Cyclophosphamide, Methotrexate, Fluorouracil, Prednisone
CMFVP	Cyclophosphamide, Methotrexate, Fluorouracil, Vincristine, Prednisone

Name	Therapeutic agents
CMV	Cisplatin, Methotrexate, Vinblastine
CNF	Cyclophosphamide, Mitoxantrone, Fluorouracil
CNOP	Cyclophosphamide, Mitoxantrone, Vincristine, Prednisone
COB	Cisplatin, Vincristine, Bleomycin
CODE	Cisplatin, Vincristine, Doxorubicin, Etoposide
COMLA	Cyclophosphamide, Vincristine, Methotrexate, Leucovorin, Cytarabine
COMP	Cyclophosphamide, Vincristine, Methotrexate, Prednisone
Cooper Regimen	Cyclophosphamide, Methotrexate, Fluorouracil, Vincristine, Prednisone
COP	Cyclophosphamide, Vincristine, Prednisone
COPE	Cyclophosphamide, Vincristine, Cisplatin, Etoposide
COPP	Cyclophosphamide, Vincristine, Procarbazine, Prednisone
CP(Chronic lymphocytic leukemia)	Chlorambucil, Prednisone
CP (Ovarian Cancer)	Cyclophosphamide, Cisplatin
CVD	Cisplatin, Vinblastine, Dacarbazine
CVI	Carboplatin, Etoposide, Ifosfamide, Mesna
CVP	Cyclophosphamide, Vincristine, Prednisome
CVPP	Lomustine, Procarbazine, Prednisone
CYVADIC	Cyclophosphamide, Vincristine, Doxorubicin, Dacarbazine
DA	Daunorubicin, Cytarabine
DAT	Daunorubicin, Cytarabine, Thioguanine
DAV	Daunorubicin, Cytarabine, Etoposide
DCT	Daunorubicin, Cytarabine, Thioguanine
DHAP	Cisplatin, Cytarabine, Dexamethasone
DI	Doxorubicin, Ifosfamide
DTIC/Tamoxifen	Dacarbazine, Tamoxifen
DVP	Daunorubicin, Vincristine, Prednisone
EAP	Etoposide, Doxorubicin, Cisplatin

Name	Therapeutic agents
EC	Etoposide, Carboplatin
EFP	Etoposie, Fluorouracil, Cisplatin
ELF	Etoposide, Leucovorin, Fluorouracil
EMA 86	Mitoxantrone, Etoposide, Cytarabine
EP	Etoposide, Cisplatin
EVA	Etoposide, Vinblastine
FAC	Fluorouracil, Doxorubicin, Cyclophosphamide
FAM	Fluorouracil, Doxorubicin, Mitomycin
FAMTX	Methotrexate, Leucovorin, Doxorubicin
FAP	Fluorouracil, Doxorubicin, Cisplatin
F-CL	Fluorouracil, Leucovorin
FEC	Fluorouracil, Cyclophosphamide, Epirubicin
FED	Fluorouracil, Etoposide, Cisplatin
FL	Flutamide, Leuprolide
FZ	Flutamide, Goserelin acetate implant
HDMTX	Methotrexate, Leucovorin
Hexa-CAF	Altretamine, Cyclophosphamide, Methotrexate, Fluorouracil
IDMTX/6-MP	Methotrexate, Mercaptopurine, Leucovorin
IE	Ifosfamide, Etoposie, Mesna
IfoVP	Ifosfamide, Etoposide, Mesna
IPA	Ifosfamide, Cisplatin, Doxorubicin
M-2	Vincristine, Carmustine, Cyclophosphamide, Prednisone, Melphalan
MAC-III	Methotrexate, Leucovorin, Dactinomycin, Cyclophosphamide
MACC	Methotrexate, Doxorubicin, Cyclophosphamide, Lomustine
MACOP-B	Methotrexate, Leucovorin, Doxorubicin, Cyclophosphamide, Vincristine, Bleomycin, Prednisone
MAID	Mesna, Doxorubicin, Ifosfamide, Dacarbazine

Name	Therapeutic agents
m-BACOD	Bleomycin, Doxorubicin, Cyclophosphamide, Vincristine, Dexamethasone, Methotrexate, Leucovorin
MBC	Methotrexate, Bleomycin, Cisplatin
MC	Mitoxantrone, Cytarabine
MF	Methotrexate, Fluorouracil, Leucovorin
MICE	Ifosfamide, Carboplatin, Etoposide, Mesna
MINE	Mesna, Ifosfamide, Mitoxantrone, Etoposide
mini-BEAM	Carmustine, Etoposide, Cytarabine, Melphalan
MOBP	Bleomycin, Vincristine, Cisplatin, Mitomycin
MOP	Mechlorethamine, Vincristine, Procarbazine
MOPP	Mechlorethamine, Vincristine, Procarbazine, Prednisone
MOPP/ABV	Mechlorethamine, Vincristine, Procarbazine, Prednisone, Doxorubicin, Bleomycin, Vinblastine
MP (multiple myeloma)	Melphalan, Prednisone
MP (prostate cancer)	Mitoxantrone, Prednisone
MTX/6-MO	Methotrexate, Mercaptopurine
MTX/6-MP/VP	Methotrexate, Mercaptopurine, Vincristine, Prednisone
MTX-CDDPAdr	Methotrexate, Leucovorin, Cisplatin, Doxorubicin
MV (breast cancer)	Mitomycin, Vinblastine
MV (acute myelocytic leukemia)	Mitoxantrone, Etoposide
M-VAC Methotrexate	Vinblastine, Doxorubicin, Cisplatin
MVP Mitomycin	Vinblastine, Cisplatin
MVPP	Mechlorethamine, Vinblastine, Procarbazine, Prednisone
NFL	Mitoxantrone, Fluorouracil, Leucovorin
NOVP	Mitoxantrone, Vinblastine, Vincristine
OPA	Vincristine, Prednisone, Doxorubicin
OPPA	Add Procarbazine to OPA.
PAC	Cisplatin, Doxorubicin
PAC-I	Cisplatin, Doxorubicin, Cyclophosphamide

Name	Therapeutic agents
PA-CI	Cisplatin, Doxorubicin
PCV	Lomustine, Procarbazine, Vincristine
PFL	Cisplatin, Fluorouracil, Leucovorin
POC	Prednisone, Vincristine, Lomustine
ProMACE	Prednisone, Methotrexate, Leucovorin, Doxorubicin, Cyclophosphamide, Etoposide
ProMACE/cytaBOM	Prednisone, Doxorubicin, Cyclophosphamide, Etoposide, Cytarabine, Bleomycin, Vincristine, Methotrexate, Leucovorin, Cotrimoxazole
PRoMACE/MOPP	Prednisone, Doxorubicin, Cyclophosphamide, Etoposide, Mechlorethamine, Vincristine, Procarbazine, Methotrexate, Leucovorin
Pt/VM	Cisplatin, Teniposide
PVA	Prednisone, Vincristine, Asparaginase
PVB	Cisplatin, Vinblastine, Bleomycin
PVDA	Prednisone, Vincristine, Daunorubicin, Asparaginase
SMF	Streptozocin, Mitomycin, Fluorouracil
TAD	Mechlorethamine, Doxorubicin, Vinblastine, Vincristine, Bleomycin, Etoposide, Prednisone
TTT	Methotrexate, Cytarabine, Hydrocortisone
Topo/CTX	Cyclophosphamide, Topotecan, Mesna
VAB-6	Cyclophosphamide, Dactinomycin, Vinblastine, Cisplatin, Bleomycin
VAC	Vincristine, Dactinomycin, Cyclophosphamide
VACAdr	Vincristine, Cyclophosphamide, Doxorubicin, Dactinomycin, Vincristine
VAD	Vincristine, Doxorubicin, Dexamethasone
VATH	Vinblastine, Doxorubicin, Thiotepa, Flouxymesterone
VBAP	Vincristine, Carmustine, Doxorubicin, Prednisone
VBCMP	Vincristine, Carmustine, Melphalan, Cyclophosphamide, Prednisone

Name	Therapeutic agents
VC	Vinorelbine, Cisplatin
VCAP	Vincristine, Cyclophosphamide, Doxorubicin, Prednisone
VD	Vinorelbine, Doxorubicin
VelP	Vinblastine, Cisplatin, Ifosfamide, Mesna
VIP	Etoposide, Cisplatin, Ifosfamide, Mesna
VM	Mitomycin, Vinblastine
VMCP	Vincristine, Melphalan, Cyclophosphamide, Prednisone
VP	Etoposide, Cisplatin
V-TAD	Etoposide, Thioguanine, Daunorubicin, Cytarabine
5 + 2	Cytarabine, Daunorubicin, Mitoxantrone
7 + 3	Cytarabine with/, Daunorubicin or Idarubicin or Mitoxantrone
"8 in 1"	Methylprednisolone, Vincristine, Lomustine, Procarbazine, Hydroxyurea, Cisplatin, Cytarabine, Dacarbazine

In certain embodiments, the conjoint therapies of the disclosure comprise conjoint administration with other types of chemotherapeutic agents, such as immuno-oncology agents. Cancer cells often have specific cell surface antigens that can be recognized by the immune system. Thus, immuno-oncology agents, such as monoclonal antibodies, can selectively bind to cancer cell antigens and effect cell death. Other immuno-oncology agents can suppress tumor-mediated inhibition of the native immune response or otherwise activate the immune response and thus facilitate recognition of the tumor by the immune system. Exemplary antibody immuno-oncology agents, include, but are not limited to, abagovomab, adecatumumab, afutuzumab, alemtuzumab, anatumomab mafenatox, apolizumab, blinatumomab, BMS-936559, catumaxomab, durvalumab, epacadostat, epratuzumab, indoximod, inotuzumab ozogamicin, intelumumab, ipilimumab, isatuximab, lambrolizumab, MED14736, MPDL3280A, nivolumab, obinutuzumab, ocaratuzumab, ofatumumab, olatatumab, pembrolizumab, pidilizumab, rituximab, ticilimumab, samalizumab, and tremelimumab. In some embodiments, the antibody immuno-oncology agents are selected from anti-CD73 monoclonal antibody (mAb), anti-CD39 mAb, anti-PD-1 mAb, and anti-CTLA4 mAb. Thus, in some embodiments, the methods of the

disclosure comprise conjoint administration of one or more immuno-oncology agents, such as the agents mentioned above.

In some embodiments, the combination therapy comprises conjoint administration of a compound of the disclosure, such as a compound of Formula (I) or (II) or (III), with SH2 inhibitors, such as CGP78850, CPG85793, C90, C126, G7-18NATE, G7-B1, and NSC642056.

In some embodiments, the combination therapy comprises conjoint administration of a compound of the disclosure, such as a compound of Formula (I) or (II) or (III), with MEK inhibitors, such as trametinib, cobimetinib, binimetinib, selumetinib, PD-325901, CI-1040, and TAK-733.

In some embodiments, the combination therapy comprises conjoint administration of a compound of the disclosure, such as a compound of Formula (I) or (II) or (III), with a MET inhibitor selected from JNJ-38877605, PF-04217903, foretinib, AMG 458, tivantinib, cabozantinib, capmatinib hydrochloride, tepotinib hydrochloride, savolitinib, and crizotinib.

In some embodiments, the combination therapy comprises conjoint administration of a compound of the disclosure, such as Formula (I) or (II) or (III), with a SHP2 inhibitor selected from TNO-155, RMC-4630, JAB-3068, or RLY-1971.

In some embodiments, an ataxia-telangiectasia mutated (ATM) kinase inhibitor can be used in combination with compounds of the present disclosure. Non-limiting examples of ATM inhibitors include M-4076 and AZD-1390.

In some embodiments, the combination therapy comprises conjoint administration of a compound of the disclosure with an EGFR inhibitor selected from osimertinib, gefitinib, erlotinib, afatinib or dacomitinib.

In some embodiments, the combination therapy comprises conjoint administration of a compound of the disclosure with a RAS inhibitor selected from aliskiren, captopril, losartan, irbesartan, olmesartan, candesartan, valsartan, fimasartan, azilsartan, telmisartan, eprosartan, benazepril, enalapril, lisinopril, perindopril, quinapril, ramipril, and trandolapril.

In some embodiments, the combination therapy comprises conjoint administration of a compound of the disclosure with anti-PD-1 therapy. In certain embodiments, the combination therapy comprises conjoint administration of a compound of the disclosure

with oxaliplatin. In other embodiments, the combination therapy comprises conjoint administration of a compound of the disclosure with doxorubicin.

In certain embodiments, a compound of the disclosure may be conjointly administered with non-chemical methods of cancer treatment. In certain embodiments, a compound of the disclosure may be conjointly administered with radiation therapy. In certain embodiments, a compound of the disclosure may be conjointly administered with surgery, with thermoablation, with focused ultrasound therapy, with cryotherapy, or with any combination of these.

In certain instances, it may be advantageous to administer a compound of the present disclosure in combination with one or more additional therapeutic agent(s). For example, it may be advantageous to administer a compound of the present disclosure (*e.g.*, a compound of Formula I, or a subformula thereof, or a pharmaceutically acceptable salt of the foregoing) in combination with one or more additional therapeutic agents, *e.g.*, independently selected from an anti-cancer agent (*e.g.*, chemotherapeutic agent), anti-allergic agent, anti-emetic, pain reliever, immunomodulator and cytoprotective agent, to treat cancer.

In some embodiments, a compound of the present disclosure is administered in combination with radiation therapy. Non-limiting examples of radiation therapy include external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (*e.g.*, At211, I131, I125, Y90, Re186, Re188, Sm153, Bi212, P32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I125, I131, Yb169, Ir192 as a solid source, I125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), *e.g.*, a solution of I125 or I131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au198, Y90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive microspheres.

Compounds of the present disclosure may be effective in sensitizing abnormal cells to radiation therapy. Thus, also provided herein is a method for sensitizing abnormal cells in a subject (*e.g.*, subject in need thereof) to treatment with radiation, comprising administering to the subject an amount of a compound of the present disclosure effective to sensitize abnormal cells to treatment with radiation. The amount of a compound of the present disclosure effective to sensitize abnormal cells to treatment with radiation can be determined by a person of ordinary skill in the art, for example, according to the means for ascertaining effective amounts described herein.

In some embodiments, standard of care therapy includes radiation therapy. DNA damaging agents can also be used in combination with a compound of the present disclosure. As used herein, "DNA damaging agent" refers to any agent that directly or indirectly damages DNA in such a way that homologous recombination could repair the damage. Non-limiting examples of DNA damaging agents are DNA damaging chemicals, chemotherapeutic agents, radiochemotherapy and ionizing or ultraviolet radiation. Non-limiting examples of DNA damaging chemotherapeutic agents include alkylating agents, nitrosoureas, anti-metabolites, plant alkaloids, plant extracts and radioisotopes. Non-limiting examples of DNA damaging chemotherapeutic agents also include DNA-damaging drugs, for example, 5-fluorouracil (5-FU), capecitabine, gemcitabine, temozolomide, S-1 (Tegafur, 5-chloro-2,4-dihydroxypyridine and oxonic acid), 5-ethynyluracil, arabinosylcytosine (ara-C), 5-azacytidine (5-AC), 2' ,2' -difluoro-2' -deoxycytidine (dFdC), purine antimetabolites (*e.g.*, mercaptopurine, azathiopurine, thioguanine), gemcitabine hydrochlorine (Gemzar), pentostatin, allopurinol, 2-fluoro-arabinosyl-adenine (2F-ara-A), hydroxyurea, sulfur mustard (bischloroetyhylsulfide), mechlorethamine, melphalan, chlorambucil, cyclophosphamide, ifosfamide, thiotepa, AZQ, mitomycin C, dianhydrogalactitol, dibromoducitol, alkyl sulfonate (busulfan), nitrosoureas (BCNU, CCNU, 4-methyl CCNU or ACNU), procarbazine, decarbazine, rebeccamycin, anthracyclins such as doxorubicin (adriamycin; ADR), daunorubicin (Cerubicine), idarubicin (Idamycin) and epirubicin (Ellence), anthracyclin analogs such as mitoxantrone, actinomycin D, topoisomerase inhibitors (*e.g.*, non-intercalating topoisomerase inhibitors such as epipodophyllotoxins (etoposide or VP16, teniposide or VM-26)), PARP inhibitors, podophylotoxin, bleomycin (Blea), pepleomycin, compounds that form adducts with nucleic acid including platinum derivatives, *e.g.*, cisplatin (CDDP), trans analog of cisplatin, carboplatin, iproplatin, tetraplatin and oxaliplatin, as

well as camptothecin, topotecan, irinotecan (CPT-11), and SN-38. Radiation, *e.g.*, ultraviolet (UV), infrared (IR), or α-, β-, or γ-radiation, is also a DNA damaging agent. In some embodiments, standard of care therapy includes a DNA damaging agent, such as a DNA crosslinking agent.

Agents that induce endoplasmic reticulum (ER) stress can also be used in combination with a compound of the present disclosure. Non-limiting examples of agents that induce ER stress include agents that increase levels of reactive oxygen species (ROS) (*e.g.*, napabucasin), chaperone inhibitors, HSP90 inhibitors, HSP70 inhibitors, PDI inhibitors and proteasome inhibitors. Further non-limiting examples of agents that induce ER stress include GSK2606414, GSK2656157, STF-083010, TKI (*e.g.*, sorafenib), phosphor-eif2α phosphatase (*e.g.*, Sal003), diindolylmethane derivatives, proteasome inhibitors (*e.g.*, bortezomib), levistolide A, andrographolide, tolfenamic acid, cantharidin, carnosic acid, casticin, cryptotanshinone, curcumin, flavokawain B, fucoidan, 2-3,4-dihydroxyphenylethanol, 7-dimethoxyflavone, SMIP004 (*N*-(4-butyl-2-methyl-phenylacetamide), licochalcone A, neferine, paeonol, pardaxin, parthenolide, piperine, polyphenon E, polyphyllin D, resveratrol, dehydrocostuslactone, γ-tocotrienol, Ω-hydroxyundec-9-enoic acid, ampelopsin, ardisianone, genistein, guttiferone H, guggulsterone, marchantin M, sarsasapogenin, saxifragifolin, prodigiosin, quercetin, honokiol, brefeldin A, A-tocopheryl succinate, verrucarin A, vitamin E succinate, ultrafine and zerumbone. *See*, for example, Walczak, A., *et al. Oxidative Medicine and Cellular Longevity* Volume 2019, Article ID 5729710, the entire content of which is incorporated herein by reference.

Anti-cancer agents of particular interest for use in combination with the compounds of the present disclosure include:

Topoisomerase inhibitors, including Type I topoisomerase inhibitors, such as irinotecan, topotecan, and camptothecin, and Type 2 topoisomerase inhibitors, such as etoposide, doxorubicin, and epirubicin.

Poly(ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, rucaparib, niraparib, talazoparib, veliparib, pamiparib and iniparib.

In some embodiments, a compound of the present disclosure is administered in combination with DNA crosslinking agents, such as cisplatin, carboplatin and oxaliplatin. Agents that increase levels of reactive oxygen species (ROS), such as napabucasin. PARP inhibitors, such as olaparib, rucaparib, niraparib, veliparib and talazoparib.

Purine antimetabolites and/or inhibitors of de novo purine synthesis, such as pemetrexed (Alimta®), gemcitabine (Gemzar®), 5-fluorouracil (Adrucil®, Carac® and Efudex®), methotrexate (Trexall®), capecitabine (Xeloda®), floxuridine (FUDR®), decitabine (Dacogen®), azacitidine (Vidaza® and Azadine®), 6-mercaptopurine (Purinethol®), cladribine (Leustatin®, Litak® and Movectro®), fludarabine (Fludara®), pentostatin (Nipent®), nelarabine (Arranon®), clofarabine (Clolar® and Evoltra®), and cytarabine (Cytosar®).

Anti-angiogenesis agents, such as matrix metalloproteinase (MMP) inhibitors (*e.g.*, MMP-2 inhibitors, MMP-9 inhibitors), rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib and bevacizumab, as well as COX-II inhibitors, such as CELEBREX™ (alecoxib), valdecoxib and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24,1996), WO 96/27583 (published March 7,1996), European Patent Application No. 97304971.1 (filed July 8,1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26,1998), WO 98/03516 (published January 29,1998), WO 98/34918 (published August 13,1998), WO 98/34915 (published August 13,1998), WO 98/33768 (published August 6,1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13,1994), European Patent Publication 931, 788 (published July 28,1999), WO 90/05719 (published May 31,1990), WO 99/52910 (published October 21,1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17,1999), PCT International Application No. PCT/IB98/01113 (filed July 21,1998), European Patent Application No. 99302232.1 (filed March 25,1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12,1999), United States Patent 5,863, 949 (issued January 26,1999), United States Patent 5,861, 510 (issued January 19,1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Embodiments of MMP-2 and/or MMP-9 inhibitors include those that have little or no activity inhibiting MMP-1. Other embodiments include MMP inhibitors that selectively inhibit MMP-2 and/or MMP-9 relative to other matrix metalloproteinases (*e.g.*, MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12 and/or MMP-13). Specific examples of MMP inhibitors useful in some embodiments include AG-3340, RO 323555 and RS 13-0830.

In some embodiments, a compound of the present disclosure is administered in combination with autophagy inhibitors, such as chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4-imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside and vinblastine, as well as antisense or siRNA that inhibits expression of proteins including but not limited to ATG5 (which are implicated in autophagy).

In some embodiments, a compound of the present disclosure is administered in combination with B-cell lymphoma 2 (BCL-2) inhibitors, such as venetoclax.

In some embodiments, a compound of the present disclosure is administered in combination with B-cell receptor signaling antagonists, such as a Bruton's tyrosine kinase (BTK) inhibitor (*e.g.*, ibrutinib).

In some embodiments, a compound of the present disclosure is administered in combination with Bromodomain inhibitors. A bromodomain inhibitor inhibits at least one bromodomain protein, such as Brd2, Brd3, Brd4 and/or BrdT, for example, Brd4. Non-limiting examples of bromodomain inhibitors include JQ-1 (Nature 2010 Dec 23;468(7327):1067-73), BI2536 (ACS Chem. Biol. 2014 May 16;9(5):1160-71; Boehringer Ingelheim), TG101209 (ACS Chem. Biol. 2014 May 16;9(5):1160-71), OTX015 (Mol. Cancer Ther. November 201312; C244; Oncoethix), IBET762 (J Med Chem. 2013 Oct 10;56(19):7498-500; GlaxoSmithKline), IBET151 (Bioorg. Med. Chem. Lett. 2012 Apr 15;22(8):2968-72; GlaxoSmithKline), PFI-1 (J. Med. Chem. 2012 Nov 26;55(22):9831-7; Cancer Res. 2013 Jun 1;73(11):3336-46; Structural Genomics Consortium), CPI-0610 (Constellation Pharmaceuticals). In some embodiments, the bromodomain inhibitor is TG101209, BI2536, OTX015, C244, IBET762, IBET151, or PFI-1.

Histone deacetylase (HDAC) inhibitors. HDAC proteins may be grouped into classes based on homology to yeast HDAC proteins with Class I made up of HDAC1, HDAC2, HDAC3 and HDAC 8; Class IIa made up of HDAC4, HDAC5, HDAC7 and HDAC 9; Class IIb made up of HDAC6 and HDAC10; and Class IV made up of HDAC11. Non-limiting examples of HDAC inhibitors include trichostatin A, vorinostat (Proc. Natl. Acad. Sci. U.S.A. 1998 Mar 17;95(6):3003-7), givinostat, abexinostat (Mol. Cancer Ther. 2006 May;5(5):1309-17), belinostat (Mol. Cancer Ther. 2003 Aug;2(8):721-8),

panobinostat (Clin. Cancer Res. 2006 Aug 1;12(15):4628-35), resminostat (Clin. Cancer Res. 2013 Oct 1;19(19):5494-504), quisinostat (Clin. Cancer Res. 2013 Aug 1;19(15):4262-72), depsipeptide (Blood. 2001 Nov 1;98(9):2865-8), entinostat (Proc. Natl. Acad. Sci. U.S.A. 1999 Apr 13;96(8):4592-7), mocetinostat (Bioorg. Med. Chem. Lett. 2008 Feb 1;18(3):106771) and valproic acid (EMBO J. 2001 Dec 17;20(24):6969-78). In some embodiments, the HDAC inhibitor is panobinostat, vorinostat, MS275, belinostat, SAHA or LBH589.

In some embodiments, a compound of the present disclosure is administered in combination with epidermal growth factor receptor tyrosine kinase (EGFR) inhibitors, such as erlotinib, osimertinib, cetuximab, gefitinib, necitumumab, lapatinib, neratinib, panitumumab, vandetanib, and necitumumab. A combination of a compound as described herein and an EGFR inhibitor may be useful, for example, in the treatment of cancers that are related to EGFR dysregulation, such as non-small-cell lung cancer (NSCLC), pancreatic cancer, breast cancer, and colon cancer. EGFR may be dysregulated, for example, due to activating mutations in exons 18, 19, 20, or 21. In particular embodiments, the EGFR inhibitor is erlotinib or osimertinib. In particular embodiments, the combination of a compound of the present disclosure and an EGFR inhibitor is used to treat EGFR-mutated NSCLC. In particular embodiments, the combination of a compound of the present disclosure and an EGFR inhibitor is used to treat an EGFR inhibitor-resistant cancer, for example, and the compound of the present disclosure sensitizes the cancer to the EGFR inhibitor.

EGFR antibodies, such as cetuximab (Erbitux®).

Methylthioadenosine phosphorylase (MTAP) inhibitors, such as (3R,4S)-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-((methylthio)methyl)pyrrolidin-3-ol (MT-DADMe-Immucillin-A, CAS 653592-04-2).

Methylthioadenosine ((2R,3R,4S,5S)-2-(6-amino-9H-purin-9-yl)-5-((methylthio)methyl)tetrahydrofuran-3,4-diol, CAS 2457-80-9).

Epidermal growth factor receptor (EGFR) inhibitors, such as erlotinib hydrochloride (Tarceva®) and gefitnib (Iressa®).

Mesenchymal-epithelial transition (MET) inhibitors, such as capmatinib (INC280, CAS 1029712-80-8).

In some embodiments, a compound of the present disclosure is administered in combination with platelet-derived growth factor (PDGF) receptor inhibitors, such as

imatinib (Gleevec®); linifanib (N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea, also known as ABT 869, available from Genentech); sunitinib malate (Sutent®); quizartinib (AC220, CAS 950769-58-1); pazopanib (Votrient®); axitinib (Inlyta®); sorafenib (Nexavar®); vargatef (BIBF1120, CAS 928326-83-4); telatinib (BAY57-9352, CAS 332012-40-5); vatalanib dihydrochloride (PTK787, CAS 212141-51-0); and motesanib diphosphate (AMG706, CAS 857876-30-3, N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide, described in PCT Publication No. WO 02/066470).

In some embodiments, a HER2 (Receptor tyrosine-protein kinase erbB-2) antibody can be used in combination with the compounds as described herein. In some embodiments, the HER2 antibody or biologics is fam-trastuzumab deruxtecan-nxki, trastuzumab, pertuzumab, ado-trastuzumab emtansine, or margetuximab-cmkb.

In some embodiments, a compound of the present disclosure is administered in combination with phosphoinositide 3-kinase (PI3K) inhibitors, such as 4-[2-(1H-indazol-4-yl)-6-[[4-(methylsulfonyl)piperazin-1-yl]methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine (also known as GDC 0941 and described in PCT Publication Nos. WO 09/036082 and WO 09/055730); 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine (also known as BKM120 or NVP-BKM120, and described in PCT Publication No. WO 2007/084786); alpelisib (BYL719); (5Z)-5-[[4-(4-pyridinyl)-6-quinolinyl]methylene]-2,4-thiazolidinedione (GSK1059615, CAS 958852-01-2); 5-[8-methyl-9-(1-methylethyl)-2-(4-morpholinyl)-9H-purin-6-yl]-2-pyrimidinamine (VS-5584, CAS 1246560-33-7); and everolimus (AFINITOR®).

Cyclin-dependent kinase (CDK) inhibitors, such as ribociclib (LEE011, CAS 1211441-98-3); aloisine A; alvocidib (also known as flavopiridol or HMR-1275, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3*S*,4*R*)-3-hydroxy-1-methyl-4-piperidinyl]-4-chromenone, and described in U.S. Patent No. 5,621,002); crizotinib (PF-02341066, CAS 877399-52-5); 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(2*R*,3*S*)-2-(hydroxymethyl)-1-methyl-3-pyrrolidinyl]-4*H*-1-benzopyran-4-one, hydrochloride (P276-00, CAS 920113-03-7); 1-methyl-5-[[2-[5-(trifluoromethyl)-1*H*-imidazol-2-yl]-4-pyridinyl]oxy]-*N*-[4-(trifluoromethyl)phenyl]-1*H*-benzimidazol-2-amine (RAF265, CAS 927880-90-8); indisulam (E7070); roscovitine (CYC202); 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-d]pyrimidin-7-one, hydrochloride (PD0332991); dinaciclib (SCH727965); *N*-[5-[[(5-*tert*-butyloxazol-2-

yl)methyl]thio]thiazol-2-yl]piperidine-4-carboxamide (BMS 387032, CAS 345627-80-7); 4-[[9-chloro-7-(2,6-difluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-yl]amino]-benzoic acid (MLN8054, CAS 869363-13-3); 5-[3-(4,6-difluoro-1*H*-benzimidazol-2-yl)-1*H*-indazol-5-yl]-*N*-ethyl-4-methyl-3-pyridinemethanamine (AG-024322, CAS 837364-57-5); 4-(2,6-dichlorobenzoylamino)-1*H*-pyrazole-3-carboxylic acid *N*-(piperidin-4-yl)amide (AT7519, CAS 844442-38-2); 4-[2-methyl-1-(1-methylethyl)-1*H*-imidazol-5-yl]-*N*-[4-(methylsulfonyl)phenyl]-2-pyrimidinamine (AZD5438,CAS 602306-29-6); palbociclib (PD-0332991); and (2*R*,3*R*)-3-[[2-[[3-[[*S(R)*]-*S*-cyclopropylsulfonimidoyl]-phenyl]amino]-5-(trifluoromethyl)-4-pyrimidinyl]oxy]-2-butanol (BAY 10000394).

In some embodiments, a compound of the present disclosure is administered in combination with p53-MDM2 inhibitors, such as (*S*)-1-(4-chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2*H*-isoquinolin-3-one, (*S*)-5-(5-chloro-1-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-1-isopropyl-5,6-dihydro-1*H*-pyrrolo[3,4-d]imidazol-4-one, [(4*S*,5*R*)-2-(4-*tert*-butyl-2-ethoxyphenyl)-4,5-bis(4-chlorophenyl)-4,5-dimethylimidazol-1-yl]-[4-(3-methylsulfonylpropyl)piperazin-1-yl]methanone (RG7112), 4-[[(2*R*,3*S*,4*R*,5*S*)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethylpropyl)pyrrolidine-2-carbonyl]amino]-3-methoxybenzoic acid (RG7388), SAR299155, 2-((3*R*,5*R*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (AMG232), {(3*R*,5*R*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-[(2*S*,3*S*)-2-hydroxy-3-pentanyl]-3-methyl-2-oxo-3-piperidinyl}acetic acid (AM-8553), (±)-4-[4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one (Nutlin-3), 2-methyl-7-[phenyl(phenylamino)methyl]-8-quinolinol (NSC 66811), 1-*N*-[2-(1*H*-indol-3-yl)ethyl]-4-*N*-pyridin-4-ylbenzene-1,4-diamine (JNJ-26854165), 4-[4,5-bis(3,4-chlorophenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxyl]-piperazin-2-one (Caylin-1), 4-[4,5-bis(4-trifluoromethyl-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxyl]-piperazin-2-one (Caylin-2), 5-[[3-dimethylamino)propyl]amino]-3,10-dimethylpyrimido[4,5-b]quinoline-2,4(3*H*,10*H*)-dione dihydrochloride (HLI373) and trans-4-iodo-4′-boranyl-chalcone (SC204072).

In some embodiments, a compound of the present disclosure is administered in combination with mitogen-activated protein kinase (MEK) inhibitors, such as XL-518 (also known as GDC-0973, CAS No. 1029872-29-4, available from ACC Corp.); selumetinib (5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzimidazole-6-carboxamide, also known as AZD6244 or ARRY 142886, described in PCT Publication No. WO 2003/077914); 2-[(2-chloro-4-iodophenyl)amino]-*N*-(cyclopropylmethoxy)-3,4-difluoro-benzamide (also known as CI-1040 or PD184352 and described in PCT Publication No. WO 2000/035436); *N*-[(2*R*)-2,3-dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]- benzamide (also known as PD0325901 and described in PCT Publication No. WO 2002/006213); 2,3-bis[amino[(2-aminophenyl)thio]methylene]-butanedinitrile (also known as U0126 and described in U.S. Patent No. 2,779,780); *N*-[3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-6-methoxyphenyl]-1-[(2*R*)-2,3-dihydroxypropyl]-cyclopropanesulfonamide (also known as RDEA119 or BAY869766 and described in PCT Publication No. WO 2007/014011); (3*S*,4*R*,5*Z*,8*S*,9*S*,11*E*)-14-(ethylamino)-8,9,16-trihydroxy-3,4-dimethyl-3,4,9; 19-tetrahydro-1*H*-2-benzoxacyclotetradecine-1,7(8*H*)-dione] (also known as E6201 and described in PCT Publication No. WO 2003/076424); 2'-amino-3'-methoxyflavone (also known as PD98059 available from Biaffin GmbH & Co., KG, Germany); (*R*)-3-(2,3-dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (TAK-733, CAS 1035555-63-5); pimasertib (AS-703026, CAS 1204531-26-9); trametinib dimethyl sulfoxide (GSK-1120212, CAS 1204531-25-80); 2-(2-fluoro-4-iodophenylamino)-*N*-(2-hydroxyethoxy)-1,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (AZD 8330); 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-*N*-(2-hydroxyethoxy)-5-[(3-oxo-[1,2]oxazinan-2-yl)methyl]benzamide (CH 4987655 or Ro 4987655); and 5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzimidazole-6-carboxamide (MEK162).

B-RAF inhibitors, such as regorafenib (BAY73-4506, CAS 755037-03-7); tuvizanib (AV951, CAS 475108-18-0); vemurafenib (ZELBORAF®, PLX-4032, CAS 918504-65-1); encorafenib (also known as LGX818); 1-methyl-5-[[2-[5-(trifluoromethyl)-1*H*-imidazol-2-yl]-4-pyridinyl]oxy]-*N*-[4-(trifluoromethyl)phenyl-1*H*-benzimidazol-2-amine (RAF265, CAS 927880-90-8); 5-[1-(2-hydroxyethyl)-3-(pyridin-4-yl)-1*H*-pyrazol-4-yl]-2,3-dihydroinden-1-one oxime (GDC-0879, CAS 905281-76-7); 5-[2-[4-[2-

(dimethylamino)ethoxy]phenyl]-5-(4-pyridinyl)-1*H*-imidazol-4-yl]-2,3-dihydro-1*H*-inden-1-one oxime (GSK2118436 or SB590885); (+/-)-methyl (5-(2-(5-chloro-2-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl)carbamate (also known as XL-281 and BMS908662); dabrafenib (TAFINLAR®); and *N*-(3-(5-chloro-1*H*-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (also known as PLX4720).

In some embodiments, a compound of the present disclosure is administered in combination with proteasome inhibitors, such as bortezomib (VELCADE®), N-5-benzyloxycarbonyl-Ile-Glu(O-tert-butyl)-Ala-leucinal (PSI), carfilzomib and ixazomib, marizomib (NPI-0052), delanzomib (CEP-18770), and O-methyl-N-[(2-methyl-5-thiazolyl)carbonyl]-L-seryl-O-methyl-N-[(1S)-2-[(2R)-2-methyl-2-oxiranyl]-2-oxo-1-(phenylmethyl)ethyl]-L-serinamide (oprozomib, ONX-0912, PR-047) (*e.g.*, bortezomib), *e.g.*, for the treatment of multiple myeloma.

A host of chemotherapeutic agents can be used in combination with the compound of the present disclosure. In some embodiments, the chemotherapeutic agent is selected from the group consisting of mitotic inhibitors (*e.g.*, paclitaxel, nab-paclitaxel), alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

In some embodiments, a compound of the present disclosure is administered in combination with a secondary chemotherapeutic agent selected from alkylating agents such as thiotepa and cyclosphosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, Casodex®, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin,

marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK.RTM.; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g., paclitaxel (TAXOLTM , Bristol-Myers Squibb Oncology, Princeton, N.J.), docetaxel (TAXOTERETM, Rhone-Poulenc Rorer, Antony, France) and cabazitaxel (JEVTANA, Sanofi Genzyme); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Further non-limiting examples of chemotherapeutic agents for use in combination with a compound of the present disclosure (*e.g.*, in combination therapy, in a pharmaceutical combination) include bortezomib, capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), doxorubicin hydrochloride (Adriamycin®, Rubex®), erlotinib, fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), FOLFIRINOX, gemcitabine (difluorodeoxycitidine), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), nabpaclitaxel, pentostatin, 6-thioguanine, thiotepa, and topotecan hydrochloride for injection (Hycamptin®). Yet further non-limiting examples of chemotherapeutic agents for use in combination with a compound of the present

disclosure (*e.g.*, in combination therapy, in a pharmaceutical combination) include erlotinib, afatinib, gefitinib, GDC0941, MLN1117, BYL719 (alpelisib), BKM120 (buparlisib), CYT387, GLPG0634, baricitinib, lestaurtinib, momelotinib, pacritinib, ruxolitinib, TG101348, crizotinib, tivantinib, AMG337, cabozantinib, foretinib, onartuzumab, NVP-AEW541, dasatinib, ponatinib, saracatinib, bosutinib, trametinib, selumetinib, cobimetinib, PD0325901, RO5126766, axitinib, bevacizumab, cetuximab, fostamatinib, imatinib, lapatinib, lenvatinib, ibrutinib, nilotinib, panitumumab, pazopanib, pegaptanib, ranibizumab, sorafenib, sunitinib, SU6656, trastuzumab, tofacitinib, vandetanib, vemurafenib, irinotecan, Taxol, docetaxel, rapamycin and MLN0128. More non-limiting examples of chemotherapeutic agents for use in combination with a compound of the present disclosure (*e.g.*, in combination therapy, in a pharmaceutical combination) include capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), doxorubicin hydrochloride (Adriamycin®, Rubex®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), gemcitabine (difluorodeoxycitidine), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), pentostatin, 6-thioguanine, thiotepa, and topotecan hydrochloride for injection (Hycamptin®).

Commonly prescribed anti-cancer drugs can also be used in combination with a compound of the present disclosure. Non-limiting examples of commonly prescribed anti-cancer drugs include Herceptin®, Avastin®, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, ABVD, AVICINE, Abagovomab, Acridine carboxamide, Adecatumumab, 17-N-Allylamino-17-demethoxygeldanamycin, Alpharadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastic, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Biricodar, Brostallicin, Bryostatin, Buthionine sulfoximine, CBV (chemotherapy), Calyculin, cell-cycle nonspecific antineoplastic agents, Dichloroacetic acid, Discodermolide, Elsamitrucin, Enocitabine, Epothilone, Eribulin, Everolimus, Exatecan, Exisulind, Ferruginol, Forodesine, Fosfestrol, ICE chemotherapy regimen, IT-101, Imexon, Imiquimod, Indolocarbazole, Irofulven, Laniquidar, Larotaxel, Lenalidomide, Lucanthone,

Lurtotecan, Mafosfamide, Mitozolomide, Nafoxidine, Nedaplatin, Olaparib, Ortataxel, PAC-1, Pawpaw, Pixantrone, Proteasome inhibitor, Rebeccamycin, Resiquimod, Rubitecan, SN-38, Salinosporamide A, Sapacitabine, Stanford V, Swainsonine, Talaporfin, Tariquidar, Tegafur-uracil, Temodar, Tesetaxel, Triplatin tetranitrate, Tris(2-chloroethyl)amine, Troxacitabine, Uramustine, Vadimezan, Vinflunine, ZD6126 or Zosuquidar.

Chemotherapeutic cell conditioners can also be used in combination with compound of the present disclosure. Non-limiting examples of chemotherapeutic cell conditioners include anti-hormonal agents that act to regulate or inhibit hormone action on tumors, such as anti-estrogens, including, for example, tamoxifen, (NolvadexTM), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone and toremifene (Fareston); and anti-androgens, such as flutamide, nilutamide, bicalutamide, leuprolide and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs, such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomeRASe inhibitor RFS 2000; and difluoromethylornithine (DMFO).

mTOR inhibitors can also be used in combination with a compound of the present disclosure. Non-limiting examples of mTOR inhibitors include, *e.g.*, temsirolimus; ridaforolimus (formally known as deferolimus, (1R,2R,4S)-4-[(2R)-2 [(1R,9S,12S,15R,16E,18R,19R,21R, 23S,24E,26E,28Z,30S,32S,35R)- 1,18-dihydroxy-19,30-dimethoxy-15,17,21,23, 29,35-hexamethyl-2,3,10,14,20-pentaoxo-11,36-dioxa-4-azatricyclo[30.3.1.$0^{4,9}$] hexatriaconta-16,24,26,28-tetraen-12-yl]propyl]-2-methoxycyclohexyl dimethylphosphinate, also known as AP23573 and MK8669, and described in PCT Publication No. WO 03/064383); everolimus (Afinitor® or RAD001); rapamycin (AY22989, Sirolimus®); simapimod (CAS 164301-51-3); emsirolimus, (5-{2,4-Bis[(3S)-3-methylmorpholin-4-yl]pyrido[2,3-d]pyrimidin-7-yl}-2-methoxyphenyl)methanol (AZD8055); 2-Amino-8-[trans-4-(2-hydroxyethoxy)cyclohexyl]-6-(6- methoxy-3-pyridinyl)-4-methyl-pyrido[2,3-d]pyrimidin-7(8H)-one (PF04691502, CAS 1013101-36-4); and N^2-[1,4-dioxo-4-[[4-(4-oxo-8-phenyl-4H-1-benzopyran-2-yl)morpholinium-4-yl]methoxy]butyl]-L-

arginylglycyl-L-α-aspartylL-serine- inner salt (SEQ ID NO: 1482) (SF1126, CAS 936487-67-1) and XL765.

Some patients may experience allergic reactions to compounds of the present disclosure and/or other therapeutic agent(s) (*e.g.*, anti-cancer agent(s)) during or after administration. Therefore, anti-allergic agents can be administered in combination with compounds of the present disclosure and/or other therapeutic agent(s) (*e.g.*, anti-cancer agent(s)) to minimize the risk of an allergic reaction. Suitable anti-allergic agents include corticosteroids (Knutson, S., *et al.*, *PLoS One*, DOI:10.1371/journal.pone.0111840 (2014)), such as dexamethasone (*e.g.*, DECADRON®), beclomethasone (*e.g.*, BECLOVENT®), hydrocortisone (also known as cortisone, hydrocortisone sodium succinate, hydrocortisone sodium phosphate, sold under the tradenames ALA-CORT®, hydrocortisone phosphate, SOLU-CORTEF®, HYDROCORT ACETATE® and LANACORT®), prednisolone (sold under the tradenames DELTA-CORTEL®, ORAPRED®, PEDIAPRED® and PRELONE®), prednisone (sold under the tradenames DELTASONE®, LIQUID RED®, METICORTEN® and ORASONE®), methylprednisolone (also known as 6-methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, sold under the tradenames DURALONE®, MEDRALONE®, MEDROL®, M-PREDNISOL® and SOLU-MEDROL®); antihistamines, such as diphenhydramine (*e.g.*, BENADRYL®), hydroxyzine, and cyproheptadine; and bronchodilators, such as the beta-adrenergic receptor agonists, albuterol (*e.g.*, PROVENTIL®), and terbutaline (BRETHINE®).

Some patients may experience nausea during and after administration of the compounds described herein and/or other therapeutic agent(s) (*e.g.*, anti-cancer agent(s)). Therefore, anti-emetics can be used in combination with compounds of the present disclosure and/or other therapeutic agent(s) (*e.g.*, anti-cancer agent(s)) to prevent nausea (upper stomach) and vomiting. Suitable anti-emetics include aprepitant (EMEND®), ondansetron (ZOFRAN®), granisetron HCl (KYTRIL®), lorazepam (ATIVAN®, dexamethasone (DECADRON®), prochlorperazine (COMPAZINE®), casopitant (REZONIC® and ZUNRISA®), and combinations thereof.

Medication to alleviate the pain experienced during the treatment period is often prescribed to make the patient more comfortable. Common over-the-counter analgesics, such TYLENOL®, can also be used in combination with compounds of the present disclosure and/or other therapeutic agent(s) (*e.g.*, anti-cancer agent(s)). Opioid

analgesic drugs such as hydrocodone/paracetamol or hydrocodone/acetaminophen (*e.g.*, VICODIN®), morphine (*e.g.*, ASTRAMORPH® or AVINZA®), oxycodone (*e.g.*, OXYCONTIN® or PERCOCET®), oxymorphone hydrochloride (OPANA®), and fentanyl (*e.g.*, DURAGESIC®) can be useful for moderate or severe pain, and can be used in combination with compounds of the present disclosure and/or other therapeutic agent(s) (*e.g.*, anti-cancer agent(s)).

In an effort to protect normal cells from treatment toxicity and to limit organ toxicities, cytoprotective agents (such as neuroprotectants, free-radical scavengers, cardioprotectors, anthracycline extravasation neutralizers, nutrients and the like) may be used as an adjunct therapy in combination with compounds of the present disclosure. Suitable cytoprotective agents include amifostine (ETHYOL®), glutamine, dimesna (TAVOCEPT®), mesna (MESNEX®), dexrazoxane (ZINECARD® or TOTECT®), xaliproden (XAPRILA®), and leucovorin (also known as calcium leucovorin, citrovorum factor and folinic acid).

In an effort to protect normal cells from treatment toxicity and to limit organ toxicities, cytoprotective agents (such as neuroprotectants, free-radical scavengers, cardioprotectors, anthracycline extravasation neutralizers, nutrients and the like) may be used as an adjunct therapy in combination with compounds of the present disclosure. Suitable cytoprotective agents include amifostine (ETHYOL®), glutamine, dimesna (TAVOCEPT®), mesna (MESNEX®), dexrazoxane (ZINECARD® or TOTECT®), xaliproden (XAPRILA®), and leucovorin (also known as calcium leucovorin, citrovorum factor and folinic acid).

In the combination therapies of the present disclosure, the compound of the present disclosure and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the present disclosure and the other therapeutic agent may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.*, in the case of a kit comprising the compound of the present disclosure and the other therapeutic agent); (ii) by the physician (or under the guidance of a physician) shortly before administration; (iii) in the patient themselves, *e.g.*, during sequential administration of the compound of the present disclosure and the other therapeutic agent.

Pharmaceutical Compositions

In certain embodiments, the present disclosure provides a pharmaceutical preparation suitable for use in a human patient, comprising any of the compounds shown above (e.g., a compound of the disclosure, such as a compound of Formula (I) or (II) or (III), and one or more pharmaceutically acceptable excipients. In certain embodiments, the pharmaceutical preparations may be for use in treating or preventing a condition or disease as described herein. Any of the disclosed compounds may be used in the manufacture of medicaments for the treatment of any diseases or conditions disclosed herein.

The compositions and methods of the present disclosure may be utilized to treat a subject in need thereof. In certain embodiments, the subject is a mammal such as a human, or a non-human mammal. When administered to subject, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the disclosure and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In a preferred embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, suspension, cream, gel, ointment, aerosol infusion, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound or to enable manufacturing such as a compound of the disclosure. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a

pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a self-emulsifying drug delivery system or a self-microemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the disclosure. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for

application to the tongue); absorption through the oral mucosa (e.g., sublingually); anally, rectally or vaginally (for example, as a pessary, cream or foam); parenterally (including intramuscularly, intravenously, subcutaneously or intrathecally as, for example, a sterile solution or suspension); nasally; intraperitoneally; subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin, or as an eye drop). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the disclosure, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present disclosure with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the disclosure suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present

disclosure as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired

release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or more active compounds with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the pharmaceutical compositions for administration to the mouth may be presented as a mouthwash, or an oral spray, or an oral ointment.

Alternatively, or additionally, compositions can be formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams, or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present disclosure to the body. Such dosage forms can be made by dissolving or dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this disclosure. Exemplary ophthalmic formulations are described in U.S. Publication Nos. 2005/0080056, 2005/0059744, 2005/0031697 and 2005/004074 and U.S. Patent No. 6,583,124, the contents of each of which are incorporated herein by reference. If desired, liquid ophthalmic formulations have properties similar to that of lacrimal fluids, aqueous humor or vitreous humor or are compatible with such fluids. A preferred route of administration is local administration (*e.g.*, topical administration, such as eye drops, or administration via an implant).

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form.

Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

For use in the methods of this disclosure, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs, including proteinacious biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the subject being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that required in order to achieve the desired

therapeutic effect and gradually increase the dosage until the desired effect is achieved. By "therapeutically effective amount" is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the subject's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the disclosure. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher *et al.* (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

In general, a suitable daily dose of an active compound used in the compositions and methods of the disclosure will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of the present disclosure, the active compound may be administered two or three times daily. In certain embodiments, the active compound will be administered once daily.

In certain embodiments, compounds of the disclosure may be used alone or conjointly administered with another type of therapeutic agent. As used herein, the phrase "conjoint administration" refers to any form of administration of two or more different therapeutic compounds such that the second compound is administered while the previously administered therapeutic compound is still effective in the body (*e.g.*, the two compounds are simultaneously effective in the subject, which may include synergistic effects of the two compounds). For example, the different therapeutic compounds can be administered either in the same formulation or in a separate formulation, either concomitantly or sequentially. In certain embodiments, the different therapeutic compounds can be administered within one hour, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, or a week of one another. Thus, a subject who receives such treatment can benefit from a combined effect of different therapeutic compounds.

In certain embodiments, conjoint administration of compounds of the disclosure with one or more additional therapeutic agent(s) (e.g., one or more additional chemotherapeutic agent(s)) provides improved efficacy relative to each individual administration of the compound of the disclosure (e.g., compound of Formula (I) or (II) or (III)) or the one or more additional therapeutic agent(s). In certain such embodiments, the conjoint administration provides an additive effect, wherein an additive effect refers to the sum of each of the effects of individual administration of the compound of the disclosure and the one or more additional therapeutic agent(s).

This disclosure includes the use of pharmaceutically acceptable salts of compounds of the disclosure in the compositions and methods of the present disclosure. In certain embodiments, contemplated salts of the disclosure include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts of the disclosure include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts of the disclosure include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Phamaceutically acceptable anionic salts include acetate, aspartate, benzenesulfonate, benzoate, besylate, bicarbonate, bitartrate, bromide, camsylate, carbonate, chloride, citrate, decanoate, edetate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolate, hexanoate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, octanoate, oleate, pamoate, pantothenate, phosphate, polygalacturonate, propionate, salicylate, stearate, acetate, succinate, sulfate, tartrate, teoclate, and tosylate.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents,

sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

The disclosure now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present disclosure, and are not intended to limit the disclosure.

Examples

General Synthetic Procedures

The starting materials and reagents used in preparing these compounds are either available from commercial supplier such as Aldrich Chemical Co., Bachem, etc., or can be made by methods well known in the art. The schemes are merely illustrative of some methods by which the compounds disclosed herein can be synthesized and various modifications to these schemes can be made and will be suggested to one of skill in the art having referred to this disclosure. The starting materials and the intermediates and the final products of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography, and the like and may be characterized using conventional means, including physical constants and spectral data.

Unless specified otherwise, the reactions described herein take place at atmospheric pressure over a temperature range from about -78 °C to about 150 °C.

Abbreviations	Definition
EA, EtOAc	Ethyl acetate
PE	Petroleum ether
SFC	Supercritical fluid chromatography
DIAD	Diethyl azodicarboxylate

Abbreviations	Definition
THF	Tetrahydrofuran
DCM	Dichloromethane
DMF	*N,N*-dimethylformamide
V/V	Volume/volume
LC/MS, LC-MS, LCMS	Liquid chromatography-mass spectrometry
MeOH	Methanol
EtOH	Ethanol
MS	Mass spectrometry
DIPEA	N,N-diisopropylethylamine
DMSO	Dimethyl sulfoxide
IPA	Isopropyl alcohol
NMP	N-methyl pyrrolidinone
NMR	Nuclear magnetic resonance
TEA	Triethylamine
ppm	Parts per million
ATP	Adenosine triphosphate
TFA	Trifluoroacetic acid
FA	Formic acid
ESI	Electrospray ionization
sat.	saturated
TLC	Thin layer chromatography
DIBAL, DIBAL-H	Diisobutylaluminium hydride
AcOH, HOAc	Acetic acid
TES	Triethylsilane
BuLi	Butyllithium
LDA	Lithium diisopropylamide
NBS	N-Bromosuccinimide
NIS	N-Iodosuccinimide
NCS	N-Chlorosuccinimide
DME	Dimethoxyethane
DMP	Dess-Martin periodinane
DEA	Diethylamine
DMF-DMA	Dimethylformamide dimethylacetal
NMO	N-Methylmorpholine N-oxide
TBSCl	tert-Butyldimethylsilyl chloride
HPLC	High-pressure liquid chromatography
KOAc	Potassiuma acetate
Prep	Preperative
SM	Starting material
wt	Wild-type
rt, r.t.	Room-temperature
TMSOK	Potassium trimethylsilanolate
$Pd(dppf)Cl_2$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)-palladium(0)
K_2CO_3	Potassium Carbonate
CuI	Copper Iodine

Abbreviations	Definition
$[Ir(OMe)(cod)_2]$	Cyclooctadiene iridium methoxide dimer
MBTE	tert-Butyl methyl ether
Na_2SO_4	Sodium Sulfate
Na_2CO_3	Sodium carbonate
$LiAlH_4$	Lithium Aluminium hydride
Pd/C	Palladium on Carbon
N_2	Nitrogen
dtbpy	4,4′-Di-tert-butyl-2,2′-dipyridyl
TsCl	Tosyl Chloride
HNO_3	Nitric acid
BrCN	Cyanogen Bromide
tBuONa	Sodium tertbutoxide
NH_4CO_3	Ammonium carbonate
NaH	Sodium hydride
Zn	Zinc
HOBt	Hydroxybenzotriazole
DIC	N,N'-Diisopropylcarbodiimide
$NaBH_4$	Sodium borohydride
$NaBH(OAc)_3$	Triacetoxy borohydride
NH_4Cl	Ammonium chloride
HATU	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
C18	octadecane
HCHO	Formaldehyde
NH_4Cl	Ammonium Chloride
HCl	Hydrochloric acid
NaOH	Sodium hydroxide
PtO_2	Platinium oxide
Cs_2CO_3	Cesium Carbonate
TMEDA	Tetramethylethylenediamine
HMDS	Hexamethyldisilazane
PTSA	p-Toluenesulfonic Acid
ACN	Acetonitrile
PMBCl	para-methoxybenzyl chloride
DAST	Diethylaminosulfur trifluoride
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
mCPBA	meta-Chloroperoxybenzoic acid
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
DiMeIHeptCl)Pd(cinnamyl)Cl	1H-Imidazolium, 1,3-bis[2,6-bis[3-methyl-1-(2-methylpropyl)butyl]phenyl]-4,5-dichloro- Palladium(π-cinnamyl) chloride

The compounds of the invention can be prepared by a variety of synthetic methods, as further described and illustrated herein. It will be understood by those with skill in the art that the following general synthetic methods are representative and not intended to be limiting.

Those having skill in the art will recognize that the starting materials and reaction conditions may be varied, the sequence of the reactions altered, and additional steps employed to produce compounds encompassed by the present disclosure, as demonstrated by the following examples. In some cases, protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general, the need for such protecting groups as well as the conditions necessary to attach and remove such groups will be apparent to experienced organic chemists. The disclosures of all articles and references mentioned in this application, including patents, are incorporated herein by reference.

The preparation of the compounds of the present disclosure is illustrated further by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures and compounds described in them.

Analytical Methods

LCMS data was collected using one of the following methods:

Method	Method Details
A	**Instrument**: SHIMADZU 2020 **Column**: Poroshell HPH C-18, 50×3.0 mm I.D., 2.7 μm **Mobile phase**: A is H_2O / 5 mM NH_4CO_3 and B is CH3CN **Run Time**: 10%B (0.01 min); 95% B (2.0 min); 95% B (2.7 min); 10% B (2.75 min); stop (3.0 min) **Flow rate**: 1.2 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm
B	**Instrument**: SHIMADZU 2020 **Column**: SHIM-Pack Scepter C18, 33 * 3.0 mm, 3.0 μm **Mobile phase**: A is H_2O (+ 0.1%TFA) and B is CH_3CN **Run Time**: 10%B (0.01 min); 95% B (1.2 min); 95% B (1.8 min); 95% B (1.82 min); stop (2.0 min) **Flow rate**: 1.5 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm

Method	Method Details
C	**Instrument**: SHIMADZU 2020 **Column**: Halo C18, 30 * 3.0 mm, 2.0 µm **Mobile phase**: A is H_2O (+ 0.05%TFA) and B is CH_3CN (+ 0.05% TFA) **Run Time**: 5%B (0.01 min); 100% B (1.2 min); 100% B (1.8 min); 5% B (1.82 min); stop (2.0 min) **Flow rate**: 1.3 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm
D	**Instrument**: SHIMADZU 2020 **Column**: Halo C18, 30 * 3.0 mm, 2.0 µm **Mobile phase**: A is H_2O (+ 0.05%TFA) and B is CH_3CN (+ 0.05% TFA) **Run Time**: 20%B (0.01 min); 60% B (1.7 min); 95% B (2.3 min); 95% B (2.8 min); 5% (2.83 min); stop (3.0 min) **Flow rate**: 1.3 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm
E	**Instrument**: SHIMADZU 2020 **Column**: Shim-pack GIST C18 50 *4.6 mm, 5 µm **Mobile phase**: A is H_2O (+ 0.1% FA) and B is CH_3CN **Run Time**: 20%B (0. 1 min); 95% B (1.7 min); 95% B (2.4 min); 20% B (2.8 min); stop (3.0 min) **Flow rate**: 2.5 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm
F	**Instrument**: SHIMADZU 2020 **Column**: Halo C18, 30 * 3.0 mm, 2.0 µm **Mobile phase**: A is H_2O (+ 0.1%FA) and B is CH_3CN (+ 0.1% FA) **Run Time**: 20%B (0.01 min); 60% B (1.7 min); 95% B (2.3 min); 95% B (2.8 min); 5% (2.83 min); stop (3.0 min) **Flow rate**: 1.3 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm
G	**Instrument**: SHIMADZU 2020 **Column**: YMC Triart C18, 50 * 4.6 mm, 5.0 µm **Mobile phase:** A is H_2O/CH_3CN/TFA (90/10/0.1) and B is H_2O/CH_3CN/TFA (10/90/0.1) **Run Time**: 20%B (0.4 min); 95% B (3.4 min); 95% B (4.2 min) **Flow rate**: 2.5 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm
H	**Instrument**: SHIMADZU 2020 **Column**: YMC Triart C18, 50 * 4.6 mm, 5.0 µm **Mobile phase:** A is $H_2O/CH_3CN/NH_3$ (90/10/0.1) and B is H_2O/CH_3CN/TFA (10/90/0.1) **Run Time**: 20%B (0.4 min); 95% B (3.4 min); 95% B (4.2 min) **Flow rate**: 2.5 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm

Method	Method Details
I	**Instrument**: SHIMADZU 2020 **Column**: Halo C18, 30 * 3.0 mm, 2.0 μm **Mobile phase**: A is H_2O (+ 0.05%TFA) and B is CH_3CN (+ 0.05% TFA) **Run Time**: 20%B (0.01 min); 70% B (1.7 min); 100% B (2.3 min); 100% B (2.8 min); 5% (2.83 min); stop (3.0 min) **Flow rate**: 1.3 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm
J	**Instrument**: SHIMADZU 2020 **Column**: Shim-Pack Scepter, 33 * 3.0 mm, 3.0 μm **Mobile phase**: A is H_2O (+ 5mM NH_4CO_3) and B is CH_3CN **Run Time**: 10%B (0.01 min); 95% B (1.2 min); 95% B (1.8 min); 10% B (1.82 min); stop (2.0 min) **Flow rate**: 1.5 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm
K	**Instrument**: SHIMADZU 2020 **Column**: YMC Triart C18, 50 * 4.6 mm, 5.0 μm **Mobile phase:** A is H_2O/CH_3CN/FA (90/10/0.05) and B is CH_3CN **Run Time**: 20%B (0.01 min); 95% B (1.79 min); 95% B (2.49 min) **Flow rate**: 2.3 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm
L	**Instrument**: SHIMADZU 2020 **Column**: L-column3 C18, 30 * 3.0 mm, 3.0 μm **Mobile phase:** A is H_2O (+ 5mM NH_4CO_3) and B is CH_3CN **Run Time**: 20% B (0.01 min); 95% B (1.20 min); 95% B (1.80 min), 10% B (1.82 min), stop (2 min) **Flow rate**: 1.5 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm
M	**Instrument**: SHIMADZU 2020 **Column**: Shim-Pack Scepter, 33 * 3.0 mm, 3.0 μm **Mobile phase**: A is H_2O (+ 5mM NH_4CO_3) and B is CH_3CN **Run Time**: 30%B (0.01 min); 70% B (1.7 min); 95% B (2.3 min); 95% B (2.80 min); 10%B (2.83 min); stop (3.00 min) **Flow rate**: 1.5 mL / min **Column temperature**: 40 °C **Wavelength**: 220 nm / 254 nm

Exemplified Synthesis

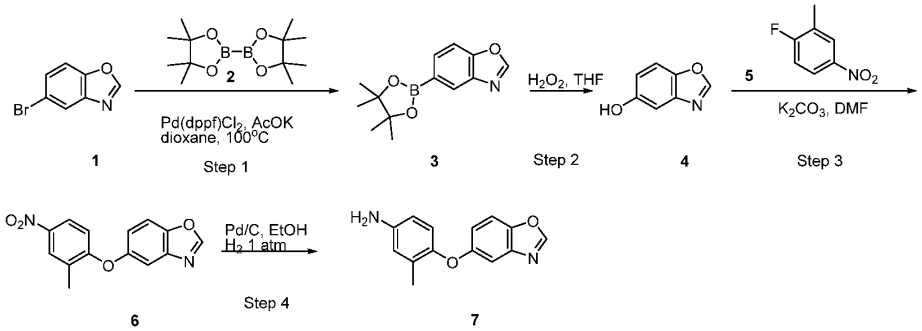
Several variables are used in the exempflied synthesis, e.g., the exemplified general synthetic schemes. As used herein, each occurrence of X is independently CR_5, or N as valency permits; R_{1a} is hydrogen, halogen, or optionally substituted alkyl; R_{2a} is

hydrogen, halogen, optionally substituted alkyl, or optionally substituted alkoxy; R_5 is independently halo, optionally substituted alkyl, or optionally substituted alkoxy; R_{2b} is hydrogen or optionally substituted alkyl; R_{1d} is hydrogen, halo, or optionally substituted alkyl; R_{3a} is halo, optionally substituted alkyl, or optionally substituted heterocyclyl; R_{4a} is hydrogen, halo, or optionally substituted alkoxy; R_{5a} is hydrogen, optionally substituted alkyl or heterocyclyl; R_{6a} is hydrogen or halo; alkenyl or alkynyl, each of which is optionally substituted by ne or more occurrences of R^a (R^a is as defined in this application); each occurrence of A is C or N as valency permits; PG is a nitrogen protecting group when attached to nitrogen or an oxygen protecting group when attached to oxygen.

Exemplified compounds in Figures 1-17 can be synthesized using the following procedures from the corresponding starting materials and commercially available reagents.

Synthesis of Intermediates

Synthesis of 4-(benzo[d]oxazol-5-yloxy)-3-methylaniline 7



1 3 4 6 7

Step 1: A mixture of 5-bromobenzo[d]oxazole **1** (2.00 g, 10.10 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (1.65 g, 2.02 mmol, 0.20 equiv.), AcOK (2.97 g, 30.30 mmol, 3.00 equiv.) and bis(pinacolato)diboron **2** (3.85 g, 15.15 mmol, 1.50 equiv.) in dioxane (50.00 mL) was stirred at 100 °C for 6 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% MeOH in DCM) to afford 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazole **3** (2.10 g, 85%) as a yellow solid. LCMS (ESI, *m/z*): 246 {$[M+H]^+$.

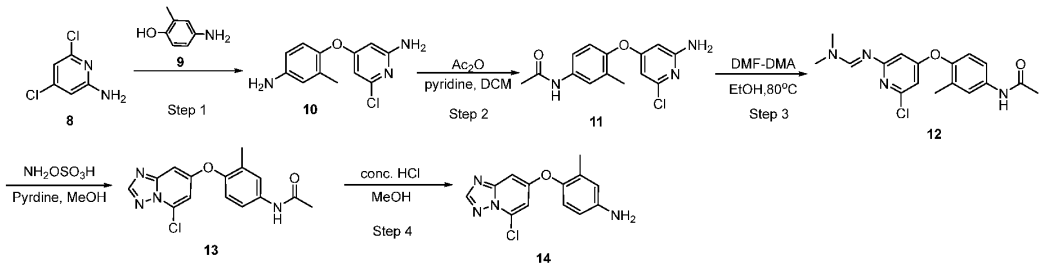
Step 2: A mixture of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazole **3** (2.00 g, 8.16 mmol, 1.00 equiv.) and H_2O_2 (30%, 50.00 mL, 2.00

equiv.) in THF (60.00 mL) was stirred at 0 °C for 1 h and then concentrated under vacuum to afford benzo[d]oxazol-5-ol **4** (crude, 2.30 g) as a black oil, which was used for the next step without further purification. LCMS (ESI, *m/z*): 136 $[M+H]^+$.

Step 3: A mixture of benzo[d]oxazol-5-ol **4** (1.28 g, 8.16 mmol, 1.00 equiv.), 1-fluoro-2-methyl-4-nitrobenzene **5** (1.39 g, 8.98 mmol, 1.10 equiv.) and K_2CO_3 (3.38 g, 24.48 mmol, 3.00 equiv.) in DMF (30.00 mL) was stirred at 50 °C for 16 h. The resulting mixture was diluted with water and extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% MeOH in DCM) to afford 5-(2-methyl-4-nitrophenoxy)benzo[d]oxazole **6** (610.0 mg, 28%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.84 (s, 1H), 8.26 (s, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.63 (s, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 9.2 Hz, 1H), 2.43 (s, 3H). LCMS (ESI, *m/z*): 271 $[M + H]^+$.

Step 4: A mixture of 5-(2-methyl-4-nitrophenoxy)benzo[d]oxazole **6** (250.0 mg, 0.92 mmol, 1.00 equiv.) and Pd/C (wet, 10%, 25.0 mg, 1/10 w/w) in EtOH (5.00 mL) was stirred at ambient temperature for 2 h under H_2 atmosphere and then filtered. The filtrate was concentrated under vacuum to afford 4-(benzo[d]oxazol-5-yloxy)-3-methylaniline **7** (crude, 210.0 mg) as a yellow solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 241 $[M + H]^+$.

Synthesis of *N*-(4-(5-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-*d*]pyrimidin-4-amine 14



Step 1: To a stirred solution of 4-amino-2-methylphenol **8** (3.2 g, 25.9 mmol) in DMSO (50 mL) was added potassium tert-butoxide (7.0 g, 61.3 mmol). After stirring at r.t for 0.5 h, 4,6-dichloropyridin-2-amine **9** (5.0 g, 30.7 mmol) was added. The reaction was

stirred at 80 °C under N_2 for 18 hrs. After cooling to r.t., the reaction mixture was poured into water (150 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography (0 - 100% of EtOAc in PE) to give 4-(4-amino-2-methylphenoxy)-6-chloropyridin-2-amine **10** (4.9 g, 52.2% yield) as a yellow solid. LCMS (ESI) (m/z): 250 $[M+H]^+$.

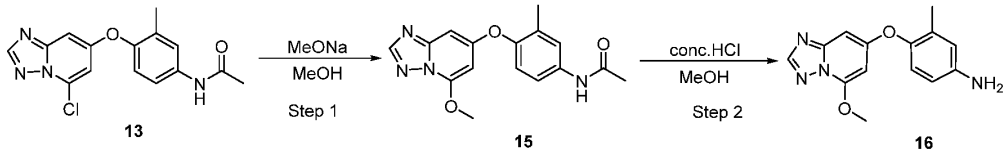
Step 2: To a stirred solution of 4-(4-amino-2-methylphenoxy)-6-chloropyridin-2-amine **10** (3.0 g, 12.0 mmol) in DCM (20 mL) were added pyridine (1.4 g, 18.0 mmol) and acetic anhydride (1.2 g, 12.0 mmol) at 0 °C. The reaction was stirred at r.t for 1 h, and then concentrated to dryness. The residue was purified by flash chromatography (0 - 33% of EtOAc in PE) to give N-(4-((2-amino-6-chloropyridin-4-yl)oxy)-3-methylphenyl)acetamide **11** (2.5 g , 71.3% yield) as a yellow oil. LCMS (ESI) m/z: 292 $[M+H]^+$.

Step 3: To a solution of N-(4-((2-amino-6-chloropyridin-4-yl)oxy)-3-methylphenyl)acetamide **11** (2.5 g, 8.6 mmol) in EtOH (20 mL) was added DMF-DMA (3.1 g, 25.7 mmol). The reaction was degassed with N_2 and stirred at 80 °C for 36 hrs. The reaction was concentrated to dryness. The residue was purified by flash chromatography (0 - 66% of EtOAc in PE) to give (E)-N-(4-((2-chloro-6-(((dimethylamino)methylene)amino)pyridin-4-yl)oxy)-3-methylphenyl)acetamide **12** (2.5 g , 84.1% yield) as a yellow solid. LCMS ESI (m/z): 347 $[M+H]^+$.

Step 4: To a stirred solution of (E)-N-(4-((2-chloro-6-(((dimethylamino)methylene)amino)pyridin-4-yl)oxy)-3-methylphenyl)acetamide **12** (1.0 g, 2.9 mmol) in MeOH (20 mL) were added hydroxylamine-O-sulfonic acid (0.3 g, 3.0 mmol) and pyridine (0.3 g, 4.3 mmol) at 0 °C. The mixture was degassed with N_2 and stirred at r.t for 18 hrs. The reaction was concentrated to dryness. The residue was dissolved in THF (20 mL) and trifluoroacetic anhydride (0.7 g, 3.5 mmol) was added. The reaction was stirred at 40 oC overnight, then quenched with ice water (0.5 mL) and concentrated to dryness. The residue was purified by flash chromatography (0 - 100% of EtOAc in PE) to give N-(4-((5-chloro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)-3-methylphenyl)acetamide **13** (150 mg, 12.3% yield) as a yellow oil. LCMS ESI (m/z): 317 $[M+H]^+$.

Step 5: To a stirred solution of N-(4-((5-chloro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)-3-methylphenyl)acetamide **13** (150 mg, 0.5 mmol) in MeOH (2 mL) was added conc. HCl (0.2 mL, 12 N). The reaction was stirred at 80 ºC for 18 hrs. The reaction was concentrated and purified by prep-TLC (DCM : MeOH = 10 : 1) to give 4-((5-chloro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)-3-methylaniline **14** (80 mg, 61.5% yield) as a yellow solid. LCMS ESI (m/z): 275 $[M+H]^+$.

Synthesis of 4-((5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)-3-methylaniline 16

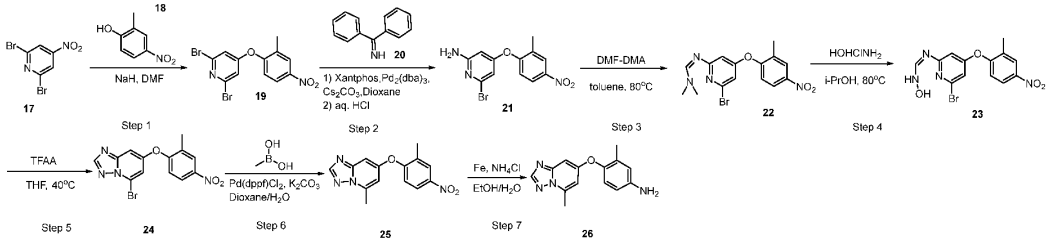


13 15 16

Step 1: To a solution of *N*-[4-({5-chloro-[1,2,4]triazolo[1,5-a]pyridin-7-yl}oxy)-3-methylphenyl]acetamide **13** (150 mg, 0.5 mmol) in MeOH (5.0 mL) was added sodium methoxide (256 mg, 1.4 mmol). The reaction was stirred at 70 °C for 4 hours. After cooling to r.t., the reaction was quenched by the addition of saturated aqueous NH_4Cl. The reaction mixture was extracted with EA (2 x 10 mL). The combined extracts were washed with water (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give crude *N*-[4-({5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl}oxy)-3-methylphenyl]acetamide **15** (148 mg, 100%) as a brown solid. The residue was used directly in the next step. LCMS ESI (m/z): 313 $[M+H]^+$.

Step 2: To a solution of *N*-[4-({5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl}oxy)-3-methylphenyl]acetamide **15** (140 mg, 0.5 mmol) in MeOH (5.0 mL) was added conc. HCl (1.0 mL). The reaction was stirred at 70 °C overnight. After cooling to 0°C, the reaction mixture was neutralized with aq. NH_3 and then concentrated in vacuo. The residue was purified by prep-TLC (6% of MeOH in DCM) to give 4-((5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)-3-methylaniline **16** (42 mg, 34.7%) as a light yellow solid. LCMS (ESI) m/z: 271$[M+H]^+$.

Synthesis of 3-methyl-4-({5-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl}oxy)aniline 26



Step 1: To a stirred solution of 2-methyl-4-nitrophenol **17** (2.70 g, 17.7 mmol) in DMF (50 mL) was added NaH (0.71 g, 17.7 mmol, 60% in mineral oil) at 0 °C under N_2. After stirring at 0 °C for 30 min, a solution of 2,6-dibromo-4-nitropyridine **18** (5.0 g, 17.7 mmol) in DMF (30 mL) was added at 0 °C. The reaction was stirred at 70 °C overnight, then quenched with sat. NH_4Cl (10 mL) and extracted with EtOAc (100 mL x 2). The combined organic solution was dried over Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (PE:EtOAc = 5:1) to give 2,6-dibromo-4-(2-methyl-4-nitrophenoxy)pyridine **19** (4.4 g, 48.6% yield) as a yellow solid. LCMS (ESI) m/z: 387/389/391 $[M+H]^+$.

Step 2: To a stirred solution of 2,6-dibromo-4-(2-methyl-4-nitrophenoxy)pyridine **19** (4.40 g, 8.66 mmol) and diphenylmethanimine **20** (1.5 mL, 8.66 mmol) in dioxane (100 mL), were added Xantphos (1.0 g, 1.73 mmol), $Pd_2(dba)_3$ (0.79 g, 0.87 mmol) and Cs_2CO_3 (5.64 g, 17.3 mmol) at 25 °C. After stirring at 80 °C for 4 h under N_2, LCMS showed the reaction worked well. HCl (26 mL, 1M) was then added to this solution at 25 °C. This reaction was stirred at 25 °C for 1 h. Then $NaHCO_3$ solution was added to adjust the PH > 7. Then the mixture was extracted with EtOAc (100 mL x 2). The combined organic solution was dried over Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (PE:EtOAc = 3:1) to give 6-bromo-4-(2-methyl-4-nitrophenoxy)pyridin-2-amine **21** (1.21 g, 43.1% yield) as a yellow solid. LCMS (ESI) m/z: 324/326 $[M+H]^+$.

Step 3: To a stirred solution of 6-bromo-4-(2-methyl-4-nitrophenoxy)pyridin-2-amine **21** (1.21 g, 3.74 mmol) in toluene (20 mL) was added DMF-DMA (0.58 g, 4.86 mmol) at 25 °C. The reaction was stirred at 80 °C overnight. LCMS showed the reaction worked well. Then the reaction mixture was concentrated to give crude product (*Z*)-*N*'-[6-

bromo-4-(2-methyl-4-nitrophenoxy)pyridin-2-yl]-*N,N*-dimethylmethanimidamide **22** (1.42 g, 80.2% yield) as a brown oil. LCMS (ESI) m/z: 379/381 $[M+H]^+$.

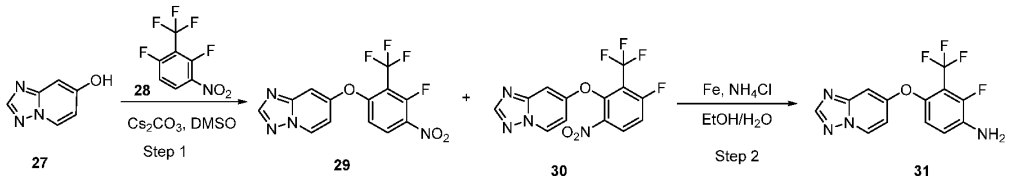
Step 4: To a stirred solution of (*Z*)-*N'*-[6-bromo-4-(2-methyl-4-nitrophenoxy)pyridin-2-yl]-*N,N*-dimethylmethanimidamide **22** (1.42 g, 3.75 mmol) in *i*-PrOH (20 mL) was added hydroxylamine. HCl salt (0.29 g, 4.12 mmol) at 25 °C. After stirring at 80 °C for 1 h, LCMS showed the reaction worked well. The mixture was diluted by DCM (60 mL) and washed by water (20 mL). This separated organic solution was dried over Na_2SO_4 and concentrated to give crude product (Z)-N'-[6-bromo-4-(2-methyl-4-nitrophenoxy)pyridin-2-yl]-N-hydroxymethanimidamide **23** (1.38 g, 70.5% yield) as a yellow solid. LCMS (ESI) m/z: 367/369 $[M+H]^+$.

Step 5: To a stirred solution of (*Z*)-*N'*-[6-bromo-4-(2-methyl-4-nitrophenoxy)pyridin-2-yl]-*N*-hydroxymethanimidamide **23** (1.38 g, 3.759 mmol) in THF (20 mL) was added trifluoroacetic anhydride (0.87 g, 4.13 mmol) at 25°C. After stirring at 40 °C overnight under N_2, LCMS showed the reaction worked well. The reaction mixture was added $NaHCO_3$ solution to adjust the PH to greater than 7. And then the mixture was extracted with EtOAc (20 mLx2), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (PE:EtOAc = 2:1) to give 5-bromo-7-(2-methyl-4-nitrophenoxy)-[1,2,4]triazolo[1,5-a]pyridine **24** (300 mg, 22.9% yield) as a yellow solid. LCMS (ESI) m/z: 349/351 $[M+H]^+$.

Step 6: To a stirred solution of 5-bromo-7-(2-methyl-4-nitrophenoxy)-[1,2,4]triazolo[1,5-a]pyridine **24** (300 mg, 0.86 mmol) and methylboronic acid (61.7 mg, 1.03 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was added $Pd(dppf)Cl_2$ (126 mg, 0.17 mmol) and K_2CO_3 (238 mg, 1.72 mmol) at r.t. The reaction was degassed under N_2 atmosphere for three times and stirred at 80 °C overnight. The reaction was cooled to r.t, diluted with EtOAc (25 mL). This organic solution was washed with brine (25 mL), dried over Na_2SO_4 and concentrated to give crude product 5-methyl-7-(2-methyl-4-nitrophenoxy)-[1,2,4]triazolo[1,5-*a*]pyridine **25** (244 mg, 80.0% yield) as a black solid. LCMS (ESI) m/z: 285 $[M+H]^+$.

Step 7: To a mixture of 5-methyl-7-(2-methyl-4-nitrophenoxy)-[1,2,4]triazolo[1,5-*a*]pyridine **25** (244 mg, 0.86 mmol) in EtOH (5 mL) and water (1 mL) were added iron powder (479 mg, 8.58 mmol) and NH_4Cl (459 mg, 8.58 mmol). This mixture was stirred at 80 °C for 2 hours. Then this mixture was filtered immediately and concentrated. The residue was purified by column chromatography on silica gel (PE:EA=0:1) to give 3-methyl-4-({5-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl}oxy)aniline **26** (133 mg, 61.0% yield) as a yellow solid. LCMS (ESI) m/z: 255 $[M+H]^+$.

Synthesis of 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-(trifluoromethyl)aniline 31

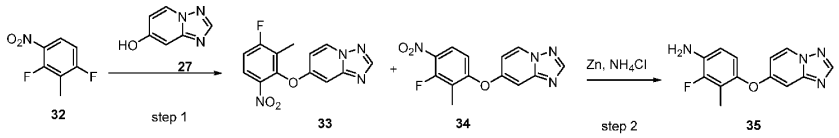


Step 1: To a stirred mixture of Cs_2CO_3 (1.44 g, 4.44 mmol) in DMSO (10 mL), was added a solution of [1,2,4]triazolo[4,3-*a*]pyridin-7-ol **27** (500 mg, 3.70 mmol) and 1,3-difluoro-4-nitro-2-(trifluoromethyl)benzene **28** (1.68 g, 7.40 mmol) in DMSO (10 mL) dropwise at room temperature. Then the resulting mixture was stirred at room temperature for 15 min. LCMS showed the reaction was completed. The reaction mixture was quenched by adding ice-water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to dryness to give a mixture of 7-(3-fluoro-4-nitro-2-(trifluoromethyl)phenoxy)-[1,2,4]triazolo[1,5-*a*]pyridine **29** and 7-(3-fluoro-6-nitro-2-(trifluoromethyl)phenoxy)-[1,2,4]triazolo[1,5-*a*]pyridine **30** (1.10 g, crude) as a yellow solid. The crude product was directly used in the next step without any further purification. LCMS ESI (m/z): 343 $[M+H]^+$.

Step 2: To a solution of 7-(3-fluoro-4-nitro-2-(trifluoromethyl)phenoxy)-[1,2,4]triazolo[1,5-*a*]pyridine and 7-(3-fluoro-6-nitro-2-(trifluoromethyl)phenoxy)-[1,2,4]triazolo[1,5-*a*]pyridine (1.10 g, crude) in EtOH (30 mL) and H_2O (10 mL), were added Fe (0.90 g, 16.02 mmol) and NH_4Cl (1.72 g, 32.11 mmol). Then the resulting mixture was stirred at 75°C for 1 h. LCMS showed the reaction was completed. The reaction

mixture was concentrated *in vacuo* to give the residue. The residue was purified by flash chromatography with EtOAc in PE (0 - 10%, V/V) to give 4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-2-fluoro-3-(trifluoromethyl)aniline **31** (320 mg, 27.6%, yield over two steps) as a yellow solid. LCMS ESI (m/z): 313 $[M+H]^+$.

Synthesis of 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylaniline 35

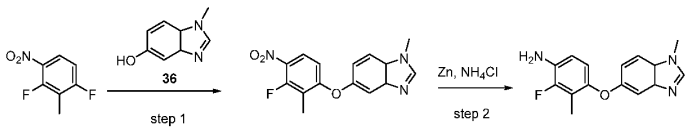


Step 1: To a stirred mixture of Cs_2CO_3 (21.7 g, 66.6 mmol) in DMSO (150 mL), were added a solution of 1,3-difluoro-2-methyl-4-nitrobenzene **32** (23.1 g, 133.5 mmol) and [1,2,4]triazolo[1,5-a]pyridin-7-ol **27** (9.0 g, 66.7 mmol) in DMSO (300 mL) dropwise at 80°C in a period of 1 h. Then the resulting mixture was stirred at 80°C for another 0.5 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature, diluted with water (800 mL) and extracted with EtOAc (3 × 600 mL). The combined organic phases were washed with brine (600 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a mixture of 7-(3-fluoro-2-methyl-4-nitrophenoxy)-[1,2,4]triazolo[1,5-*a*]pyridine **33** and 7-(3-fluoro-2-methyl-6-nitrophenoxy)-[1,2,4]triazolo[1,5-*a*]pyridine **34** (21.1 g, crude) as a yellow oil. The crude product was directly used in the next step without further purification. LCMS ESI (m/z): 289 $[M+H]^+$

Step 2: To a mixture of 7-(3-fluoro-2-methyl-4-nitrophenoxy)-[1,2,4]triazolo[1,5-*a*]pyridine and 7-(3-fluoro-2-methyl-6-nitrophenoxy)-[1,2,4]triazolo[1,5-*a*]pyridine (21.1 g, crude) in EtOH (200 mL), were added Fe (18.7 g, 333.7 mmol), NH_4Cl (35.4 g, 667.4 mmol) and water (60 mL). Then the resulting mixture was stirred at 80°C for 1 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature, diluted with EtOAc (600 mL) and filtered. The filtrate was washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by flash column chromatography on silica gel with EtOAc in PE (30 - 70%, V/V) to give pure 4-([1,2,4]triazolo[1,5-*a*]pyridin-7-

yloxy)-2-fluoro-3-methylaniline **35** (3.91 g, 22.7%, yield over two steps) as a light yellow solid and some crude product as a gray solid. LCMS ESI (m/z): 259 $[M+H]^+$

Synthesis of 2-fluoro-3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline 38

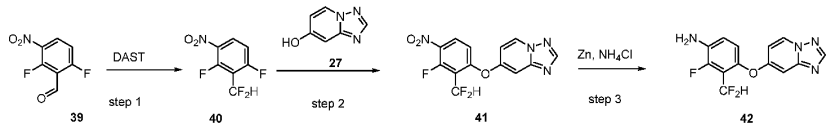


32 37 38

Step 1: A mixture of 1-methyl-1H-benzo[d]imidazol-5-ol **36** (5.5 g, 37.16 mol, 1.00 equiv), 1,3-difluoro-2-methyl-4-nitrobenzene (12.8 g, 74.32 mol, 2.00 equiv) **32** and K_2CO_3 (15.4 g, 111.48 mol, 3.00 equiv) in DMF (50.0 mL) was stirred at ambient temperature for 16 h and then filtered through a pad of celite. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (0-70% acetonitrile in water (containing 0.05% NH_4HCO_3)) to afford 5-(3-fluoro-2-methyl-4-nitrophenoxy)-1-methyl-1H-benzo[d]imidazole **37** (1.4 g, 12%) as a yellow solid. LCMS (ESI, m/z): 304 $[M + H]^+$.

Step 2: A mixture of 5-(3-fluoro-2-methyl-4-nitrophenoxy)-1-methyl-1H-benzo[d]imidazole **37** (1.4 g, 4.65 mol, 1.00 equiv) and zinc powder (1.5 g, 23 mol, 5.00 equiv) in MeOH (22.4 mL) and water (5.6 mL) was stirred at 70 °C for 3 h and then filtered through a pad of celite. The filtrate was diluted with water and the mixture was extracted with DCM 3 times. The organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford 2-fluoro-3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline **38** (crude, 3.0 g) as a yellow solid, which was used for the next step without further purification. 1H NMR (300 MHz, DMSO-d6) δ 8.36 (s, 1H), 7.59 (d, J = 9.0 Hz, 1H), 7.00-6.96 (m, 2H), 6.60 (t, J = 9.0 Hz, 1H), 6.51 (d, J = 8.7 Hz, 1H), 4.96 (s, 2H), 3.88 (s, 3H), 1.95 (d, J = 5.4 Hz, 3H). LCMS (ESI, m/z): 274 $[M + H]^+$.

Synthesis of 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-(difluoromethyl)aniline 42



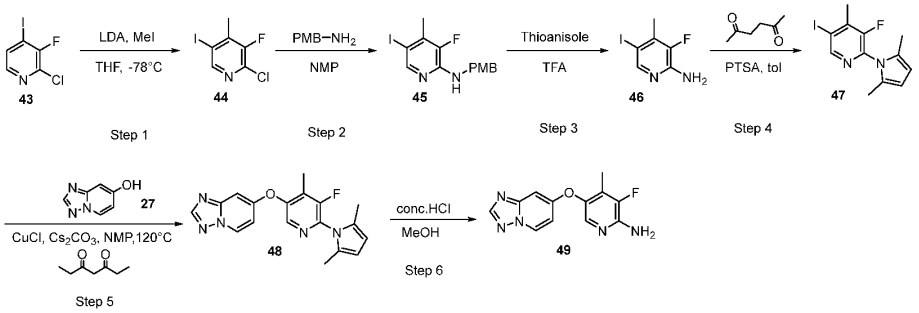
39 40 41 42

Step 1: To a stirred solution of 2,6-difluoro-3-nitrobenzaldehyde **39** (4.50 g, 24.05 mmol, 1.00 equiv) in DCM (30.0 mL) was added dropwise a solution of DAST (11.6 g, 72.15 mmol, 3.0 equiv) in DCM (10 mL) at -78 °C under N_2 atmosphere. The resulting mixture was stirred at this temperature for 4 h and then quenched at 0 °C with water/ice and extracted with DCM 3 times. The combined organic layers were concentrated under vacuum to afford 2-(difluoromethyl)-1,3-difluoro-4-nitrobenzene **40** (crude, 4.70 g), which was used in the next step directly without further purification.

Step 2: To a stirred mixture of 2-(difluoromethyl)-1,3-difluoro-4-nitrobenzene **40** (3.60 g, 17.21 mmol, 1.00 equiv) and [1,2,4]triazolo[1,5-a]pyridin-7-ol **27** (2.56 g, 18.93 mmol, 1.10 equiv) in acetonitrile (20.0 mL) at ambient temperature was added DIEA (6.68 g, 51.65 mmol, 3.00 equiv). The resulting mixture was stirred at this temperature for 4 h and then diluted with water and extracted with EtOAc 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford 7-[2-(difluoromethyl)-3-fluoro-4-nitrophenoxy]-[1,2,4]triazolo[1,5-a]pyridine **41** (850 mg, 14%) as a yellow solid. LCMS (ESI, *m/z*): 325 $[M + H]^+$.

Step 3: To a stirred mixture of 7-[2-(difluoromethyl)-3-fluoro-4-nitrophenoxy]-[1,2,4]triazolo[1,5-a]pyridine **41** (500.0 mg, 1.54 mmol, 1.00 equiv) in THF (10 mL) and water (2 mL) was added Zn powder (806.6 mg, 12.33 mmol, 8.00 equiv) and NH_4Cl (659.9 mg, 12.33 mmol, 8.00 equiv). The resulting mixture was stirred at 70 °C for 3 h and filtered. The filtrate was concentrated under vacuum. The residue was diluted with water and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford 3-(difluoromethyl)-2-fluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline **42** (crude, 420 mg) as a yellow solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 295 $[M + H]^+$.

Synthesis of 5-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluoro-4-methylpyridin-2-amine 49



Step 1: To a solution of LDA (21.3 mL, 42.73 mmol, 2.0 M in toluene) in THF (60 mL) was added a solution of 2-chloro-3-fluoro-4-iodopyridine **43** (10.0 g, 38.84 mmol) in THF (20 mL). Then the resulting mixture was stirred under N_2 at -78 °C for 4 h, iodomethane (2.7 mL, 42.73 mmol) was added and the reaction mixture was stirred at -78 °C for additional 1 h. After additional 1 h, the reaction was quenched with sat. aqueous NH_4Cl solution (50 mL), warmed to room temperature and extracted EtOAc (2 × 80 mL). The organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with EtOAc in PE (0 - 3%, V/V) to give 2-chloro-3-fluoro-5-iodo-4-methylpyridine **44** (6.10 g, 57.8% yield) as a yellow oil. LC/MS ESI (m/z): 272/274 $[M+H]^+$.

Step 2: To a solution of 2-chloro-3-fluoro-5-iodo-4-methylpyridine **44** (2.50 g, 9.20 mmol) in NMP (10 mL) was added (4-methoxyphenyl)methanamine (1.80 mL, 13.81 mmol). Then the resulting mixture was stirred at 120 °C for 16 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature, diluted with water (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (2 × 25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with EtOAc in PE (0 - 5%, V/V) to give 3-fluoro-5-iodo-*N*-(4-methoxybenzyl)-4-methylpyridin-2-amine **45** (1.40 g, 40.8% yield) as a yellow oil. LCMS ESI (m/z): 373 $[M+H]^+$.

Step 3: To a solution of 3-fluoro-5-iodo-*N*-(4-methoxybenzyl)-4-methylpyridin-2-amine **45** (650 mg, 1.74 mmol) in TFA (10 mL), was added thioanisole (10 mg, 0.087 mmol). Then the resulting mixture was degassed under N_2 for twice and stirred at room temperature for 16 h. LCMS showed the reaction was completed. The reaction mixture was concentrated *in vacuo* to give the residue, the residue was basified by adding sat. aqueous $NaHCO_3$ solution to pH ~ 8 and extracted with DCM (3 × 20 mL). The organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with EtOAc in PE (0 - 10%, V/V) to give 3-fluoro-5-iodo-4-methylpyridin-2-amine **46** (410 mg, 93.1% yield) as a white solid. LCMS ESI (m/z): 253 $[M+H]^+$.

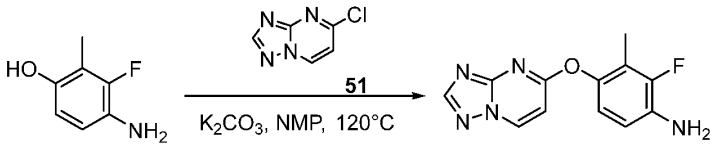
Step 4: To a solution of 3-fluoro-5-iodo-4-methylpyridin-2-amine **46** (410 mg, 1.62 mmol) in toluene (10 mL), were added hexane-2,5-dione (557 mg, 4.88 mmol) and PTSA (14 mg, 0.081 mmol). Then the resulting mixture was stirred at 120 °C for 16 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature and concentrated *in vacuo* to give the residue. The residue was diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with EtOAc in PE (0 - 5%, V/V) to give 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-fluoro-5-iodo-4-methylpyridine **47** (440 mg, 81.9% yield) as a yellow oil. LCMS ESI (m/z): 331$[M+H]^+$.

Step 5: To the solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-fluoro-5-iodo-4-methylpyridine **47** (296 mg, 0.89 mmol) in NMP (15 mL), were added [1,2,4]triazolo[1,5-*a*]pyridin-7-ol (242 mg, 1.79 mmol), CuCl (27 mg, 0.26 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (64 mg, 0.44 mmol) and Cs_2CO_3 (584 mg, 1.79 mmol). The reaction mixture was degassed under N_2 for three times and stirred at 120 °C for 16 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature, diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with EtOAc in PE (0 - 30%, V/V) to give 7-((6-(2,5-

dimethyl-1*H*-pyrrol-1-yl)-5-fluoro-4-methylpyridin-3-yl)oxy)-[1,2,4]triazolo[1,5-*a*]pyridine **48** (54 mg, 17.8% yield) as a yellow solid. LCMS ESI (m/z): 338 $[M+H]^+$.

Step 6: To a solution of 7-((6-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluoro-4-methylpyridin-3-yl)oxy)-[1,2,4]triazolo[1,5-*a*]pyridine **48** (54 mg, 0.16 mmol) in MeOH (3 mL) was added conc. HCl (3 mL). Then the resulting mixture was stirred at 60 °C for 16 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature and concentrated *in vacuo* to give the residue. The residue was basified by adding sat. aqueous $NaHCO_3$ solution to pH ~ 8 and extracted with DCM (3 × 15 mL). The combined organic phases were washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with MeOH in DCM (0 - 7%, V/V) to give 5-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-fluoro-4-methylpyridin-2-amine **49** (38 mg, 91.6% yield) as a yellow solid. LCMS ESI (m/z): 260 $[M+H]^+$.

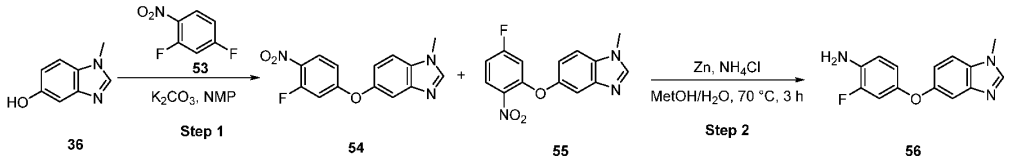
Synthesis of 4-([1,2,4]triazolo[1,5-a]pyrimidin-5-yloxy)-2-fluoro-3-methylaniline 52



50 **52**

Step 1: To a stirred solution of 4-amino-3-fluoro-2-methylphenol **50** (92 mg, 0.65 mmol, synthesized based on the preparation disclosed in WO2010051373) and 5-chloro-[1,2,4]triazolo[1,5-*a*]pyrimidine **51** (120 mg, 0.78 mmol) in NMP (4 mL), was added K_2CO_3 (270 mg, 1.96 mmol). Then the resulting mixture was stirred at 120 °C for 2 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature, diluted with sat. aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with sat. aqueous NH_4Cl solution (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was triturated with MeOH/DCM (1/30, V/V) to give 4-([1,2,4]triazolo[1,5-*a*]pyrimidin-5-yloxy)-2-fluoro-3-methylaniline **52** (111 mg, 65.7% yield) as a brown solid. LCMS ESI (m/z): 260 $[M+H]^+$

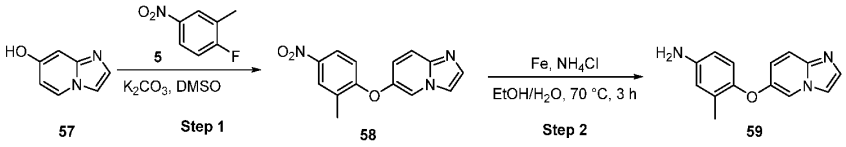
Synthesis of 2-fluoro-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]aniline 56



Step 1: A mixture of 1-methyl-1,3-benzodiazol-5-ol **36** (500 mg, 3.38 mmol, 1 equiv), 2,4-difluoro-1-nitrobenzene **53** (644.25 mg, 4.05 mmol, 1.2 equiv) and K_2CO_3 (1.40 g, 10.14 mmol, 3 equiv) in NMP (6 mL) was stirred at ambient temperature for 3 h and then filtered. The filtrate was diluted with EtOAc. The organic solution was washed with water twice and brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0 - 10% MeOH in DCM) to afford a mixture of **54** and **55** (900 mg, 92%) as a yellow solid. LCMS (ESI, *m/z*): 288 $[M + H]^+$.

Step 2: A mixture of 5-(3-fluoro-4-nitrophenoxy)-1-methyl-1,3-benzodiazole (980 mg, 3.41 mmol, 1 equiv), Zn (2.23 g, 34.12 mmol, 10 equiv) and NH_4Cl (1.82 g, 34.12 mmol, 10 equiv) in MeOH (5 mL) and H_2O (5 mL) was stirred at 70 °C for 3 h under N_2 atmosphere and then filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0 - 10% MeOH in DCM) to afford 2-fluoro-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]aniline (470 mg, 53%) **56** as a yellow solid. LCMS (ESI, *m/z*): 258 $[M + H]^+$.

Synthesis of 4-(imidazo[1,2-a]pyridin-7-yloxy)-3-methylaniline 59

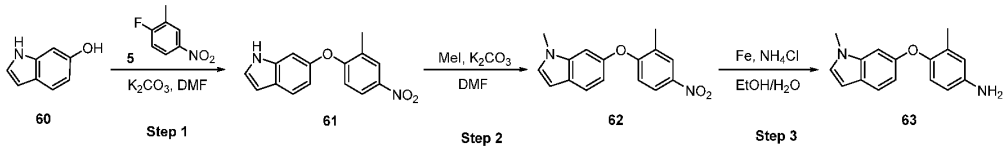


Step 1: To a solution of imidazo[1,2-*a*]pyridin-7-ol **57** (300 mg, 2.24 mmol) in DMSO (5 mL), were added 1-fluoro-2-methyl-4-nitrobenzene **5** (347 mg, 2.27 mmol) and K_2CO_3 (927 mg, 6.69 mmol). Then the resulting mixture was stirred at 100 °C for 16 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature, diluted with sat. aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude

product was purified by column chromatography on silica gel with EtOAc in PE (0 - 50%, V/V) to give 7-(2-methyl-4-nitrophenoxy)imidazo[1,2-*a*]pyridine **58** (380 mg, 63.1% yield) as a yellow solid. LCMS ESI (m/z): 270 $[M+H]^+$.

Step 2: To a solution of 7-(2-methyl-4-nitrophenoxy)imidazo[1,2-*a*]pyridine **58** (380 mg, 1.41 mmol) in EtOH (10 mL) and water (2 mL), were added iron powder (788 mg, 14.11 mmol) and ammonium chloride (755 mg, 14.11 mmol). Then the resulting mixture was stirred at 80 °C for 3 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with EtOAc in PE (0 - 90%, V/V) to give 4-(imidazo[1,2-*a*]pyridin-7-yloxy)-3-methylaniline **59** (180 mg, 53.30% yield) as a yellow solid. LCMS ESI (m/z): 240 $[M+H]^+$.

Synthesis of 3-methyl-4-((1-methyl-1H-indol-6-yl)oxy)aniline 63



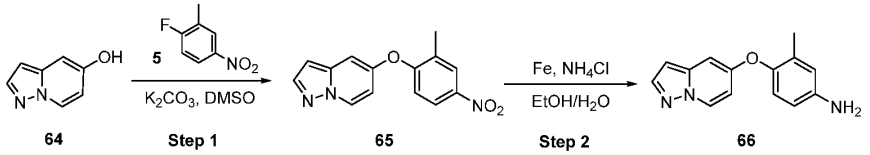
Step 1: To a solution of 1*H*-indol-6-ol **60** (940 mg, 7.1 mmol) in DMF (10 mL), were added 1-fluoro-2-methyl-4-nitrobenzene **5** (1.0 g, 6.45 mmol) and K_2CO_3 (1.49 g, 10.76 mmol). Then the resulting mixture was stirred at 80 °C for 16 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature, diluted with sat. aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with sat. aqueous NH_4Cl solution (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by column chromatography on silica gel with EtOAc in PE (0 - 50%, V/V) to give 6-(2-methyl-4-nitrophenoxy)-1*H*-indole **61** (1.00 g, 57.8%) as a yellow gum. LCMS ESI (m/z): 269 $[M+H]^+$.

Step 2: To a solution of 6-(2-methyl-4-nitrophenoxy)-1*H*-indole **61** (686 mg, 2.56 mmol) in DMF (10 mL), were added K_2CO_3 (707 mg, 5.10 mmol) and iodomethane (545 mg, 3.84 mmol) was added in sequence. Then the resulting mixture was stirred at 80 °C for 16 h. LCMS showed the reaction was completed. The reaction mixture was diluted with

sat. aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with sat. aqueous NH_4Cl solution (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by column chromatography on silica gel with EtOAc in PE (0 - 50%, V/V) to give 1-methyl-6-(2-methyl-4-nitrophenoxy)-1*H*-indole **62** (650 mg, 90.0% yield) as a yellow gum. LCMS ESI (m/z): 283 $[M+H]^+$.

Step 3: To a solution of 1-methyl-6-(2-methyl-4-nitrophenoxy)-1*H*-indole **62** (200 mg, 0.71 mmol) in EtOH (8 mL) and water (3 mL), were added iron powder (198 mg, 3.54 mmol) and ammonium chloride (379 mg, 7.08 mmol). Then the resulting mixture was stirred at 75°C for 0.5 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with EtOAc in PE (0 - 90%, V/V) to give 3-methyl-4-((1-methyl-1*H*-indol-6-yl)oxy)aniline **63** (135 mg, 75.5% yield) as a light-yellow gum. LCMS ESI (m/z): 253 $[M+H]^+$.

Synthesis of 3-methyl-4-(pyrazolo[1,5-a]pyridin-5-yloxy)aniline 66

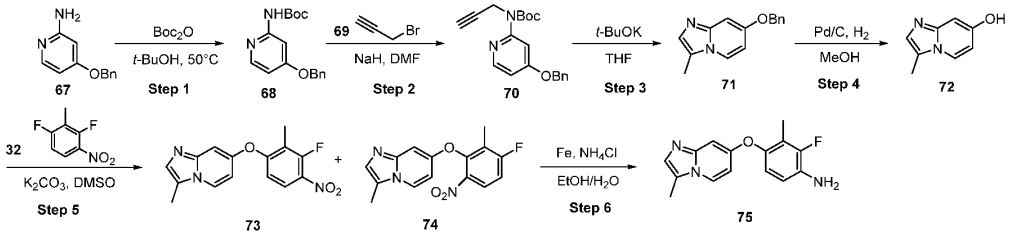


64 Step 1 65 Step 2 66

Step 1: To a solution of pyrazolo[1,5-*a*]pyridin-5-ol **64** (150 mg, 1.12 mmol) in DMSO (5 mL), were added 1-fluoro-2-methyl-4-nitrobenzene **5** (173 mg, 1.12 mmol) and K_2CO_3 (464 mg, 3.36 mmol). Then the resulting mixture was stirred at 100 °C for 16 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature, diluted with sat. aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by column chromatography on silica gel with EtOAc in PE (0 - 50%, V/V) to give 5-(2-methyl-4-nitrophenoxy)pyrazolo[1,5-*a*]pyridine **65** (250 mg, 83.0% yield) as a yellow solid. LCMS ESI (m/z):270 $[M+H]^+$.

Step 2: To a solution of 5-(2-methyl-4-nitrophenoxy)pyrazolo[1,5-*a*]pyridine **65** (250 mg, 0.93 mmol) in EtOH (10 mL) and water (2 mL), were added iron powder (518 mg, 9.28 mmol) and ammonium chloride (496 mg, 9.28 mmol). Then the resulting mixture was stirred at 80 °C for 3 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with EtOAc in PE (0 - 90%, V/V) to give 3-methyl-4-(pyrazolo[1,5-*a*]pyridin-5-yloxy)aniline **66** (200 mg, 90.0% yield) as a yellow solid. LCMS ESI (m/z): 240 $[M+H]^+$.

Synthesis of 2-fluoro-3-methyl-4-((3-methylimidazo[1,2-a]pyridin-7-yl)oxy)aniline 75



Step 1: To a solution of 4-(benzyloxy)pyridin-2-amine **67** (5.00 g, 0.025 mol) in *t*-BuOH (75 mL) was added Boc_2O (6.00 g, 0.027 mmol) dropwise at room temperature. Then the resulting mixture was stirred at 50 °C for 1 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with EtOAc in PE (0 - 50%, V/V) to give *tert*-butyl (4-(benzyloxy)pyridin-2-yl)carbamate **68** (6.63 g, 88.5% yield) as a white solid. LCMS ESI (m/z): 301 $[M+H]^+$.

Step 2: To a stirred solution of *tert*-butyl (4-(benzyloxy)pyridin-2-yl)carbamate **68** (6.50 g, 21.6 mmol) in DMF (50 mL), was added NaH (1.30 g, 32.5 mmol, 60% in mineral oil) at 0 °C. After stirring at 0 °C for 1 h, a solution of 3-bromoprop-1-yne **69** (2.78 mL, 32.5 moml) in DMF (15 mL) was added dropwise. Then the resulting mixture was stirred at room temperature for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with sat. aqueous NH_4Cl solution (100 mL) and extracted with

EtOAc (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with EtOAc in PE (0 - 50%, V/V) to give *tert*-butyl (4-(benzyloxy)pyridin-2-yl)(prop-2-yn-1-yl)carbamate **70** (6.08 g, 83.1% yield) as a yellow oil. LCMS ESI (m/z): 339 $[M+H]^+$.

Step 3: To a solution of *tert*-butyl (4-(benzyloxy)pyridin-2-yl)(prop-2-yn-1-yl)carbamate **70** (6.07 g, 17.96 mmol) in THF (60 mL) was added a solution of *t*-BuOK (2.42 g, 21.56 mmol) in THF (10 mL) dropwise at room temperature. Then the resulting mixture was stirred at room temperature for 1 h. LCMS showed the reaction was completed. The reaction mixture was quenched with sat. aqueous NH_4Cl solution (60 mL) and extracted with EtOAc (3 × 60 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the residue. The residue was purified by flash chromatography with EtOAc in PE (0 - 60%, V/V) to give 7-(benzyloxy)-3-methylimidazo[1,2-*a*]pyridine **71** (3.34 g, 78.2% yield) as a yellow solid.
LCMS ESI (m/z): 239 $[M+H]^+$.

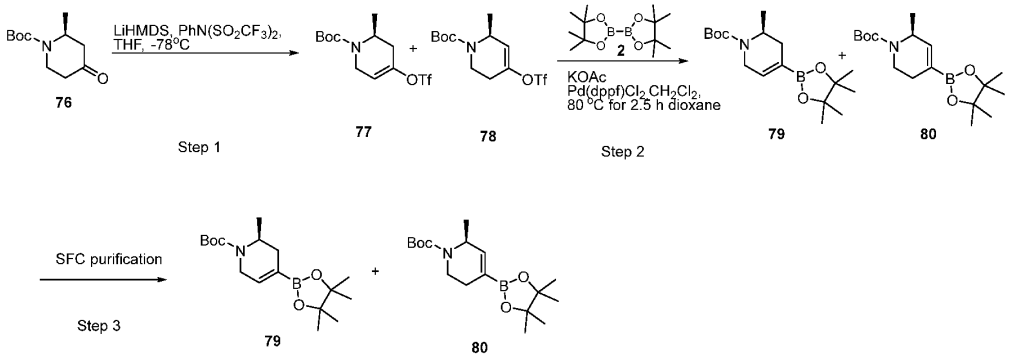
Step 4: To a solution of 7-(benzyloxy)-3-methylimidazo[1,2-*a*]pyridine **71** (3.34 g, 14.05 mmol) in MeOH (30 mL) was added Pd/C (1.67 g, 10% *wt*). Then the resulting mixture was degassed with H_2 for three times and stirred at room temperature for overnight. LCMS showed the reaction was completed. The reaction mixture was filtered and concentrated *in vacuo* to give 3-methylimidazo[1,2-*a*]pyridin-7-ol **72** (1.44 g, 69.6% yield) as a yellow solid. LCMS ESI (m/z): 149 $[M+H]^+$.

Step 5: To a stirred mixture of K_2CO_3 (4.04 g, 29.25 mmol) in DMSO (30 mL) was added a solution of 3-methylimidazo[1,2-*a*]pyridin-7-ol **72** (1.44 g, 9.75 mmol) and 1,3-difluoro-2-methyl-4-nitrobenzene **32** (2.02 g, 11.70 mmol) in DMSO (5 mL) dropwise at room temperature. Then the resulting mixture was stirred at room temperature for 3 h. LCMS showed the reaction was completed. The reaction mixture was quenched by adding water (60 mL) and extracted with EtOAc (3 × 60 mL). The combined organic phases were washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a mixture of 7-(3-fluoro-2-methyl-4-nitrophenoxy)-3-methylimidazo[1,2-*a*]pyridine **73** and 7-(3-fluoro-2-methyl-6-nitrophenoxy)-3-methylimidazo[1,2-*a*]pyridine

74 (1.30 g, crude) as a yellow oil. The crude product was directly used in the next step without any further purification. LCMS ESI (m/z): 302 $[M+H]^+$.

Step 6: To a solution of 7-(3-fluoro-2-methyl-4-nitrophenoxy)-3-methylimidazo[1,2-*a*]pyridine and 7-(3-fluoro-2-methyl-6-nitrophenoxy)-3-methylimidazo[1,2-*a*]pyridine (1.30 g, crude) in EtOH (15 mL) and water (3 mL), were added iron power (1.21 g, 21.59 mmol) and NH_4Cl (2.31 g, 43.18 mmol). Then the resulting mixture was stirred at 80 °C for 1 h. LCMS showed the reaction was completed. The reaction mixture was cooled down to room temperature and concentrated *in vacuo* to give the crude product. The crude product was purified by flash chromatography with EtOAc in PE (0 - 70%, V/V) to give 2-fluoro-3-methyl-4-((3-methylimidazo[1,2-*a*]pyridin-7-yl)oxy)aniline **75** (134 mg, 5.1% yield over two steps) as a white solid. LCMS ESI (m/z): 272 $[M+H]^+$.

Synthesis of tert-butyl (S)-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate 80



The synthesis was based on the procedures from WO2019163865. **Step 1**: To a stirred solution of tert-butyl (S)-2-methyl-4-oxopiperidine-1-carboxylate **76** (50.00 g, 234.7 mmol, 1.00 equiv) in THF (500 mL) at -78 °C was added dropwise LiHMDS (1 M in THF, 305 mL, 305 mmol, 1.3 equiv) under N_2 atmosphere. The resulting mixture was stirred at -60 °C for 1.5 h. To this at -78 °C was added dropwise a solution of 1,1,1-trifluoro-N-phenyl-N-trifluoromethanesulfonylmethanesulfonamide (100.56 g, 281.6 mmol, 1.2 equiv) in THF (400 mL). The resulting mixture was allowed to warm up to ambient temperature and stirred for another 2.5 h. The reaction was quenched with saturated NH_4Cl solution and extracted with DCM 3 times. The combined organic layers were washed with water 3 times,

dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (Petroleum ether: EtOAc = 20:1) to afford a mixture of isomers of tert-butyl (S)-2-methyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (**77** and **78**) (62.5 g, 77%) as yellow oil. LCMS ESI (m/z): 346 $[M+H]^+$.

Step 2: To a stirred mixture of tert-butyl (S)2-methyl-4-(trifluoromethanesulfonyloxy)-3,6-dihydro-2H-pyridine-1-carboxylate **77** and **78** (62.4 g, 180.8 mmol, 1.00 equiv) and bis(pinacolato)diboron (55.1 g, 217.0 mmol, 1.2 equiv) in 1,4-dioxane at ambient temperature was added KOAc (35.4 g, 361.6 mmol, 2 equiv) and $Pd(dppf)Cl_2.CH_2Cl_2$ (22.1 g, 27.1 mmol, 0.15 equiv) under N_2 atmosphere. The resulting mixture was stirred at 80 °C for 2.5 h and then concentrated under vacuum. The residue was re-dissolved in DCM. The organic solution was washed with water 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (Petroleum ether: EtOAc = 20:1) to afford a mixture of isomers of tert-butyl (S)-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**79** and **80**) (67.1 g, >100%) as yellow oil. LCMS ESI (m/z): 324 $[M+H]^+$.

Step 3: The mixture of **79** and **80** was purified under SFC conditions using Water Thar 80 preparative SFC (ChiralPaK C-IG, 250x21.2 mm I.D., 5 μm, mobile phase A for CO_2 and B for MeOH, gradient B: 20%, flow rate 40 mL/min, back pressure 100 bar, column temperature 35°C, cycle time 4 min, eluted time 3h).

Compound 79: ^1H NMR (400 MHz, DMSO-d6) δ 6.39 (s, 1H), 4.32 (s, 1H), 4.08 (dt, J = 20.2, 3.4 Hz, 1H), 3.54 (d, J = 19.8 Hz, 1H), 2.31 – 2.16 (m, 1H), 1.97 (d, J = 17.2 Hz, 1H), 1.40 (s, 9H), 1.20 (s, 12H), 0.96 (d, J = 6.8 Hz, 3H). LCMS: Method G; Retention Time: 2.16 min; ESI (m/z): 324 $[M+H]^+$.

Compound 80: ^1H NMR (400 MHz, DMSO-d6) δ 6.33 (s, 1H), 4.32 (s, 1H), 3.90 (s, 1H), 2.68 (s, 1H), 2.14 – 1.88 (m, 2H), 1.40 (s, 9H), 1.20 (s, 12H), 1.12 (d, J = 6.6 Hz, 3H). LCMS ESI (m/z): 324 $[M+H]^+$. LCMS: Method G; Retention Time: 2.18 min; ESI (m/z): 324 $[M+H]^+$.

Synthesis of (2S)-2-(fluoromethyl)-1-[(4-methoxyphenyl)methyl]piperazine 85



81 **83** **84** **85**

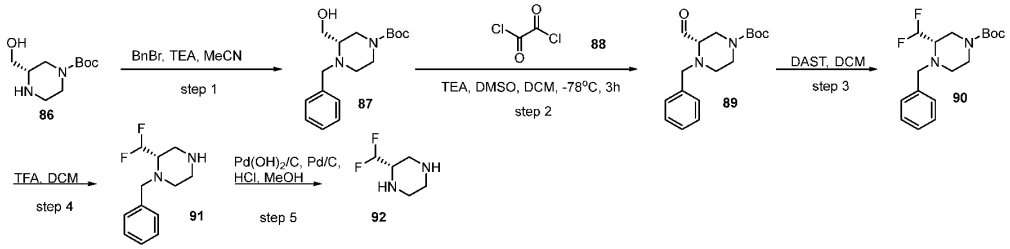
Step 1: To a stirred solution of tert-butyl (3S)-3-(hydroxymethyl)piperazine-1-carboxylate **81** (3.00 g, 13.87 mmol, 1.00 equiv) in acetonitrile (30.0 mL) at ambient temperature was added PMBCl **82** (2.60 g, 16.64 mmol, 1.20 equiv) and TEA (4.21 g, 41.61 mmol, 3.00 equiv). The resulting mixture was stirred at 60 °C for 16 h and then diluted with water and extracted with EtOAc 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-80% EtOAc in petroleum ether) to afford tert-butyl (3S)-3-(hydroxymethyl)-4-[(4-methoxyphenyl)methyl]piperazine-1-carboxylate **83** (3.1 g, 63%) as colorless oil. MS (ESI, *m/z*): 337 $[M + H]^+$.

Step 2: To a stirred solution of tert-butyl (3S)-3-(hydroxymethyl)-4-[(4-methoxyphenyl)methyl]piperazine-1-carboxylate **83** (2.00 g, 5.94 mmol, 1.00 equiv) in DCM (20.0 mL) was added dropwise a solution of DAST (2.87 g, 17.83 mmol, 3.00 equiv) in DCM (10.0 mL) at -78 °C under N_2 atmosphere. The resulting mixture was stirred at this temperature for 4 h and then quenched at 0 °C with water/ice and extracted with DCM 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-40% EtOAc in petroleum ether) to afford tert-butyl (3S)-3-(fluoromethyl)-4-[(4-methoxyphenyl)methyl]piperazine-1-carboxylate **84** (1.5 g, 67%) as colorless oil. MS (ESI, *m/z*): 339 $[M + H]^+$.

Step 3: To a stirred solution of tert-butyl (3S)-3-(fluoromethyl)-4-[(4-methoxyphenyl)methyl]piperazine-1-carboxylate **84** (200 mg, 0.591 mmol, 1 equiv) in EtOAc (5.0 mL) at 0 °C was added HMDS (476.9 mg, 2.95 mmol, 5.00 equiv) and TMSOTf (525.3 mg, 2.36 mmol, 4.00 equiv). The resulting mixture was stirred at ambient temperature for 1 h and then diluted with water and extracted with EtOAc 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford (2S)-2-(fluoromethyl)-1-[(4-methoxyphenyl)methyl]piperazine **85**

(crude, 155 mg) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 239 $[M + H]^+$.

Synthesis of (S)-2-(difluoromethyl)piperazine 92



Step 1: A mixture of tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate **86** (800.0 mg, 3.70 mmol, 1.00 equiv), benzyl bromide (1.26 g, 7.40 mmol, 2.00 equiv) and TEA (747.4 mg, 7.40 mmol, 2.00 equiv) in acetonitrile (20.00 mL) was stirred at 60 °C for 2 h. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-70% EtOAc in petroleum ether) to afford tert-butyl (S)-4-benzyl-3-(hydroxymethyl)piperazine-1-carboxylate **87** (510.0 mg, 45%) as yellow oil. MS (ESI, *m/z*): 307 $(M + H)^+$.

Step 2: To a stirred solution of oxalyl chloride **88** (621.3 mg, 4.896 mmol, 3.00 equiv) in DCM (10.00 mL) was added DMSO (509.9 mg, 6.53 mmol, 4.00 equiv) dropwise at -78 °C under N_2 atmosphere. The resulting mixture was stirred at this temperature for 0.5 h and to this was added tert-butyl (S)-4-benzyl-3-(hydroxymethyl)piperazine-1-carboxylate **87** (500.0 mg, 1.63 mmol, 1.00 equiv) and TEA (495.3 mg, 4.89 mmol, 3.00 equiv). The resulting mixture was stirred at ambient temperature for additional 1 h and then diluted with water and extracted with DCM 3 times. The organic layers were combined and concentrated under vacuum to afford tert-butyl (S)-4-benzyl-3-formylpiperazine-1-carboxylate **89** (crude, 450.0 mg) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 305 $(M + H)^+$.

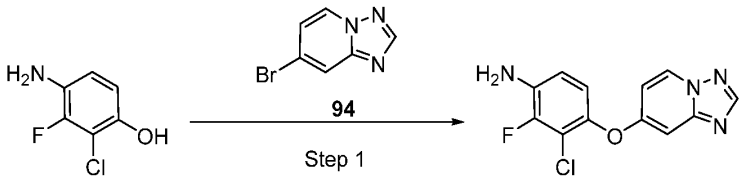
Step 3: To a stirred solution of tert-butyl (S)-4-benzyl-3-formylpiperazine-1-carboxylate **89** (350.0 mg, 1.15 mmol, 1.00 equiv) in DCM (5.00 mL) at -78 °C was added DAST (463.3 mg, 2.87 mmol, 2.50 equiv) under N_2 atmosphere. The resulting mixture was stirred at ambient temperature for 2 h and then quenched with $NaHCO_3$ solution and

extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-85% acetonitrile in water (containing 0.05% NH_4HCO_3)) to afford tert-butyl (S)-4-benzyl-3-(difluoromethyl)piperazine-1-carboxylate **90** (210.0 mg, 56%) as yellow oil. MS (ESI, *m/z*): 327 $(M + H)^+$.

Step 4: To a stirred solution of tert-butyl (S)-4-benzyl-3-(difluoromethyl)piperazine-1-carboxylate **90** (200.0 mg, 0.61 mmol, 1.00 equiv) in DCM (8.00 mL) at 0 °C was added TFA (695.4 mg, 6.10 mmol, 10.00 equiv). The resulting mixture was stirred at ambient temperature for 1 h and then concentrated under vacuum to afford (S)-1-benzyl-2-(difluoromethyl)piperazine trifluoroacetate **91** (crude, 150.0 mg) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 227 $(M + H)^+$.

Step 5: A mixture of (S)-1-benzyl-2-(difluoromethyl)piperazine trifluoroacetate **91** (150.0 mg, 0.44 mmol, 1.00 equiv), $Pd(OH)_2/C$ (15.0 mg, 10% w/w), Pd/C (wet, 10%, 15.0 mg, 10% w/w) and HCl (0.60 mL, 19.81 mmol, 148.94 equiv) in MeOH (5.00 mL) was stirred at ambient temperature for 16 h under H_2 atmosphere and then filtered. The filtrate was concentrated under vacuum to afford (S)-2-(difluoromethyl)piperazine hydrochloride **92** (crude, 80.0 mg) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 137 $(M + H)^+$.

Synthesis of 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chloro-2-fluoroaniline 95

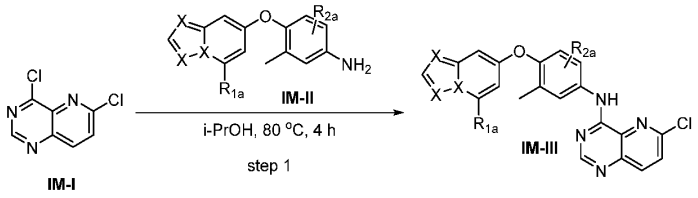


93 **95**

Step 1: A mixture of 4-amino-2-chloro-3-fluorophenol **93** (1.0 g, 6.21 mmol, 1.00 equiv), 7-bromo-[1,2,4]triazolo[1,5-a]pyridine **94** (1.8 g, 9.32 mmol, 1.50 equiv) and K_2CO_3 (1.7 g, 12.42 mmol, 2.00 equiv) in NMP (10.0 mL) was stirred at 80 °C for 4 h under N_2 atmosphere and then filtered through a pad of celite. The filtrate was diluted with H_2O and extracted with EtOAc 3 times. The combined organic layers were

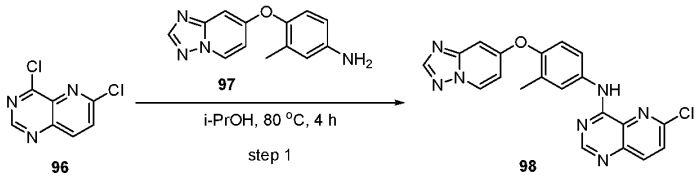
washed with brine, dried over Na_2SO_4 and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-80% EtOAc in petroleum ether) to afford 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chloro-2-fluoroaniline **95** (950.0 mg, 55%) as a brown solid. MS (ESI, *m/z*): 279, 281 $[M + H]^+$.

General synthetic method for Intermediate IM-III



Step 1: A mixture of 4,6-dichloropyrido[3,2-d]pyrimidine **IM-I** (1.00 equiv.) and intermediate **IM-II** (1.00 equiv.) in i-PrOH (4.00 mL) was stirred at 80 °C for 4 h and then concentrated under vacuum to intermediate **IM-III** (crude) which was used for the next step without further purification.

Synthesis of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-chloropyrido[3,2-d]pyrimidin-4-amine 98

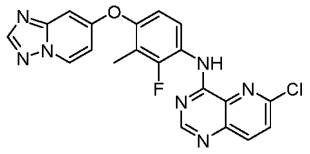
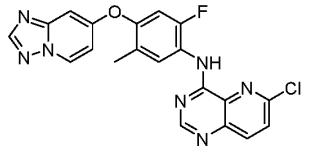
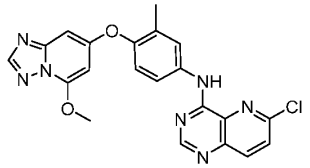


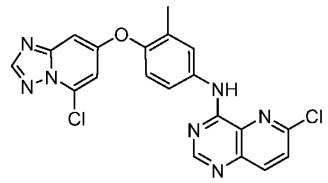
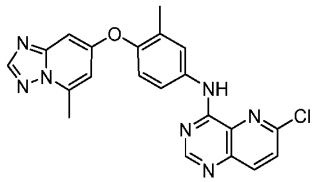
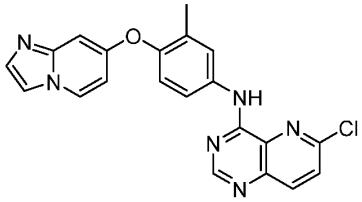
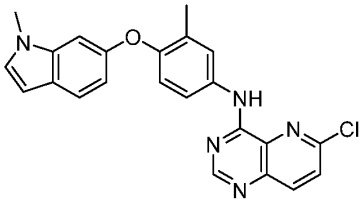
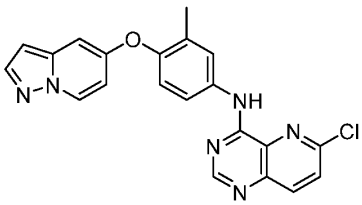
Step 1: A mixture of 4,6-dichloropyrido[3,2-d]pyrimidine **96** (200.00 mg, 1.00 mmol, 1.00 equiv.) and 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline **97** (240.24 mg, 1.00 mmol, 1.00 equiv.) in i-PrOH (4.00 mL) was stirred at 80 °C for 4 h and then concentrated under vacuum to afford N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-chloropyrido[3,2-d]pyrimidin-4-amine **98** (crude, 300.00 mg) as a brown

solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 404, 406 $[M + H]^+$.

The following intermediates in **Table 2** were obtained following above-mentioned method using the appropriate starting materials.

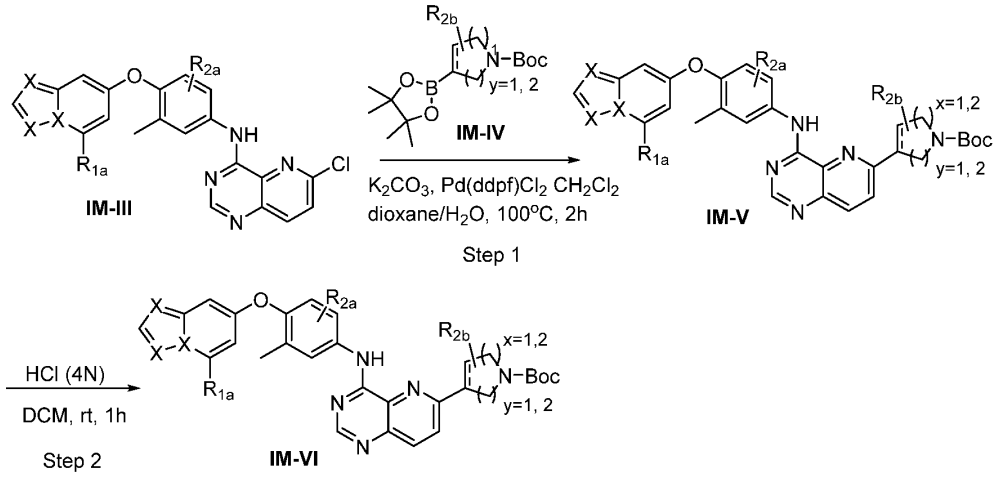
Table 2: Intermediates

Intermediate #	**Compound Structure**	**Physical Data MS [ESI, *m/z*]**
99	 N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-chloropyrido[3,2-d]pyrimidin-4-amine	422 $[M + H]^+$
100	 N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6-chloropyrido[3,2-d]pyrimidin-4-amine	422 $[M + H]^+$
101	 6-chloro-N-(4-(5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)pyrido[3,2-d]pyrimidin-4-amine	434 $[M+H]^+$

102	 6-chloro-N-(4-((5-chloro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)-3-methylphenyl)pyrido[3,2-d]pyrimidin-4-amine	438 $[M+H]^+$
103	 6-chloro-*N*-[3-methyl-4-({5-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl}oxy)phenyl]pyrido[3,2-d]pyrimidin-4-amine	418 $[M+H]^+$
104	 6-chloro-N-(4-(imidazo[1,2-a]pyridin-7-yloxy)-3-methylphenyl)pyrido[3,2-d]pyrimidin-4-amine	403 $[M+H]^+$
105	 6-chloro-N-(3-methyl-4-((1-methyl-3a,7a-dihydro-1H-indol-6-yl)oxy)phenyl)pyrido[3,2-d]pyrimidin-4-amine	418 $[M+H]^+$
106		403 $[M+H]^+$

	6-chloro-N-(3-methyl-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)pyrido[3,2-d]pyrimidin-4-amine	

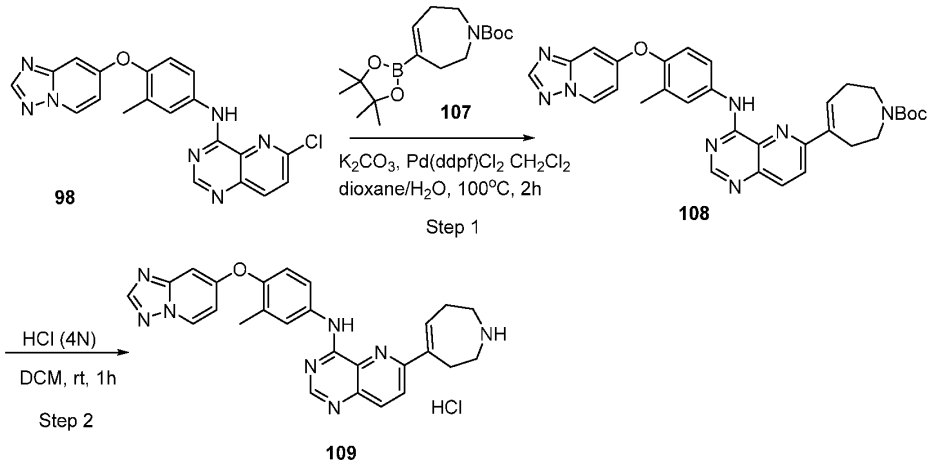
Method A: General method for intermediate IM-VI



Step 1: A mixture of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-chloropyrido[3,2-d]pyrimidin-4-amine **IM-III** (1.00 equiv.), boronic ester **IM-IV** (1.20 equiv.), K_2CO_3 (3.00 equiv.) and $Pd(dppf)Cl_2.CH_2Cl_2$ (0.10 equiv.) in dioxane and H_2O was stirred at 100 °C under N_2 atmosphere until the reaction was complete and then quenched with brine and extracted with EtOAc 3 times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% MeOH in DCM) to afford intermediate **IM-V.**

Step 2: A mixture of intermediate **IM-V** (1.00 equiv.) and HCl (4 N in 1,4-dioxane, 1.00 mL) in DCM (4.00 mL) was stirred at ambient temperature until the reaction was complete and then concentrated under vacuum to afford intermediate **IM-VI** (crude) as a yellow solid, which was used for the next step without further purification.

Synthesis of N-(3-methyl-4-[[1,2,4]triazolo[1,5-a]pyridin-7-yloxy]phenyl)-6-(2,3,6,7-tetrahydro-1H-azepin-4-yl)pyrido[3,2-d]pyrimidin-4-amine 109



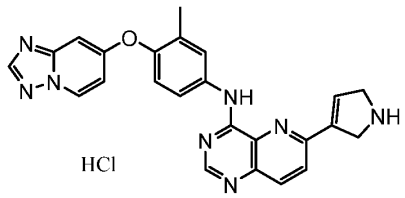
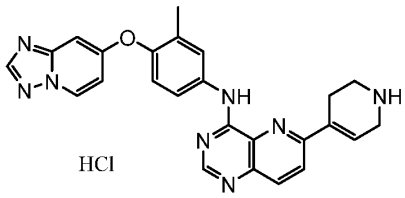
Step 1: To a stirred mixture of 6-chloro-N-(3-methyl-4- [[1,2,4] triazolo[1,5-a] pyridin-7-yloxy] phenyl) pyrido[3,2-d]pyrimidin-4-amine **98** (300.00 mg, 0.74 mmol, 1.00 equiv.), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,6,7-tetrahydroazepine-1-carboxylate **107** (288.16 mg, 0.89 mmol, 1.20 equiv.) and K_2CO_3 (308.01 mg, 2.23 mmol, 3.00 equiv.) in dioxane (15.00 mL) and H_2O (3.00 mL) at ambient temperature was added $Pd(dppf)Cl_2$ CH_2Cl_2 (60.52 mg, 0.07 mmol, 0.10 equiv.) under N_2 atmosphere. The resulting mixture was stirred at 100 °C for 2 h and then diluted with H_2O and extracted with EtOAc 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-95% acetonitrile in H_2O (containing 0.05% NH_4HCO_3)) to afford tert-butyl 4-[4-[(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]-2,3,6,7-tetrahydroazepine-1-carboxylate **108** (100 mg, 24%) as a brown solid. LCMS (ESI, *m/z*): 565 $[M + H]^+$.

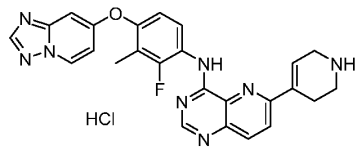
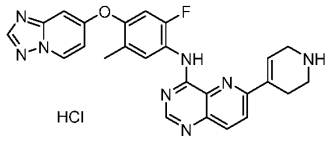
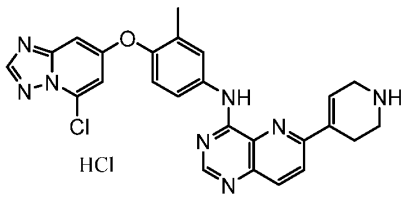
Step 2: To a stirred mixture of tert-butyl 4-[4-[(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]-2,3,6,7-tetrahydroazepine-1-carboxylate **108** (100.00 mg, 0.18 mmol, 1.00 equiv.) in DCM (4.00 mL) at ambient temperature was added HCl (4 N in 1,4-dioxane, 1.00 mL, 4.00 mmol). The resulting mixture was stirred at this temperature for 1 h and concentrated under vacuum to afford N-(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridine-7-yloxy]phenyl)-6-(2,3,6,7-tetrahydro-1H-azepin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride **109** (crude, 110 mg) as a

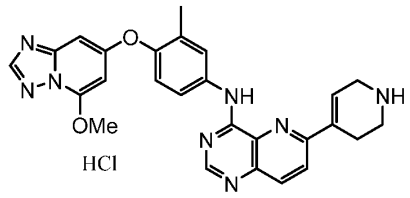
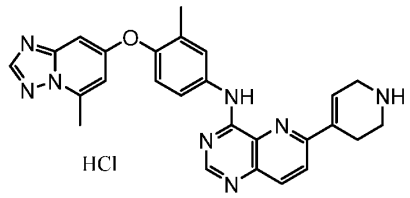
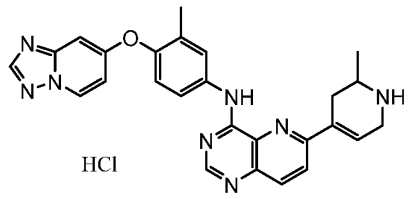
yellow solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 465 $[M + H]^+$.

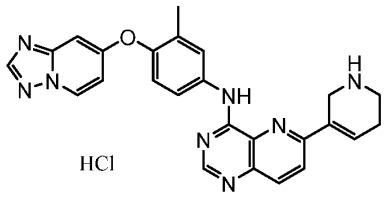
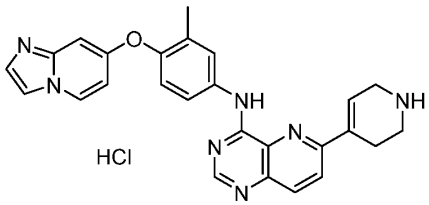
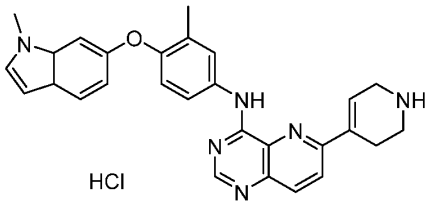
Intermediates in **Table 3** were obtained following above-mentioned method using the appropriate starting materials.

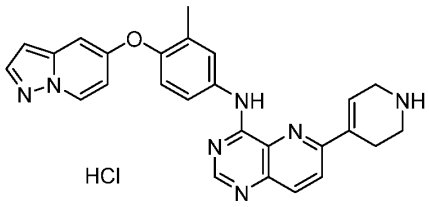
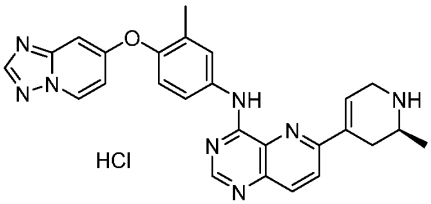
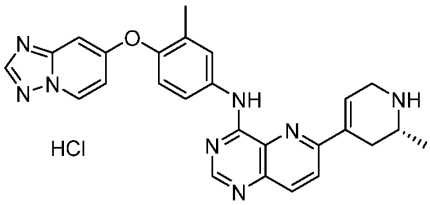
Table 3: Intermediates

Intermediate #	Compound Structure	Physical Data MS [ESI, *m/z*]
110	 HCl 6-(2,5-dihydro-1H-pyrrol-3-yl)-N-(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridin-7-yloxy]phenyl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	437 $[M + H]^+$
111	 HCl N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	451 $[M+H]^+$

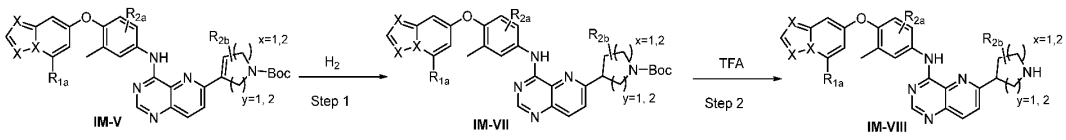
Intermediate #	Compound Structure	Physical Data MS [ESI, *m/z*]
112	 N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	469 $[M+H]^+$
113	 N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	469 $[M+H]^+$
114	 N-(4-((5-chloro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)-3-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	485 $[M+H]^+$

Intermediate #	Compound Structure	Physical Data MS [ESI, *m/z*]
115	 HCl N-(4-(5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	481 $[M+H]^+$
116	 HCl *N*-[3-methyl-4-({5-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl}oxy)phenyl]-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-*d*]pyrimidin-4-amine hydrochloride	465 $[M+H]^+$
117	 HCl N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(2-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	465 $[M+H]^+$

Intermediate #	Compound Structure	Physical Data MS [ESI, *m/z*]
118	 HCl N-(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-6-(1,2,5,6-tetrahydropyridin-3-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	451 $[M+H]^+$
119	 HCl N-(4-(imidazo[1,2-a]pyridin-7-yloxy)-3-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	450 $[M+H]^+$
120	 HCl N-(3-methyl-4-((1-methyl-3a,7a-dihydro-1H-indol-6-yl)oxy)phenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	465 $[M+H]^+$

Intermediate #	Compound Structure	Physical Data MS [ESI, *m/z*]
121	 HCl N-(3-methyl-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	450 $[M+H]^+$
122	 HCl (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(6-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	465 $[M+H]^+$
123	 HCl (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(6-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	465 $[M+H]^+$

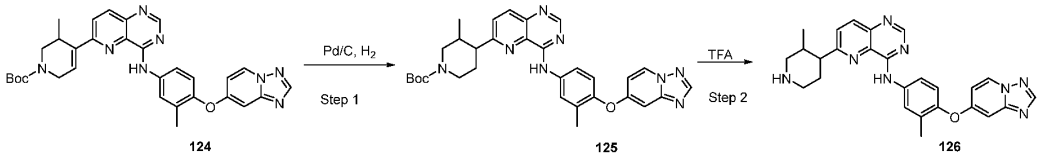
Method B: General method for intermediate IM-VIII



Step 1: A mixture of intermediate **IM-V** (1.00 equiv.) and Pd/C (wet, 10%, 0.2 equiv.) in MeOH was stirred at ambient temperature until the reaction was complete under H_2 atmosphere and then filtered through a pad of celite. The filtrate was concentrated under vacuum to afford intermediate **IM-VII** (crude) as a brown solid, which was used for the next step without further purification.

Step 2: To a stirred mixture of intermediate **IM-VII** (1.00 equiv.) in DCM at ambient temperature was added TFA. The reaction mixture was stirred at this temperature until the reaction was complete h and then concentrated under vacuum to afford intermediate **IM-VIII** (crude) as brown oil, which was used for the next step without further purification.

Synthesis of tert-butyl 4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3-methylpiperidine-1-carboxylate 126



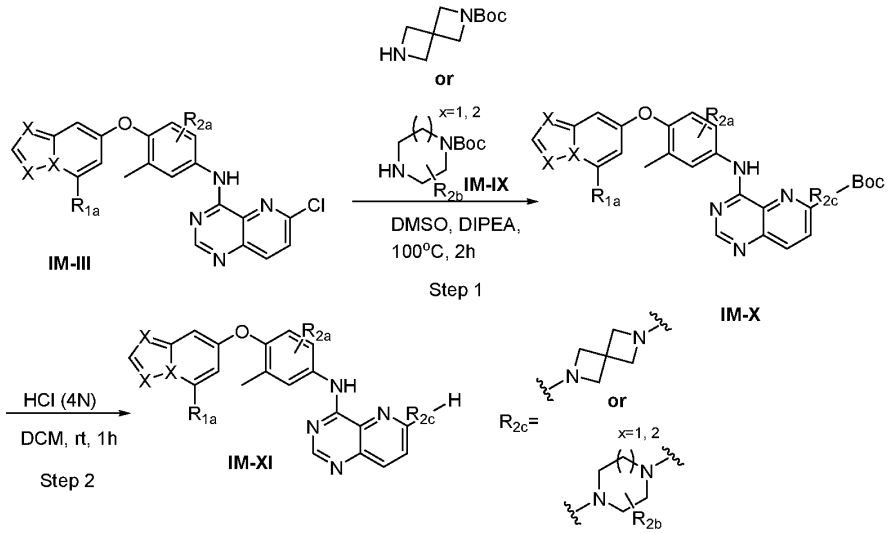
124 125 126

Step 1: A mixture of 3-methyl-4-{4-[(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate **124** (150.0 mg, 0.27 mmol, 1.00 equiv.) and Pd/C (wet, 10%, 30.0 mg) in MeOH (5.0 mL) was stirred at ambient temperature for 96 h under H_2 atmosphere and then filtered through a pad of celite. The filtrate was concentrated under vacuum to afford tert-butyl 4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3-methylpiperidine-1-carboxylate **125** (crude, 190.5 mg) as a brown solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 567 $[M + H]^+$.

Step 2: To a stirred mixture of (2R)-2-methyl-4-{4-[(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl}piperazine-1-carboxylate **125** (150.0 mg, 0.27 mmol, 1.00 equiv.) in DCM (2.0 mL) at ambient temperature was added TFA (1.0 mL). The reaction mixture was stirred at this temperature for 2 h and then concentrated under vacuum to afford N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-

methylphenyl)-6-(3-methylpiperidin-4-yl)pyrido[3,2-d]pyrimidin-4-amine trifluoroacetate **126** (crude, 40.0 mg) as brown oil, which was used for the next step without further purification. LCMS (ESI, *m/z*): 467 $[M + H]^+$.

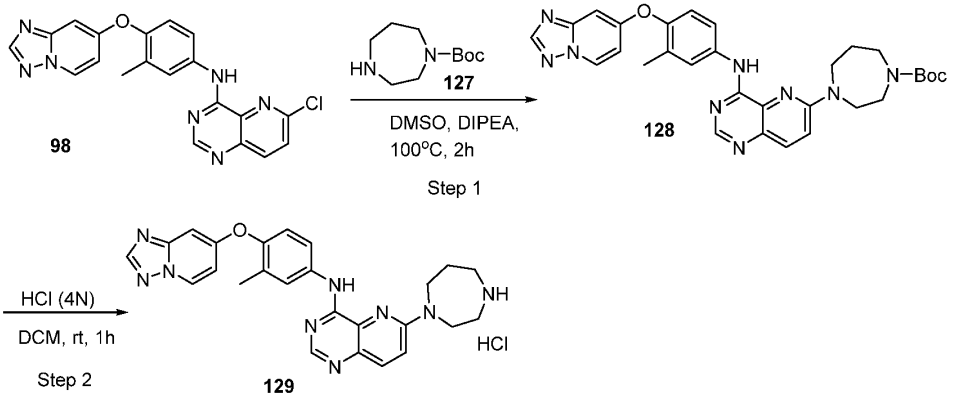
Method C: General method for intermediate IM-XI



Step 1: A mixture of intermediate **IM-III** (1.00 equiv.), N-Boc protected intermediate **IM-IX** (2.00 equiv.) and TEA (3.00 equiv.) in DMSO was stirred at 100 °C for 2 h and then diluted with water and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-95% acetonitrile in water (containing 0.05% NH_4HCO_3) to afford intermediate **IM-X.**

Step 2: A mixture of intermediate **IM-X** (1.00 equiv.) and HCl (4 N in 1,4-dioxane) in DCM (4.0 mL) was stirred at ambient temperature for 1 h and then concentrated under vacuum to afford intermediate **IM-XI** (crude) as a yellow solid, which was used for the next step without further purification.

Synthesis of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(1,4-diazepan-1-yl)pyrido[3,2-d]pyrimidin-4-amine 52



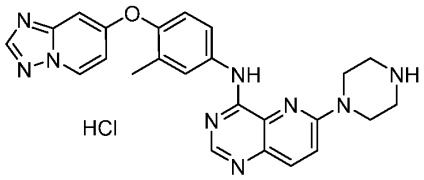
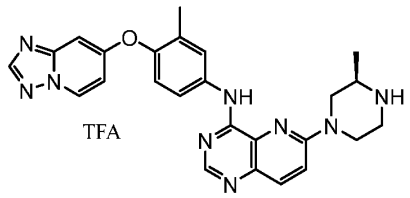
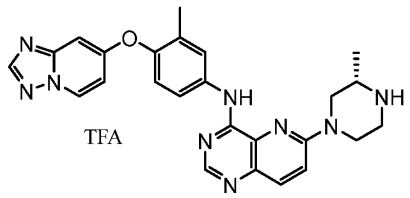
Step 1: A mixture of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-chloropyrido[3,2-d]pyrimidin-4-amine **98** (250.0 mg, 0.62 mmol, 1.00 equiv.), tert-butyl 1,4-diazepane-1-carboxylate **127** (248.1 mg, 1.24 mmol, 2.00 equiv.) and TEA (187.9 mg, 1.86 mmol, 3.00 equiv.) in DMSO (7.5 mL) was stirred at 100 °C for 2 h and then diluted with water and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-95% acetonitrile in water (containing 0.05% NH_4HCO_3) to afford tert-butyl 4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-1,4-diazepane-1-carboxylate **128** (100.0 mg, 28%) as brown oil. LCMS (ESI, *m/z*): 568 $[M + H]^+$.

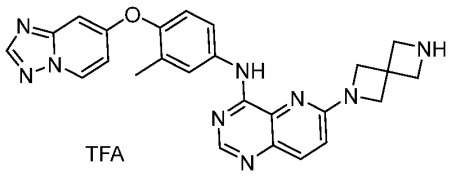
Step 2: A mixture of tert-butyl 4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-1,4-diazepane-1-carboxylate **128** (130.0 mg, 0.23 mmol, 1.00 equiv.) and HCl (4 N in 1,4-dioxane, 4.0 mL) in DCM (4.0 mL) was stirred at ambient temperature for 1 h and then concentrated under vacuum to afford N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(1,4-diazepan-1-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride **129** (crude, 160.0 mg) as a yellow solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 468 $[M + H]^+$.

Alternatively, TFA in DCM (1/1) could be used to remove Boc protecting group instead of HCl (4 N in 1,4-dioxane). After completion of the reaction, the reaction mixture was concentrated under vacuum to afford the desired intermediate as TFA salt.

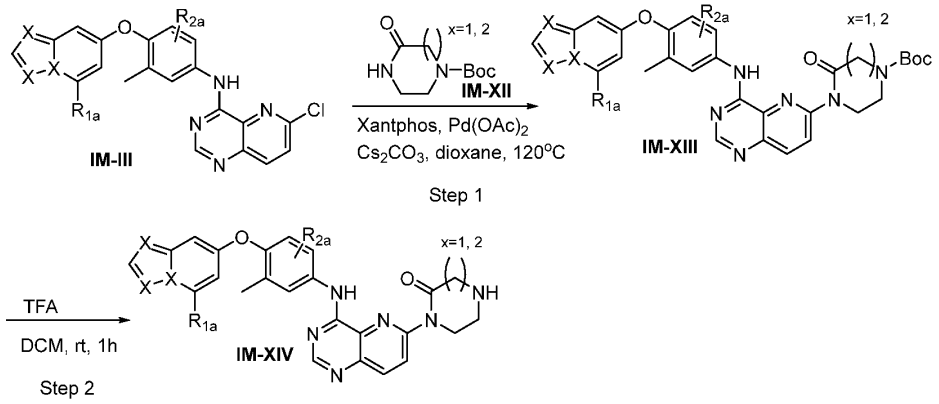
The following intermediates in **Table 4** were obtained following above-mentioned method using the appropriate starting materials.

Table 4: Intermediates

Example	Compound Structure	Physical Data MS [ESI, *m/z*]
130	 HCl N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(piperazin-1-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride	454 $[M + H]^+$
131	 TFA N-(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-6-[(3R)-3-methylpiperazin-1-yl]pyrido[3,2-d]pyrimidin-4-amine trifluoroacetate	468 $[M + H]^+$
132	 TFA N-(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-6-[(3S)-3-	468 $[M + H]^+$

Example	Compound Structure	Physical Data MS [ESI, *m/z*]
	methylpiperazin-1-yl]pyrido[3,2-d]pyrimidin-4-amine trifluoroacetate	
133	 TFA N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(2,6-diazaspiro[3.3]heptan-2-yl)pyrido[3,2-d]pyrimidin-4-amine 2,2,2-trifluoroacetate	466 $[M + H]^+$

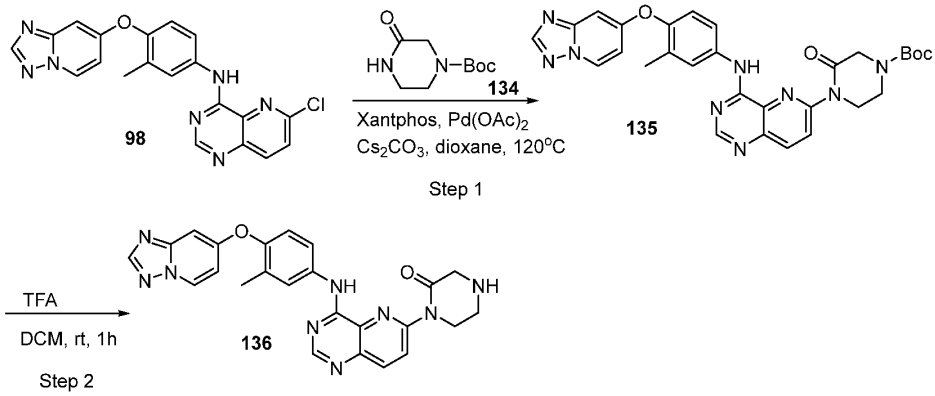
Method D: General method for intermediate IM-XIV



Step 1: A mixture of intermediate **IM-III** (1.00 equiv.), tert-butyl 3-oxopiperazine-1-carboxylate **IM-XII** (1.20 equiv.), Xantphos (143.28 mg, 0.25 mmol, 0.20 equiv.), $Pd(OAc)_2$ (0.10 equiv.) and Cs_2CO_3 (3.00 equiv.) in dioxane was stirred at 120 °C under N_2 atmosphere until the reaction was complete and then filtered. The filtrate was concentrated under vacuum to afford intermediate **IM-XIII** (crude) as a brown solid, which was used for the next step without further purification.

Step 2: To a stirred mixture of intermediate **IM-XIII** (1.00 equiv.) in DCM at ambient temperature was added TFA. The resulting mixture was stirred at this temperature until the reaction was complete and then concentrated under vacuum to afford intermediate **IM-XIV** (crude) as a brown solid, which was used for the next step without further purification.

Synthesis of 1-[4-[(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]piperazin-2-one 136

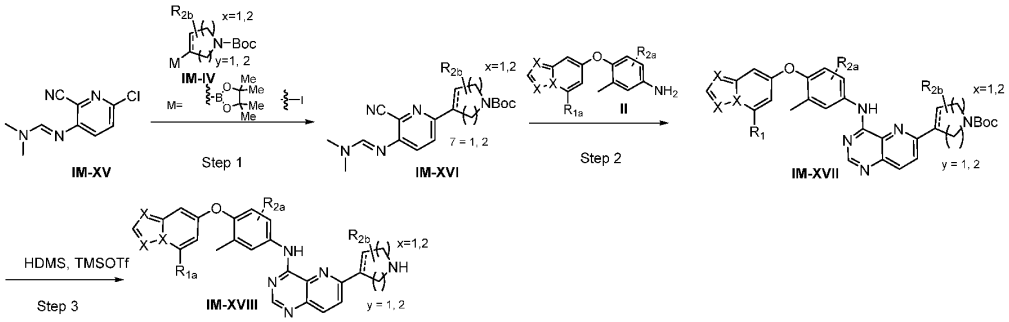


Step 1: A mixture of 6-chloro-N-(3-methyl-4-[[1,2,4]triazolo[1,5-a]pyridin-7-yloxy]phenyl)pyrido[3,2-d]pyrimidin-4-amine **98** (500.00 mg, 1.24 mmol, 1.00 equiv.), tert-butyl 3-oxopiperazine-1-carboxylate **134** (297.51 mg, 1.49 mmol, 1.20 equiv.), Xantphos (143.28 mg, 0.25 mmol, 0.20 equiv.), $Pd(OAc)_2$ (27.80 mg, 0.12 mmol, 0.10 equiv.) and Cs_2CO_3 (1.21 g, 3.71 mmol, 3.00 equiv.) in dioxane (8.00 mL) was stirred at 120 °C for 6 h under N_2 atmosphere and then filtered. The filtrate was concentrated under vacuum to afford tert-butyl 4-[4-[(3-methyl-4-[[1,2,4]triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]-3-oxopiperazine-1-carboxylate **135** (crude, 600 mg) as a brown solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 568 $[M + H]^+$.

Step 2: To a stirred mixture of tert-butyl 4-[4-[(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]-3-oxopiperazine-1-carboxylate **135** (600.00 mg, 1.06 mmol, 1.00 equiv.) in DCM (6.00 mL) at ambient temperature was added TFA (6 mL). The resulting mixture was stirred at this temperature

for 2 h and then concentrated under vacuum to afford 1-[4-[(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]piperazin-2-one trifluoroacetate **136** (crude, 120 mg) as a brown solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 468 $[M + H]^+$.

Method E: General method for intermediate IM-XVIII



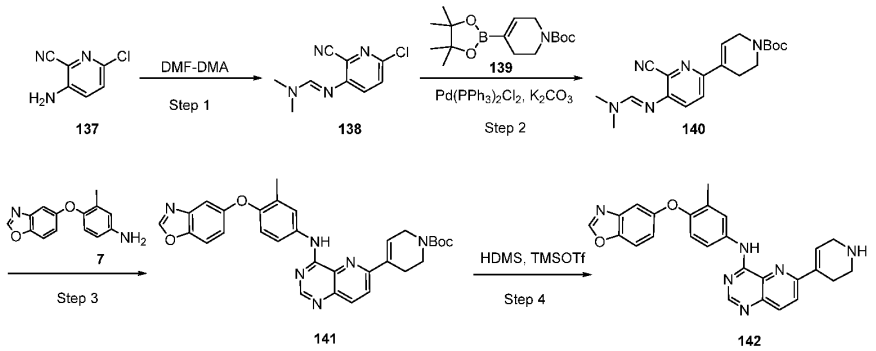
Step 1: A mixture of (*E*)-N'-(6-chloro-2-cyanopyridin-3-yl)-N,N-dimethylformimidamide **IM-XV** (1.00 equiv.), boronic ester **IM-IV** (1.50 equiv.), $Pd(PPh_3)_2Cl_2$ (0.10 equiv.) and K_2CO_3 (3.00 equiv.) in DME / H_2O / EtOH (2 / 2 / 1) was stirred at 95 °C under N_2 atmosphere until the reaction was complete. The resulting mixture was diluted with water and extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% MeOH in DCM) to afford desired intermediate **IM-XVI**.

Step 2: A mixture of aniline **IM-II** (1.00 equiv.) and intermediate **IM-XVI** (1.10 equiv.) in AcOH was stirred at 80 °C until the reaction was complete and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-70% acetonitrile in water (containing0.05% NH_4HCO_3)) to afford desired intermediate **IM-XVII**.

Step 3: To a stirred mixture of intermediate **IM-XVII** (1.00 equiv.) and HMDS (2.50 equiv.) in EtOAc at ambient temperature was added TMSOTf (2.00 equiv.). The resulting mixture was stirred at this temperature until the reaction was complete and then diluted

with water and extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford intermediate **IM-XVIII** which was used for the next step without further purification.

Synthesis of N-(4-(benzo[d]oxazol-5-yloxy)-3-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine 65



Step 1: A mixture of 3-amino-6-chloropicolinonitrile **137** (750.0 mg, 4.90 mmol, 1.00 equiv.) and DMF-DMA (1.75 g, 14.70 mmol, 3.00 equiv.) in toluene (15.00 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The mixture was concentrated under vacuum to afford (E)-N'-(6-chloro-2-cyanopyridin-3-yl)-N,N-dimethylformimidamide **138** (crude, 950.0 mg) as a yellow solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 209, 211 $[M+H]^+$.

Step 2: A mixture of (E)-N'-(6-chloro-2-cyanopyridin-3-yl)-N,N-dimethylformimidamide **138** (950.0 mg, 4.56 mmol, 1.00 equiv.), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **139** (2.12 g, 6.85 mmol, 1.50 equiv.), $Pd(PPh_3)_2Cl_2$ (320.0 mg, 0.45 mmol, 0.10 equiv.) and K_2CO_3 (1.88 g, 13.68 mmol, 3.00 equiv.) in DME (10.00 mL), H_2O (10.00 mL) and EtOH (5.00 mL) was stirred at 95 °C for 2 h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% MeOH in DCM) to afford tert-butyl (E)-6-cyano-5-(((dimethylamino)methylene)amino)-3',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate **140** (810.0 mg, 50%) as a yellow solid. ^1H NMR (400 MHz, DMSO-*d*6) δ 8.12

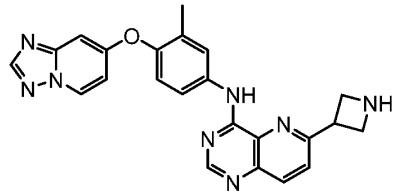
(s, 1H), 7.77-7.66 (m, 2H), 6.58 (s, 1H), 4.03 (d, J = 3.2 Hz, 2H), 3.55-3.48 (m, 2H), 3.10 (s, 3H), 3.02 (s, 3H), 2.54-2.51 (m, 2H), 1.42 (s, 9H). LCMS (ESI, *m/z*): 356 $[M+H]^+$.

Step 3: A mixture of 4-(benzo[d]oxazol-5-yloxy)-3-methylaniline **7** (210.0 mg, 0.87 mmol, 1.00 equiv.) and tert-butyl (E)-6-cyano-5-(((dimethylamino)methylene)amino)-3',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate **140** (341.0 mg, 0.96 mmol, 1.10 equiv.) in AcOH (6.00 mL) was stirred at 80 ºC for 2 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-70% acetonitrile in water (containing 0.05% NH_4HCO_3)) to afford tert-butyl 4-(4-((4-(benzo[d]oxazol-5-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate **141** (140.0 mg, 29%) as a yellow solid. LCMS (ESI, *m/z*): 551 $[M + H]^+$.

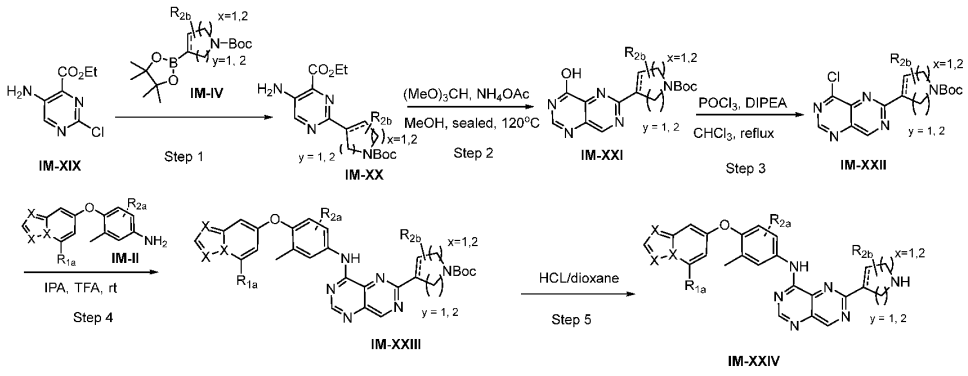
Step 4: To a stirred mixture of tert-butyl 4-(4-((4-(benzo[d]oxazol-5-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate **141** (140.0 mg, 0.25 mmol, 1.00 equiv.) and HMDS (102.5 mg, 0.64 mmol, 2.50 equiv.) in EtOAc (5.00 mL) at ambient temperature was added TMSOTf (111.0 mg, 0.50 mmol, 2.00 equiv.). The resulting mixture was stirred at this temperature for 1 h and then diluted with water and extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford N-(4-(benzo[d]oxazol-5-yloxy)-3-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine **142** (crude, 120.0 mg) as a yellow solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 451 $[M + H]^+$.

The following intermediates in **Table 5** were obtained following above-mentioned method using the appropriate starting materials.

Table 5: Intermediates

Example	Compound Structure	Physical Data MS [ESI, *m/z*]
143	 N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(azetidin-3-yl)pyrido[3,2-d]pyrimidin-4-amine	425 $[M + H]^+$

Method F: General method for intermediate IM-XXIV



Step 1: A mixture of ethyl 5-amino-2-chloropyrimidine-4-carboxylate **IM-XIX** (1.0 equiv.), $Pd(dppf)Cl_2$ (0.001-0.01 equiv.), boronic ester **IM-IV** (1.5 equiv.) and K_2CO_3 (3 equiv.) in dioxane and H_2O was charged with N_2 twice. Then this mixture was stirred at 100 °C overnight. The mixture was diluted with dichloromethane, then washed with water and brine. The organic extract was then dried over Na_2SO_4, filtered, and concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel (e.g., 20% EtOAc/Hexanes) to give intermediate **IM-XX**.

Step 2: A mixture of intermediate **IM-XX** (1.0 equiv.), trimethoxymethane (2.97 equiv.), ammonium acetate (2.97 equiv.) in MeOH was charged with N_2 twice and sealed

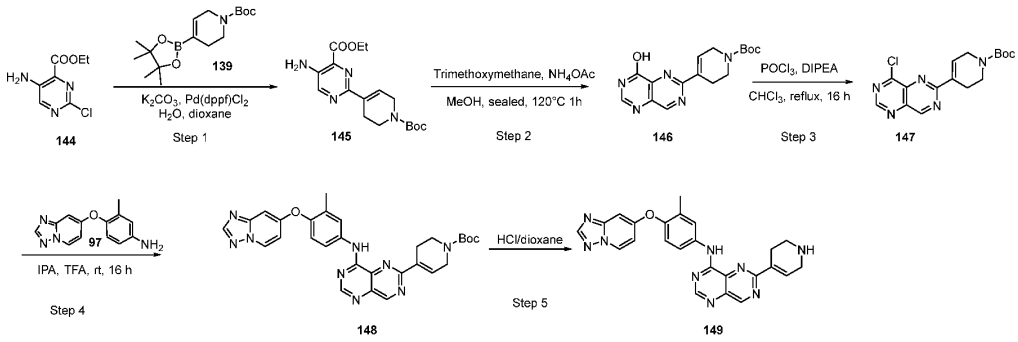
in tube. Then this mixture was stirred at 120 °C until the reaction was complete. The mixture was cooled and diluted with dichloromethane. Then this mixture was washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (e.g., EA/PE = 0 - 50%) to give intermediate **IM-XXI**.

Step 3: Intermediate **IM-XXI** (1.0 equiv.) was suspended in $CHCl_3$. DIPEA (3.0 equiv.) was added followed by addition of $POCl_3$ (3.0 equiv.) at room temperature. The reaction was heated to reflux until the reaction waS complete to give a clear orange solution. After cooling the reaction to room temperature, it was concentrated under reduced pressure followed by adding water. Then this mixture was extracted with dichloromethane. The combined organic solution was washed with water and brine, dried over anhydrous Na_2SO_4, concentrated in vacuo to give the crude intermediate **IM-XXII** which was used for next reaction step immediately within a few minutes without any further purification.

Step 4: To a solution of intermediate **IM-XXII** (1.0 equiv.) in *i*-PrOH, was added aniline **IM-II** (1.0 equiv.) at 25°C. TFA was added, and stirred at 20 °C until the reaction was complete. The reaction was quenched by adding water, then extracted with dichloromethane. The combined organic solution was washed with sat. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, concentrated in vacuo to give the crude product. This crude was purified by flash (EA/PE = 0 - 50%) to give intermediate **IM-XXIII**.

Step 5: The solution of intermediate **IM-XXIII** (1.0 equiv.) was treated with HCl (4N in dioxane), and then the reaction mixture was stirred at 20 °C until the reaction was complete. The reaction mixture was concentrated in vacuo to remove solvent to give intermediate **IM-XXIV** which was used directly for next reaction step without purification.

Synthesis of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimido[5,4-d]pyrimidin-4-amine 72



Step 1: A mixture of ethyl 5-amino-2-chloropyrimidine-4-carboxylate **144** (1.0 g, 4.96 mmol), $Pd(dppf)Cl_2$ (5.12 mg, 0.007 mmol), tert-butyl 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate **139** (1.99 g, 6.45 mmol) and K_2CO_3 (2.06 g, 14.9 mmol) in dioxane (30 mL) and H_2O (2 mL) was charged with N_2 twice. Then this mixture was stirred at 100 °C overnight. The mixture was diluted with dichloromethane (50 mL), then washed with water and brine. The organic extract was then dried over Na_2SO_4, filtered, and concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel (20% EtOAc/Hexanes) to give ethyl 5-amino-2-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-4-carboxylate **145** (850 mg, 49.1% yield). LCMS ESI (m/z): 349 $[M+H]^+$.

Step 2: A mixture of ethyl 5-amino-2-{1-[(tert-butoxy)carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}pyrimidine-4-carboxylate **145** (600 mg, 1.72 mmol), trimethoxymethane (0.56 mL, 5.12 mmol), ammonium acetate (398 mg, 5.12 mmol) in MeOH (10 mL) was charged with N_2 twice and sealed in tube. Then this mixture was stirred at 120 °C for 16 hours. The mixture was cooled and diluted with dichloromethane (50 mL). Then this mixture was washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EA/PE = 0 - 50%) to give tert-butyl 4-{8-hydroxy-[1,3]diazino[5,4-*d*]pyrimidin-2-yl}-1,2,3,6-tetrahydropyridine-1-carboxylate **146** (200 mg, 35.3% yield). LCMS ESI (m/z): 330 $[M+H]^+$.

Step 3: tert-butyl 4-{8-hydroxy-[1,3]diazino[5,4-d]pyrimidin-2-yl}-1,2,3,6-tetrahydropyridine-1-carboxylate **146** (100 mg, 0.30 mmol) was suspended in 10 mL of $CHCl_3$. Ethylbis(propan-2-yl) amine (DIPEA, 0.15 mL, 0.90 mmol) was added followed

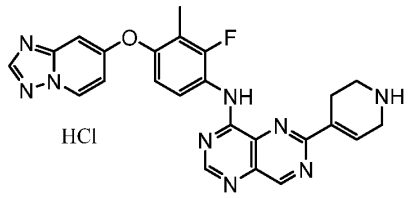
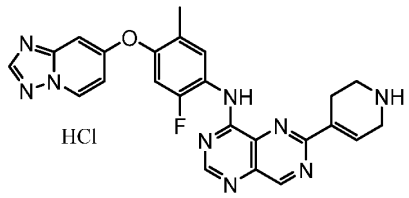
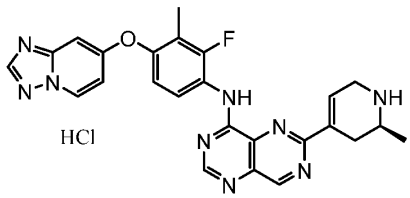
by addition of $POCl_3$ (137.8 mg, 0.90 mmol) at room temperature. The reaction was heated to reflux for 24 hours to give a clear orange solution. After cooling the reaction to room temperature, it was concentrated under reduced pressure followed by adding water (10 mL). Then this mixture was extracted with dichloromethane (3 ×10 mL). The combined organic solution was washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo to give the crude tert-butyl 4-{8-chloro-[1,3]diazino[5,4-d]pyrimidin-2-yl}-1,2,3,6-tetrahydropyridine-1-carboxylate **147** (200 mg, purity: 50%) as a brown gum which was used for next reaction step immediately within a few minutes without any further purification. LCMS ESI (m/z): 348 $[M+H]^+$.

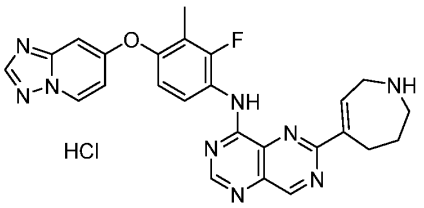
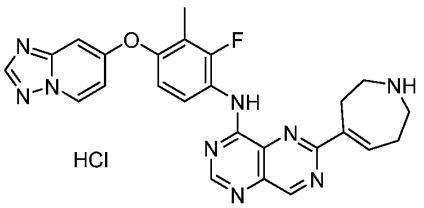
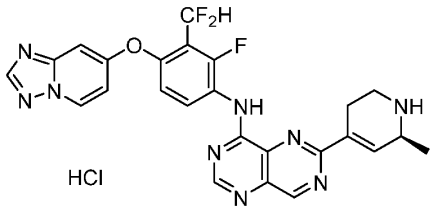
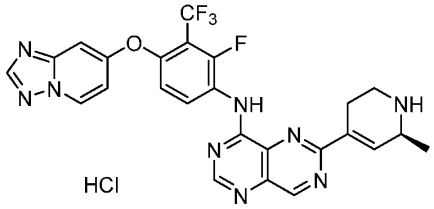
Step 4: To a solution of tert-butyl 4-{8-chloro-[1,3]diazino[5,4-d]pyrimidin-2-yl}-1,2,3,6-tetrahydropyridine-1-carboxylate **147** (200 mg, purity: 50%, 0.288 mmol) in *i*-PrOH (5 mL), was added 3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline **97** (69 mg, 0.29 mmol) at 25°C. TFA (0.1 mL) was added, and stirred at 20 °C for another 16 hours. The reaction was quenched by adding water (5 mL), then extracted with dichloromethane (3 ×10 mL). The combined organic solution was washed with sat. $NaHCO_3$ (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo to give the crude product. This crude was purified by flash (EA/PE = 0 - 50%) to give tert-butyl 4-{8-[(3-methyl-4-{[1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy}phenyl)amino]pyrimido[5,4-*d*][1,3] diazin-2-yl}-1,2,3,6-tetrahydropyridine-1-carboxylate **148** (95 mg, 72% yield) as a yellow gum. LCMS (ESI): m/z 552 $[M+H]^+$.

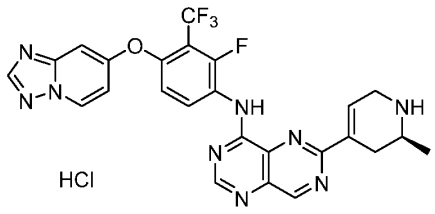
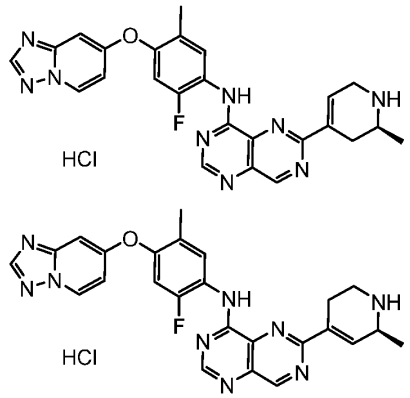
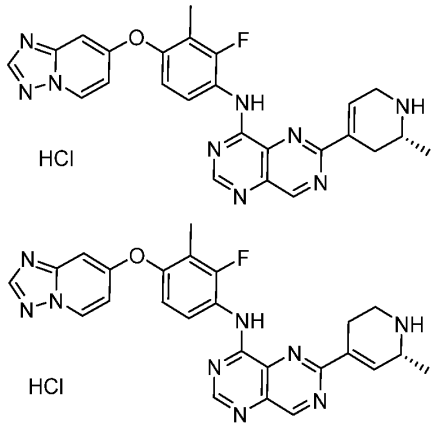
Step 5: The solution of tert-butyl 4-{8-[(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]pyrimido[5,4-d][1,3]diazin-2-yl}-1,2,3,6-tetrahydropyridine-1-carboxylate **148** (95 mg, 0.172 mmol) was treated with HCl (2 mL, 4N in dioxane), and then the reaction mixture was stirred at 20 °C for 1 hour. After 1 hour, the reaction mixture was concentrated in vacuo to remove solvent to give N-(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimido[5,4-d][1,3]diazin-4-amine hydrochloride **149** (70 mg, 90% yield) as a brown gum which was used directly for next reaction step without purification. LCMS (ESI): m/z 452 $[M+H]^+$.

The following intermediates in **Table 6** were obtained following above-mentioned method using the appropriate starting materials.

Table 6: Intermediates

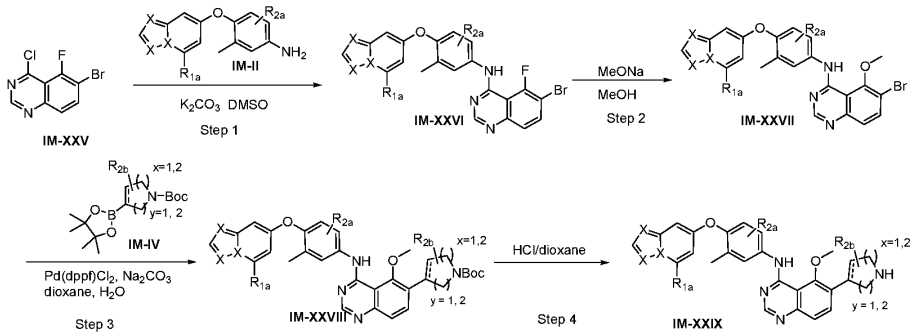
Example	Compound Structure	Physical Data MS [ESI, *m/z*]
150	 HCl *N*-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	470 $[M + H]^+$
151	 HCl N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	470 $[M + H]^+$
152	 HCl (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(2-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	484 $[M + H]^+$

153	 HCl  HCl N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(2,3,6,7-tetrahydro-1H-azepin-4-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	484 $[M + H]^+$
154	 HCl N-[3-(difluoromethyl)-2-fluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl]-6-[(2S)-2-methyl-1,2,3,6-tetrahydropyridin-4-yl]-[1,3]diazino[5,4-d]pyrimidin-4-amine hydrochloride	520 $[M + H]^+$
155	 HCl	538 $[M + H]^+$

	 HCl (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-(trifluoromethyl)phenyl)-6-(2-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	
156	 HCl HCl N-(2-fluoro-5-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-6-[(2S)-2-methyl-1,2,3,6-tetrahydropyridin-4-yl]-[1,3]diazino[5,4-d]pyrimidin-4-amine hydrochloride	484 $[M + H]^+$
157	 HCl HCl	484 $[M + H]^+$

	(R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(2-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	

Method G: General method for intermediate IM-XXIX



Step 1: To a solution of aniline **IM-II** (1.0 equiv.) in DMSO were added K_2CO_3 (2.9 equiv,) and 6-bromo-4-chloro-5-fluoroquinazoline **IM-XXV** (1.0 equiv.) at room temperature. After stirring at 100 °C until the reaction was complete, TLC showed the reaction was completed. The reaction mixture was diluted by EtOAc (20 mL). The organic layer was washed by sat. NH_4Cl and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (e.g., PE:EtOAc = 1:2) to afford intermediate **IM-XXVI**.

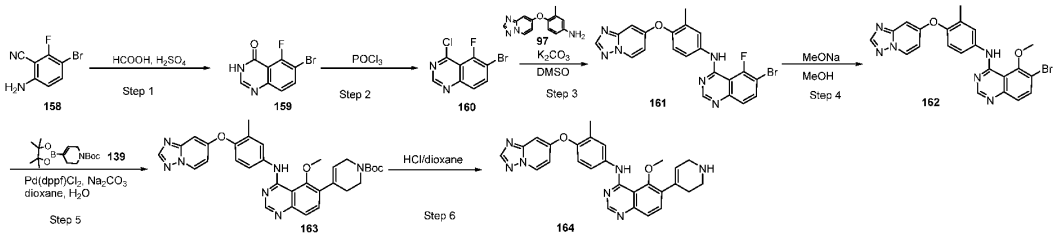
Step 2: To a mixture of intermediate **IM-XXVI** (1.0 equiv.) in MeOH was added a solution of MeONa (3.0 equiv., 30%wt) in MeOH at room temperature. The reaction was stirred at 50 °C until the reaction was complete, then concentrated directly. The residue was diluted with EtOAc (10 mL), washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give intermediate **IM-XXVII**.

Step 3: To a stirred solution of intermediate **IM-XXVII** (1.0 equiv.) and boronic ester **IM-IV** (1.2 equiv.) in 1,4-dioxane and water, were added Na_2CO_3 (3.0 equiv.) and $Pd(dppf)Cl_2$ (0.1 equiv.) at room temperature. The reaction was degassed under

N_2 atmosphere for three times and stirred at 100 °C until the reaction was complete. The reaction was cooled to r.t, filtered and the solid was washed with EtOAc. The filtrate was washed with water and brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (DCM:MeOH = 15:1) to give intermediate **IM-XXVIII**.

Step 4: To a stirred solution of intermediate **IM-XXVIII** (1.0 equiv.) in ethyl acetate was added HCl-dioxane at 0 °C under N_2. After stirring at 0 °C until the reaction was complete, the reaction was concentrated to give intermediate **IM-XXIX**.

Synthesis of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-5-methoxy-6-(1,2,3,6-tetrahydropyridin-4-yl)quinazolin-4-amine hydrochloride 164



Step 1: To a suspension of 6-amino-3-bromo-2-fluorobenzonitrile **158** (5.0 g, 23 mmol) in formic acid (30 mL) was added a mixture of conc. H_2SO_4 (2 mL) and formic acid (5 mL). The mixture was stirred at 115°C for 1hr. LCMS showed that the reaction was completed. The mixture was cooled down to r.t. and poured into ice water (100 mL). This mixture was stirred at r.t for 15minutes and filtered. The filtered cake was washed with water (5 mL) and ethanol (100 mL) to give 6-bromo-5-fluoro-3, 4-dihydroquinazolin-4-one **159** (5.0 g, 89%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 8.06 (dd, J = 8.8, 7.1 Hz, 1H), 7.46 (dd, J = 8.8, 1.2 Hz, 1H). LCMS ESI (m/z):242 $[M+H]^+$.

Step 2: A suspension of 6-bromo-5-fluoro-3,4-dihydroquinazolin-4-one **159** (1.0 g, 4.1 mmol) in $POCl_3$ (10 mL) was stirred and refluxed for 18 hours. TLC showed that 30% of desired product. The mixture was concentrated to give the crude product, which was purified by column chromatography on silica gel (PE : EtOAc =10 : 1 - 2 : 1) to afford 6-

bromo-4-chloro-5-fluoroquinazoline **160** (0.24 g , 22%) as a yellow solid. LCMS ESI (m/z):262 $[M+H]^+$.

Step 3: To a solution of 4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylaniline **97** (400 mg, 1.70 mmol) in DMSO (5 mL) were added K_2CO_3 (690 mg, 5.00 mmol) and 6-bromo-4-chloro-5-fluoroquinazoline **160** (435 mg, 1.70 mmol) at room temperature. After stirring at 100 °C for 16 h, TLC showed the reaction was completed. The reaction mixture was diluted by EtOAc (20 mL). The organic layer was washed by sat. NH_4Cl (30 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc = 1:2) to afford *N*-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)-6-bromo-5-fluoroquinazolin-4-amine **161** (300 mg, 38.7%) as a white solid. LCMS ESI (m/z):465/467 $[M+H]^+$.

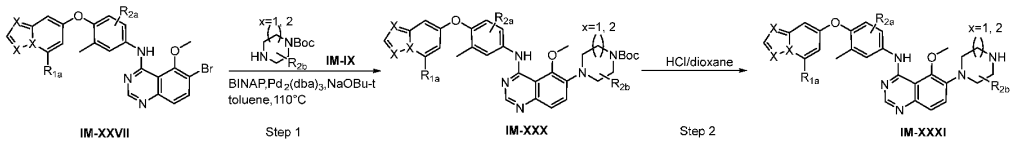
Step 4: To a mixture of *N*-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)-6-bromo-5-fluoroquinazolin-4-amine **161** (100 mg, 0.22 mmol) in MeOH (2 mL) was added a solution of MeONa (116 mg, 0.65 mmol, 30%wt) in MeOH at room temperature. The reaction was stirred at 50 °C for 12 hours, then concentrated directly. The residue was diluted with EtOAc (10 mL), washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give *N*-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)-6-bromo-5-methoxyquinazolin-4-amine **162** (97 mg, 95% yield) as a white solid. LCMS (ESI) (m/z): 477/479 $[M+H]^+$.

Step 5: To a stirred solution of *N*-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)-6-bromo-5-methoxyquinazolin-4-amine **162** (90 mg, 0.19 mmol) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **139** (64 mg, 0.21 mmol) in 1,4-dioxane (1 mL) and water (0.2 mL), were added Na_2CO_3 (60 mg, 0.57 mmol) and $Pd(dppf)Cl_2$ (14 mg, 0.02 mmol) at room temperature. The reaction was degassed under N_2 atmosphere for three times and stirred at 100 °C for 4 hours. The reaction was cooled to r.t, filtered and the solid was washed with EtOAc (15 mL). The filtrate was washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (DCM:MeOH = 15:1) to give tert-butyl 4-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-7-

yloxy)-3-methylphenyl)amino)-5-methoxyquinazolin-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **163** (108 mg, 98.8% yield) as a yellow oil. LCMS (ESI) (m/z): 580 $[M+H]^+$.

Step 6: To a stirred solution of tert-butyl 4-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)amino)-5-methoxyquinazolin-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **163** (108 mg, 0.19 mmol) in EA (2 mL) was added HCl-dioxane (2 mL, 4 M) at 0 °C under N_2. After stirring at 0 °C for 1 h, the reaction was concentrated to give *N*-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)-5-methoxy-6-(1,2,3,6-tetrahydropyridin-4-yl)quinazolin-4-amine hydrochloride **164** (95 mg, 99% yield) as a white solid. LCMS (ESI) (m/z): 480 $[M+H]^+$.

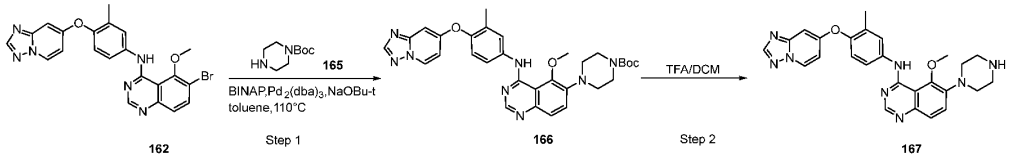
Method H: General method for intermediate IM-XXXI



Step 1: To a solution of intermediate **IM-XXVII** (1.0 equiv.) in toluene were added BINAP (0.2 equiv.), and $Pd_2(dba)_3$ (0.05 equiv.) and ^{t}BuONa (2.0 equiv.) and tert-butyl piperazine-1-carboxylate **IM-IX** (1.3 equiv.), then the mixture was stirred at 110°C overnight. After overnight, the reaction mixture was quenched by NH_4Cl aq. This mixture was extracted with ethyl acetate. The combined organic solution was washed with sat NH_4Cl aq and brine, dried over anhydrous Na_2SO_4, concentrated in vacuo to give the residue. The residue was purified by prep-TLC to give intermediate **IM-XXX**.

Step 2: To a solution of intermediate **IM-XXX** (1.0 equiv.) in DCM was added TFA. Then the mixture was stirred at r.t. until the reaction was complete. The mixture was concentrated in vacuo to give the residue. The reaction mixture was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. This organic solution was separated, dried over anhydrous Na_2SO_4, concentrated in vacuo to give the residue. The residue was purified by flash to give intermediate **IM-XXXI**.

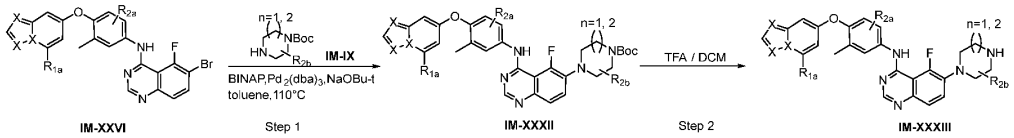
Synthesis of 5-methoxy-*N*-(3-methyl-4-{[1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy}phenyl)-6-(piperazin-1-yl)quinazolin-4-amine 167



Step 1: To a solution of 6-bromo-5-methoxy-*N*-(3-methyl-4-{[1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy}phenyl)quinazolin-4-amine **162** (20 mg, 0.042 mmol) in toluene (0.5 mL) were added BINAP (5.2 mg, 0.008 mmol), and $Pd_2(dba)_3$ (1.9 mg, 0.002 mmol) and ^{t}-BuONa (8 mg, 0.084 mmol) and tert-butyl piperazine-1-carboxylate **165** (9.36 mg, 0.050 mmol), then the mixture was stirred at 110°C overnight. After overnight, the reaction mixture was quenched by NH_4Cl aq. This mixture was extracted with EA (3 × 10 mL). The combined organic solution was washed with sat NH_4Cl aq (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo to give the residue. The residue was purified by prep-TLC (MeOH/DCM = 0 - 20%) to give tert-butyl 4-{5-methoxy-4-[(3-methyl-4-{[1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy}phenyl)amino]quinazolin-6-yl}piperazine-1-carboxylate **166** (18 mg, 73.7% yield) as a yellow solid. LCMS ESI (m/z): 583 $[M+H]^+$.

Step 2: To a solution of tert-butyl 4-{5-methoxy-4-[(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]quinazolin-6-yl}piperazine-1-carboxylate **166** (86 mg, 0.148 mmol) in DCM (1 mL) was added TFA (0.8 mL). Then the mixture was stirred at r.t. for 2 hours. After 2 hours, this mixture was concentrated in vacuo to give the residue. The reaction mixture was partitioned between EA and saturated aqueous $NaHCO_3$ solution. This organic solution was seperated, dried over anhydrous Na_2SO_4, concentrated in vacuo to give the residue. The residue was purified by flash (MeOH/DCM = 0 - 20%) to give 5-methoxy-N-(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-6-(piperazin-1-yl)quinazolin-4-amine **167** (60 mg, 84.2% yield) as a yellow oil. LCMS ESI (m/z): 483 [M+H]+.

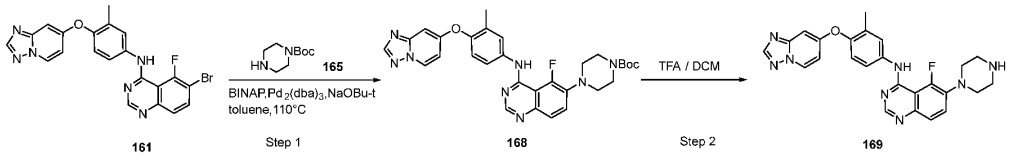
Method I: General method for intermediate IM-XXXIII



Step 1: To a solution of intermediate **IM-XXVI** (1.0 equiv.) in toluene were added Boc protected amine **IM-IX** (1.2 equiv.), NaOtBu (2.0 equiv.), BINAP (0.2 equiv.) and $Pd_2(dba)_3$ (0.04 equiv.) under N_2. Then this mixture was stirred at 120 °C until the reaction was complete. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (DCM: MeOH) to intermediate **IM-XXXII** as a yellow solid.

Step 2: To a solution of **IM-XXXII** (1.0 equiv.) in DCM was added TFA. The resulting mixture was stirred at room temperature until the reaction was complete. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (DCM: MeOH) to give intermediate **IM-XXXIII**.

Synthesis of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-5-fluoro-6-(piperazin-1-yl)quinazolin-4-amine 169



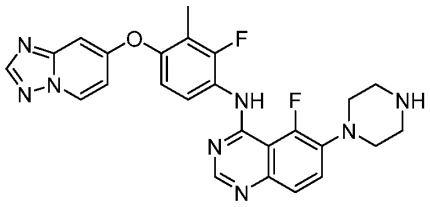
Step 1: To a solution of N-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)-6-bromo-5-fluoroquinazolin-4-amine **161** (200 mg, 0.43 mmol) in toluene (10 mL) were added tert-butyl piperazine-1-carboxylate **165** (96 mg, 0.52 mmol), NaO^{t}Bu (82 mg, 0.86 mmol), BINAP (53 mg, 0.086 mmol) and $Pd_2(dba)_3$ (17 mg, 0.021 mmol) under N_2. Then this mixture was stirred at 120 °C for 24 hours. The reaction mixture was

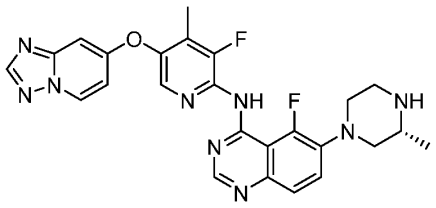
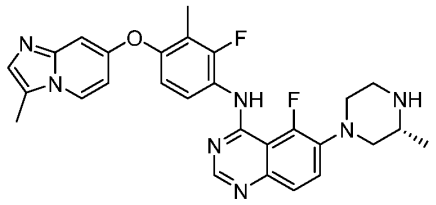
quenched with saturated $NaHCO_3$ and extracted with DCM (5 mL x 2). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (DCM: MeOH = 20:1, V/V) to give tert-butyl 4-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)amino)-5-fluoroquinazolin-6-yl)piperazine-1-carboxylate **168** (90 mg, 36.7% yield) as a yellow solid. LCMS ESI (m/z):571 $[M+H]^+$.

Step 2: To a solution of tert-butyl 4-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)amino)-5-fluoroquinazolin-6-yl)piperazine-1-carboxylate **168** (90 mg, 0.16 mmol) in DCM (1 mL) was added TFA (0.5 mL, 6.7 mmol). The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with DCM (5 mL x 2). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (DCM: MeOH = 15:1, V/V) to give N-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)-5-fluoro-6-(piperazin-1-yl)quinazolin-4-amine **169** (66 mg, 88.9% yield) as a yellow oil. LCMS ESI (m/z):471 $[M+H]^+$.

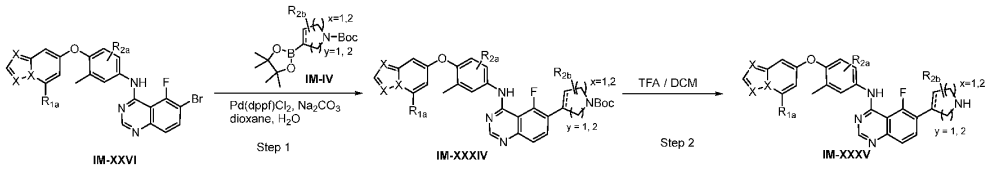
The following intermediates in **Table 7** were obtained following above-mentioned method using the appropriate starting materials.

Table 7. Intermediate

Example	Compound Structure	Physical Data MS [ESI, *m/z*]
170	 N-(5-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-fluoro-4-methylpyridin-2-yl)-5-fluoro-6-(piperazin-1-yl)quinazolin-4-amine	490 $[M + H]^+$

171	 (*R*)-N-(5-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-fluoro-4-methylpyridin-2-yl)-5-fluoro-6-(3-methylpiperazin-1-yl)quinazolin-4-amine	504 $[M + H]^+$
172	 tert-butyl (R)-4-(5-fluoro-4-((2-fluoro-3-methyl-4-((3-methylimidazo[1,2-a]pyridin-7-yl)oxy)phenyl)amino)quinazolin-6-yl)-2-methylpiperazine-1-carboxylate	616 $[M + H]^+$

Method J: General method for intermediate IM-XXXV

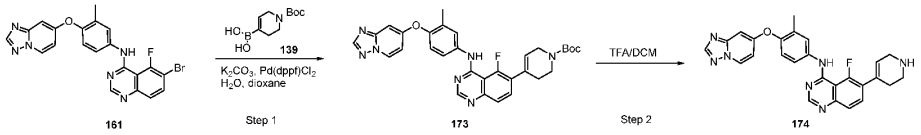


Step 1: To a solution of intermediate **IM-XXVI** (1 equiv.) in dioxane and water were added boronic ester **IM-IV** (1.2 equiv.), $Pd(dppf)Cl_2$ (0.1 equiv.) and K_2CO_3 (2.0 equiv.). Then this mixture was stirred at 100°C until the reaction was complete. After cooling to r.t., this mixture was concentrated, diluted with H_2O, and then extracted with EtOAc. The combined organic solutions were dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE:EA = 0:1) to give intermediate **IM-XXXIV**.

Step 2: A solution of intermediate **IM-XXXIV** (1.0 equiv.) in TFA and DCM was stirred at r.t. until the reaction was complete. Then this mixture was concentrated, basified

with saturated aqueous $NaHCO_3$ and extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated to give intermediate **IM-XXXV**.

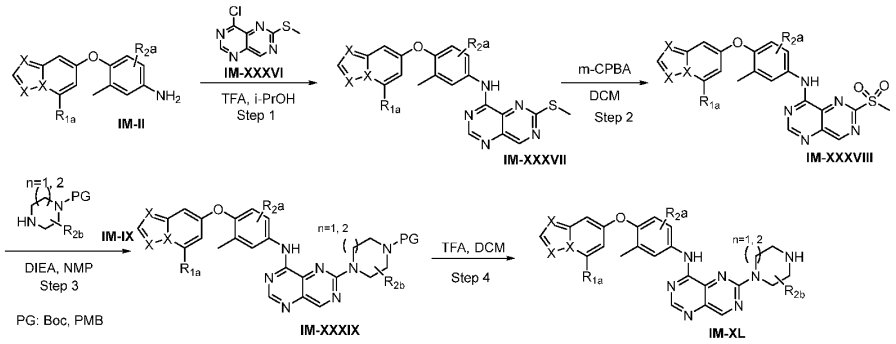
Synthesis of 5-fluoro-N-(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)quinazolin-4-amine 174



Step 1: To a solution of 6-bromo-5-fluoro-*N*-(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)quinazolin-4-amine **161** (200 mg, 0.430 mmol) in dioxane (4 mL) and water (1 mL) were added {1-[(tert-butoxy)carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}boronic acid **139** (107 mg, 0.473 mmol), $Pd(dppf)Cl_2$ (31.4 mg, 0.043 mmol) and K_2CO_3 (119 mg, 0.860 mmol). Then this mixture was stirred at 100°C for 16 hours. After cooling to r.t., this mixture was concentrated, diluted with H_2O, and then extracted with EtOAc (10 mL x 3). The combined organic solutions were dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE:EA = 0:1) to give tert-butyl4-{5-fluoro-4-[(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]quinazolin-6-yl}-1,2,3,6-tetrahydropyridine-1-carboxylate **173** (88 mg, yield: 37%) as a yellow solid. LCMS (ESI) m/z: 568.1$[M+H]^+$.

Step 2: A solution of tert-butyl 4-{5-fluoro-4-[(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]quinazolin-6-yl}-1,2,3,6-tetrahydropyridine-1-carboxylate **173** (88 mg, 0.155 mmol) in TFA (2 mL) and DCM (2 mL) was stirred at r.t. for 1hour. Then this mixture was concentrated, basified with saturated aqueous $NaHCO_3$ and extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated to give 5-fluoro-N-(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)quinazolin-4-amine **174** (135 mg, yield: 82.8%) as a white solid. LCMS (ESI) m/z: 466.1$[M-H]^+$.

Method K: General method for intermediate IM-XL



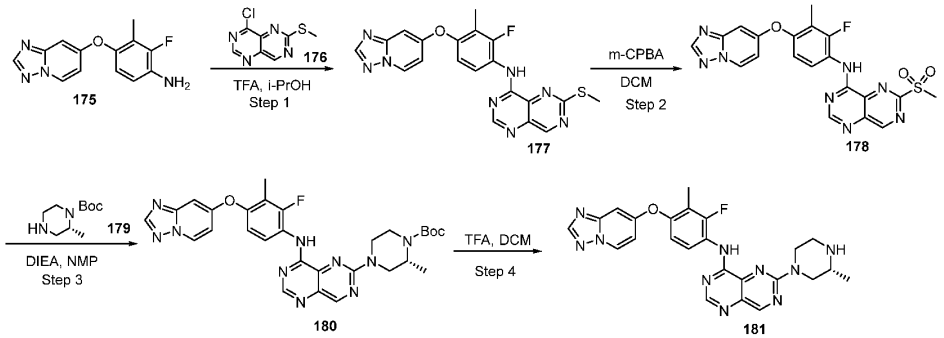
Step 1: To intermediate **IM-II** (1.0 equiv.) in i-PrOH was added 8-chloro-2-(methylsulfanyl)[1,3]diazino[5,4-d]pyrimidine **IM-XXXVI** (1.0 equiv.) and TFA, then the mixture was stirred at room temperature until the reaction was complete. LCMS showed the reaction was completed. The reaction mixture was concentrated, basified by saturated $NaHCO_3$ and filtered. The filter cake was washed with water twice and dried under vacuum to give intermediate **IM-XXXVII**.

Step 2: To the intermediate **IM-XXXVII** (1.0 equiv.) in DCM was added m-CPBA (2.0 equiv.) at 0°C, then the mixture was stirred at room temperature until the reaction was complete. LCMS showed the consumption of starting material. The reaction mixture was quenched by saturated $NaHCO_3$ and extracted with DCM. The organic solution was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give intermediate **IM-XXXVIII** which was used directly in the next step.

Step 3: To intermediate **IM-XXXVIII** (1.0 equiv.) in NMP were added DIPEA (4.0 equiv.) and intermediate **IM-IX** (2 equiv.), then the mixture was stirred at 50°C until the reaction was complete. LCMS showed the reaction was completed. The reaction mixture was quenched by ice water and extracted with EtOAc. The organic solution was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (DCM 95%-MeOH 5%) to give intermediate **IM-XXXIX**.

Step 4: To intermediate **IM-XXXIX** (1 equiv.) in DCM was added TFA, then the mixture was stirred at room temperature until the reaction was complete. LCMS showed the reaction was completed. The reaction mixture was concentrated to dryness to give intermediate **IM-XL** which was used directly in the next step.

Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-d]pyrimidin-4-amine 181



Step 1: To 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylaniline **175** (200 mg, 0.77 mmol) in i-PrOH (10 mL) was added 8-chloro-2-(methylsulfanyl)[1,3]diazino[5,4-d]pyrimidine **176** (164 mg, 0.77 mmol) and TFA (0.3 mL), then the mixture was stirred at room temperature for 16 hours. LCMS showed the reaction was completed. The reaction mixture was concentrated, basified by saturated $NaHCO_3$ and filtered. The filter cake was washed with water twice and dried under vacuum to give N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(methylthio)pyrimido[5,4-d]pyrimidin-4-amine **177** (310 mg, yield: 92.1%) as a yellow solid. LCMS ESI (m/z): 435$[M+H]^+$.

Step 2: To the mixture of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(methylthio)pyrimido[5,4-d]pyrimidin-4-amine **177** (100 mg, 0.23 mmol) in DCM (5 mL) was added m-CPBA (93.5 mg, 0.46 mmol, 85% wt) at 0°C, then the mixture was stirred at room temperature for 2 hours. LCMS showed the consumption of starting material. The reaction mixture was quenched by saturated $NaHCO_3$ and extracted with DCM. The organic solution was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-

yloxy)-2-fluoro-3-methylphenyl)-6-(methylsulfonyl)pyrimido[5,4-d]pyrimidin-4-amine **178** (105 mg, yield: 97.8%) as a yellow solid which was used directly in the next step. LCMS ESI (m/z): 467 [M+H]+ and 451 (sulfone) $[M+H]^+$.

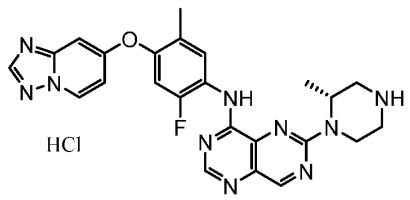
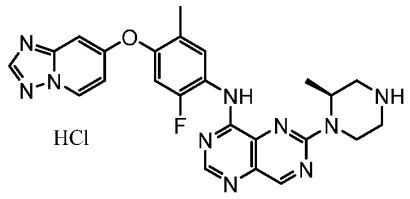
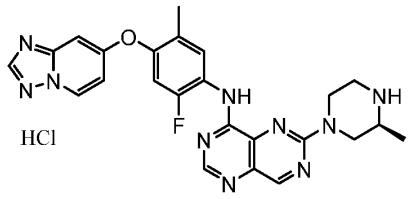
Step 3: To the mixture of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(methylsulfonyl)pyrimido[5,4-d]pyrimidin-4-amine **178** (105 mg, 0.22 mmol) in NMP (3 mL) were added DIPEA (116 mg, 0.90 mmol) and tert-butyl (R)-2-methylpiperazine-1-carboxylate **179** (90 mg, 0.45 mmol), then the mixture was stirred at 50°C for 16 hours. LCMS showed the reaction was completed. The reaction mixture was quenched by ice water and extracted with EtOAc. The organic solution was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (DCM 95%-MeOH 5%) to give (R)-tert-butyl 4-(8-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenylamino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate **180** (120 mg, yield: 90.8%) as yellow solid. LCMS ESI (m/z): 587 $[M+H]^+$.

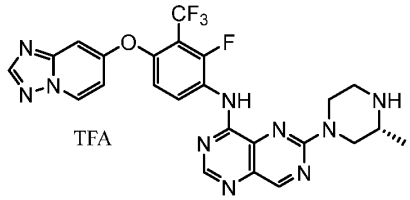
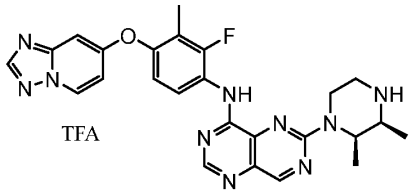
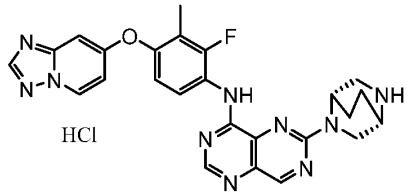
Step 4: To the mixture of tert-butyl (R)-4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate **180** (120 mg, 0.21 mmol) in DCM (4 mL) was added TFA (2 mL), then the mixture was stirred at room temperature for 2 hours. LCMS showed the reaction was completed. The reaction mixture was concentrated to dryness to give the mixture of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-d]pyrimidin-4-amine **181** (90 mg, yield: 90.4%) as a yellow oil which was used directly in the next step. LCMS ESI (m/z): 487 $[M+H]^+$.

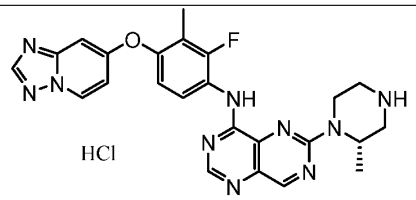
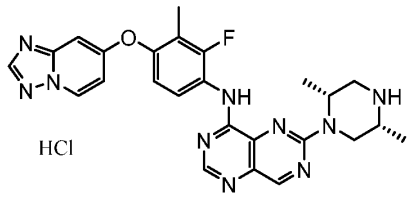
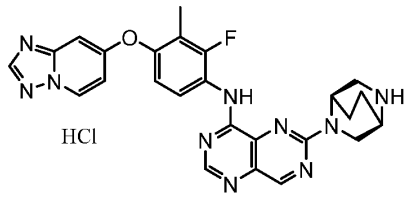
Alternatively, HCl (4N in 1,4-dioxane) in DCM could be used to remove the Boc protecting group instead of TFA in DCM. After completion of the reaction, the reaction mixture was concentrated under vacuum to afford the desired intermediate as HCl salt.

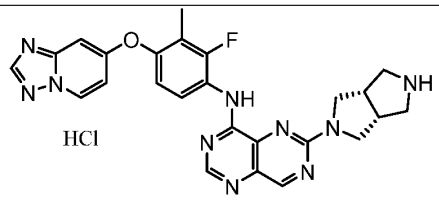
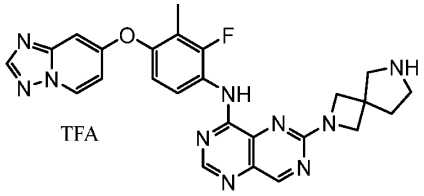
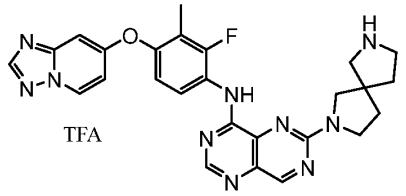
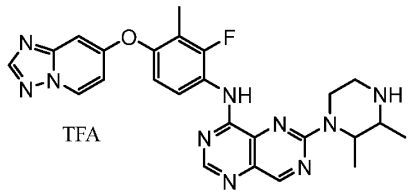
The following intermediates in **Table 8** were obtained following above-mentioned method using the appropriate starting materials.

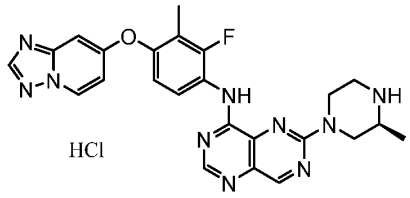
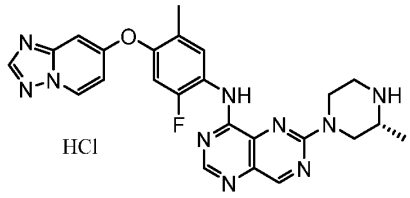
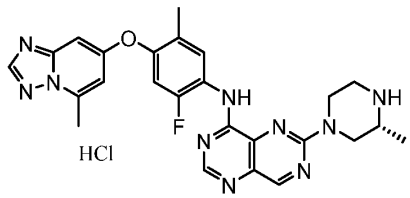
Table 8: Intermediates

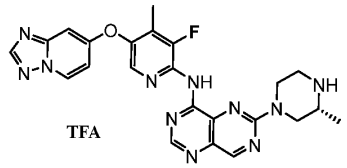
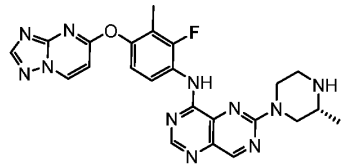
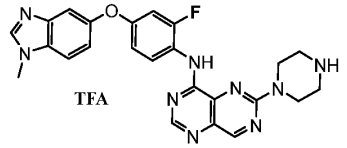
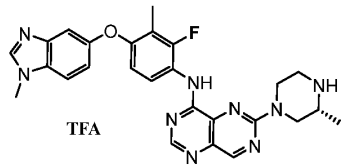
Example	Compound Structure	Physical Data MS [ESI, *m/z*]
182	 HCl (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6-(2-methylpiperazin-1-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	487 $[M + H]^+$
183	 HCl (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6-(2-methylpiperazin-1-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	487 $[M + H]^+$
184	 HCl (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	487 $[M + H]^+$
185		541 $[M + H]^+$

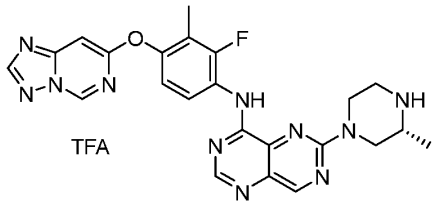
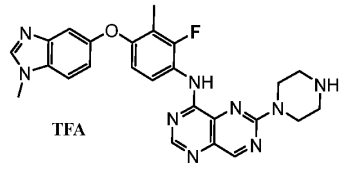
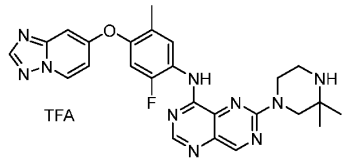
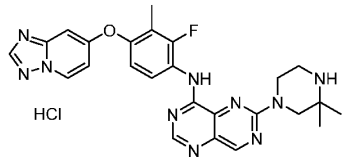
Example	Compound Structure	Physical Data MS [ESI, *m/z*]
	 TFA (*R*)-*N*-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-2-fluoro-3-(trifluoromethyl)phenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-*d*]pyrimidin-4-amine trifluoroacetate	
186	 TFA relative stereochemistry 6-(2,3-dimethylpiperazin-1-yl)-N-(2-fluoro-3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-[1,3]diazino[5,4-d]pyrimidin-4-amine trifluoroacetate	501 $[M + H]^+$
187	 HCl N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-((1S,4S)-2,5-diazabicyclo[2.2.2]octan-2-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	499 $[M + H]^+$
188		487 $[M + H]^+$

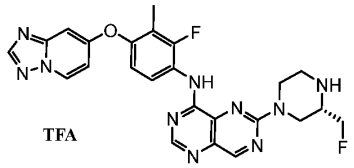
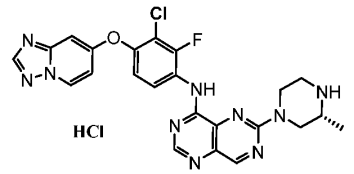
Example	Compound Structure	Physical Data MS [ESI, *m/z*]
	 HCl (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(2-methylpiperazin-1-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	
189	 HCl 6-[(2R,5R)-2,5-dimethylpiperazin-1-yl]-N-(2-fluoro-3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)pyrimido[5,4-d][1,3]diazin-4-amine hydrochloride	501 $[M + H]^+$
190	 HCl N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-((1R,4R)-2,5-diazabicyclo[2.2.2]octan-2-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	499 $[M + H]^+$
191		499 $[M + H]^+$

Example	Compound Structure	Physical Data MS [ESI, *m/z*]
	 HCl N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimido[5,4-d]pyrimidin-4-amine	
192	 TFA N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(2,6-diazaspiro[3.4]octan-2-yl)pyrimido[5,4-d]pyrimidin-4-amine trifluoroacetate	499 $[M + H]^+$
193	 TFA N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(2,7-diazaspiro[4.4]nonan-2-yl)pyrimido[5,4-d]pyrimidin-4-amine trifluoroacetate	513 $[M + H]^+$
194	 TFA	501 $[M + H]^+$

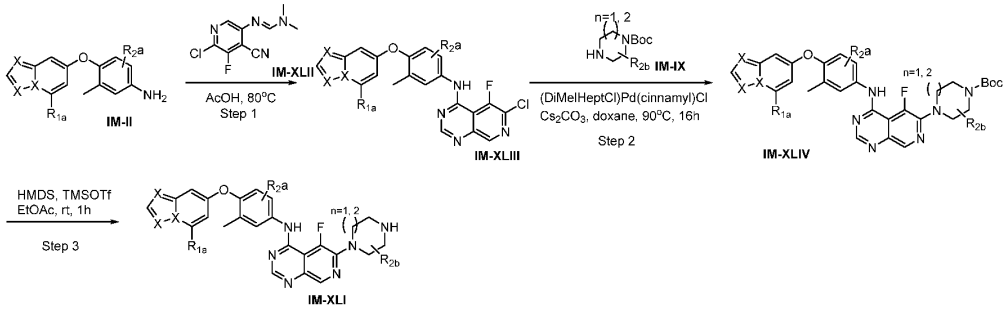
Example	Compound Structure	Physical Data MS [ESI, *m/z*]
	6-(2,3-dimethylpiperazin-1-yl)-N-(2-fluoro-3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-[1,3]diazino[5,4-d]pyrimidin-4-amine trifluoroacetate	
195	 HCl (*S*)-*N*-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-*d*]pyrimidin-4-amine hydrochloride	487 $[M + H]^+$
196	 HCl (*R*)-*N*-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-*d*]pyrimidin-4-amine hydrochloride	487 $[M + H]^+$
197	 HCl (R)-N-(2,6-difluoro-3-methyl-4-((5-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)phenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	501 $[M + H]^+$

Example	Compound Structure	Physical Data MS [ESI, *m/z*]
198	 TFA (*R*)-*N*-(5-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-fluoro-4-methylpyridin-2-yl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-*d*]pyrimidin-4-amine trifluoroacetate	488 $[M + H]^+$
199	 (*R*)-*N*-(4-([1,2,4]triazolo[1,5-*a*]pyrimidin-5-yloxy)-2-fluoro-3-methylphenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-*d*]pyrimidin-4-amine	488 $[M + H]^+$
200	 TFA N-(2-fluoro-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6-(piperazin-1-yl)pyrimido[5,4-d]pyrimidin-4-amine trifluoroacetate	472 $[M + H]^+$
201	 TFA N-{2-fluoro-3-methyl-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]phenyl}-6-[(3R)-3-methylpiperazin-1-yl]pyrimido[5,4-d][1,3]diazin-4-amine trifluoroacetate	500 $[M + H]^+$

Example	Compound Structure	Physical Data MS [ESI, *m/z*]
202	 TFA (*R*)-*N*-(4-([1,2,4]triazolo[1,5-*c*]pyrimidin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-*d*]pyrimidin-4-amine trifluoroacetate	488 $[M + H]^+$
203	 TFA *N*-(2-fluoro-3-methyl-4-((1-methyl-1*H*-benzo[*d*]imidazol-5-yl)oxy)phenyl)-6-(piperazin-1-yl)pyrimido[5,4-*d*]pyrimidin-4-amine trifluoroacetate	486 $[M + H]^+$
204	 TFA 6-(3,3-dimethylpiperazin-1-yl)-N-(2-fluoro-5-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-[1,3]diazino[5,4-d]pyrimidin-4-amine trifluoroacetate	501 $[M + H]^+$.
205	 HCl 6-(3,3-dimethylpiperazin-1-yl)-N-(2-fluoro-3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-[1,3]diazino[5,4-d]pyrimidin-4-amine hydrochloride	501 $[M + H]^+$.

Example	Compound Structure	Physical Data MS [ESI, *m/z*]
206	 TFA N-(2-fluoro-3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)-6-[(3S)-3-(fluoromethyl)piperazin-1-yl]pyrimido[5,4-d][1,3]diazin-4-amine trifluoroacetate	505 $[M + H]^+$.
207	 HCl (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chloro-2-fluorophenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-d]pyrimidin-4-amine hydrochloride	507 / 509 $[M + H]^+$.

Method L: General method for intermediate IM-XLI

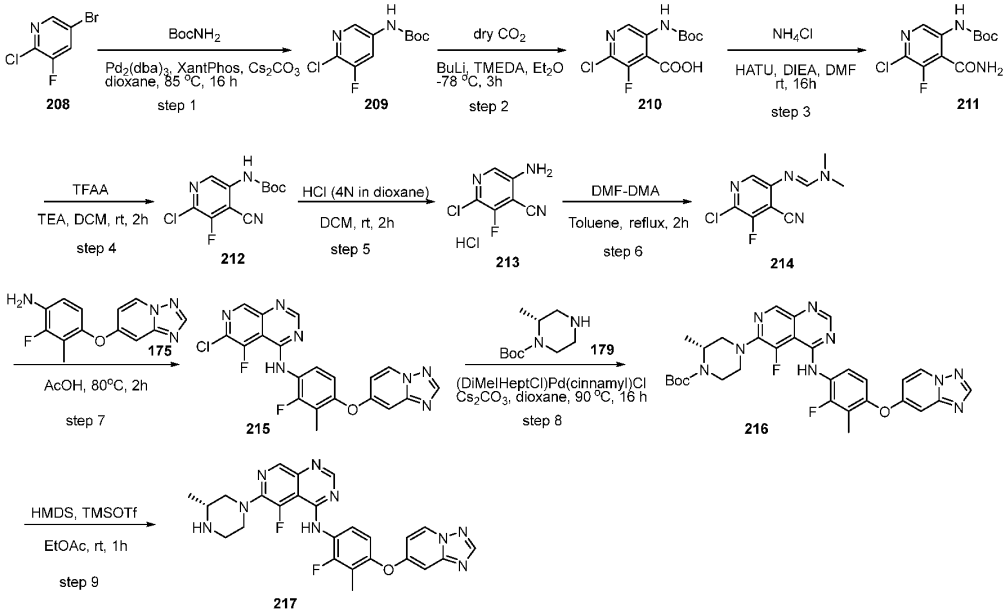


Step 1: To intermediate **IM-II** (1.1 equiv.) in acetic acid was added (E)-N'-(6-chloro-4-cyano-5-fluoropyridin-3-yl)-N,N-dimethylformimidamide **IM-XLII** (1.0 equiv.) then the mixture was stirred at 80°C until the reaction was complete. LCMS showed the reaction was completed. The reaction mixture was concentrated. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-80% acetonitrile in water (containing 0.05% NH_4HCO_3) to afford intermediate **IM-XLIII** as a yellow solid.

Step 2: A mixture of intermediate **IM-XLIII** (1.0 equiv.) and **IM-IX** (1.1 equiv.), (DiMeIHeptCl)Pd(cinnamyl)Cl (0.1 equiv.) and Cs_2CO_3 (2.0 equiv.) in dioxane was stirred at 90°C until the reaction was complete under N_2 atmosphere. LCMS showed the consumption of starting material. The resulting mixture was diluted with water and extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-70% acetonitrile in water (containing 0.05% NH_4HCO_3)) to afford intermediate **IM-XLIV.**

Step 3: To a stirred mixture intermediate **IM-XLIV** (1.0 equiv.) and HMDS (5.0 equiv.) in EtOAc at 0°C was added TMSOTf (4.0 equiv.) The resulting mixture was stirred at this temperature until the reaction was complete and then quenched with $NaHCO_3$ solution and extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford intermediate **IM-XLI**.

Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-5-fluoro-6-(3-methylpiperazin-1-yl)pyrido[3,4-d]pyrimidin-4-amine 217



Step 1: A mixture of 5-bromo-2-chloro-3-fluoropyridine **208** (10.00 g, 47.85 mmol, 1.00 equiv.), $BocNH_2$ (5.65 g, 48.33 mmol, 1.01 equiv.), $Pd_2(dba)_3$ (4.39 g, 4.79 mmol, 0.10 equiv.), XantPhos (5.53 g, 9.57 mmol, 0.20 equiv.) and Cs_2CO_3 (31.20 g, 95.70 mmol, 2.00 equiv.) in dioxane (100.00 mL) was stirred at 85 °C for 16 h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% MeOH in DCM) to afford tert-butyl (6-chloro-5-fluoropyridin-3-yl)carbamate **209** (9.40 g, 80%) as a yellow solid. LCMS (ESI, *m/z*): 247 $[M + H]^+$.

Step 2: To a stirred mixture of tert-butyl (6-chloro-5-fluoropyridin-3-yl)carbamate **209** (5.00 g, 20.32 mmol, 1.00 equiv.) and TMEDA (7.07 g, 60.96 mmol, 3.00 equiv.) in Et_2O (100.00 mL) at -78 °C was added dropwise nBuLi (2 M in THF, 30.48 mL, 60.96 mmol, 3.00 equiv.) under N_2 atmosphere. The resulting mixture was stirred at -20 °C for 1 h. To this at -78 °C was added dry ice (excess). The resulting mixture was allowed to warm up to ambient temperature and stirred for 2 h. The reaction was quenched with NH_4Cl solution at 0 °C and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-80% acetonitrile in water (containing 0.05% TFA)) to afford 5-((tert-butoxycarbonyl)amino)-2-chloro-3-fluoroisonicotinic acid **210** (4.80 g, 81%) as a white solid. LCMS (ESI, *m/z*): 291 $[M + H]^+$.

Step 3: To a stirred mixture of 5-((tert-butoxycarbonyl)amino)-2-chloro-3-fluoroisonicotinic acid **210** (4.80 g, 16.55 mmol, 1.00 equiv.), HATU (8.18 g, 21.52 mmol, 1.30 equiv.) and DIEA (12.81 g, 99.30 mmol, 6.00 equiv.) in DMF (50.00 mL) at ambient temperature was added NH_4Cl (2.68 g, 49.65 mmol, 3.00 equiv.). The resulting mixture was stirred at this temperature for 16 h and then diluted with water and extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% EtOAc in petroleum ether) to afford tert-butyl (4-carbamoyl-6-chloro-5-fluoropyridin-3-yl)carbamate **211** (2.50 g, 52%) as a yellow solid. LCMS (ESI, *m/z*): 290 $[M + H]^+$.

Step 4: To a stirred mixture of tert-butyl (4-carbamoyl-6-chloro-5-fluoropyridin-3-yl)carbamate **211** (2.00 g, 6.92 mmol, 1.00 equiv.) and TEA (2.10 g, 20.76 mmol, 3.00 equiv.) in DCM (20.00 mL) at ambient temperature was added trifluoroacetic anhydride (2.91 g, 13.84 mmol, 2.00 equiv.). The resulting mixture was stirred at this temperature for 2 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-80% acetonitrile in water (containing 0.05% NH_4HCO_3)) to afford tert-butyl (6-chloro-4-cyano-5-fluoropyridin-3-yl)carbamate **212** (850.0 mg, 45%) as a yellow solid. LCMS (ESI, *m/z*): 272 $[M + H]^+$.

Step 5: To a stirred solution of tert-butyl (6-chloro-4-cyano-5-fluoropyridin-3-yl)carbamate **212** (850.0 mg, 3.12 mmol, 1.00 equiv.) in DCM (15.00 mL) at ambient temperature was added HCl (4 N in dioxane, 4.00 mL). The resulting mixture was stirred at this temperature for 2 h and then concentrated under vacuum to afford 5-amino-2-chloro-3-fluoroisonicotinonitrile hydrochloride **213** (crude, 900.0 mg) as a yellow solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 172 $[M + H]^+$.

Step 6: A mixture of 5-amino-2-chloro-3-fluoroisonicotinonitrile hydrochloride **213** (900.0 mg, 5.23 mmol, 1.00 equiv.) and DMF-DMA (934.0 mg, 7.85 mmol, 1.50 equiv.) in toluene (10.00 mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-80% acetonitrile in water (containing 0.05% NH_4HCO_3)) to afford (E)-N'-(6-chloro-4-cyano-5-fluoropyridin-3-yl)-N,N-dimethylformimidamide **214** (410.0 mg, 34%) as a yellow solid. LCMS (ESI, *m/z*): 227 $[M + H]^+$.

Step 7: A mixture of (E)-N'-(6-chloro-4-cyano-5-fluoropyridin-3-yl)-N,N-dimethylformimidamide **214** (400.0 mg, 1.77 mmol, 1.00 equiv.) and 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylaniline **175** (502.3 mg, 1.95 mmol, 1.10 equiv.) in AcOH (3.00 mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-80% acetonitrile in water (containing 0.05% NH_4HCO_3)) to afford N-(4-

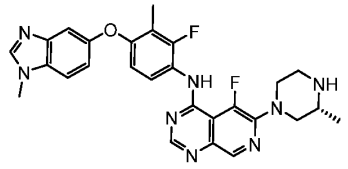
([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-chloro-5-fluoropyrido[3,4-d]pyrimidin-4-amine **215** (420.0 mg, 54%) as a yellow solid. LCMS (ESI, *m/z*): 440 $(M + H)^+$.

Step 8: A mixture of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-chloro-5-fluoropyrido[3,4-d]pyrimidin-4-amine **215** (200.0 mg, 0.46 mmol, 1.00 equiv.), tert-butyl (R)-2-methylpiperazine-1-carboxylate **179** (100.2 mg, 0.50 mmol, 1.10 equiv.), (DiMeIHeptCl)Pd(cinnamyl)Cl (CAS: 2138491-47-9, 58.35 mg, 0.05 mmol, 0.10 equiv.) and Cs_2CO_3 (299.9 mg, 0.92 mmol, 2.00 equiv.) in dioxane (4.00 mL) was stirred at 90 °C for 16 h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-70% acetonitrile in water (containing 0.05% NH_4HCO_3)) to afford tert-butyl (R)-4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)-5-fluoropyrido[3,4-d]pyrimidin-6-yl)-2-methylpiperazine-1-carboxylate **216** (110.0 mg, 39%) as a yellow solid. LCMS (ESI, *m/z*): 604 $[M + H]^+$

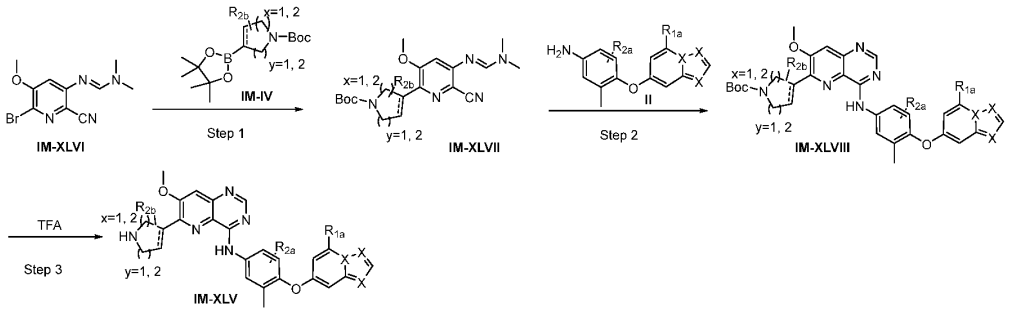
Step 9: To a stirred mixture of tert-butyl (R)-4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)-5-fluoropyrido[3,4-d]pyrimidin-6-yl)-2-methylpiperazine-1-carboxylate **216** (100.0 mg, 0.17 mmol, 1.00 equiv.) and HMDS (136.8 mg, 0.85 mmol, 5.00 equiv.) in EtOAc (3.00 mL) at 0 °C was added TMSOTf (150.9 mg, 0.68 mmol, 4.00 equiv.). The resulting mixture was stirred at this temperature for 1 h and then quenched with $NaHCO_3$ solution and extracted with EtOAc 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-5-fluoro-6-(3-methylpiperazin-1-yl)pyrido[3,4-d]pyrimidin-4-amine **217** (crude, 90.0 mg) as a yellow solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 504 $[M + H]^+$.

The following intermediates in **Table 9** were obtained following above-mentioned method using the appropriate starting materials.

Table 9: Intermediate

Example	Compound Structure	Physical Data MS [ESI, *m/z*]
218	 (R)-5-fluoro-N-(2-fluoro-3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6-(3-methylpiperazin-1-yl)pyrido[3,4-d]pyrimidin-4-amine	517 $[M + H]^{1+}$

Method M: General method for intermediate IM-XLV



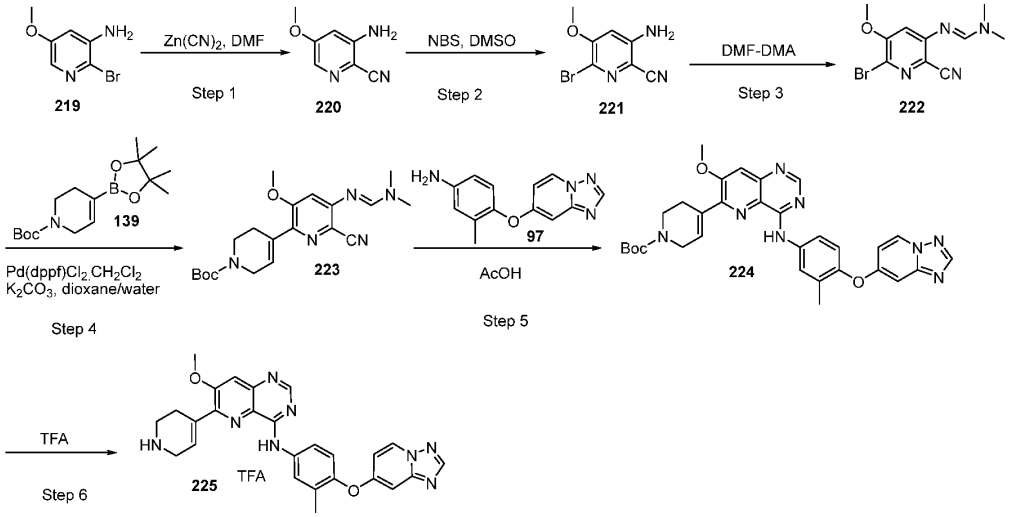
Step 1: A mixture of intermediate **IM-XLVI** (1.00 equiv), **IM-IV** (1.30 equiv), K_2CO_3 (3.00 equiv) and $Pd(dppf)Cl_2.CH_2Cl_2$ (0.10 equiv) in dioxane and water was stirred at 80 °C until the reaction was complete under N_2 atmosphere. The resulting mixture was diluted with water and extracted with DCM 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0 to 5% MeOH in DCM) to afford intermediate **IM-XLVII** as a brown oil.

Step 2: A mixture of intermediate **IM-XLVII** (1.00 equiv) and **IM-II** (1.00 equiv) in AcOH was stirred at 80 °C until the reaction was complete and then diluted with water. The mixture was neutralized with saturated $NaHCO_3$ to pH 8 and then extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated

under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5 to 60% acetonitrile in water (containing 0.05% NH_4HCO_3) to afford intermediate **IM-XLVIII** as a yellow solid.

Step 3: To a stirred mixture intermediate **IM-XLVIII** (1.0 equiv.) in DCM at ambient temperature was added TFA. The resulting mixture was stirred at ambient temperature until the reaction was complete and then concentrated under vacuum to **IM-XLV** as brown oil,

Synthesis of 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-7-methoxypyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one 225



Step 1: A mixture of 2-bromo-5-methoxypyridin-3-amine **219** (2.0 g, 9.90 mmol, 1.00 equiv), $Zn(CN)_2$ (1.16 g, 9.90 mmol, 1.00 equiv) and $Pd(PPh_3)_4$ (1.14 g, 0.99 mmol, 0.10 equiv) in DMF (60.0 mL) was stirred at 120 °C for 16 h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (50 to 80% EtOAc in petroleum ether) to afford 3-amino-5-methoxypicolinonitrile **220** (1.0 g, 68%) as a yellow solid. LCMS (ESI, *m/z*): 150 $[M + H]^+$.

Step 2: To a stirred solution of 3-amino-5-methoxypicolinonitrile **220** (1.0 g, 6.71 mmol, 1.00 equiv) in DMSO (25.0 mL) and water (2.5 mL) was added NBS (3.6 g, 20.13 mmol, 3.00 equiv) at ambient temperature. The resulting mixture was stirred at ambient temperature for 16 h and then diluted with EtOAc. The organic solution was washed with water twice and brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (40% to 80% EtOAc in petroleum ether) to afford 3-amino-6-bromo-5-methoxypicolinonitrile **221** (930.0 mg, 61%) as a white solid. LCMS (ESI, *m/z*): 228, 230 $[M + H]^+$.

Step 3: A mixture of 3-amino-6-bromo-5-methoxypicolinonitrile **221** (930.0 mg, 4.10 mmol, 1.00 equiv) and DMF-DMA (1.5 g, 12.30 mmol, 3.00 equiv) in toluene (30.0 mL) was stirred at 80 °C for 2 h. The resulting mixture was concentrated under vacuum to afford (E)-N'-(6-bromo-2-cyano-5-methoxypyridin-3-yl)-N,N-dimethylformimidamide **222** (crude, 950.0 mg) as a white solid, which was used for the next step without further purification. LCMS (ESI, *m/z*): 283, 285 $[M + H]^+$.

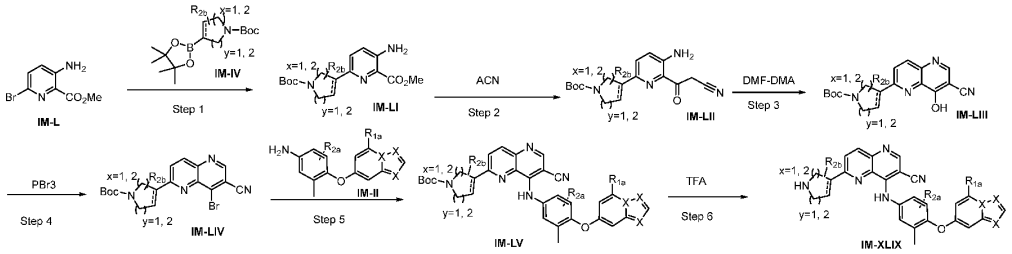
Step 4: A mixture of (E)-N'-(6-bromo-2-cyano-5-methoxypyridin-3-yl)-N,N-dimethylformimidamide **222** (300.0 mg, 1.06 mmol, 1.00 equiv), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **139** (427.3 mg, 1.38 mmol, 1.30 equiv), K_2CO_3 (438.8 mg, 3.18 mmol, 3.00 equiv) and $Pd(dppf)Cl_2.CH_2Cl_2$ (114.2 mg, 0.14 mmol, 0.10 equiv) in dioxane (8.0 mL) and water (0.8 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with DCM 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0 to 5% MeOH in DCM) to afford tert-butyl (E)-6-cyano-5-(((dimethylamino)methylene)amino)-3-methoxy-3',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate **223**(340.0 mg, 83%) as a brown oil. LCMS (ESI, *m/z*): 386 $[M + H]^+$.

Step 5: A mixture of tert-butyl (E)-6-cyano-5-(((dimethylamino)methylene)amino)-3-methoxy-3',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate **223** (340.0 mg, 0.88 mmol, 1.00 equiv) and 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline **97** (211.9 mg, 0.88 mmol, 1.00 equiv) in AcOH (14.0 mL) was stirred at 80 °C for 2 h and

then diluted with water. The mixture was neutralized with saturated $NaHCO_3$ to pH 8 and then extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5 to 60% acetonitrile in water (containing 0.05% NH_4HCO_3) to afford tert-butyl 4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-7-methoxypyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate **224** (105.0 mg, 21%) as a yellow solid. LC/MS (ESI, *m/z*): 581 $[M + H]^+$.

Step 6: To a stirred mixture of tert-butyl 4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-7-methoxypyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate **224** (100.0 mg, 0.17 mmol, 1.00 equiv) in DCM (3.0 mL) at ambient temperature was added TFA (1.0 mL). The resulting mixture was stirred at ambient temperature for 1 h and then concentrated under vacuum to afford N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-7-methoxy-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine trifluoroacetate **225** (crude, 140.0 mg) as brown oil, which was used for the next step without further purification. LCMS (ESI, *m/z*): 481 $[M + H]^+$.

Method N: General method for intermediate IM-XLIX



Step 1: A mixture of intermediate **IM-L** (1.00 equiv), **IM-IV** (1.20 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.10 equiv) and K_2CO_3 (2.00 equiv) in dioxane and water was stirred until the reaction was complete at 80 °C under N_2 atmosphere and then filtered through a pad of celite. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-80% EtOAc in petroleum ether) to intermediate **IM-LI**.

Step 2: To a stirred solution of acetonitrile (5.00 equiv) in THF at -78 °C was added dropwise n-BuLi (2.5 M in hexane, 5.50 equiv) under N2 atmosphere for 30 min. To this was added a solution of intermediate IM-LI (1.00 equiv) in THF. The resulting mixture was stirred at ambient temperature until the reaction was complete and then quenched with NH_4Cl solution and extracted with EtOAc 3 times. The organic layers were combined, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-70% EtOAc in petroleum ether) to afford intermediate **IM-LII**.

Step 3: A mixture of intermediate **IM-LII** (1.00 equiv) and DMF-DMA (3.00 equiv) in toluene was stirred at 100 °C under N_2 atmosphere until the reaction was complete and then concentrated under vacuum. The residue is purified by flash chromatography on silica gel (0-70% EtOAc in petroleum ether) to afford intermediate **IM-LIII.**

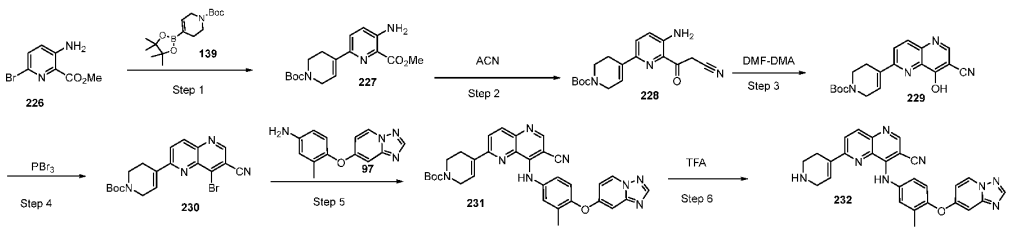
Step 4: To a stirred solution of intermediate **IM-LIII** (1.00 equiv) in DMF at 0 °C was added phosphorus tribromide (1.50 equiv) dropwise under N_2 atmosphere. The resulting mixture was stirred at ambient temperature until the reaction was complete and then quenched with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford intermediate **IM-LIV**

Step 5: A mixture of intermediate **IM-LIV** (1.00 equiv), **IM-II** (1.00 equi.), $Pd_2(dba)_3$ (0.20 equiv), XantPhos (0.20 equiv) and Cs_2CO_3 (2.00 equiv) in dixoane was stirred at 100 °C under N_2 atmosphere until the reaction was complete. The resulting mixture was diluted with water and extracted with EtOAc 3 times. The combined organic layers were concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-80% EtOAc in petroleum ether) to afford intermediate **LV**.

Step 6: To a mixture of intermediate **IM-LV** (1.00 equiv) in DCM at ambient temperature was added TFA (10.00 equiv). The resulting mixture was stirred at this

temperature until the reaction was complete and concentrated under vacuum to intermediate **IM-LVI** which was used for the next step without further purification.

Synthesis of 4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6-(1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridine-3-carbonitrile 232



Step 1: A mixture of methyl 3-amino-6-bromopyridine-2-carboxylate **226** (3.7 g, 16.08 mmol, 1.00 equiv), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate **139** (5.9 g, 19.30 mmol, 1.20 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (1.3 g, 1.60 mmol, 0.10 equiv) and K_2CO_3 (4.4 g, 32.16 mmol, 2.00 equiv) in dioxane (30.0 mL) and water (3.0 mL) was stirred for 2 h at 80 °C under N_2 atmosphere and then filtered through a pad of celite. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-80% EtOAc in petroleum ether) to afford 1'-(tert-butyl) 6-methyl 5-amino-3',6'-dihydro-[2,4'-bipyridine]-1',6(2'H)-dicarboxylate **227** (3.2 g, 59%) as yellow oil. MS (ESI, *m/z*): 334 $[M + H]^+$.

Step 2: To a stirred solution of acetonitrile (615.7 mg, 15.00 mmol, 5.00 equiv) in THF (16.0 mL) at -78 °C was added dropwise n-BuLi (2.5 M in hexane, 6.6 mL, 16.50 mmol, 5.50 equiv) under N_2 atmosphere for 30 min. To this was added a solution of 1'-tert-butyl 6-methyl 5-amino-3',6'-dihydro-2'H-[2,4'-bipyridine]-1',6-dicarboxylate **227** (1.0 g, 3.00 mmol, 1.00 equiv) in THF (2.0 mL). The resulting mixture was stirred at ambient temperature for further 1 h and then quenched with NH_4Cl solution and extracted with EtOAc 3 times. The organic layers were combined, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-70% EtOAc in petroleum ether) to afford tert-butyl 5-amino-6-(2-cyanoacetyl)-3',6'-dihydro-

[2,4'-bipyridine]-1'(2'H)-carboxylate **228** (790.0 mg, 76%) as a yellow oil. MS (ESI, m/z): 343 $[M + H]^+$.

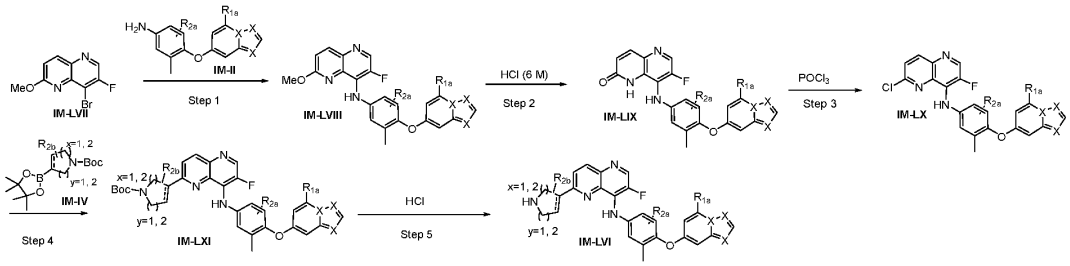
Step 3: A mixture of tert-butyl 5-amino-6-(2-cyanoacetyl)-3',6'-dihydro-2'H-[2,4'-bipyridine]-1'-carboxylate **228** (580.0 mg, 1.69 mmol, 1.00 equiv) and DMF-DMA (117.0 mg, 5.08 mmol, 3.00 equiv) in toluene (10.0 mL) was stirred for 2 h at 100 oC under N2 atmosphere and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-70% EtOAc in petroleum ether) to afford tert-butyl 4-(7-cyano-8-hydroxy-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **229** (322.0 mg, 53%) as a yellow solid. MS (ESI, m/z): 353 $[M + H]^+$.

Step 4: To a stirred solution of tert-butyl 4-(7-cyano-8-hydroxy-1,5-naphthyridin-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate **229** (320.0 mg, 0.91 mmol, 1.00 equiv) in DMF (3.2 mL) at 0 °C was added phosphorus tribromide (368.7 mg, 1.36 mmol, 1.50 equiv) dropwise under N_2 atmosphere. The resulting mixture was stirred at ambient temperature for 2 h and then quenched with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford tert-butyl 4-(8-bromo-7-cyano-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **230** (220.0 mg, 58%) as an off-white solid. MS (ESI, *m/z*): 415, 417 $[M + H]^+$.

Step 5: A mixture of tert-butyl 4-(7-cyano-8-hydroxy-1,5-naphthyridin-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate **230** (220.0 mg, 0.53 mmol, 1.00 equiv), $Pd(dba)_2$ (63.25 mg, 0.11 mmol, 0.20 equiv), XantPhos (63.58 mg, 0.11 mmol, 0.20 equiv) and Cs_2CO_3 (345.5 mg, 1.06 mmol, 2.00 equiv) in dixoane (2.0 mL) was stirred at 100 °C for 4 h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with EtOAc 3 times. The combined organic layers were concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-80% EtOAc in petroleum ether) to afford tert-butyl 4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-7-cyano-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **231** (280.0 mg, 91%) as a brown solid. MS (ESI, *m/z*): 575 $[M + H]^+$.

Step 6: To a mixture of tert-butyl 4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-7-cyano-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **231** (210.00 mg, 0.36 mmol, 1.00 equiv) in DCM (2.0 mL) at ambient temperature was added TFA (410.4 mg, 3.60 mmol, 10.00 equiv). The resulting mixture was stirred at this temperature for 1 h and concentrated under vacuum to afford 4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6-(1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridine-3-carbonitrile 2,2,2-trifluoroacetate **232** (crude, 200.0 mg) as a yellow oil, which was used for the next step without further purification. MS (ESI, m/z): 475 $[M + H]^+$.

Method O: General method for intermediate IM-LVI.



Step 1: A mixture of intermediate **IM-LVII** (1.00 equiv), **IM-II** (1.50 equiv), $Pd_2(dba)_3$ (0.20 equiv), XantPhos (0.10 equiv) and Cs_2CO_3 (3.00 equiv) in dioxane was stirred at 120 °C until the reaction was complete under N_2 atmosphere. The resulting mixture was quenched with brine and extracted with EtOAc 3 times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (e.g., 0-70% acetonitrile in water (containing 0.05% NH_4HCO_3)) to afford intermediate **IM-LVIII.**

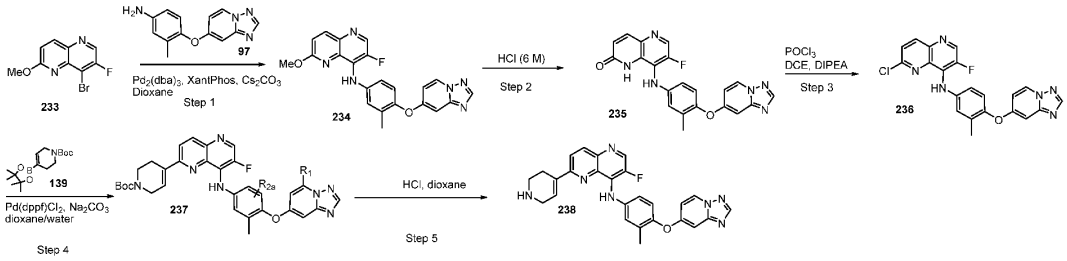
Step 2: A mixture of intermediate **IM-LVIII** (1.00 equiv) in HCl (6 M) was stirred at 90 °C until the reaction was complete and then concentrated under vacuum to afford intermediate **IM-LIX** (crude) which was used for the next step without further purification.

Step 3: A mixture of intermediate **IM-LIX** (1.00 equiv), $POCl_3$ (3.00 equiv) and DIEA (2.00 equiv) in DCE was stirred at 80 °C until the reaction was complete. The resulting mixture was concentrated under vacuum to afford intermediate **IM-LX** (crude) which was used for the next step without further purification.

Step 4: A mixture of intermediate **IM-LX** (1.00 equiv), **IM-IV** (2.00 equiv), Na_2CO_3 (3.00 equiv) and $Pd(dppf)Cl_2$ (0.20 equiv) in dioxane and water was stirred at 100 °C for 4 h under N_2 atmosphere. The reaction was quenched with brine and extracted with EtOAc 3 times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (e.g., 0-20% MeOH in DCM) to afford intermediate **IM-LXI**.

Step 5: A mixture of intermediate **IM-LXI** (1.00 equiv) and HCl (1.00 mL) in DCM (3.00 mL) was stirred at ambient temperature until the reaction was complete. The resulting mixture was concentrated under vacuum to afford intermediate **IM-LXII** hydrochloride (crude) which was used for the next step without further purification.

Synthesis of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-fluoro-6-(1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-4-amine 238



Step 1: A mixture of 8-bromo-7-fluoro-2-methoxy-1,5-naphthyridine **233** (400 mg, 1.56 mmol, 1.00 equiv), 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline **97** (560.8 mg, 2.33 mmol, 1.50 equiv), $Pd_2(dba)_3$ (285.0 mg, 0.31 mmol, 0.20 equiv), XantPhos (90.1 mg, 0.16 mmol, 0.10 equiv) and Cs_2CO_3 (1.52 g, 4.67 mmol, 3.00 equiv) in dioxane (8.00 mL) was stirred at 120 °C for 16 h under N_2 atmosphere. The resulting mixture was quenched with brine and extracted with EtOAc 3 times. The organic layers

were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (0-70% acetonitrile in water (containing 0.05% NH_4HCO_3)) to afford N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-fluoro-6-methoxy-1,5-naphthyridin-4-amine **234** (560 mg, 73%) as a light-yellow solid. MS (ESI, *m/z*): 417 $[M + H]^+$.

Step 2: A mixture of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-fluoro-6-methoxy-1,5-naphthyridin-4-amine **234** (560 mg, 1.35 mmol, 1.00 equiv) in HCl (6 M, 10.00 mL) was stirred at 90 °C for 16 h and then concentrated under vacuum to afford 8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-7-fluoro-1,5-naphthyridin-2(1H)-one **235** (crude, 500.00 mg) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 403 $[M + H]^+$.

Step 3: A mixture of 8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-7-fluoro-1,5-naphthyridin-2(1H)-one **235** (200.00 mg, 0.50 mmol, 1.00 equiv), $POCl_3$ (228.6 mg, 1.49 mmol, 3.00 equiv) and DIEA (128.50 mg, 0.99 mmol, 2.00 equiv) in DCE (4.00 mL) was stirred at 80 °C for 4 h. The resulting mixture was concentrated under vacuum to afford N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-chloro-3-fluoro-1,5-naphthyridin-4-amine **236** (crude, 180 mg) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 421, 423 $[M + H]^+$.

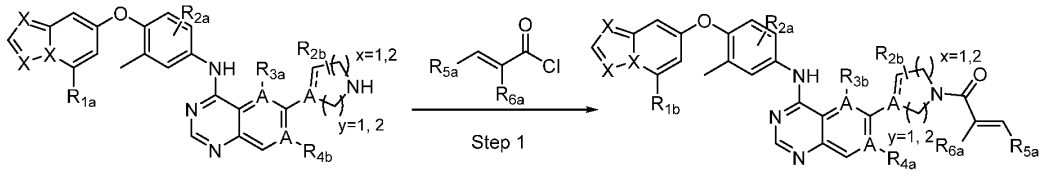
Step 4: A mixture of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-chloro-3-fluoro-1,5-naphthyridin-4-amine **236** (160.00 mg, 0.38 mmol, 1.00 equiv), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **139** (235.12 mg, 0.76 mmol, 2.00 equiv), Na_2CO_3 (120.89 mg, 1.14 mmol, 3.00 equiv) and $Pd(dppf)Cl_2$ (61.94 mg, 0.076 mmol, 0.20 equiv) in dioxane (3.00 mL) and water (0.60 mL) was stirred at 100 °C for 4 h under N_2 atmosphere. The reaction was quenched with brine and extracted with EtOAc 3 times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% MeOH in DCM) to afford tert-butyl 4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-7-fluoro-1,5-

naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **237** (230 mg, 93%) as a yellow solid. MS (ESI, *m/z*):568 $[M + H]^+$.

Step 5: A mixture of tert-butyl 4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-7-fluoro-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **237** (130.00 mg, 0.229 mmol, 1.00 equiv) and HCl (4 N in 1,4-dioxane, 1.00 mL) in DCM (3.00 mL) was stirred at ambient temperature for 1 h. The resulting mixture was concentrated under vacuum to afford N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-fluoro-6-(1,2,3,6-tetrahydropyridin-4-yl)-1,5-naphthyridin-4-amine hydrochloride **238** (crude, 130.00 mg) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 469 $[M + H]^+$.

General method for final analog IM-LXIII

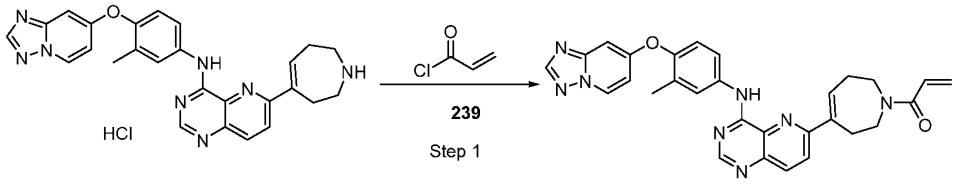
Coupling Condition A:



IM-LXIV **IM-LXV** **IM-LXIII**

Step 1: To a stirred mixture of intermediate **IM-LXIV** (1.00 equiv.) and TEA (3.00 equiv.) in DCM at 0 °C was added dropwise acryloyl chloride **IM-LXV** (1.00 equiv.). The resulting mixture was stirred at ambient temperature until the reacitonw was complete and then diluted with H_2O and extracted with EtOAc 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 silica gel (5-65% acetonitrile in H_2O (containing 0.05% TFA)) to afford desired final product **IM-LXIII**.

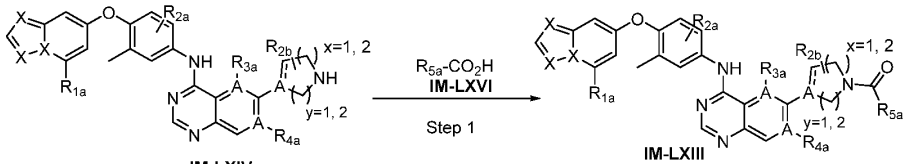
Synthesis of 1-(4-[4-[(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]-2,3,6,7-tetrahydroazepin-1-yl)prop-2-en-1-one Example 1



109 Example 1

Step 1: To a stirred mixture of N-(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridin-7-yloxy]phenyl)-6-(2,3,6,7-tetrahydro-1H-azepin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride **109** (110.00 mg, 0.22 mmol, 1.00 equiv.) and TEA (66.66 mg, 0.66 mmol, 3.00 equiv.) in DCM (4.00 mL) at 0 °C was added dropwise acryloyl chloride **239** (19.80 mg, 0.22 mmol, 1.00 equiv.). The resulting mixture was stirred at this temperature for 2 h and then diluted with H_2O and extracted with EtOAc 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% MeOH in DCM) and further purified by Prep-HPLC (NH_4HCO_3 system) to afford 1-(4-[4-[(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]-2,3,6,7-tetrahydroazepin-1-yl)prop-2-en-1-one **Example 1** (20.9 mg, 18%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.82 (brs, 1H), 8.92 (d, J = 9.0 Hz 1H), 8.62 (s, 1H), 8.37 (s, 1H), 8.19-8.08 (m, 2H), 7.98-7.90 (m, 2H), 7.27-7.18 (m, 1H), 7.06-6.92 (m, 2H), 6.92-6.74 (m, 2H), 6.17-6.08 (m, 1H), 5.72-5.64 (m, 1H), 4.34 (dd, J = 9.6, 5.1 Hz, 2H), 3.88-3.67 (m, 2H), 3.26-2.96 (m, 2H), 2.20 (s, 3H), 2.06-1.89 (m, 2H). MS (ESI, *m/z*): 519 (M + H)$^+$, LCMS: Method A; Retention Time: 1.45 min; MS (ESI, *m/z*): 519.15 [M + H]$^+$.

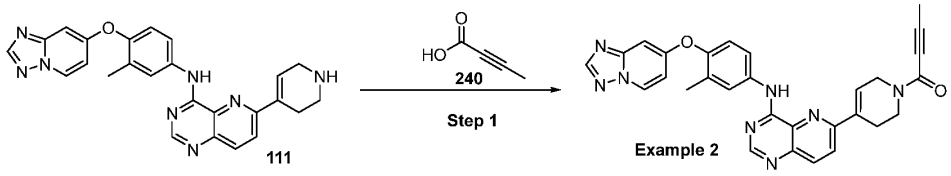
Coupling Condition B:



IM-LXIV IM-LXIII

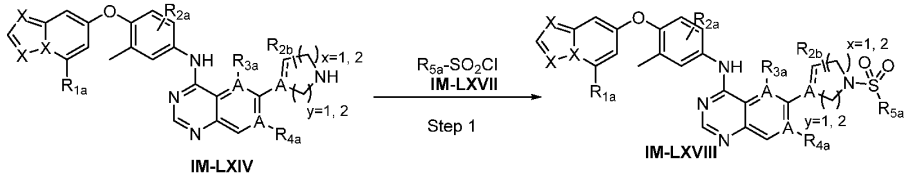
Step 1: A mixture of intermediate **IM-LXIV**(1.00 equiv.), carboxylic acid **IM-LXVI** (1.20 equiv.), HATU (1.50 equiv.) and DIEA (3.00 equiv.) in DMF was stirred at ambient temperature until the reaction was complete. The reaction was diluted with brine and extracted with EtOAc 3 times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-HPLC (NH_4HCO_3 system) to desired final product **IM-LXIII**.

Synthesis of 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)but-2-yn-1-one Example 2



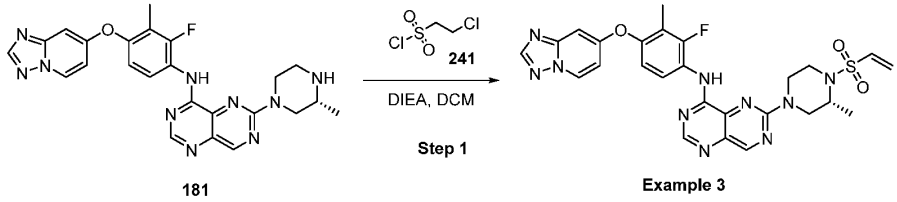
A mixture of N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidin-4-amine hydrochloride **111** (107.89 mg, 0.222 mmol, 1.00 equiv.), but-2-ynoic acid **240** (22.39 mg, 0.266 mmol, 1.20 equiv.), HATU (126.60 mg, 0.333 mmol, 1.50 equiv.) and DIEA (86.07 mg, 0.666 mmol, 3.00 equiv.) in DMF (2.00 mL) was stirred at ambient temperature for 1 h. The reaction was diluted with brine and extracted with EtOAc 3 times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-HPLC (NH_4HCO_3 system) to afford 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]- 239 -yridine-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)but-2-yn-1-one **Example 2** (45.5 mg, 39%) as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ9.84 (s, 1H), 8.95 (d, *J* = 7.6 Hz, 1H), 8.65 (s, 1H), 8.38 (s, 1H), 8.21-8.14 (m, 2H), 8.04-7.95 (m, 2H), 7.29-7.22 (m, 1H), 7.09-7.00 (m, 2H), 6.80 (d, *J* = 2.8 Hz, 1H), 4.56-4.25 (m, 2H), 4.02-3.74 (m, 2H), 3.02-2.84 (m, 2H), 2.22 (s, 3H), 2.10-2.02 (m, 3H). LCMS: Method A; Retention Time: 1.49 min; LCMS (ESI, m/z): 517 $[M + H]^+$,

Coupling Condition C:



Step 1: A mixture of intermediate **IM-LXIV** (1.00 equiv.), Sulfonyl chloride **IM-LXVII** (1.20 equiv.), and DIEA (3.00 equiv.) in DCM was stirred at -10°C until the reaction was complete. The reaction was diluted with brine and extracted with EtOAc 3 times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-HPLC to desired final product **IM-LXVIII**.

Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]- 240 -yridine-7-yloxy)-2-fluoro-3-methylphenyl)-6-(3-methyl-4-(vinylsulfonyl)piperazin-1-yl)pyrimido[5,4-d]pyrimidin-4-amine, example 3.

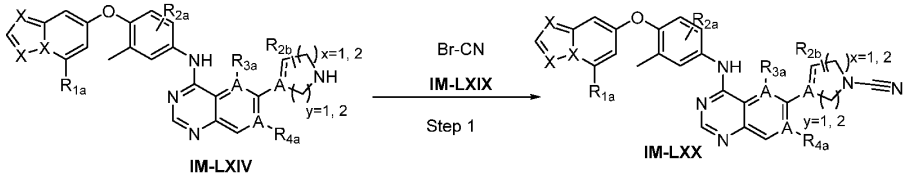


Step 1: To a stirred mixture of (*R*)-*N*-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-*d*]pyrimidin-4-amine (79 mg, crude) in DCM (5 mL), were added DIEA (0.2 mL) and 2-chloroacetyl chloride **241** (23 mg, 0.14 mmol) in sequence at -10 °C. Then the resulting mixture was stirred at -10 °C for 1 h. LCMS showed the reaction was completed. The reaction mixture was quenched by adding water (5 mL) and extracted with DCM (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by prep-TLC (MeOH/DCM = 1/15, V/V) and prep-HPLC (Column: AZZOTA C18 GEMINI 250*20mm 10um, MeCN in H_2O with 0.1% HCOOH) to give the desired product (8.1 mg, 10.3% yield over two steps) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 9.15 (s,

1H), 8.98 (d, *J* = 7.4 Hz, 1H), 8.42 (s, 1H), 8.40 (s, 1H), 7.83 (t, *J* = 8.7 Hz, 1H), 7.19 – 7.12 (m, 1H), 7.07 (dd, *J* = 7.5, 2.6 Hz, 1H), 6.95 – 6.86 (m, 2H), 6.14 (d, *J* = 16.4 Hz, 1H), 6.07 (d, *J* = 9.9 Hz, 1H), 4.82 (d, *J* = 39.2 Hz, 2H), 4.08 (dt, *J* = 6.4, 3.0 Hz, 1H), 3.59 – 3.50 (m, 1H), 3.41 – 3.36 (m, 1H), 3.30 – 3.18 (m, 2H), 2.17 (d, *J* = 1.9 Hz, 3H), 1.19 (d, *J* = 6.7 Hz, 3H).

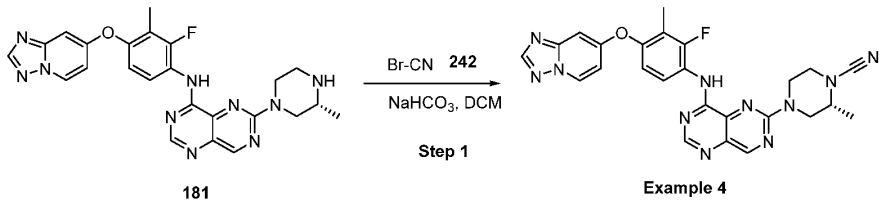
LC/MS: Method K; Retention Time: 1.63 min MS (ESI, m/z): 577 $[M + H]^+$.

Coupling Condition D:



Step 1: A mixture of intermediate **IM-LXIV** (1.00 equiv.), and $NaHCO_3$ (5.00 equiv.) in DCM and water was stirred at 0°C. Cyanic bromide (1.0 equiv.) was added dropwise at 0°C and stirred for 10 min. The reaction mixture was stirred overnight. Upon completion, the mixture was diluted with brine and extracted with DCM 3 times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-HPLC to desired final product **IM-LXX.**

Synthesis of (R)-4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazine-1-carbonitrile, Example 4



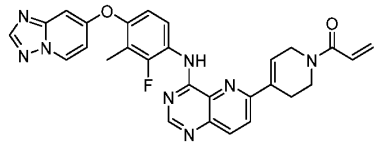
Step 1: To a stirred mixture of (*R*)-*N*-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6-(3-methylpiperazin-1-yl)pyrimido[5,4-*d*]pyrimidin-4-amine (65 mg, crude) and $NaHCO_3$ (50 mg, 0.6 mmol) in H_2O (3.6 mL) and DCM (1 mL), was added

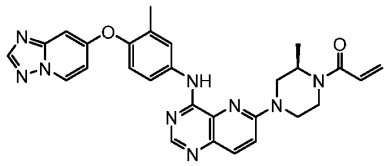
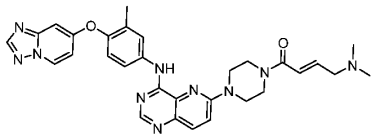
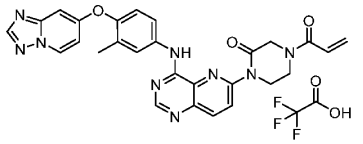
cyanic bromide **242** (14 mg, 0.13mmol) in DCM (1 mL) dropwise at 0 °C. Then the resulting mixture was stirred at 0 °C for 10 min. After 10 min, the reaction mixture was warmed to room temperature and stirred overnight. LCMS showed the reaction was completed. The reaction mixture was quenched by adding water (5 mL) and extracted with DCM (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by prep-TLC (MeOH/DCM = 1/15, V/V) and prep-HPLC (Column: AZZOTA C18 GEMINI 250*20mm 10um, MeCN in H_2O with 0.1% HCOOH) to give the desired product (15.7 mg, 26.17 % yield over two steps) as a yellow solid.

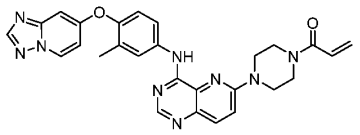
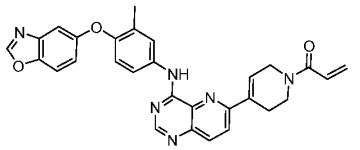
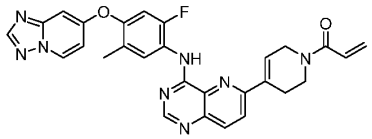
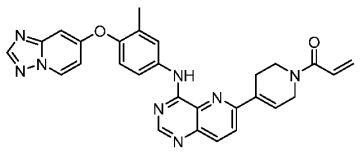
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.68 (s, 1H), 9.16 (s, 1H), 8.98 (d, *J* = 7.4 Hz, 1H), 8.41 (d, *J* = 6.0 Hz, 2H), 7.77 (t, *J* = 8.7 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 7.07 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 4.77 (t, *J* = 14.5 Hz, 2H), 3.56 (d, *J* = 12.0 Hz, 1H), 3.44 – 3.33 (m, 3H), 3.07 (dd, *J* = 13.4, 9.7 Hz, 1H), 2.17 (s, 3H), 1.31 (d, *J* = 6.4 Hz, 3H). LC/MS: Method G; Retention Time: 1.28 min MS (ESI, m/z): 512 [M + H]+

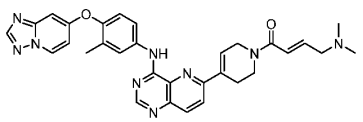
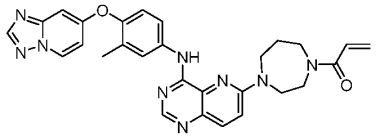
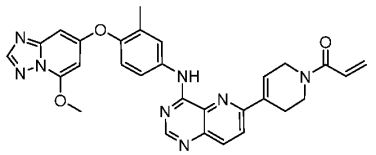
The following compounds in **Table 10** were obtained following above-mentioned method using the appropriate starting materials.

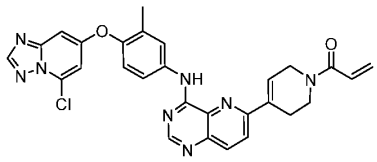
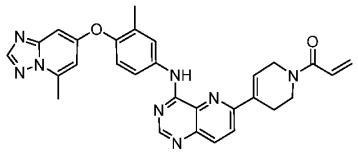
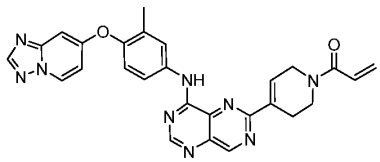
Table 10: Compounds

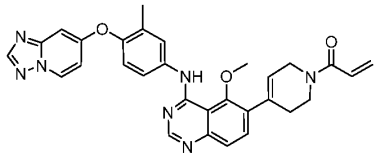
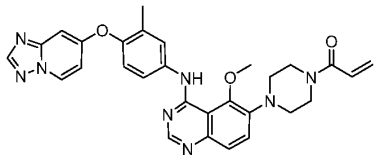
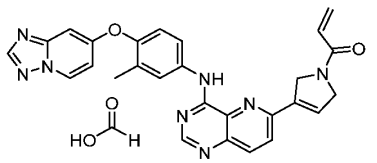
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
5	A	A	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.81-9.70 (m, 1H), 8.97 (d, *J* = 7.6 Hz, 1H), 8.63 (s, 1H), 8.41 (s, 1H), 8.26-8.17 (m, 2H), 8.16-8.01 (m, 1H), 7.19-7.13 (m, 1H), 7.10-7.01 (m, 2H), 6.97-6.80 (m, 2H), 6.22-6.11 (m, 1H), 5.77-5.69 (m, 1H), 4.51-4.28 (m, 2H), 3.94-3.73 (m, 2H), 2.95-2.79 (m, 2H), 2.22-2.14 (m, 3H). LCMS: Method A; Retention Time: 1.28 min; MS (ESI, *m/z*): 523 [M + H]$^+$

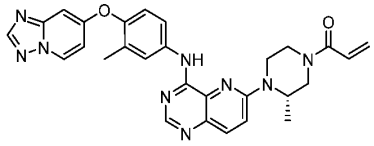
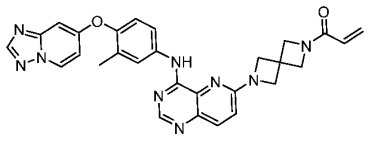
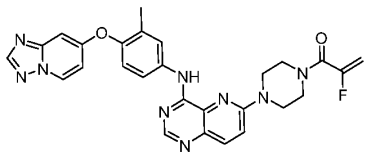
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
6	C	A	 1-[(2R)-2-methyl-4-{4-[(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl}piperazin-1-yl]prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d*6*) δ 9.37 (s, 1H), 8.94 (d, *J* = 7.5 Hz, 1H), 8.44 (s, 1H), 8.38 (s, 1H), 8.02-7.92 (m, 3H), 7.58 (d, *J* = 9.3 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.03 (dd, *J* = 7.5, 2.7 Hz, 1H), 6.92-6.78 (m, 2H), 6.17 (dd, *J* = 16.5, 2.4 Hz, 1H), 5.73 (dd, *J* = 10.5, 2.4 Hz, 1H), 4.81-4.56 (m, 2H), 4.53-4.37 (m, 2H), 4.34-4.03 (m, 1H), 3.44 (d, *J* = 12.3 Hz, 1H), 3.25-3.07 (m, 1H), 2.21 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 3H). LCMS: Method B; Retention Time: 0.98 min; MS (ESI, *m/z*): 522 $[M + H]^+$
7	C	A	 (E)-1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)piperazin-1-yl)-4-(dimethylamino)but-2-en-1-one	1H NMR (300 MHz, DMSO-*d6*) δ 9.39 (brs, 1H), 8.94 (d, *J* = 7.2 Hz, 1H), 8.46 (s, 1H), 8.38 (s, 1H), 8.06-7.93 (m, 3H), 7.60 (d, *J* = 9.3 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 7.03 (dd, *J* = 7.5, 2.7 Hz, 1H), 6.79 (d, *J* = 2.7 Hz, 1H), 6.71-6.63 (m, 2H), 3.92-3.82 (m, 4H), 3.80-3.68 (m, 4H), 3.09-3.04 (m, 2H), 2.33-2.14 (m, 9H). LCMS: Method B; Retention Time: 0.92 min; MS (ESI, m/z): 5652 $[M + H]^+$
8	D	A	 1-[4-[(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]-4-(prop-2-enoyl)piperazin-2-one; trifluoroacetate	^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.07 (brs, 1H), 8.96 (brs, 1H), 8.71 (s, 1H), 8.51-8.44 (m, 1H), 8.39 (s, 1H), 8.29-8.22 (m, 1H), 7.97-7.83 (m, 2H), 7.30-7.25 (m, 1H), 7.24-7.09 (m, 1H), 7.04 (dd, *J* = 7.6, 2.4 Hz, 1H), 6.98 (s, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 6.28-6.18 (m, 1H), 5.84-5.74 (m, 1H), 4.63-4.53 (m, 2H), 3.97-3.91 (m, 2H), 2.22 (s, 3H), 1.52 (d, *J* = 7.2 Hz, 2H). LCMS: Method C; Retention Time: 0.78 min; MS (ESI, *m/z*): 522 $[M + H]^+$, 262 $([M + 2 H] / 2)^+$.

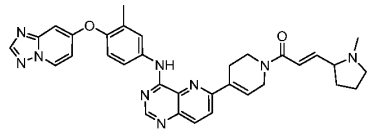
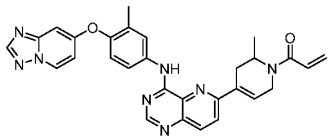
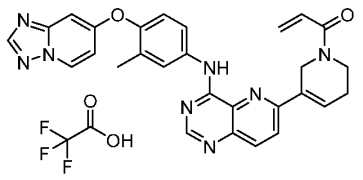
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
9	C	A	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)piperazin-1-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.95 (d, J = 7.5 Hz, 1H), 8.46 (s, 1H), 8.39 (s, 1H), 8.06-7.92 (m, 3H), 7.60 (d, J = 9.6 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.04 (dd, J = 7.5, 2.7 Hz, 1H), 6.95-6.86 (m, 1H), 6.79 (d, J = 2.7 Hz, 1H), 6.21-6.14 (m, 1H), 5.77-5.72 (m, 1H), 3.95-3.81 (m, 4H), 3.79-373. (m, 4H), 2.21 (s, 3H). LCMS: Method A; Retention Time: 1.35 min; MS (ESI, m/z): 508 $[M + H]^+$
10	E	A	 1-(4-(4-((4-(benzo[d]oxazol-5-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-$d6$) δ 9.79 (s, 1H), 8.76 (s, 1H), 8.62 (s, 1H), 8.16-8.13 (m, 2H), 7.92-7.84 (m, 2H), 7.78 (d, J = 9.0 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 7.13-6.87 (m, 4H), 6.22-6.12 (m, 1H), 5.78-5.70 (m, 1H), 4.34-4.43 (m, 2H), 3.83-3.85 (m, 2H), 2.94-2.90 (m, 2H), 2.26 (s, 3H). LCMS: Method D; Retention Time: 1.20 min; MS (ESI, m/z): 505 $[M + H]^+$.
11	A	A	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86-9.77 (m, 1H), 8.98 (d, J = 7.6 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.42 (s, 1H), 8.26-8.15 (m, 2H), 8.06-7.93 (m, 1H), 7.36 (d, J = 10.8 Hz, 1H), 7.12-6.99 (m, 2H), 7.08-6.92 (m, 2H), 6.22-6.12 (m, 1H), 5.77-5.68 (m, 1H), 4.48-4.26 (m, 2H), 3.89-3.73 (m, 2H), 2.95-2.80 (m, 2H), 2.21 (s, 3H). LCMS: Method B; Retention Time: 1.02 min; MS (ESI, m/z): 523 $[M + H]^+$
12	A	A	 1-(4-[4-[(3-methyl-4-[[1,2,4]triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.86 (brs, 1H), 8.95 (d, J = 7.6 Hz, 1H), 8.65 (s, 1H), 8.39 (s, 1H), 8.19 (s, 2H), 8.00 (d, J = 7.6 Hz, 2H), 7.28-7.23 (m, 1H), 7.12-7.02 (m, 2H), 6.96-6.82 (m, 1H), 6.81 (d, J = 2.4 Hz, 1H), 6.22-6.10 (m, 1H), 5.76-5.69 (m, 1H), 4.44 (s, 1H), 4.35 (s, 1H), 3.93-3.76 (m, 2H), 2.93 (d, J = 20.8 Hz, 2H), 2.22 (s, 3H). LCMS: Method C; Retention Time: 0.68 min; MS (ESI, m/z): 505 $[M + H]^+$

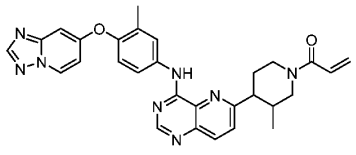
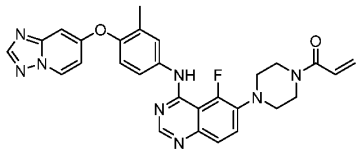
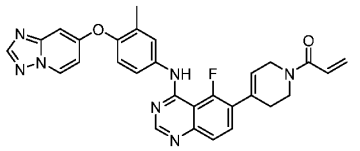
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
13	A	A	 (E)-1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)-4-(dimethylamino)but-2-en-1-one	1H NMR (400 MHz, DMSO-*d6*) δ 9.86 (s, 1H), 8.96-8.92 (m, 1H), 8.65 (s, 1H), 8.39 (s, 1H), 8.21-8.15 (m, 2H), 8.00-7.96 (m, 2H), 7.28-7.23 (m, 1H), 7.11-7.02 (m, 2H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.73-6.61 (m, 2H), 4.44-4.31 (m, 2H), 3.87-3.78 (m, 2H), 3.08-3.03 (m, 2H), 2.97-2.86 (m, 2H), 2.22 (s, 3H), 2.17 (s, 6H). LCMS: Method A; Retention Time: 1.35 min; MS (ESI, m/z): 562 $[M+H]^+$, 281 $([M+2H]/2)^+$, 302 $([M+\text{acetonitrile}+2H]/2)^+$.
14	C	A	 1-(4-[4-[(3-methyl-4-[[1,2,4]triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]-1,4-diazepan-1-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.38 (brs, 1H), 8.94 (d, *J* = 7.5 Hz, 1H), 8.44 (d, *J* = 4.2 Hz, 1H), 8.39 (s, 1H), 8.02-7.85 (m, 3H), 7.52-7.42 (m, 1H), 7.29-7.19 (m, 1H), 7.07-6.99 (m, 1H), 6.83-6.64 (m, 2H), 6.16-5.80 (m, 1H), 5.71-5.41 (m, 1H), 4.11-4.04 (m 2H), 3.93-3.74 (m, 4H), 3.60-3.45 (m, 2H), 2.22 (s, 3H), 1.98-1.83 (m, 2H). LCMS: Method A; Retention Time: 1.36 min; MS (ESI, *m/z*): 522 $[M+H]^+$, 262 $([M+2H]/2)^+$.
15	A	A	 1-(4-(4-(4-(5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenylamino)pyrido[3,2-d]pyrimidin-6-yl)-5,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, MeOD) δ 8.82 (s, 1H), 8.41 – 8.26 (m, 2H), 8.20 (d, *J* = 9.0 Hz, 1H), 7.98 – 7.78 (m, 2H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.11 (d, *J* = 25.1 Hz, 1H), 6.96 – 6.76 (m, 1H), 6.64 (d, *J* = 2.1 Hz, 1H), 6.41 (s, 1H), 6.28 (d, *J* = 15.5 Hz, 1H), 5.82 (d, *J* = 10.9 Hz, 1H), 4.48 (d, *J* = 14.8 Hz, 2H), 4.24 (s, 3H), 4.23 (m, 1H), 3.95 (s, 2H), 3.08 – 2.95 (m, 2H), 2.31 (s, 3H) LCMS: Method G; Retention Time: 2.22 min MS (ESI, *m/z*): 535 $[M+H]^+$

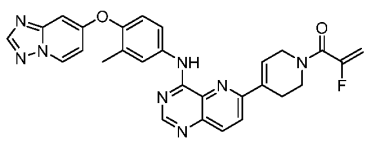
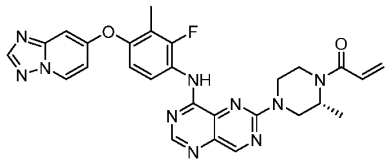
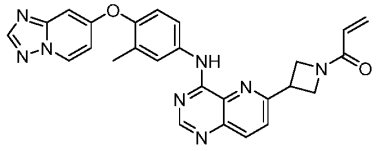
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
16	A	A	 1-(4-(4-((4-((5-chloro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, MeOD) δ 8.62 (s, 1H), 8.38 (s, 1H), 8.20 (d, *J* = 8.9 Hz, 1H), 8.12 (d, *J* = 8.9 Hz, 1H), 7.97 – 7.93 (m, 2H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 21.7 Hz, 1H), 6.92 – 6.78 (m, 3H), 6.28 (d, *J* = 16.6 Hz, 1H), 5.81 (d, *J* = 10.6 Hz, 1H), 4.46 (d, *J* = 14.2 Hz, 2H), 3.96 (d, *J* = 5.5 Hz, 2H), 3.01 (d, *J* = 18.8 Hz, 2H), 2.28 (s, 3H). LCMS: Method G; Retention Time: 2.22 min MS (ESI, *m/z*): 539 [M + H]$^+$
17	A	A	 1-(4-(4-((4-((5-Methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 9.85 (s, 1H), 8.65 (s, 1H), 8.39 (s, 1H), 8.22 – 8.13 (m, 2H), 8.03 – 7.95 (m, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 16.8 Hz, 1H), 6.99 (s, 1H), 6.96 – 6.81 (m, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 6.18 (d, *J* = 16.8 Hz, 1H), 5.75 (d, *J* = 10.8 Hz, 1H), 4.39 (d, *J* = 34.8 Hz, 2H), 3.91 – 3.79 (m, 2H), 2.93 (d, *J* = 20.8 Hz, 2H), 2.73 (s, 3H), 2.22 (s, 3H). LCMS: Method E; Retention Time: 1.25 min MS (ESI, *m/z*): 519 [M + H]$^+$
18	F	A	 1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.13 (s, 1H), 9.43 (s, 1H), 8.94 (d, *J* = 7.5 Hz, 1H), 8.73 (s, 1H), 8.39 (s, 1H), 7.97 (d, *J* = 4.0 Hz, 2H), 7.54 (d, *J* = 21.6 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.05 (dd, *J* = 7.5, 2.6 Hz, 1H), 7.00 – 6.83 (m, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.18 (d, *J* = 16.6 Hz, 1H), 5.75 (dd, *J* = 10.5, 2.3 Hz, 1H), 4.43 (d, *J* = 40.3 Hz, 2H), 3.85 (d, *J* = 7.2 Hz, 2H), 2.92 (d, *J* = 17.2 Hz, 2H), 2.23 (s, 3H). LCMS: Method E; Retention Time: 1.28 min MS (ESI, *m/z*): 506 [M + H]$^+$

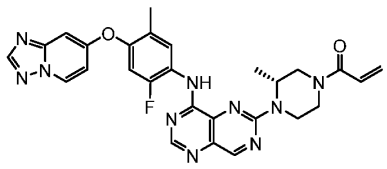
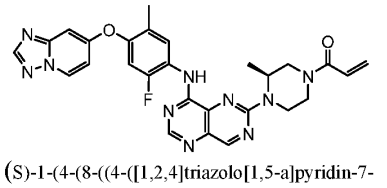
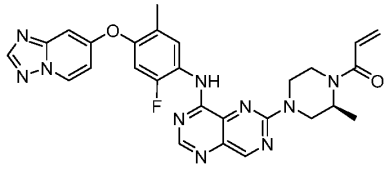
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
19	G	A	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-5-methoxyquinazolin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 10.24 (s, 1H), 8.94 (d, *J* = 7.6 Hz, 1H), 8.58 (s, 1H), 8.38 (s, 1H), 7.95 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.87 (d, *J* = 2.8 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.03 (dd, *J* = 7.6, 2.8 Hz, 1H), 6.98 – 6.82 (m, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.18 (d, *J* = 16.4 Hz, 1H), 6.11 – 6.04 (m, 1H), 5.77 – 5.71 (m, 1H), 4.29 (d, *J* = 38.8 Hz, 2H), 3.92 (s, 3H), 3.88 – 3.78 (m, 2H), 2.69 – 2.53 (m, 2H), 2.21 (s, 3H). LCMS: Method E; Retention Time: 1.01 min MS (ESI, *m/z*): 534 $[M + H]^+$
20	H	A	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-5-methoxyquinazolin-6-yl)piperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 10.36 (s, 1H), 8.92 (d, *J* = 7.5 Hz, 1H), 8.48 (s, 1H), 8.37 (s, 1H), 7.97 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 9.1 Hz, 1H), 7.56 (d, *J* = 9.0 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.02 (dd, *J* = 7.5, 2.6 Hz, 1H), 6.88 (dd, *J* = 16.7, 10.4 Hz, 1H), 6.78 (d, *J* = 2.5 Hz, 1H), 6.16 (dd, *J* = 16.6, 2.3 Hz, 1H), 5.73 (dd, *J* = 10.4, 2.3 Hz, 1H), 4.15 (s, 3H), 3.80 (s, 4H), 3.15 (s, 4H), 2.20 (s, 3H). LCMS: Method E; Retention Time: 0.80 min MS (ESI, *m/z*): 537 $[M + H]^+$
21	A	A	 1-(3-[4-[(3-methyl-4-[[1,2,4] triazolo[1,5-a]pyridin-7-yloxy]phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl]-2,5-dihydropyrrol-1-yl)prop-2-en-1-one formate	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.90 (brs, 1H), 8.94 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.63 (d, *J* = 5.1 Hz, 1H), 8.37 (s, 1H), 8.35-8.23 (m, 1H), 8.22-8.14 (m, 1H), 8.06-7.86 (m, 2H), 7.31-7.20 (m, 1H), 7.12 (s, 1H), 7.03 (dd, *J* = 7.5, 2.7 Hz, 1H), 6.92-6.60 (m, 2H), 6.33-6.17 (m, 1H), 5.86-5.69 (m, 1H), 5.07 (s, 1H), 4.85 (s, 1H), 4.72 (s, 1H), 4.48 (s, *J* = 3.2 Hz, 1H), 2.21 (s, 3H). LCMS: Method F; Retention Time: 1.16 min. MS (ESI, *m/z*): 491 $[M + H]^+$ 246 ([M + 2 H] / 2)$^+$, 267 ([M + H + acetonitrile] / 2)$^+$.

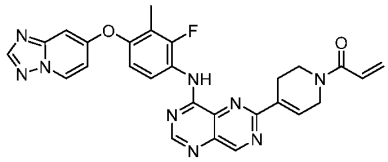
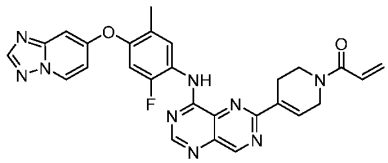
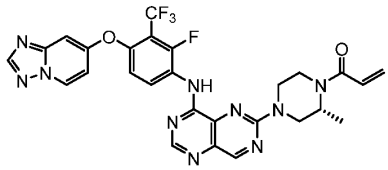
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
22	C	A	 (S)-1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.94 (dd, J = 7.5, 0.6 Hz, 1H), 8.44 (s, 1H), 8.37 (s, 1H), 8.01-7.94 (m, 3H), 7.53 (d, J = 9.0 Hz, 1H), 7.21 (d, J = 9.0 Hz, 1H), 7.02 (dd, J = 7.5, 2.7 Hz, 1H), 6.90-6.85 (m 1H), 6.79-6.78 (m, 1H), 6.16 (d, J = 18.0 Hz, 1H), 5.76 (dd, J = 12.0, 2.4 Hz, 1H), 4.95-4.86 (m, 1H), 4.59-4.01 (m, 3H), 3.64-3.34 (m, 1H), 3.31-2.87 (m, 2H), 2.21 (s, 3H), 1.11 (d, J = 6.0 Hz, 3H). LCMS: Method B; Retention Time: 0.99 min. MS (ESI, m/z): 522 $[M + H]^+$
23	C	A	 1-(6-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-2,6-diazaspiro[3.3]heptan-2-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.81 (d, J = 7.5 Hz, 1H), 8.35 (s, 1H), 8.26 (s, 1H), 7.92-7.77 (m, 3H), 7.11 (d, J = 9.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 6.92-6.89 (m, 1H), 6.67 (d, J = 3.0 Hz, 1H), 6.25-6.16 (m, 1H), 6.02-5.96 (m, 1H), 5.59-5.54 (m, 1H), 4.36 (s, 2H), 4.26 (s, 4H), 4.06 (s, 2H), 2.08 (s, 3H). LCMS: Method B; Retention Time: 0.93 min. MS (ESI, m/z): 520 $[M + H]^+$260 ($[M + 2H]/2)^+$.
24	C	B	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)piperazin-1-yl)-2-fluoroprop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-$d6$) δ 9.37 (s, 1H), 8.92 (d, J = 7.5 Hz, 1H), 8.44 (s, 1H), 8.36 (s, 1H), 8.02-7.89 (m, 3H), 7.56 (d, J = 9.0 Hz, 1H), 7.21 (d, J = 9.0 Hz, 1H), 7.01 (dd, J = 7.5, 2.7 Hz, 1H), 6.76 (d, J = 3.0 Hz, 1H), 5.38-5.17 (d, J = 6.0 Hz, 2H), 3.92-3.89 (m, 4H), 3.71-3.69 (m, 4H), 2.18 (s, 3H). LCMS: Method B; Retention Time: 1.03 min. MS (ESI, m/z): 526 $[M + H]^+$

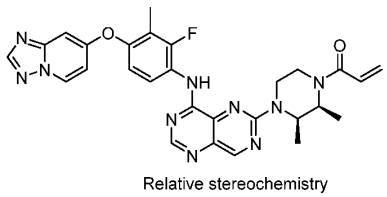
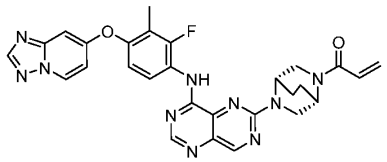
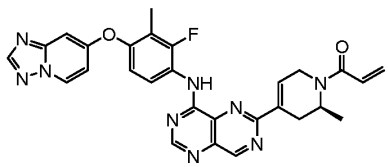
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
25	A	A	 (E)-1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)-3-(1-methylpyrrolidin-2-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.88-8.79 (m, 1H), 8.53 (s, 1H), 8.26 (s, 1H), 8.07 (s, 2H), 7.89-7.87 (m, 2H), 7.14 (d, J = 9.0 Hz, 1H), 7.02-6.88 (m, 2H), 6.69 (d, J = 3.0 Hz, 1H), 6.63-6.33 (m, 2H), 4.30-4.21 (m, 2H), 3.90-3.75 (m, 2H), 2.93-2.82 (m, 3H), 2.66-2.63 (m, 1H), 2.10-2.02 (m, 7H), 1.93-1.78 (m, 1H), 1.61-1.58 (m, 2H), 1.45-1.42 (m, 1H). LCMS: Method B; Retention Time: 0.99 min. MS (ESI, m/z): 588 $[M + H]^+$, 294 $([M + 2H]/2)^+$, 315 $([M + 2H + \text{acetonitrile}]/2)^+$.
26	A	A	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-2-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.72 (d, J = 6.0 Hz, 1H), 8.83 (d, J = 7.5 Hz, 1H), 8.53 (s, 1H), 8.27 (s, 1H), 8.14-8.00 (m, 2H), 8.02-7.95 (m, 2H), 7.14 (d, J = 9.0 Hz, 1H), 7.00-6.75 (m, 3H), 6.69 (d, J = 3.0 Hz, 1H), 6.06-6.01 (m, 1H), 5.63-5.89 (m, 1H), 5.25-4.10 (m, 3H), 3.11-2.61 (m, 2H), 2.10 (s, 3H), 1.35-0.96 (m, 3H). LCMS: Method B; Retention Time: 1.03 min. MS (ESI, m/z): 519 $[M + H]^+$
27	A	A	 1-(3-{4-[(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]pyrido[3,2-d]pyrimidin-6-yl}-5,6-dihydro-2H-pyridin-1-yl)prop-2-en-1-one trifluoroacetate	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (brs, 1H), 9.01-8.88 (m, 2H), 8.48-8.32 (m, 2H), 8.25 (d, J = 8.8 Hz, 1H), 7.89-7.75 (m, 2H), 7.31 (d, J = 17.6 Hz, 2H), 7.22-7.01 (m, 2H), 7.00-6.79 (m, 2H), 6.26-6.14 (m, 1H), 5.82-5.71 (m, 1H), 4.83 (d, J = 20.4 Hz, 2H), 3.83-3.72 (m, 2H), 2.50-2.46 (m, 1H), 2.26 (s, 3H). LCMS: Method D; Retention Time: 1.32 min. MS (ESI, m/z): 505 $[M + H]^+$

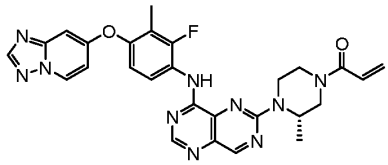
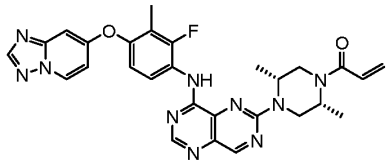
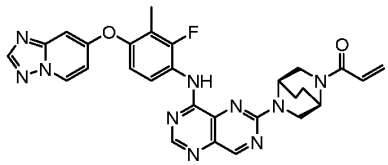
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
28	B	A	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3-methylpiperidin-1-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d6) δ 9.79 (s, 1H), 8.95 (d, J = 7.5 Hz, 1H), 8.67 (s, 1H), 8.39 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.08-7.95 (m, 2H), 7.87 (d, J = 8.7 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 7.04 (dd, J = 7.5, 2.7 Hz, 1H), 6.95-6.83 (m, 1H), 6.80 (d, J = 2.7 Hz, 1H), 6.20-6.09 (m, 1H), 5.76-5.63 (m, 1H), 4.82-4.49 (m, 1H), 4.33-4.05 (m, 1H), 3.53-3.41 (m, 2H), 3.17-3.00 (m, 1H), 2.86-2.69 (m, 1H), 2.43-2.33 (m, 1H), 2.22 (s, 3H), 2.00-1.89 (m, 1H), 0.59 (d, J = 6.9 Hz, 3H). LCMS: Method D; Retention Time: 1.09 min. MS (ESI, m/z): 521 $[M + H]^+$
29	I	A	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-5-fluoroquinazolin-6-yl)piperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (d, J = 13.6 Hz, 1H), 8.94 (d, J = 7.6 Hz, 1H), 8.51 (s, 1H), 8.39 (s, 1H), 7.83-7.79 (m, 2H), 7.74 (t, J = 9.2 Hz, 1H), 7.63 (d, J = 9.2 Hz, 1H), 7.27 – 7.16 (m, 1H), 7.04 (dd, J = 7.6, 2.8 Hz, 1H), 6.90 (dd, J = 16.8, 10.4 Hz, 1H), 6.80 (d, J = 2.8 Hz, 1H), 6.18 (dd, J = 16.8, 2.4 Hz, 1H), 5.74 (dd, J = 10.4, 2.4 Hz, 1H), 3.83 – 3.72 (m, 4H), 3.21 – 3.16 (m, 4H), 2.20 (s, 3H). LCMS: Method H; Retention Time: 2.64 min. MS (ESI, m/z): 525 $[M + H]^+$
30	J	A	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-5-fluoroquinazolin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, J = 13.6 Hz, 1H), 8.94 (d, J = 7.6 Hz, 1H), 8.59 (s, 1H), 8.38 (s, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.76 (dd, J = 11.2, 2.4 Hz, 2H), 7.63 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.03 (dd, J = 7.6, 2.6 Hz, 1H), 6.18 (d, J = 16.4 Hz, 2H), 5.74 (dd, J = 10.4, 2.4 Hz, 1H), 4.30 (d, J = 38.6 Hz, 2H), 3.87 – 3.76 (m, 2H), 3.32 (s, 2H), 2.60 (d, J = 20.0 Hz, 2H), 2.19 (s, 3H). LCMS: Method G; Retention Time: 3.26 min. MS (ESI, m/z): 522 $[M + H]^+$

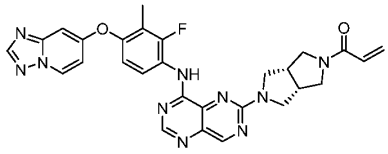
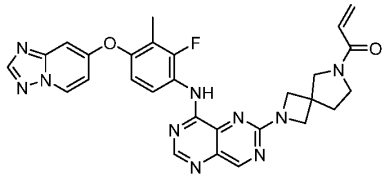
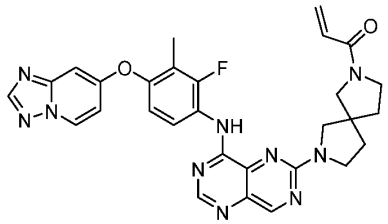
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
31	A	B	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)-2-fluoroprop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d6) δ 9.86 (brs, 1H), 8.95 (s, 1H), 8.65 (s, 1H), 8.39 (s, 1H), 8.19 (s, 2H), 8.04-7.97 (m, 2H), 7.30-7.21 (m, 1H), 7.13-7.01 (m, 2H), 6.81 (d, *J* = 2.7 Hz, 1H), 5.44-5.16 (m, 2H), 4.33-4.30 (m, 2H), 3.82 (t, *J* = 5.7 Hz, 2H), 3.11-2.98 (m, 2H), 2.22 (s, 3H). LCMS: Method C; Retention Time: 0.90 min MS (ESI, *m/z*): 523 $[M + H]^+$
32	K	A	 (R)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.64 (s, 1H), 9.16 (s, 1H), 8.98 (d, J = 7.6 Hz, 1H), 8.42 (d, J = 4.3 Hz, 2H), 7.95 – 7.83 (m, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.10 – 7.05 (m, 1H), 6.97 – 6.93 (m, 1H), 6.92 – 6.83 (m, 1H), 6.21 – 6.11 (m, 1H), 5.79 – 5.69 (m, 1H), 4.96 – 4.46 (m, 4H), 3.67 – 3.61 (m, 2H), 3.20 – 3.15 (m, 1H), 2.18 (s, 3H), 1.21 – 1.13 (m, 3H). LCMS: Method H; Retention Time: 1.31 min MS (ESI, m/z): 541 $[M + H]^+$
33	E	A	 1-(3-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)azetidin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (brs, 1H), 8.95 (d, *J* = 7.6 Hz, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 8.00-7.88 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.04 (dd, *J* = 7.6, 2.8 Hz, 1H), 6.80 (d, *J* = 2.8 Hz, 1H), 6.47-6.38 (m, 1H), 6.16 (dd, *J* = 16.0, 2.8 Hz, 1H), 5.71 (dd, *J* = 10.8, 2.4 Hz, 1H), 4.76-4.64 (m, 2H), 4.47-4.28 (m, 3H), 2.22 (s, 3H). MS (ESI, *m/z*): 479 $(M + H)^+$. LCMS: Method B; Retention Time: 0.86 min MS (ESI, *m/z*): 479 $[M + H]^+$

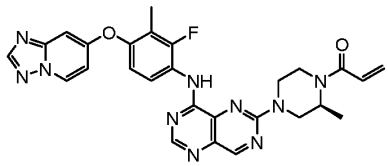
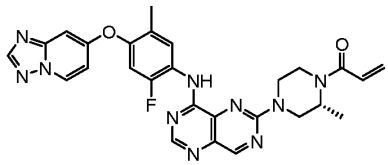
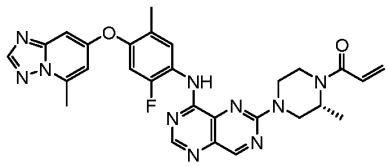
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
34	K	A	 (R)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 9.69 (s, 1H), 9.19 (d, *J* = 8.3 Hz, 1H), 9.02 (d, *J* = 7.5 Hz, 1H), 8.45 (d, *J* = 4.6 Hz, 2H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 10.8 Hz, 1H), 7.10 (dd, *J* = 7.5, 2.5 Hz, 1H), 7.03 – 6.87 (m, 2H), 6.24 (d, *J* = 16.5 Hz, 1H), 5.79 (dd, *J* = 10.5, 2.1 Hz, 1H), 5.37 – 5.06 (m, 1H), 4.94 – 4.72 (m, 1H), 4.45 (dd, *J* = 50.1, 13.0 Hz, 1H), 4.28 – 4.02 (m, 1H), 3.68 – 3.40 (m, 1H), 3.31 – 2.92 (m, 2H), 2.24 (s, 3H), 1.20 (d, *J* = 4.8 Hz, 3H). LCMS: Method H; Retention Time: 2.92 min MS (ESI, m/z): 541 $[M + H]^+$
35	K	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 9.66 (s, 1H), 9.17 (s, 1H), 8.98 (d, *J* = 7.5 Hz, 1H), 8.42 (d, *J* = 4.8 Hz, 2H), 7.88 (d, *J* = 9.1 Hz, 1H), 7.34 (d, *J* = 10.7 Hz, 1H), 7.07 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.98 – 6.85 (m, 2H), 6.25 – 6.14 (m, 1H), 5.80 – 5.71 (m, 1H), 5.25 – 5.02 (m, 1H), 4.89 – 4.68 (m, 1H), 4.42 (dd, *J* = 49.7, 12.8 Hz, 1H), 4.27 – 3.99 (m, 1H), 3.58 – 3.41 (m, 1H), 3.22 – 2.84 (m, 2H), 2.21 (s, 3H), 1.16 (s, 3H). LCMS: Method H; Retention Time: 2.97 min MS (ESI, m/z): 541 $[M + H]^+$
36	K	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 9.68 (s, 1H), 9.15 (s, 1H), 8.98 (d, J = 7.5 Hz, 1H), 8.41 (d, J = 10.6 Hz, 2H), 7.86 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 10.7 Hz, 1H), 7.06 (dd, J = 7.5, 2.6 Hz, 1H), 6.93 (d, J = 2.5 Hz, 1H), 6.88 (dd, J = 16.6, 10.5 Hz, 1H), 6.21 – 6.11 (m, 1H), 5.77 – 5.70 (m, 1H), 5.00 – 4.72 (m, 2H), 4.70 – 3.87 (m, 2H), 3.44 – 3.38 (m, 1H), 3.27 – 2.92 (m, 2H), 2.20 (s, 3H), 1.17 (m, 3H).LCMS: Method H; Retention Time: 1.31 min MS (ESI, m/z): 541 $[M + H]^+$

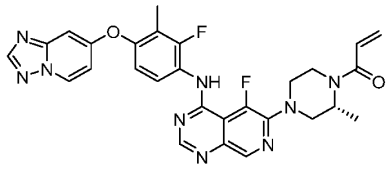
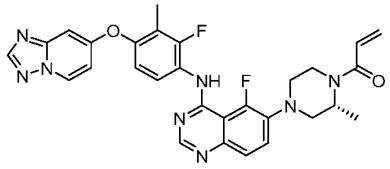
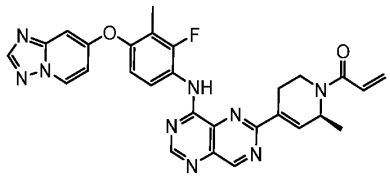
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
37	F	A	 1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 10.07 (d, *J* = 13.0 Hz, 1H), 9.47 (s, 1H), 8.98 (d, *J* = 7.5 Hz, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.90 – 7.78 (m, 1H), 7.49 (d, *J* = 19.3 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.07 (dd, *J* = 7.5, 2.6 Hz, 1H), 7.00 – 6.81 (m, 2H), 6.16 (d, *J* = 16.7 Hz, 1H), 5.73 (dd, *J* = 10.5, 2.3 Hz, 1H), 4.39 (d, *J* = 24.8 Hz, 2H), 3.89 – 3.79 (m, 2H), 2.87 (d, *J* = 17.0 Hz, 2H), 2.18 (d, *J* = 1.5 Hz, 3H). LCMS: Method H; Retention Time: 2.63 min MS (ESI, m/z): 524 $[M + H]^+$
38	F	A	 1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 10.11 (s, 1H), 9.46 (s, 1H), 8.98 (d, *J* = 7.5 Hz, 1H), 8.68 (s, 1H), 8.43 (s, 1H), 7.85 (t, *J* = 10.3 Hz, 1H), 7.50 (d, *J* = 19.6 Hz, 1H), 7.36 (d, *J* = 10.7 Hz, 1H), 7.07 (dd, *J* = 7.4, 2.5 Hz, 1H), 6.99 – 6.82 (m, 2H), 6.18 (d, *J* = 16.6 Hz, 1H), 5.74 (dd, *J* = 10.5, 2.1 Hz, 1H), 4.43 (d, *J* = 42.0 Hz, 2H), 3.89 – 3.81 (m, 2H), 2.93 – 2.83 (m, 2H), 2.21 (s, 3H). LCMS: Method H; Retention Time: 2.81 min MS (ESI, m/z): 524 $[M + H]^+$
39	K	A	 (R)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-(trifluoromethyl)phenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 9.76 (s, 1H), 9.17 (s, 1H), 9.02 (d, *J* = 7.5 Hz, 1H), 8.47 (s, 1H), 8.42 (s, 1H), 8.27 (t, *J* = 8.6 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 7.30 (d, *J* = 2.5 Hz, 1H), 7.13 (dd, *J* = 7.5, 2.7 Hz, 1H), 6.87 (dd, *J* = 16.5, 10.3 Hz, 1H), 6.21 – 6.13 (m, 1H), 5.76 – 5.70 (m, 1H), 4.90 – 4.15 (m, 4H), 3.44 – 3.35 (m, 2H), 3.22 – 3.14 (m, 1H), 1.20 – 1.11 (m, 3H) LCMS: Method H; Retention Time: XX min MS (ESI, m/z): 595 $[M + H]^+$

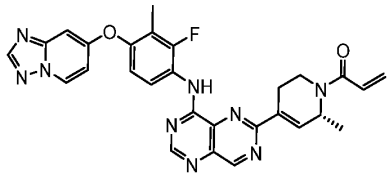
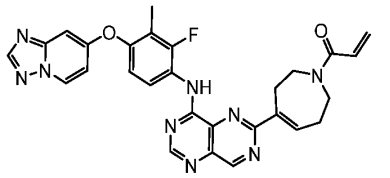
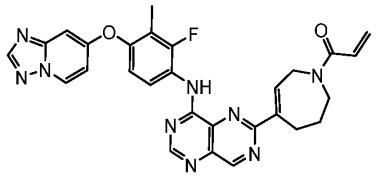
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
40	K	A	 Relative stereochemistry 1-(4-{8-[(2-fluoro-3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]-[1,3]diazino[5,4-d]pyrimidin-2-yl}-2,3-dimethylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.50 (s, 1H), 9.15 (s, 1H), 8.98 (d, *J* = 7.6 Hz, 1H), 8.42 (d, *J* = 2.4 Hz, 2H), 8.03-7.94 (m, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.07 (dd, *J* = 7.6, 2.8 Hz, 1H), 6.93 (d, *J* = 2.8 Hz, 1H), 6.85-6.75 (m, 1H), 6.12 (dd, *J* = 16.8, 2.4 Hz, 1H), 5.68 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.06-4.96 (m, 1H), 4.61-4.49 (m, 2H), 4.06-3.98 (m, 1H), 3.66-3.56 (m, 2H), 2.17 (d, *J* = 2.0 Hz, 3H), 1.37-1.32 (m, 6H) LCMS: Method I; Retention Time: 1.15 min MS (ESI, m/z): 555 $[M+H]^+$
41	K	A	 1-((1S,4S)-5-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2,5diazabicyclo[2.2.2]octan-2-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69-9.27 (m, 1H), 9.19-9.09 (m, 1H), 9.03-8.92 (m, 1H), 8.46-8.35 (m, 2H), 8.18-7.79 (m, 1H), 7.17-7.04 (m, 2H), 6.95-6.91 (m, 1H), 6.90-6.55 (m, 1H), 6.25-6.12 (m, 1H), 5.76-5.66 (m, 1H), 5.43-5.11 (m, 1H), 4.86-4.54 (m, 1H), 3.90-3.77 (m, 3H), 3.69-3.60 (m, 1H), 2.17 (s, 3H), 2.02-1.81 (m, 4H) LCMS: Method A; Retention Time: 1.01 min MS (ESI, m/z): 553 $[M+H]^+$
42	F	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	1H NMR (300 MHz, DMSO-d6) δ 10.00 (brs, 1H), 9.44 (s, 1H), 8.99 (d, J = 7.5 Hz, 1H), 8.69 (s, 1H), 8.43 (s, 1H), 7.93-7.84 (m, 1H), 7.56-7.46 (m, 1H), 7.16 (dd, J = 1.5, 9.0 Hz, 1H), 7.09 (dd, J = 2.7, 7.5 Hz, 1H), 7.18-6.85 (m, 2H), 6.18 (dd, J = 2.1, 16.5 Hz, 1H), 5.74 (dd, J = 2.4, 10.5 Hz, 1H), 5.17-4.69 (m, 2H), 4.22-3.81 (m, 1H), 3.13 (d, J = 17.7 Hz, 1H), 2.80-2.64 (m, 1H), 2.19 (d, J = 2.1 Hz, 3H), 1.26-1.10 (m, 3H). LCMS: Method A; Retention Time: 1.04 min MS (ESI, m/z): 538 $[M+H]^+$

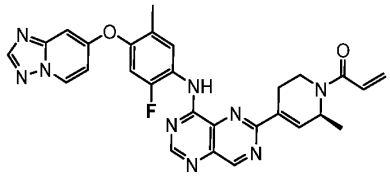
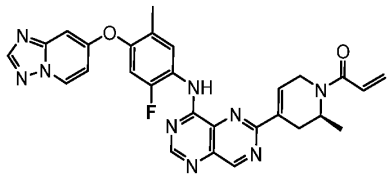
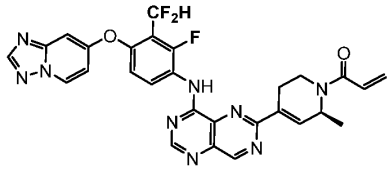
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
43	K	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.17 (s, 1H), 8.98 (d, J = 7.5, 1H), 8.42 (s, 2H), 7.99-7.84 (m, 1H), 7.15 (dd, J = 9.0, 1.5 Hz, 1H), 7.08 (dd, J = 7.5, 2.7 Hz, 1H), 7.01-6.83 (m, 2H), 6.21 (d, J = 16.5 Hz, 1H), 5.76 (dd, J = 10.5, 2.4 Hz, 1H), 5.23-5.03 (m, 1H), 4.86-4.62 (m, 1H), 4.55-4.30 (m, 1H), 4.25-4.02 (m, 1H), 3.60-2.89 (m, 3H), 2.17 (d, J = 2.1 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H) LCMS: Method J; Retention Time: 1.05 min MS (ESI, m/z): 541 $[M+H]^+$
44	K	A	 1-[(2R,5R)-4-{8-[(2-fluoro-3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]pyrimido[5,4-d][1,3]diazin-2-yl}-2,5-dimethylpiperazin-1-yl]prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.49 (s, 1H), 9.12 (s, 1H), 8.98 (d, J = 7.2 Hz, 1H), 8.40 (d, J = 6.4 Hz, 2H), 7.97 (s, 1H), 7.21-7.12 (m, 1H), 7.07 (dd, J = 7.6, 2.8 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 6.81 (s, 1H), 6.12 (d, J = 16.4 Hz, 1H), 5.67 (dd, J = 10.4, 2.4 Hz, 1H), 4.99 (s, 1H), 4.60-4.16 (m, 3H), 3.24 (d, J = 12.4 Hz, 2H), 2.17 (d, J = 2.0 Hz, 3H), 1.26 (d, J = 6.0 Hz, 3H), 1.21 (s, 3H) LCMS: Method J; Retention Time: 1.08 min MS (ESI, m/z): 555 $[M+H]^+$
45	K	A	 1-((1R,4R)-5-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2,5diazabicyclo[2.2.2]octan-2-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.70-9.32 (m, 1H), 9.18-9.12 (m, 1H), 8.98 (d, J = 7.6 Hz, 1H), 8.50-8.36 (m, 2H), 8.21-7.78 (m, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.07 (dd, J = 7.6, 2.8 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.91-6.56 (m, 1H), 6.25-6.11 (m, 1H), 5.78-5.66 (m, 1H), 5.43-5.10 (m, 1H), 4.87-4.54 (m, 1H), 4.01-3.71 (m, 3H), 3.69-3.60 (m, 1H), 2.17 (s, 3H), 2.10-1.78 (m, 4H). LCMS: Method A; Retention Time: 1.04 min MS (ESI, m/z): 553 $[M+H]^+$

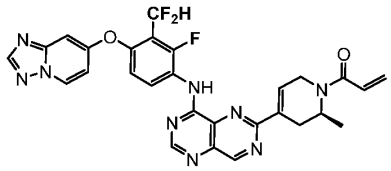
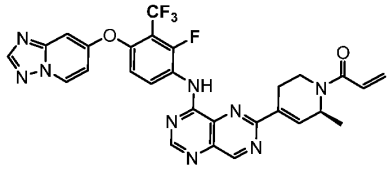
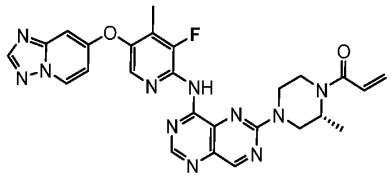
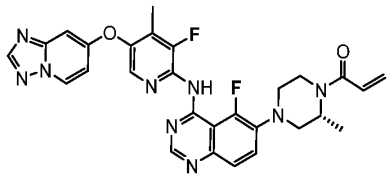
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
46	K	A	 1-((3aR,6aS)-5-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (s, 1H), 9.01 (s, 1H), 8.85 (d, J = 7.2 Hz, 1H), 8.30 (d, J = 6.9 Hz, 2H), 8.03 (s, 1H), 7.11-6.87 (m, 2H), 6.81 (d, J = 2.4 Hz, 1H), 6.51-6.42 (m, 1H), 6.01 (d, J = 16.8 Hz, 1H), 5.63-5.45 (m, 1H), 3.80-3.74 (m, 3H), 3.63-3.56 (m, 1H), 3.53-3.40 (m, 3H), 3.33-3.28 (m, 1H), 3.05-2.96 (m, 2H), 2.04 (s, 3H). LCMS: Method J; Retention Time: 0.97 min MS (ESI, m/z): 553 $[M+H]^+$
47	K	A	 1-(2-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2,6-diazaspiro[3.4]octan-6-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (d, J = 8.8 Hz, 1H), 9.15 (d, J = 2.4 Hz, 1H), 8.98 (d, J = 7.6 Hz, 1H), 8.50-8.39 (m, 2H), 8.24-8.14 (m, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.12-7.05 (m, 1H), 6.94 (s, 1H), 6.66-6.51 (m, 1H), 6.16 (d, J = 16.8 Hz, 1H), 5.69 (d, J = 10.4 Hz, 1H), 4.25-4.14 (m, 4H), 3.90-3.84 (m, 1H), 3.72-3.63 (m, 2H), 3.50-3.46 (m, 1H), 2.30-2.23 (m, 1H), 2.20-2.12 (m, 4H) LCMS: Method J; Retention Time: 0.96 min MS (ESI, m/z): 553 $[M+H]^+$
48	K	A	 1-(7-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2,7-diazaspiro[4.4]nonan-2-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.33 (d, J = 14.4 Hz, 1H), 9.12 (s, 1H), 8.97 (d, J = 7.5 Hz, 1H), 8.41 (s, 2H), 8.20-8.02 (m, 1H), 7.14 (d, J = 8.7 Hz, 1H), 7.10-7.02 (m, 1H), 6.93 (d, J = 2.7 Hz, 1H), 6.68-6.53 (m, 1H), 6.21-6.10 (m, 1H), 5.73-5.61 (m, 1H), 3.84-3.60 (m, 6H), 3.56 -3.48 (m, 2H), 2.16 (d, J = 2.1 Hz, 3H), 2.11-1.90 (m, 4H). LCMS: Method J; Retention Time: 1.01 min MS (ESI, m/z): 567 $[M+H]^+$

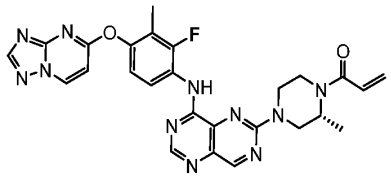
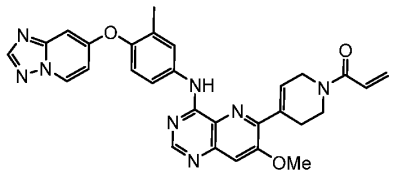
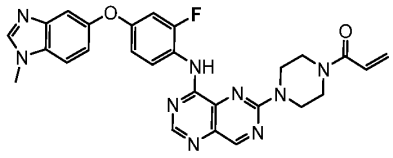
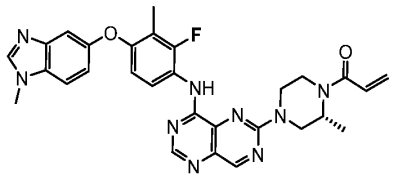
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
49	K	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino) pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 9.63 (s, 1H), 9.16 (s, 1H), 8.98 (d, *J* = 7.5 Hz, 1H), 8.42 (d, *J* = 4.2 Hz, 2H), 7.88 (t, *J* = 8.8 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.10 – 7.06 (m, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.92 – 6.84 (m, 1H), 6.20 – 6.13 (m, 1H), 5.76 – 5.71 (m, 1H), 4.94 – 4.43 (m, 4H), 3.51 – 3.48 (m, 2H), 3.22 – 3.16 (m, 1H), 2.18 (s, 3H), 1.21 – 1.13 (m, 3H). LCMS: Method H; Retention Time: 2.39 min MS (ESI, m/z): 541 $[M + H]^+$
50	K	A	 (R)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino) pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 9.66 (s, 1H), 9.14 (s, 1H), 8.97 (d, *J* = 7.4 Hz, 1H), 8.40 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.33 (d, *J* = 10.7 Hz, 1H), 7.05 (dd, *J* = 7.5, 2.6 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 16.7, 10.5 Hz, 1H), 6.15 (dd, *J* = 16.6, 2.0 Hz, 1H), 5.72 (dd, *J* = 10.4, 2.2 Hz, 1H), 4.77 (s, 2H), 4.71 – 3.98 (m, 2H), 3.37 (d, *J* = 12.4 Hz, 1H), 3.17 (s, 2H), 2.20 (s, 3H), 1.16 (s, 3H). LCMS: Method H; Retention Time: 2.75 min MS (ESI, m/z): 541 $[M + H]^+$
51	K	A	 (R)-1-(4-(8-((2-fluoro-5-methyl-4-((5-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)phenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 9.66 (s, 1H), 9.14 (s, 1H), 8.41 (d, *J* = 9.8 Hz, 2H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.30 (d, *J* = 10.7 Hz, 1H), 7.02 (s, 1H), 6.93 – 6.76 (m, 2H), 6.16 (d, *J* = 16.3 Hz, 1H), 5.73 (d, *J* = 12.6 Hz, 1H), 4.90 – 3.53 (m, 6H), 3.23 – 3.08 (m, 1H), 2.74 (s, 3H), 2.20 (s, 3H), 1.26 – 1.08 (m, 3H). LCMS: Method H; Retention Time: 2.70 min MS (ESI, m/z): 555 $[M + H]^+$

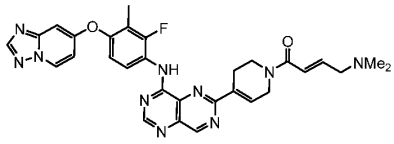
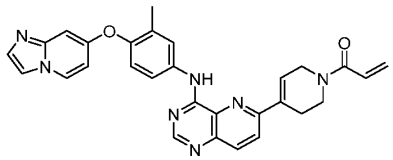
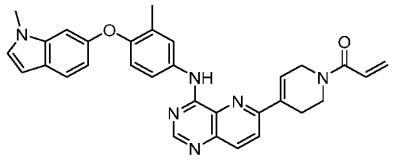
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
52	J	A	 (R)-1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)-5-fluoropyrido[3,4-d]pyrimidin-6-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.28 (s, 1H), 8.99 (d, *J* = 7.6 Hz, 1H), 8.81 (s, 1H), 8.49 (s, 1H), 8.43 (s, 1H), 7.80 (s, 1H), 7.17-7.05 (m, 2H), 6.95 (d, *J* = 2.8 Hz, 1H), 6.92-6.81 (m, 1H), 6.17 (d, *J* = 17.2 Hz, 1H), 5.78-5.69 (m, 1H), 4.77-4.38 (m, 2H), 4.02-3.99 (m, 1H), 3.88-3.84 (m, 1H), 3.62-3.44 (m, 1H), 3.21-3.19 (m, 1H), 3.07-2.96 (m, 1H), 2.16 (s, 3H), 1.33-1.25 (m, 3H). LCMS: Method D; Retention Time: 1.18 min MS (ESI, m/z): 558 $[M + H]^+$
53	I	A	 (R)-1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)-5-fluoroquinazolin-6-yl) 2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.14 (d, *J* = 10.2 Hz, 1H), 8.98 (d, *J* = 7.5 Hz, 1H), 8.47 (s, 1H), 8.42 (s, 1H), 7.86 (t, *J* = 8.7 Hz, 1H), 7.73 (t, *J* = 9.1 Hz, 1H), 7.64 (d, *J* = 9.1 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.08 (dd, *J* = 7.4, 2.4 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.86 (dd, *J* = 16.4, 10.5 Hz, 1H), 6.17 (d, *J* = 16.7 Hz, 1H), 5.73 (d, *J* = 10.4 Hz, 1H), 4.87 – 4.05 (m, 2H), 3.49 – 3.43 (m, 3H), 3.09 – 2.86 (m, 2H), 2.16 (s, 3H), 1.39 (s, 3H). LCMS: Method H; Retention Time: 1.10 min MS (ESI, m/z): 557 $[M + H]^+$
54	F	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-6-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d6) δ 10.00 (br.s, 1H), 9.45 (s, 1H), 8.99 (dd, J = 0.6, 7.5 Hz, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.92-7.82 (m, 1H), 7.45 (s, 1H), 7.17 (dd, J = 1.5, 8.7 Hz, 1H), 7.08 (dd, J = 2.7, 7.5 Hz, 1H), 6.97-6.83 (m, 2H), 6.24-6.14 (m, 1H), 5.74 (d, J = 10.2 Hz, 1H), 5.14-4.94 (m, 1H), 4.72-4.25 (m, 1H), 3.39-2.87 (m, 1H, overlapped with H2O), 3.17-3.11 (m, 1H), 2.61-2.40 (m, 1H, overlapped with DMSO), 2.19 (s, 3H), 1.39-1.31 (m, 3H). LCMS: Method A; Retention Time: 1.065 min MS (ESI, m/z): 538 $[M + H]^+$

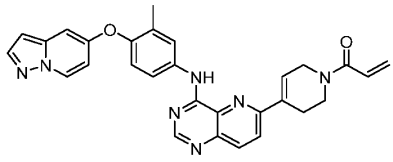
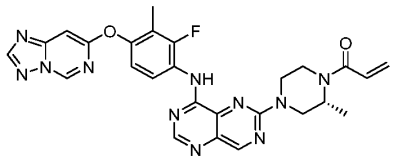
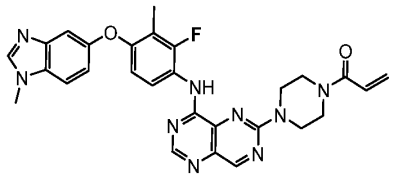
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
55	F	A	 (R)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-6-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d6) δ 10.00 (br.s, 1H), 9.45 (s, 1H), 8.99 (dd, J = 0.6, 7.5 Hz, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.92-7.82 (m, 1H), 7.45 (s, 1H), 7.17 (dd, J = 1.5, 8.7 Hz, 1H), 7.08 (dd, J = 2.7, 7.5 Hz, 1H), 6.97-6.83 (m, 2H), 6.24-6.14 (m, 1H), 5.74 (d, J = 10.2 Hz, 1H), 5.14-4.94 (m, 1H), 4.72-4.25 (m, 1H), 3.39-2.87 (m, 1H, overlapped with H2O), 3.17-3.11 (m, 1H), 2.61-2.40 (m, 1H, overlapped with DMSO), 2.19 (s, 3H), 1.39-1.31 (m, 3H). LCMS: Method A; Retention Time: 1.065 min MS (ESI, m/z): 538 $[M + H]^+$
56	F	A	 1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2,3,6,7-tetrahydro-1H-azepin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 10.10 (d, J = 14.9 Hz, 1H), 9.42 (s, 1H), 8.99 (d, J = 7.5 Hz, 1H), 8.66 (s, 1H), 8.42 (s, 1H), 7.80 – 7.66 (m, 2H), 7.16 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 6.96 (s, 1H), 6.90 – 6.82 (m, 1H), 6.15 (d, J = 16.5 Hz, 1H), 5.70 (d, J = 12.2 Hz, 1H), 3.85 – 3.73 (m, 4H), 3.28 (d, J = 3.8 Hz, 2H), 2.67 (d, J = 5.3 Hz, 2H), 2.18 (s, 3H). LCMS: Method J; Retention Time: 1.08 min MS (ESI, m/z): 538 $[M + H]^+$
57	F	A	 1-(5-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2,3,4,7-tetrahydro-1H-azepin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 10.08 (d, J = 11.9 Hz, 1H), 9.42 (s, 1H), 8.98 (d, J = 7.5 Hz, 1H), 8.67 (s, 1H), 8.42 (s, 1H), 7.80 (t, J = 8.6 Hz, 1H), 7.66 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.08 (dd, J = 7.5, 2.3 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 16.6, 10.4 Hz, 1H), 6.13 (d, J = 14.9 Hz, 1H), 5.69 (d, J = 10.5 Hz, 1H), 4.41 (dd, J = 25.0, 5.1 Hz, 2H), 3.93 – 3.69 (m, 2H), 3.14 – 3.00 (m, 2H), 2.18 (s, 3H), 2.01 – 1.91 (m, 2H). LCMS: Method J; Retention Time: 1.07 min MS (ESI, m/z): 538 $[M + H]^+$

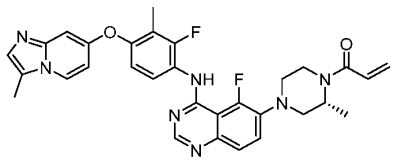
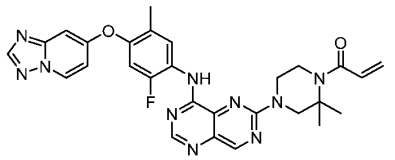
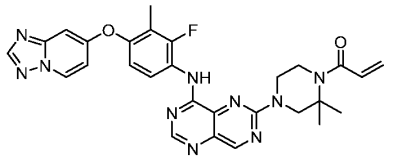
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
58	F	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-6-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 10.14 (s, 1H), 9.47 (s, 1H), 8.99 (d, J = 7.4 Hz, 1H), 8.68 (s, 1H), 8.43 (s, 1H), 7.89 – 7.79 (m, 1H), 7.62 – 7.48 (m, 1H), 7.37 (d, J = 10.7 Hz, 1H), 7.08 (dd, J = 7.5, 2.7 Hz, 1H), 6.96 (d, J = 2.6 Hz, 1H), 6.95 – 6.74 (m, 1H), 6.17 (d, J = 16.7 Hz, 1H), 5.73 (d, J = 11.1 Hz, 1H), 5.22 – 4.62 (m, 2H), 4.29 – 3.72 (m, 1H), 3.17 (d, J = 17.5 Hz, 1H), 2.86 – 2.65 (m, 1H), 2.22 (s, 3H), 1.15 (d, J = 13.2 Hz, 3H). LCMS: Method J; Retention Time: 0.94 min MS (ESI, m/z): 538 $[M+H]^+$
59	F	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 10.12 (s, 1H), 9.46 (s, 1H), 8.99 (d, J = 7.4 Hz, 1H), 8.68 (s, 1H), 8.43 (s, 1H), 7.84 (t, J = 9.3 Hz, 1H), 7.47 (s, 1H), 7.36 (d, J = 10.7 Hz, 1H), 7.07 (dd, J = 7.5, 2.6 Hz, 1H), 6.96 (d, J = 2.5 Hz, 1H), 6.90 (dd, J = 24.3, 14.3 Hz, 1H), 6.19 (t, J = 17.4 Hz, 1H), 5.74 (d, J = 9.4 Hz, 1H), 5.04 (d, J = 77.0 Hz, 1H), 4.49 (dd, J = 179.2, 8.6 Hz, 1H), 3.20 – 2.88 (m, 2H), 2.21 (s, 3H), 1.36 (dd, J = 27.2, 5.7 Hz, 3H), 1.27 – 1.10 (m, 1H). LCMS: Method G; Retention Time: .132 min MS (ESI, m/z): 538 $[M+H]^+$
60	F	A	 1-[(2S)-4-(8-{[3-(difluoromethyl)-2-fluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl]amino}-[1,3]diazino[5,4-d]pyrimidin-2-yl)-2-methyl-5,6-dihydro-2H-pyridin-1-yl]prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d6) δ 10.02 (s, 1H), 9.48 (s, 1H), 9.09-8.98 (m, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 8.16-8.01 (m, 1H), 7.64-7.32 (m, 2H), 7.32-7.19 (m, 2H), 7.16-7.10 (m, 1H), 7.01-6.83 (m, 1H), 6.27-6.11 (m, 1H), 5.81-5.67 (m, 1H), 4.76-4.20 (m, 1H), 3.82-3.71 (m, 1H), 3.26-3.13 (m, 2H), 2.71-2.65 (m, 1H), 1.46-1.22 (m, 3H). LCMS: Method J; Retention Time: 1.00 min MS (ESI, m/z): 574 $[M+H]^+$

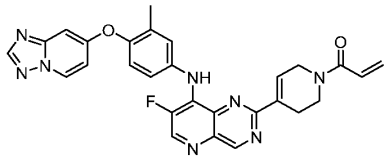
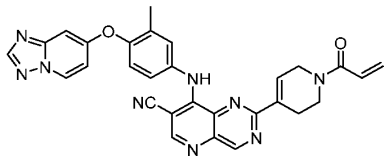
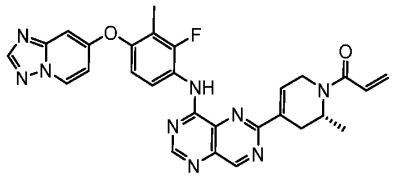
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
61	F	A	 1-[(2S)-4-(8-{[3-(difluoromethyl)-2-fluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl]amino}-[1,3]diazino[5,4-d]pyrimidin-2-yl)-2-methyl-3,6-dihydro-2H-pyridin-1-yl]prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d6) δ 10.09 (s, 1H), 9.36 (s, 1H), 8.95-8.87 (m, 1H), 8.57 (s, 1H), 8.36 (s, 1H), 8.02-7.90 (m, 1H), 7.46-7.24 (m, 2H), 7.19-7.05 (m, 2H), 7.03-6.76 (m, 2H), 6.06-6.01 (m, 1H), 5.66-5.58 (m, 1H), 4.67-4.58 (m, 1H), 3.82-3.71 (m, 1H), 3.08-2.97 (m, 2H), 2.69-2.61 (m, 1H), 1.14-0.99 (m, 3H). LCMS: Method J; Retention Time: 0.936 min MS (ESI, m/z): 574 $[M+H]^+$
62	F	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-(trifluoromethyl)phenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d6) δ 10.22 (s, 1H), 9.49 (s, 1H), 9.04 (d, J = 7.5 Hz, 1H), 8.72 (s, 1H), 8.49 (s, 1H), 8.31-8.14 (m, 1H), 7.47 (s, 1H), 7.42-7.29 (m, 1H), 7.19-7.11 (m, 1H), 7.00-6.78 (m, 1H), 6.29-6.09 (m, 1H), 5.81-5.63 (m, 1H), 5.21-4.90 (m, 1H), 4.76-4.23 (m, 1H), 3.26-3.10 (m, 1H), 3.09-2.78 (m, 1H), 2.76-2.56 (m, 1 H), 1.49-1.27 (m, 3H). LCMS: Method J; Retention Time: 1.11 min MS (ESI, m/z): 592 $[M+H]^+$
63	K	A	 (R)-1-(4-(8-((5-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluoro-4-methylpyridin-2-yl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 10.31 (s, 1H), 9.16 (s, 1H), 9.01 (d, J = 7.4 Hz, 1H), 8.45 (s, 1H), 8.38 (s, 1H), 8.31 (s, 1H), 7.17 – 7.14 (m, 1H), 7.12 (d, J = 2.4 Hz, 1H), 6.91 – 6.82 (m, 1H), 6.16 (d, J = 14.8 Hz, 1H), 5.75 – 5.71 (m, 1H), 4.83 – 4.36 (m, 4H), 3.19 – 3.11 (m, 3H), 2.26 – 2.24 (m, 3H), 1.25 – 1.22 (m, 3H). LCMS: Method K; Retention Time: 1.26 min MS (ESI, m/z): 542 $[M+H]^+$
64	K	A	 (R)-1-(4-(4-((5-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluoro-4-methylpyridin-2-yl)amino)-5-fluoroquinazolin-6-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 9.56 (s, 1H), 9.01 (d, J = 7.5 Hz, 1H), 8.64 – 8.28 (m, 2H), 8.23 (s, 1H), 7.89 – 7.43 (m, 2H), 7.17 – 7.13 (m, 1H), 7.12 – 7.06 (m, 1H), 6.91 – 6.81 (m, 1H), 6.20 – 6.11 (m, 1H), 5.76 – 5.69 (m, 1H), 4.94 – 3.83 (m, 3H), 3.47 – 3.42 (m, 2H), 3.05 – 2.83 (m, 2H), 2.22 (s, 3H), 1.37 (s, 3H). LCMS: Method K; Retention Time: 0.79 min MS (ESI, m/z): 558 $[M+H]^+$

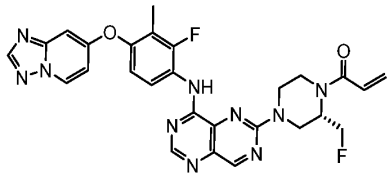
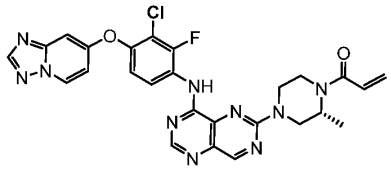
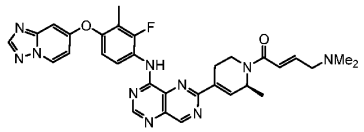
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
65	K	A	 (R)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyrimidin-5-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.38 (d, J = 7.3 Hz, 1H), 9.15 (s, 1H), 8.49 (s, 1H), 8.41 (s, 1H), 7.80 (t, J = 8.7 Hz, 1H), 7.26 – 7.18 (m, 2H), 6.88 (dd, J = 16.7, 10.5 Hz, 1H), 6.16 (dd, J = 16.8, 2.3 Hz, 1H), 5.73 (dd, J = 10.2, 2.2 Hz, 1H), 4.92 – 3.92 (m, 4H), 3.44 – 3.38 (m, 1H), 3.23 – 3.09 (m, 2H), 2.11 (d, J = 1.9 Hz, 3H), 1.17 (s, 3H). LCMS: Method K; Retention Time: 0.76 min MS (ESI, m/z): 542 $[M + H]^+$
66	M	A	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-7-methoxypyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.66 (brs, 1H), 8.93 (dd, J = 7.6, 2.4 Hz, 1H), 8.59 (d, J = 6.0 Hz, 1H), 8.37 (s, 1H), 7.97-7.95 (m, 2H), 7.61 (d, J = 6.0 Hz, 1H), 7.25-7.18 (m, 1H), 7.06-6.97 (m, 1H), 6.87-6.81 (m, 2H), 6.79 (d, J = 2.4 Hz, 1H), 6.17 (d, J = 2.4 Hz, 1H), 5.78-5.70 (m, 1H), 4.43-4.26 (m, 2H), 4.05-3.97 (m, 3H), 3.87-3.75 (m, 2H), 2.93-2.80 (m, 2H), 2.22-2.17 (m, 3H). LCMS: Method J; Retention Time: 0.71 min MS (ESI, m/z): 535$[M + H]^+$
67	K	A	 1-{4-[8-({2-fluoro-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]phenyl}amino)pyrimido[5,4-d][1,3]diazin-2-yl]piperazin-1-yl}prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d6) δ 9.64 (s, 1H), 9.12 (s, 1H), 8.32 (s, 1H), 8.24 (s, 1H), 7.67 (t, J = 8.4 Hz, 2H), 7.39 (d, J = 2.1 Hz, 1H), 7.12 (t, J = 6.6 Hz, 1H), 6.98-6.82 (m, 3H), 6.20 (dd, J = 16.8 Hz, 2.4 Hz, 1H), 5.75 (dd, J = 10.5 Hz, 2.4 Hz, 1H), 4.03-3.95 (m, 4H), 3.87 (s, 3H), 3.71-3.68 (m, 4H). LCMS: Method F; Retention Time: 1.17 min MS (ESI, m/z): 526 $[M + H]^+$
68	K	A	 1-[(2R)-4-[8-({2-fluoro-3-methyl-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]phenyl}amino)pyrimido[5,4-d][1,3]diazin-2-yl]-2-methylpiperazin-1-yl]prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d6) δ 9.59 (s, 1H), 9.12 (s, 1H), 8.35 (s, 1H), 8.22 (s, 1H), 7.66-7.54 (m, 2H), 7.23 (d, J = 2.4 Hz, 1H), 7.06 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.95-6.80 (m, 1H), 6.74-6.65 (m, 1H), 6.16 (dd, J = 16.5 Hz, 2.4 Hz, 1H), 5.73 (dd, J = 10.2 Hz, 2.4 Hz, 1H), 4.89-4.12 (m, 5H), 3.86 (s, 3H), 3.44-3.36 (m, 1H), 3.21-3.13 (m, 1H), 2.24 (d, J = 2.1 Hz, 3H), 1.17 (s, 3H). LCMS: Method F; Retention Time: 1.33 min MS (ESI, m/z): 554 $[M + H]^+$

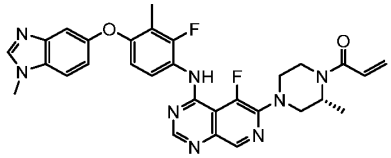
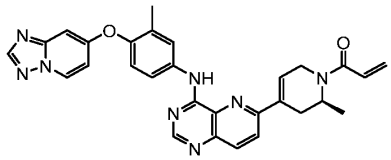
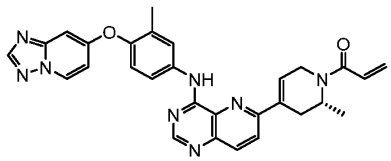
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
69	F	B	 (E)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-3,6-dihydropyridin-1(2H)-yl)-4-(dimethylamino)but-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 10.06 (s, 1H), 9.47 (s, 1H), 8.98 (d, *J* = 7.4 Hz, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.89 – 7.78 (m, 1H), 7.49 (d, *J* = 20.3 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 7.08 (dd, *J* = 7.5, 2.6 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.73 – 6.61 (m, 2H), 4.41 (d, *J* = 42.1 Hz, 2H), 3.82 (s, 2H), 3.06 (s, 2H), 2.89 (s, 2H), 2.18 (d, 3H), 2.16 (s, 6H). LCMS: Method K; Retention Time: 0.67 min MS (ESI, m/z): 581 $[M+H]^+$
70	A	A	 1-(4-(4-((4-(imidazo[1,2-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.85 (s, 1H), 8.64 (s, 1H), 8.55 (d, J = 7.4 Hz, 1H), 8.21 – 8.16 (m, 2H), 7.98 – 7.91 (m, 2H), 7.84 (s, 1H), 7.44 (d, J = 1.2 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.08 (d, J = 16.2 Hz, 1H), 7.03 – 6.83 (m, 1H), 6.81 (dd, J = 7.4, 2.5 Hz, 1H), 6.55 (d, J = 2.5 Hz, 1H), 6.17 (dd, J = 16.7, 2.1 Hz, 1H), 5.74 (d, J = 12.4 Hz, 1H), 4.39 (d, J = 34.4 Hz, 2H), 3.93 – 3.76 (m, 2H), 2.93 (d, J = 20.4 Hz, 2H), 2.23 (s, 3H). LCMS: Method K; Retention Time: 0.53 min MS (ESI, m/z): 504 $[M+H]^+$
71	A	A	 1-(4-(4-((3-methyl-4-((1-methyl-1H-indol-6-yl)oxy)phenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, MeOH-d4) δ 8.53 (s, 1H), 8.19 – 8.11 (m, 1H), 8.07 (d, J = 8.9 Hz, 1H), 7.77 (d, J = 2.6 Hz, 1H), 7.67 (dd, J = 8.7, 2.6 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.09 (d, J = 3.1 Hz, 1H), 6.95 (d, J = 18.0 Hz, 1H), 6.91 (d, J = 2.2 Hz, 1H), 6.90 – 6.79 (m, 2H), 6.76 (dd, J = 8.6, 2.2 Hz, 1H), 6.40 (dd, J = 3.2, 0.9 Hz, 1H), 6.27 (dd, J = 16.8, 1.9 Hz, 1H), 5.80 (dd, J = 10.5, 1.9 Hz, 1H), 4.44 (dd, J = 15.8, 3.3 Hz, 2H), 3.93 (q, J = 6.3, 5.9 Hz, 2H), 3.70 (s, 3H), 2.97 (d, J = 18.0 Hz, 2H), 2.34 (s, 3H). LCMS: Method K; Retention Time: 1.42 min MS (ESI, m/z): 517 $[M+H]^+$

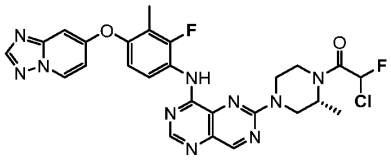
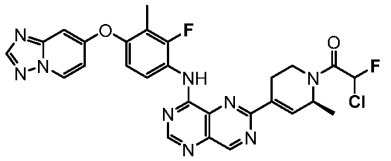
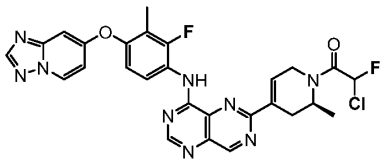
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
72	A	A	 1-(4-(4-((3-methyl-4-(pyrazolo[1,5-a]pyridin-5-yloxy)phenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.83 (s, 1H), 8.68 (d, J = 7.3 Hz, 1H), 8.64 (s, 1H), 8.18 (s, 2H), 7.98 – 7.94 (m, 2H), 7.91 (d, J = 2.2 Hz, 1H), 7.19 (d, J = 9.2 Hz, 1H), 7.08 (d, J = 16.5 Hz, 1H), 6.98 – 6.81 (m, 1H), 6.76 – 6.72 (m, 2H), 6.41 (d, J = 2.1 Hz, 1H), 6.17 (dd, J = 16.7, 2.2 Hz, 1H), 5.78 – 5.72 (m, 1H), 4.39 (d, J = 34.7 Hz, 2H), 3.88 – 3.80 (m, 2H), 2.97 – 2.88 (m, 2H), 2.22 (s, 3H). LCMS: Method K; Retention Time: 1.58 min MS (ESI, m/z): 504 $[M + H]^+$
73	K	A	 (R)-1-(4-(8-((4-([1,2,4]triazolo[1,5-c]pyrimidin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.69 (d, J = 1.2 Hz, 1H), 9.64 (s, 1H), 9.15 (s, 1H), 8.62 (s, 1H), 8.39 (s, 1H), 7.78 (t, J = 8.6 Hz, 1H), 7.34 (d, J = 1.2 Hz, 1H), 7.14 (dd, J = 9.0, 1.3 Hz, 1H), 6.88 (dd, J = 16.6, 10.5 Hz, 1H), 6.16 (dd, J = 16.8, 1.9 Hz, 1H), 5.73 (dd, J = 10.5, 2.1 Hz, 1H), 4.88 – 3.97 (m, 4H), 3.52 – 3.38 (m, 1H), 3.18 (d, J = 12.1 Hz, 2H), 2.15 (d, J = 1.9 Hz, 3H), 1.17 (s, 3H). LCMS: Method K; Retention Time: 0.97 min MS (ESI, m/z): 542 $[M + H]^+$
74	K	A	 1-{4-[8-({2-fluoro-3-methyl-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]phenyl}amino)pyrimido[5,4-d][1,3]diazin-2-yl]piperazin-1-yl}prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 9.13 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.57 (t, J = 8.9 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.08 – 7.04 (m, 1H), 6.94 – 6.85 (m, 1H), 6.69 (d, J = 8.9 Hz, 1H), 6.21 – 6.14 (m, 1H), 5.77 – 5.72 (m, 1H), 4.06 – 3.96 (m, 4H), 3.86 (s, 3H), 3.76 – 3.68 (m, 4H), 2.26 – 2.22 (m, 3H). LCMS: Method K; Retention Time: 1.14 min MS (ESI, m/z): 540 $[M + H]^+$

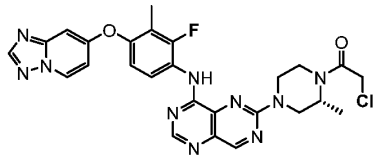
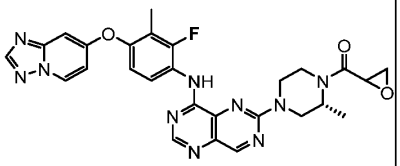
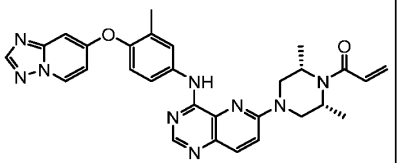
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
75	I	A	 (R)-1-(4-(5-fluoro-4-((2-fluoro-3-methyl-4-((3-methylimidazo[1,2-a]pyridin-7-yl)oxy)phenyl)amino)quinazolin-6-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.12 (d, J = 13.7 Hz, 1H), 8.45 (s, 1H), 8.30 (d, J = 7.4 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.63 (d, J = 9.0 Hz, 1H), 7.26 (s, 1H), 6.99 (d, J = 8.6 Hz, 1H), 6.90 – 6.82 (m, 2H), 6.69 (d, J = 2.3 Hz, 1H), 6.16 (dd, J = 16.6, 2.1 Hz, 1H), 5.72 (dd, J = 10.4, 2.3 Hz, 1H), 4.93 – 4.20 (m, 2H), 4.19 – 3.82 (m, 1H), 3.47 – 3.45 (m, 2H), 3.04 – 2.86 (m, 2H), 2.44 (s, 3H), 2.17 (d, J = 1.5 Hz, 3H), 1.38 (s, 3H). LCMS: Method K; Retention Time: 0.774 min MS (ESI, m/z): 570 [M + H]$^+$
76	K	A	 1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2,2-dimethylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 9.65-9.38 (m, 1H), 9.16 (s, 1H), 8.98 (d, *J* = 7.2 Hz, 1H), 8.42 (s, 2H), 8.15-7.80 (m, 1H), 7.35 (d, *J* = 10.8 Hz, 1H), 7.06 (dd, *J* = 7.6, 2.4 Hz, 1H), 6.93 (d, *J* = 2.8 Hz, 1H), 6.82-6.71 (m, 1H), 6.04 (dd, *J* = 16.8, 2.4 Hz, 1H), 5.63 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.15-4.08 (m, 2H), 3.96-3.90 (m, 2H), 3.85-3.78 (m, 2H), 2.20 (s, 3H), 1.49 (s, 6H). MS (ESI, *m/z*): 555 (M + H)$^+$. LCMS: Method D; Retention Time: 1.119 min MS (ESI, m/z): 555 [M + H]$^+$
77	K	A	 1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2,2-dimethylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 9.47 (brs, 1H), 9.16 (s, 1H), 8.98 (d, *J* = 7.5 Hz, 1H), 8.45-8.41 (m, 2H), 8.25-7.78 (m, 1H), 7.21-7.12 (m, 1H), 7.10-7.02 (m, 1H), 6.97-6.90 (m, 1H), 6.85-6.70 (m, 1H), 6.12-5.97 (m, 1H), 5.70-5.59 (m, 1H), 4.12 (s, 2H), 4.03-3.77 (m, 4H), 2.17 (s, 3H), 1.49 (s, 6H). LCMS: Method J; Retention Time: 1.09 min MS (ESI, m/z): 555 [M + H]$^+$

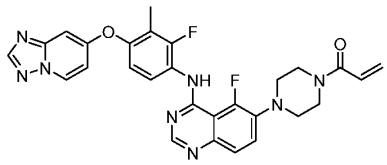
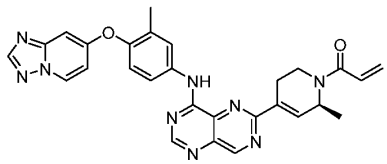
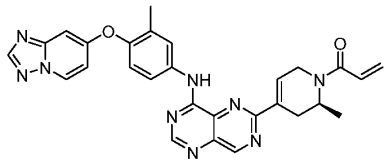
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
78	O	A	 1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-7-fluoropyrido[3,2-d]pyrimidin-2-yl)-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 8.94 (d, J = 7.6 Hz, 1H), 8.89 (s, 1H), 8.73 (d, J = 4.0 Hz, 1H), 8.38 (s, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.29 (s, 1H), 7.21-7.11 (m, 2H), 7.08-6.98 (m, 1H), 6.96-6.82 (m, 1H), 6.76 (s, 1H), 6.16 (d, J = 16.8 Hz, 1H), 5.77-5.67 (m, 1H), 4.45-4.38 (m, 1H), 4.36-4.29 (m, 1H), 3.86-3.75 (m, 2H), 2.95-2.82 (m, 2H), 2.16 (s, 3H). LCMS: Method J; Retention Time: 1.119 min MS (ESI, m/z): 522 $[M + H]^+$
79	N	A	 8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2-(1-acryloyl-1,2,3,6-tetrahydropyridin-4-yl)pyrido[3,2-d]pyrimidine-7-carbonitrile	^{1}H NMR (400 MHz, DMSO-d6) δ 10.08 (brs, 1H), 8.95 (d, J = 7.6 Hz, 1H), 8.55 (s, 1H), 8.37 (s, 1H), 8.28 (d, J = 8.8 Hz, 1H), 8.16-8.15 (m, 1H), 7.52 (d, J = 2.8 Hz, 1H), 7.43 (dd, J = 8.4, 2.8 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.15-7.05 (m, 2H), 6.98-6.79 (m, 1H), 6.17 (d, J = 16.8 Hz, 1H), 5.74 (dd, J = 10.4, 2.4 Hz, 1H), 4.42 (s, 1H), 4.36-4.31 (m, 1H), 3.85-3.78 (m, 2H), 2.94-2.89 (m, 2H), 2.20 (s, 3H). LCMS: Method J; Retention Time: 1.119 min MS (ESI, m/z): 529 $[M + H]^+$
80	F	A	 (R)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.00 (br.s, 1H), 9.47 (s, 1H), 9.00 (d, *J* = 7.6 Hz, 1H), 8.69 (s, 1H), 8.43 (s, 1H), 7.88-7.76 (m, 1H), 7.58-7.48 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.03-6.77 (m, 2H), 6.21-6.13 (m, 1H), 5.73 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.25-4.37 (m, 2H), 4.25-3.75 (m, 1H), 3.17-3.12 (m, 1H), 2.85-2.58 (m, 1H), 2.19 (s, 3H), 1.23-1.14 (m, 3H). LCMS: Method L; Retention Time: 0.822 min MS (ESI, *m/z*): 538 $(M + H)^+$.

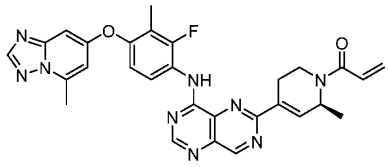
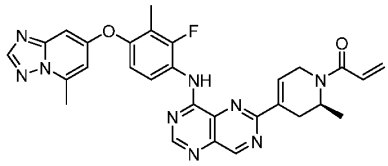
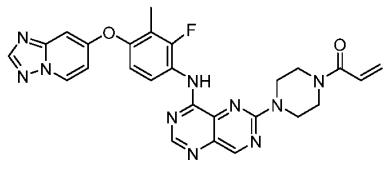
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
81	K	A	 1-[(2S)-4-{8-[(2-fluoro-3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]pyrimido[5,4-d][1,3]diazin-2-yl}-2-(fluoromethyl)piperazin-1-yl]prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d6) δ 9.64 (s, 1H), 9.15 (s, 1H), 8.99-8.94 (m, 1H), 8.41 (s, 2H), 7.91-7.82 (m, 1H), 7.18-7.12 (m, 1H), 7.09-7.04 (m, 1H), 6.95-6.84 (m, 2H), 6.23-6.12 (m, 1H), 5.78-5.70 (m, 1H), 5.02-4.86 (m, 2H), 4.75-4.60 (m, 2H), 4.57-4.38 (m, 2H), 3.53-3.36 (m, 2H), 3.11 (s, 1H), 2.20-2.12 (m, 3H). LCMS: Method J; Retention Time: 1.09 min MS (ESI, m/z): 559 $[M + H]^+$
82	K	A	 (R)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-chloro-2-fluorophenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (brs, 1H), 9.17 (s, 1H), 9.09-8.96 (m, 1H), 8.44 (d, J = 15.2 Hz, 2H), 8.01-7.89 (m, 1H), 7.38 (dd, J = 9.2, 1.6 Hz, 1H), 7.24-7.07 (m, 2H), 6.88 (dd, J = 16.4, 10.4 Hz, 1H), 6.17 (dd, J = 16.4, 2.4 Hz, 1H), 5.73 (dd, J = 10.4, 2.4 Hz, 1H), 5.05-4.43 (m, 3H), 4.42-3.93 (m, 1H), 3.53-3.01 (m, 3H), 1.17 (s, 3H). LCMS: Method J; Retention Time: 1.037 min MS (ESI, m/z): 561/563 $[M + H]^+$
83	F	B	 (2E)-4-(dimethylamino)-1-[(2S)-4-{8-[(2-fluoro-3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)amino]-[1,3]diazino[5,4-d]pyrimidin-2-yl}-2-methyl-5,6-dihydro-2H-pyridin-1-yl]but-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.47 (s, 1H), 9.03-8.97 (m, 1H), 8.70 (s, 1H), 8.43 (s, 1H), 7.91-7.78 (m, 1H), 7.47 (s, 1H), 7.20-7.15 (m, 1H), 7.12-7.06 (m, 1H), 7.01-6.95 (m, 1H), 6.77-6.62 (m, 2H), 5.20-4.98 (m, 1H), 4.77-4.53 (m, 1H), 3.22-3.11 (m, 1H), 3.10-3.03 (m, 2H), 2.97-2.86 (m, 1H), 2.24-2.19 (m, 3H), 2.17-2.12 (m, 6H), 1.44-1.27 (m, 4H). LCMS: Method J; Retention Time: 1.312 min MS (ESI, m/z): 595 $[M + H]^+$

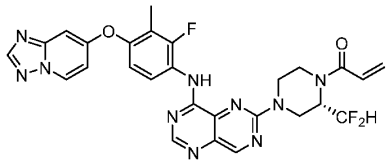
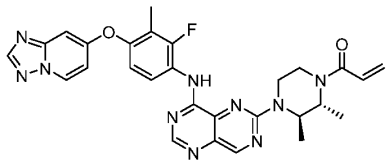
Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
84	L	A	 (R)-1-(4-(5-fluoro-4-((2-fluoro-3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)pyrido[3,4-d]pyrimidin-6-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (d, J = 10.2 Hz, 1H), 8.79 (s, 1H), 8.43 (s, 1H), 8.22 (s, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.51 (t, J = 8.7 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.07 (dd, J = 8.7, 2.1 Hz, 1H), 6.86 (dd, J = 16.5, 10.5 Hz, 1H), 6.64 (dd, J = 9.0, 1.5 Hz, 1H), 6.16 (dd, J = 16.5, 2.4 Hz, 1H), 5.72 (dd, J = 10.5, 2.4 Hz, 1H), 4.72-4.33 (m, 1H), 3.98 (d, J = 12.6 Hz, 1H), 3.86 (s, 3H), 3.84-3.80 (m, 1H), 3.19-3.10 (m, 3H), 3.00 (t, J = 12.6 Hz, 1H), 2.24 (s, 3H), 1.29 (d, J = 6.6 Hz, 3H). LCMS: Method J; Retention Time: 0.90 min MS (ESI, m/z): 571 $[M+H]^+$
85	A	A	 (S)-1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-2-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.82 (s, 1H), 8.94 (d, J = 7.5 Hz, 1H), 8.65 (s, 1H), 8.38 (s, 1H), 8.24-8.16 (m, 2H), 8.00-7.97 (m, 2H), 7.27–7.24 (m, 1H), 7.11 – 7.02 (m, 2H), 6.89-6.80 (m, 2H), 6.18-6.12 (m, 1H), 5.75-5.70 (m, 1H), 5.17-4.75 (m, 2H), 4.14-3.77 (m, 1H), 3.15-3.09 (m, 1H), 2.83-2.73 (m, 1H), 2.22 (s, 3H), 1.28-1.22 (m, 3H). LCMS: Method J; Retention Time: 1.03 min MS (ESI, m/z): 519 $[M+H]^+$
86	A	A	 (R)-1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-2-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (brs, 1H), 8.94 (d, J = 7.6 Hz, 1H), 8.65 (s, 1H), 8.38 (s, 1H), 8.20 (q, J = 8.8 Hz, 2H), 8.02-7.91 (m, 2H), 7.29-7.23 (m, 2H), 7.12 (s, 1H), 7.04 (dd, J = 7.6, 2.8 Hz, 1H), 6.81 (d, J = 2.8 Hz, 1H), 6.20-6.11 (m, 1H), 5.77-5.69 (m, 1H), 5.25-4.55 (m, 2H), 4.28-3.60 (m, 1H), 3.17-3.06 (m, 1H), 2.89-2.76 (m, 1H), 2.23 (s, 3H), 1.23 (s, 3H). LCMS: Method J; Retention Time: 1.03 min MS (ESI, m/z): 519 $[M+H]^+$

Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
87	K	B	 1-((R)-4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)-2-chloro-2-fluoroethan-1-one	^{1}H NMR (400 MHz, DMSO) δ 9.66 (d, *J* = 10.8 Hz, 1H), 9.16 (s, 1H), 8.98 (d, *J* = 7.5 Hz, 1H), 8.41 (d, *J* = 2.6 Hz, 2H), 7.89 – 7.79 (m, 1H), 7.55 – 7.21 (m, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.07 (dd, *J* = 7.5, 2.6 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 4.93 – 4.65 (m, 2H), 4.63 – 4.19 (m, 1H), 3.84 – 3.38 (m, 2H), 3.29 – 3.06 (m, 2H), 2.18 (s, 3H), 1.29 – 1.11 (m, 3H). LCMS: Method K; Retention Time: 1.41 min MS (ESI, m/z): 581/583 $[M + H]^+$
88	F	B	 1-((S)-4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-6-methyl-3,6-dihydropyridin-1(2H)-yl)-2-chloro-2-fluoroethan-1-one	^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.09 (d, *J* = 17.0 Hz, 1H), 9.47 (d, *J* = 4.5 Hz, 1H), 8.99 (d, *J* = 7.5 Hz, 1H), 8.69 (d, *J* = 5.9 Hz, 1H), 8.42 (s, 1H), 7.90 – 7.76 (m, 1H), 7.56 – 7.28 (m, 2H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.08 (dd, *J* = 7.5, 2.6 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 1H), 5.10 – 4.77 (m, 1H), 4.63 – 4.39 (m, 1H), 4.28 – 3.85 (m, 1H), 3.13 (d, *J* = 17.1 Hz, 1H), 2.91 – 2.67 (m, 1H), 2.19 (s, 3H), 1.29 – 1.15 (m, 3H). LCMS: Method K; Retention Time: 1.64 min MS (ESI, m/z): 578/580 $[M + H]^+$
89	F	B	 1-((S)-4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methyl-3,6-dihydropyridin-1(2H)-yl)-2-chloro-2-fluoroethan-1-one	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.09 (d, *J* = 19.0 Hz, 1H), 9.46 (d, *J* = 4.9 Hz, 1H), 8.99 (d, *J* = 7.5 Hz, 1H), 8.69 (d, *J* = 6.6 Hz, 1H), 8.42 (s, 1H), 7.84 (dt, *J* = 35.5, 8.7 Hz, 1H), 7.51 – 7.34 (m, 2H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.09 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.96 (s, 1H), 5.07 – 3.96 (m, 2H), 3.18 (d, *J* = 16.8 Hz, 1H), 2.66 (d, *J* = 12.0 Hz, 1H), 2.19 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 1H), 1.33 (dd, *J* = 14.4, 6.8 Hz, 3H). LCMS: Method K; Retention Time: 1.45 min MS (ESI, m/z): 578/580 $[M + H]^+$

Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
90	K	B	 (R)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)-2-chloroethan-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (s, 1H), 9.15 (s, 1H), 8.98 (d, J = 7.6 Hz, 1H), 8.41 (d, J = 4.9 Hz, 2H), 7.86 (t, J = 8.5 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.07 (dd, J = 7.5, 2.6 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 5.08 – 4.54 (m, 3H), 4.54 – 4.41 (m, 2H), 4.41 – 4.15 (m, 1H), 3.89 – 3.47 (m, 2H), 2.18 (s, 3H), 1.17 (d, J = 56.6 Hz, 4H). LCMS: Method K; Retention Time: 1.27 min MS (ESI, m/z): 563/565 $[M + H]^+$
91	K	B	 ((R)-4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methylpiperazin-1-yl)(oxiran-2-yl)methanone	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 9.15 (s, 1H), 8.97 (d, J = 7.5 Hz, 1H), 8.41 (d, J = 2.9 Hz, 2H), 7.88 (t, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.07 (dd, J = 7.5, 2.6 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 5.00 – 4.70 (m, 2H), 4.67 – 4.55 (m, 1H), 4.32 – 4.11 (m, 1H), 3.99 – 3.89 (m, 1H), 3.57 – 3.44 (m, 1H), 3.26 – 3.17 (m, 1H), 3.13 – 3.04 (m, 1H), 2.95 (s, 1H), 2.86 – 2.75 (m, 1H), 2.17 (s, 3H), 1.29 – 1.10 (m, 3H). LCMS: Method K; Retention Time: 1.30 min MS (ESI, m/z): 557 $[M + H]^+$
92	C	A	 1-((2S,6R)-4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrido[3,2-d]pyrimidin-6-yl)-2,6-dimethylpiperazin-1-yl)prop-2-en-1-one	^{1}HNMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.94 (d, J = 7.6 Hz, 1H), 8.40 (d, J = 22.0 Hz, 2H), 7.99 – 7.90 (m, 3H), 7.67 (d, J = 9.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 7.6, 2.4 Hz, 1H), 6.89 – 6.77 (m, 2H), 6.17 (dd, J = 16.4, 2.4 Hz, 1H), 5.72 (dd, J = 10.4, 2.4 Hz, 1H), 4.72 (d, J = 13.2 Hz, 2H), 4.53 (s, 2H), 3.27 (d, J = 13.6 Hz, 2H), 2.21 (s, 3H), 1.25 (d, J = 6.8 Hz, 6H. LCMS: Method G; Retention Time: 3.03 min MS (ESI, m/z): 536 $[M + H]^+$

Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
93	I	A	 1-(4-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)-5-fluoroquinazolin-6-yl)piperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO) δ 9.12 (s, 1H), 8.97 (d, J = 7.5 Hz, 1H), 8.47 (s, 1H), 8.41 (s, 1H), 7.87 (t, J = 8.8 Hz, 1H), 7.75 (t, J = 9.1 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 7.07 (dd, J = 7.5, 2.6 Hz, 1H), 6.93 (d, J = 2.5 Hz, 1H), 6.88 (dd, J = 16.7, 10.4 Hz, 1H), 6.16 (dd, J = 16.7, 2.4 Hz, 1H), 5.73 (dd, J = 10.5, 2.4 Hz, 1H), 3.77 (d, J = 12.6 Hz, 4H), 3.18 (s, 4H), 2.16 (s, 3H). LCMS: Method G; Retention Time: 1.03 min MS (ESI, m/z): 543 $[M + H]^+$
94	F	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-6-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 9.45 (s, 1H), 8.96 (d, J = 7.5 Hz, 1H), 8.74 (s, 1H), 8.40 (s, 1H), 8.00 – 7.93 (m, 2H), 7.50 (d, J = 12.8 Hz, 1H), 7.33 – 7.25 (m, 1H), 7.05 (dd, J = 7.4, 2.6 Hz, 1H), 6.97 – 6.84 (m, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.19 (t, J = 17.0 Hz, 1H), 5.75 (d, J = 10.6 Hz, 1H), 5.05 (d, J = 80.3 Hz, 1H), 4.77 – 4.20 (m, 1H), 3.40 – 3.36 (m, 1H), 3.24 (d, J = 18.0 Hz, 1H), 2.95 – 2.56 (m, 1H), 2.23 (s, 3H), 1.42 – 1.31 (m, 3H). LCMS: Method G; Retention Time: 1.29 min MS (ESI, m/z): 520 $[M + H]^+$
95	F	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.44 (s, 1H), 8.95 (d, J = 7.5 Hz, 1H), 8.73 (s, 1H), 8.39 (s, 1H), 7.98 – 7.94 (m, 2H), 7.58 (d, J = 21.3 Hz, 1H), 7.28 (d, J = 9.5 Hz, 1H), 7.04 (dd, J = 7.5, 2.7 Hz, 1H), 7.01 – 6.82 (m, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.16 (d, J = 16.7 Hz, 1H), 5.73 (dd, J = 10.5, 2.4 Hz, 1H), 5.23 – 4.66 (m, 2H), 4.26 – 3.79 (m, 1H), 3.19 (d, J = 17.8 Hz, 1H), 2.89 – 2.57 (m, 1H), 2.23 (s, 3H), 1.24 – 1.11 (m, 3H). LCMS: Method G; Retention Time: 1.29 min MS (ESI, m/z): 520 $[M + H]^+$

Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
96	F	A	 (S)-1-(4-(8-((2-fluoro-3-methyl-4-((5-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)phenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-6-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 9.47 (s, 1H), 8.69 (s, 1H), 8.43 (s, 1H), 7.83 (d, J = 10.5 Hz, 1H), 7.53 (d, J = 17.4 Hz, 1H), 7.06 – 7.04 (m, 1H), 7.03 – 6.86 (m, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.17 (d, J = 16.6 Hz, 1H), 5.74 (dd, J = 10.4, 2.4 Hz, 1H), 5.20 – 4.67 (m, 2H), 4.27 – 3.77 (m, 1H), 3.15 (d, J = 17.6 Hz, 1H), 2.84 – 2.64 (m, 4H), 2.19 (d, J = 1.9 Hz, 3H), 1.27 – 1.10 (m, 3H). LCMS: Method G; Retention Time: 1.42 min MS (ESI, m/z): 552 $[M + H]^+$
97	F	A	 (S)-1-(4-(8-((2-fluoro-3-methyl-4-((5-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)oxy)phenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-methyl-3,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.47 (s, 1H), 8.70 (s, 1H), 8.43 (s, 1H), 7.83 (dt, J = 19.1, 9.3 Hz, 1H), 7.46 (d, 1H), 7.15 (dd, J = 8.9, 1.5 Hz, 1H), 7.04 (dd, J = 2.6, 1.2 Hz, 1H), 7.01 – 6.86 (m, 1H), 6.85 (d, J = 2.6 Hz, 1H), 6.19 (t, J = 17.2 Hz, 1H), 5.79 – 5.69 (m, 1H), 5.05 (d, J = 75.7 Hz, 1H), 4.49 (dd, J = 173.8, 13.3 Hz, 1H), 3.32 – 3.24 (m, 1H), 3.17 (d, J = 17.4 Hz, 1H), 2.96 – 2.55 (m, 4H), 2.19 (d, J = 2.1 Hz, 3H), 1.45 – 1.18 (m, 3H). LCMS: Method G; Retention Time: 1.40 min MS (ESI, m/z): 552 $[M + H]^+$
98	K	A	 2-(2,5-dimethylpyrazol-3-yl)-N-{7-ethoxy-1-[2-(prop-2-enoyl)-2-azaspiro[3.4]octan-6-yl]-1,3-benzodiazol-2-yl}pyridine-4-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H), 9.17 (s, 1H), 8.99 (d, J = 7.5 Hz, 1H), 8.42 (d, J = 2.7 Hz, 2H), 7.90-7.82 (m, 1H), 7.21-7.14 (m, 1H), 7.10-7.03 (m, 1H), 6.98-6.86 (m, 2H), 6.23-6.14 (m, 1H), 5.78-5.72 (m, 1H), 4.10-3.96 (m, 4H), 3.81-3.66 (m, 4H), 2.18 (s, 3H). LCMS: Method J; Retention Time: 0.98 min MS (ESI, m/z): 527 $[M + H]^+$

Example	Synthetic Method	Coupling Method	Compound Structure	Physical Data (^{1}H NMR and MS)
99	K	A	 (S)-1-(4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2-(difluoromethyl)piperazin-1-yl)prop-2-en-1-one	^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.61 (s, 1H), 9.17 (s, 1H), 8.99-8.94 (m, 1H), 8.41 (d, *J* = 5.7 Hz, 2H), 7.98-7.85 (m, 1H), 7.19-7.11 (m, 1H), 7.10-7.03 (m, 1H), 6.98-6.85 (m, 2H), 6.55-6.27 (m, 1H), 6.26-6.15 (m, 1H), 5.85-5.71 (m, 1H), 5.17-4.62 (m, 3H), 4.53-4.11 (m, 1H), 3.57-3.38 (m, 2H), 3.26-3.03 (m, 1H), 2.16 (s, 3H). LCMS: Method J; Retention Time: 1.04 min MS (ESI, m/z): 577 $[M + H]^+$
100	K	A	 1-((2R,3R)-4-(8-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)pyrimido[5,4-d]pyrimidin-2-yl)-2,3-dimethylpiperazin-1-yl)prop-2-en-1-one	^{1}H NMR (400 MHz, DMSO-d*6*) δ 9.50 (s, 1H), 9.15 (s, 1H), 8.98 (d, *J* = 7.6 Hz, 1H), 8.42 (d, *J* = 2.4 Hz, 2H), 8.03-7.94 (m, 1H), 7.15 (d, *J* = 8.8, 1H), 7.07 (dd, *J* = 7.6, 2.8 Hz, 1H), 6.93 (d, *J* = 2.8 Hz, 1H), 6.85-6.74 (m, 1H), 6.12 (dd, *J* = 16.8, 2.4 Hz, 1H), 5.68 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.06-4.96 (m, 1H), 4.61-4.49 (m, 2H), 4.06-3.98 (m, 1H), 3.66-3.56 (m, 2H), 2.17 (d, *J* = 2.0 Hz, 3H), 1.39-1.31 (m, 6H). LCMS: Method M; Retention Time: 1.27 min MS (ESI, m/z): 555 $[M + H]^+$

Biochemical Kinase Assay

Generation of Ba/F3 Stable Cell Lines

The gene encoding HER2-A775_G776insYVMA ("HER2-YVMA") was synthesized at GeneRay, cloned into the retroviral construct pMSCV-puro (Biovector), and packaged into retroviral particles. The virus was used to infect Ba/F3 cells (RIKEN) at multiplicity of infection = 1 or 10 for 1 day. Infected cells were rescued in media (RPMI-1640 with 10% fetal bovine serum and 1% streptomycin and penicillin) supplemented with mouse IL-3 (10 ng/mL) for 2 days, and stable cell lines were selected by IL-3 withdrawal and puromycin (0.8 μg/mL) for 7 days. Monoclones were selected by single-cell dilution in IL-3-free medium containing puromycin (0.8 μg/mL). Transformation of desired genes was confirmed by Sanger sequencing and western blot using the following antibody: HER2 (CST #2242).

Besides Ba/F3s, two commercially available cell lines were also used. NCI-H1781 is a HER2 exon20 insertion cell line bearing HER2-A775_G776insV-G776C. A431 bears amplification of the wild-type EGFR gene.

Cellular Phosphorylation Assay

Ba/F3 cells were plated at 50,000 cells/well (40 μL), or NCI-H1781 cells or A431 cells were plated at 12,500 cells/well (40 μL), in a 384-well plate for 1 day. Test compounds (40 nL) were then added in a 3-fold dilution series using the TECAN EVO200 liquid handler and incubated for 5 hours. Only for pEGFR analysis in A431, the cells were briefly stimulated with EGF (30 ng/mL) for 15 minutes. Media were removed using Apricot Designs. Phosphoproteins were analyzed using the phospho-EGFR Tyr1068 AlphaLISA kit ("pEGFR"; PerkinElmer #ALSU-PEGFR-B10K;) phospho-ERK Thr202/Tyr204 AlphaLISA kit ("pERK"; PerkinElmer #ALSU-PERK-A10K) or the phospho-ErbB2 Tyr1221/1222 AlphaLISA kit ("pHER2"; PerkinElmer #ALSU-PEB2-A10K;) according to the manufacturer's instructions. Briefly, cells were lysed with lysis buffer (10 μL) containing protease-inhibitor and phosphatase-inhibitor cocktails. The lysates were transferred into a new optical plate, incubated with the acceptor mix (5 μL) for 1.5-2 hours at room temperature in darkness, and then mixed with the donor mix (5 μL) overnight in darkness. Fluorescence was measured on a plate reader using the appropriate AlphaLISA settings. Half-maximal inhibitory concentration (IC_{50}) was calculated from percent inhibition and inhibitor concentration using four-parameter logistic regression. Compound potency can be interpreted by binning IC_{50} values: bin A for high potency, $IC_{50} < 100$ nM; bin B for medium potency, 100 nM $\leq IC_{50} < 500$ nM; bin C for low potency, 500 nM $\leq IC_{50} < 1000$ nM; and bind D for very low potency, $IC_{50} \geq 1000$ nM. Exemplary data is given in **Table 11**.

HER2 is phosphorylated when activated. Therefore, phospho-HER2 indicates HER2 activity in the cells. Compounds that potently inhibit the phosphorylation of the on-target cells (Ba/F3s and NCI-H1781) are also expected to inhibit /HER2 signaling in human cancers that express HER2, providing support for the potential clinical efficacy of such compounds. Similarly, compounds that do not potently inhibit the phosphorylation of the off-target A431 cell, which bears wild-type EGFR amplification, are expected to poorly inhibit wild-type EGFR signaling in humans and hence avoid the clinical toxicity arising from wild-type EGFR inhibition.

Table 11: Cellular Phosphorylation Assay IC_{50} Summary

A < 100nM ≤ B < 500nM < C< ≤ 1000nM ≤ D

Compound #	A431 pERK	A431 pEGFR	NCI-H1781 pHER2
1	B	B	A
2	C	C	A
5	D	D	A
6	B	B	
7	B	B	
8	D	D	
9	C	B	A
10	B	A	
11		D	
12	C	C	A
13	D	B	A
14	D	D	A
15	D	D	
16	C	C	
17	D	D	
18	C	C	A
19		D	A
20	D	D	
21	D	D	A
22	C	D	
23		D	A
24		D	
25	D	D	
26	D	D	
27	D	D	
28	D	D	
29		D	
30		D	
31	D	D	
32	C		
33	D	D	
34		D	
35	D	D	
36	D	D	
37	D	C	
38		D	
39	D	D	
40	A	A	
41	A	A	
42		D	
43	B	B	
44		D	

Compound #	A431 pERK	A431 pEGFR	NCI-H1781 pHER2
45	D	D	
46		D	
47		D	
48		D	
49	D	D	A
50		D	A
51	D	D	A
52	D	D	A
53	D	D	A
54	B	C	A
55	B	D	A
56		C	A
57		B	
58	D	D	
59		D	A
60	D	C	A
61	D		
62	D	D	A
63	D	D	B
64	D	D	A
65	D	D	
66		B	
67	C	D	
68	B	C	
69	B	C	
70	B	B	
71	B	B	
72	B	A	
73	B	B	
74	A	B	
75	B	C	
76		D	
77		B	
78	D	D	
79		D	
80	C	D	
81	B	B	
82	B	A	
83	B	B	
84	B	C	
85	D	D	
86	B	B	
92		D	
93		D	
94	D	C	
95	D	D	

Compound #	A431 pERK	A431 pEGFR	NCI-H1781 pHER2
96	D	D	
97	C		
98		C	
99		A	
100	B	D	

Cell Proliferation Assay

Ba/F3 cells were plated at 1,000 cells/well (40 μL), or NCI-H1781 or A431 cells were plated at 2,000 cells/well (40 μL), in a 384-well plate for 1 day. Test compounds (40 nL) were then added in a 3-fold dilution series using the TECAN EVO200 liquid handler and incubated for 48 hours ("2days"), 72 hours ("3days"), or 48 hours followed by renewal of compound solutions and further incubation for 72 hours ("2days/3days"). The 72-hour assay was necessary for NCI-H1781 cells, which are slow-growing, and the resupply of fresh compounds on day 3 obviated the potential confounding effects arising from compound degradation in cell media over 72 hours. Plates were equilibrated at room temperature for 15 minutes followed by addition of 40 μL CellTiter-Glo reagent (Promega). Luminescence was measured on a plate reader. Half-maximal inhibitory concentration (IC_{50}) was calculated from percent inhibition and inhibitor concentration using four-parameter logistic regression. A431 and NCI-H1781 showed a biphasic growth inhibition behavior with two inflexion points: the first is associated with on-target inhibition, whereas the second is associated with off-target toxicity. In these cases, the regression curve was drawn only for the first inflexion to accurately measure on-target growth inhibitory effect. Compound potency can be interpreted by binning IC_{50} values: bin A for high potency, IC_{50} < 100 nM; bin B for medium potency, 100 nM ≤ IC_{50} < 500 nM; bin C for low potency, 500 nM ≤ IC_{50} < 1,000 nM; and bind D for very low potency, IC_{50} ≥ 1,000 nM. Exemplary data is given in **Table 12**.

Ba/F3, NCI-H1781, and A431 proliferation is driven by the oncogenes in the same way that cancer cell proliferation in humans is driven by the expression of equivalent oncogenes. Hence, compounds that potently inhibit the proliferation of the on-target cells (Ba/F3s and NCI-H1781) are also expected to inhibit human cancers that express equivalent oncogenes, providing support for the potential clinical efficacy of such compounds. Similarly, compounds that do not potently inhibit the off-target A431 cell, which bears wild-type EGFR amplification, are expected to poorly inhibit wild-type EGFR in humans and hence avoid the clinical toxicity arising from wild-type EGFR inhibition.

Table 12: Cell Proliferation Assay IC_{50} Summary

A < 100nM ≤ B < 500nM ≤ C < 1000nM ≤ D

Compound #	Ba/F3 HER2-YVMA	NCI-H1781
1	A	A
2	A	A
5	A	B
6	A	A
7	A	A
8	A	A
9	A	A
10	A	
11	A	B
12	A	A
13	A	A
14	B	
15	A	B
16	A	B
17	A	A
18	A	A
19	B	
20	A	A
21	B	B
22	A	A
23	C	
24	C	
25	B	
26	A	A
27	B	
28	B	
29	A	A
30	B	
31	D	D
32	A	A
33	B	
34	B	B
35	A	B
36	B	B
37	A	A
38	B	B
39	B	C
40	A	A
41	A	A
42	A	A
43	A	A
44	B	B
45	A	B
46	B	

Compound #	Ba/F3 HER2-YVMA	NCI-H1781
47	B	
48	B	
49	A	A
50		B
51	A	
52	A	A
53	A	A
54	A	A
55	A	
56	A	
57	A	
58	A	
59	C	
60	A	
61	B	
62	A	
63	C	
64	B	
65	B	
66	A	
67	A	
68	A	
69	A	
70	A	
71	B	
72	A	
73	A	
74	A	
75	A	
76	B	
77	A	
78	B	
79	C	
80	A	
81	A	
82	A	
83	A	
84	A	
85	A	
86	A	
92	A	
93	A	
94	A	
95	A	
96	B	
97	A	
98	A	

Compound #	Ba/F3 HER2-YVMA	NCI-H1781
99	A	
100	A	

Pharmacokinetics Assay

Rat pharmacokinetic studies: male Han Wistar rats are dosed with a test compound at 1 mg/kg by IV administration and/or 10 mg/kg by oral gavage in a suitable vehicle (for example, 20% HP-b-CD in DI water). Blood samples are collected from the jugular vein at multiple timepoints post dose. Approximately 0.2 mL of blood is collected at each time point and transferred into plastic micro centrifuge tubes containing EDTA-K2. The collection of tubes with blood samples and anti-coagulant are inverted several times for proper mixing and placed on wet ice prior to centrifugation. The blood samples are centrifuged at 4000 g for 5 min at 4 degrees Celsius to isolate the plasma. The plasma is stored at -75 degrees Celsius prior to analysis. Concentrations of a test compound in the plasma samples are analyzed using a LC-MS/MS method. WinNonlin (PhoenixTM, version 8.3) or other similar software is used for pharmacokinetic calculations. The exemplified pharmacokinetic parameters that can be calculated from the plasma concentration versus time data are as follows:

IV Bolus administration: T1/2, C0, AUClast, AUCinf, MRTlast, Cl, Vss, Number of Points for Regression.

PO administration: F, T1/2, Cmax, Tmax, MRTlast, AUCinf, AUClast, Number of Points for Regression.

Mouse pharmacokinetic studies: female Balb/C mice are dosed with a test compound at 1 mg/kg IV and/or 10 mg/kg orally in a suitable vehicle (for example 20% HP-b-CD in DI water). Blood samples are collected from the dorsal metatarsal vein or heart puncture at multiple timepoints post dose. Approximately 0.03 mL of blood sample was collected at each time point and transferred into plastic micro centrifuge tubes containing Heparin-Na. Collection tubes with blood samples and anti-coagulant are inverted several times for proper mixing and placed on wet ice prior to centrifugation. Blood samples are centrifuged at 4000 g for 5 min at 4 degrees Celsius to obtain plasma. Plasma is stored at -75 degrees Celsius prior to analysis. Concentrations of the compound in the plasma samples are analyzed using a LC-MS/MS method. WinNonlin (PhoenixTM, version 8.3) or other similar software was used for pharmacokinetic

calculations. The exemplified pharmacokinetic parameters that can be calculated from the plasma concentration versus time data are as follows:

IV Bolus administration: T1/2, C0, AUClast, AUCinf, MRTlast, Cl, Vss, Number of Points for Regression.

PO administration: F, T1/2, Cmax, Tmax, MRTlast, AUCinf, AUClast, Number of Points for Regression.

Bidirectional Permeability in NIH-MDCKII-MDR1 Cells

MDCKII-MDR1 cells from the National Institutes of Health (NIH) are seeded onto membranes in 96-well Transwell plates to form a confluent cell monolayer. Test and reference compounds are prepared in transport buffer (HBSS, HEPES, pH 7.4) at 1 μM and added to either the apical compartment (for A→B) or the basolateral compartment (for B→A). The plates are shaken and then incubated. Aliquots are taken from both the apical and basolateral sides and transferred to a new plate with quenching buffer. These plates are vortexed and centrifuged, and aliquots of the supernatant are mixed with water and analyzed by LC/MS/MS. All incubations are performed in duplicate. Monolayer integrity is confirmed with the marker Lucifer Yellow.

The apparent permeability coefficient (P_{app}), in units of centimeter per second, can be calculated for MDCK-MDR1 drug transport assays using the following equation:

$$\mathbf{P_{app} = (V_A \times [drug]_{acceptor}) / (Area \times Time \times [drug]_{initial,donor})}$$

Where V_A is the volume (in mL) in the acceptor well, Area is the surface area of the membrane (0.143 cm^2 for Transwell-96 Well Permeable Supports), and time is the total transport time in seconds.

Efflux ratio can be determined using the following equation:

$$Efflux\ Ratio = \frac{P_{app(B-A)}}{P_{app(A-B)}}$$

Where Papp (B-A) indicates the apparent permeability coefficient in basolateral to apical direction, and Papp (A-B) indicates the apparent permeability coefficient in apical to basolateral direction.

Mass balance (% recovery) can be determined using the following equation:

$$Recovery\% = \frac{[drug]_{acceptor} \times V_A + [drug]_{donor} \times V_D}{[drug]_{initial,donor} \times V_D} \times 100$$

Where VA is the volume (in mL) in the acceptor well (0.235 mL for Ap→Bl flux, and 0.075 mL for Bl→Ap), VD is the volume (in mL) in the donor well (0.075 mL for Ap→Bl flux, and 0.235 mL for Bl→Ap).

The leakage of Lucifer Yellow, in unit of percentage (%), can be calculated using the following equation:

$$\%LY\ leakage = 100\times[LY]_{acceptor}/([LY]_{donor}+[LY]_{acceptor})$$

Leakage of <1% is acceptable to indicate a well-qualified MDCK-MDR1 monolayer.

Kp and Kpuu Measurements in Rat and Mouse

The target dose (e.g., 10 mg/kg) of the test compound is prepared in a suitable formulation (e.g., 20% HP-b-CD in DI water) and administered PO to male Wistar Han rats or BALB/c mice. After a pre-specified amount of time (e.g., 1h) the animals are sacrificed, and brain and blood samples are collected. The concentrations of test compound in plasma, brain homogenate and CSF samples (for rat only) are analyzed using LC/MS/MS. Binding measurements in plasma and brain can be conducted using a Rapid Equilibrium Dialysis Device.

The unbound fraction in plasma and brain homogenate, unbound fraction in brain, and free concentration in plasma and brain of test article can be calculated as follows:

Fu mea (%) = Peak Area Ratio acceptor chamber / Peak Area Ratio donor chamber*100%

Fu plasma (%) = Fu mea (%)

Fu brain (%) = 1/D / ((1/Fu mea - 1) + 1/D)*100%

D is the dilute factor of the homogenate.

Alternatively, the unbound fraction in plasma and brain homogenate can be measured in separate in vitro experiments. For brain binding, brain tissue is obtained from exsanguinated rats or mice, weighed, and homogenized with buffer by brain weight (g) to water volume (mL) ratio 1:4. Brain homogenate and test compound is added to each vial of a new plastic plate or separate plastic tube and vortexed. An aliquot is removed and transferred to a 96-well plate to act as a control sample. The remaining sample is incubated in the CO2 incubator. After incubation, an aliquot of the spiked brain homogenate is transferred to the 96-well plate for analysis. Dialysis cells are loaded with brain homogenate sample and dialyzed against equal volume of dialysis buffer (PBS).

After dialysis, aliquots from both buffer and brain homogenate chambers are added to separate tubes for analysis. All test compounds are tested in duplicate in the brain homogenate assay.

For plasma protein binding, a similar procedure is followed, using plasma from either rat or mouse. Plasma and test compound are added to each vial of a new plastic plate or separate plastic tube and vortexed. An aliquot is removed and transferred to a 96-well plate to act as a control sample. The remaining sample is incubated in the CO2 incubator. After incubation, an aliquot of the spiked plasma is transferred to the 96-well plate for analysis. Dialysis cells are loaded with plasma sample and dialyzed against equal volume of dialysis buffer (PBS). After dialysis, aliquots from both buffer and plasma chambers are added to separate tubes for analysis. All test compounds are tested in duplicate in the plasma protein binding assay.

% Unbound = (Area ratio buffer chamber / Area ratio homogenate or plasma chamber) × 100%

% Bound = 100% - % Free

% Recovery = (Area ratio buffer chamber + Area ratio homogenate or plasma chamber) / (Area ratio Total sample) × 100

Remaining% = Area ratio 6hr / Area ratio 0hr × 100%

$$LogK = Log\left(\frac{\%\ Bound}{100 - \%\ Bound}\right)$$

% Unbound Brain=1/D/((1/(% Unbound/100)-1)+1/D) × 100

D means the dilution factor when preparing the brain homogenate.

Conc. Free-plasma = Conc. plasma * Fu plasma

Conc. Free-brain = Conc. Brain * Fu brain

Kp = Conc. Brain / Conc. Plasma

Kpuu = Conc.free Brain / Conc.free Plasma

Kinome Profiling

Test compounds are evaluated in a panel of 381 kinases using the PhosphoSens CSox-Sensor Platform (AssayQuant Technologies Inc). This assay platform uses physiological ATP concentrations (1 mM) and measures kinase activity using a fluorogenic substrates with an optimized kinase recognition motif. Briefly, the test compound is mixed with the kinase, the fluorogenic peptide substrate, and ATP in reaction buffer, and

fluorescence was recorded every 2 minutes for a total of 1.5-2 hours. When uninhibited, the kinase phosphorylates the substrate and induces fluorescence signal over time, the rate of which can be measured using the initial slope of fluorescence versus time (also called the initial velocity). Inhibition of kinase activity represses initial velocity. Inhibitory activity is calculated as the ratio between the initial velocity of the kinase in the presence and in the absence of the inhibitor, and is expressed as percent inhibition. Data are processed using GraphPad Prism or GeneData Mechanistic Action software.

PDX Study

Female athymic Nude-*Foxn1nu* mice are implanted subcutaneously in the left flank with tumor fragments from model CTG-2543 (Champions Oncology), a NSCLC tumor model harboring $HER2^{YVMA}$. In the efficacy study, mice are randomized to 5 mice per group based on tumor volume, and are administered with vehicle or test compounds. Tumor volume and body weight are measured twice per week. After the final dose , plasma samples are collected for PK analysis.

In a separate PK/PD study, CTG-2543 tumors are subcutaneously implanted in mice and allowed to grow before the mice are randomized based on tumor volume and administered with vehicle or test compounds by oral gavage. Tumor and blood samples are collected at multiple timepoints post the final dose for PK and PD analysis. Compound concentration in the plasma is determined by LC-MS/MS. Pharmacodynamic measurements include western blot, IHC assays, and transcript biomarker analysis.

N87-Luc Intracranial Efficacy Study

NCI-N87 cells stably expressing a luciferase reporter are stereotactically implanted into the right forebrains of 6- to 8-week-old female Balb/c nude mice. Two weeks after implantation, mice are randomized based on the mean bioluminescence signal into groups of n = 10 mice each and received treatment of either appropriate vehicle or different dose levels of test compounds orally. Bioluminescence and body weight are measured at regular intervals until study endpoint. At study endpoint, blood and brain samples will be collected for PK measurements.

Incorporation by Reference

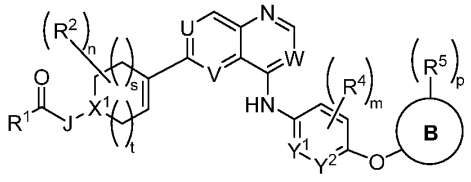
All U.S. and PCT patent publications and U.S. patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Equivalents

While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

CLAIMS

1. A compound of Formula (I-i):



(I-i)

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

wherein:

s is 0, 1, or 2;

t is 1 or 2;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, optionally substituted -O-C_{1-5} alkyl, optionally substituted -O-C_{1-5} alkylene-O-C_{1-5} alkyl, optionally substituted -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

s is 0, 1, or 2;

t is 1 or 2;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_{1-4} alkylene bridge;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

U is CR^c or N;

V is CR^d or N; provided that at least one of U and V is N;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 6-membered heterocyclic ring;

W is N or CR^e;

R^e is hydrogen, halo, or cyano;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

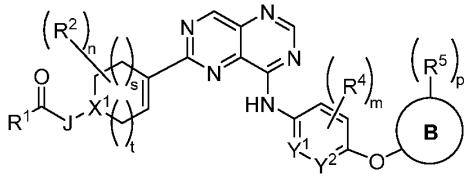
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

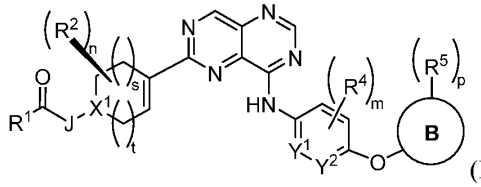
2. The compound of claim 1, wherein the compound is of Formula (I-i-a):



(I-i-a)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

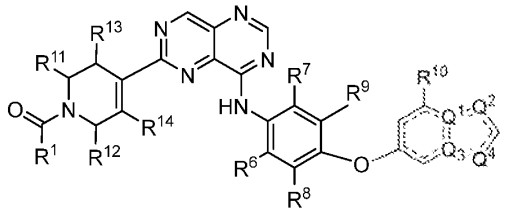
3. The compound of claim 2, wherein the compound is of Formula (I-i-a0):



(I-i-a0)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

4. The compound of claim 2, wherein the compound is of Formula (I-i-a1):



(I-i-a1)

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

wherein:

R^6, R^7, R^8, and R^9 are each independently hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

R^{10} is hydrogen, halo, or optionally substituted C_{1-5} alkyl;

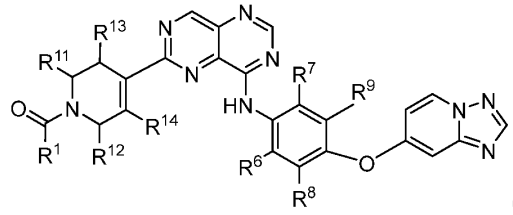
Q^1, Q^2, Q^3, and Q^4 are each independently NR^f or CR^g as valency permits, provided that at least one of Q^1, Q^2, Q^3, and Q^4 is CR^g;

R^f, independently for each occurrence, is hydrogen, optionally substituted C_{1-5} alkyl, or absent;

R^g, independently for each occurrence, is hydrogen, optionally substituted C_{1-5} alkyl, or absent; and

R^{11}, R^{12}, R^{13}, and R^{14} are each independently hydrogen or optionally substituted C_{1-5} alkyl, or two of R^{11}, R^{12}, R^{13}, and R^{14} taken together form a C_{1-4} alkylene bridge.

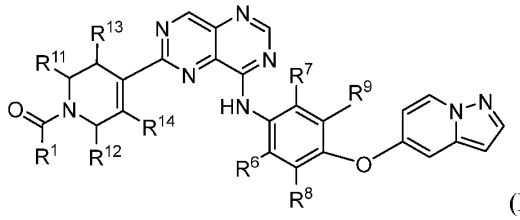
5. The compound of claim 3, wherein the compound is of Formula (I-i-a2):



(I-i-a2)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

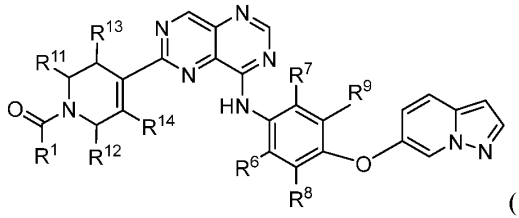
6. The compound of claim 3, wherein the compound is of Formula (I-i-a3):



(I-i-a3)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

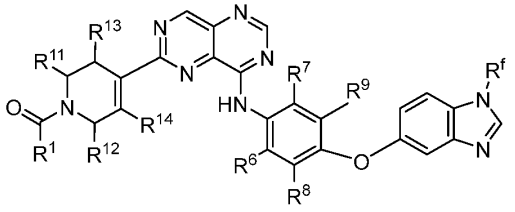
7. The compound of claim 3, wherein the compound is of Formula (I-i-a4):



(I-i-a4)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

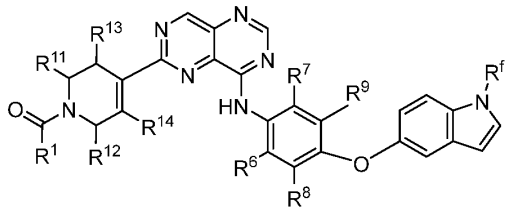
8. The compound of claim 3, wherein the compound is of Formula (I-i-a5):



(I-i-a5)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

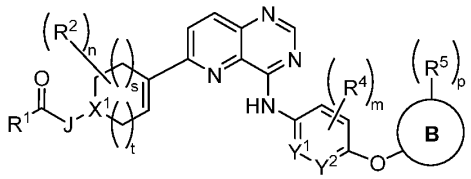
9. The compound of claim 3, wherein the compound is of Formula (I-i-a6):



(I-i-a6)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

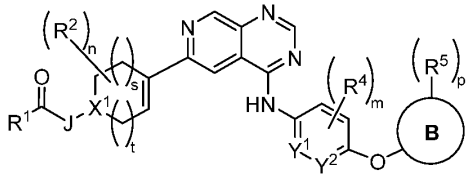
10. The compound of claim 1, wherein the compound is of Formula (I-i-b):



(I-i-b)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

11. The compound of claim 1, wherein the compound is of Formula (I-i-c):



(I-i-c)

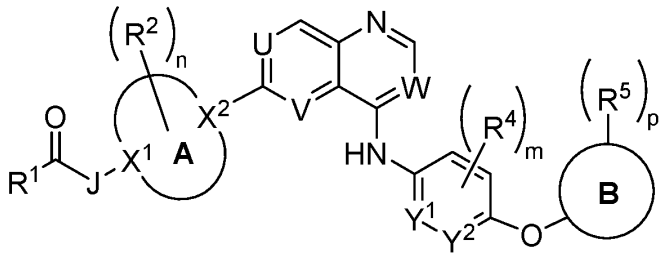
or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

12. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein s is 0 and t is 1 or 2.

13. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein s is 1 and t is 1.

14. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein s is 1 and t is 2.

15. A compound of Formula (I):



(I)

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

ring A is 6- to 10-membered bicyclic heterocyclyl or 3- to 5- or 7- to 8-membered monocyclic heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_{1-4} alkylene bridge; or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 8-membered heterocyclic ring;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

U is CR^c or N;

V is CR^d or N;

W is N or CR^e;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

R^e is hydrogen, halo (e.g., fluoro), or cyano;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

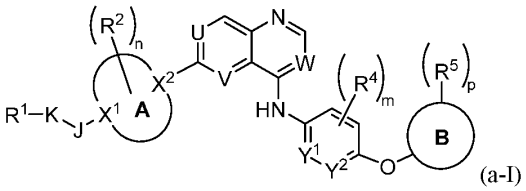
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

16. A compound of Formula (a-I):



(a-I)

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

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

K is a bond or SO_2;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge; or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 8-membered heterocyclic ring;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

U is CR^c or N;

V is CR^d or N;

W is N or CR^e;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

R^e is hydrogen, halo (e.g., fluoro), or cyano;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

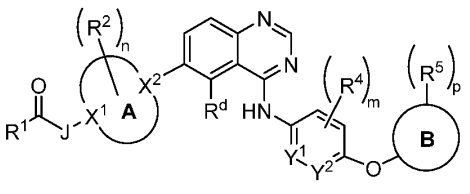
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

17. A compound of Formula (B):



(B)

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

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge; or R^d and an occurrence of R^2 taken together with the intervening atoms form a 5- to 8-membered heterocyclic ring;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

R^d is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

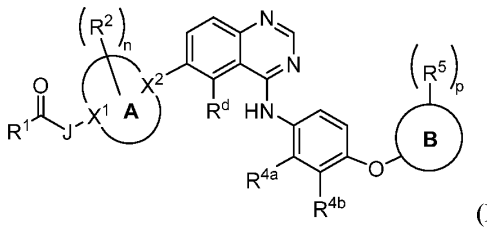
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

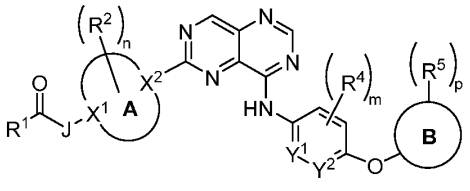
18. A compound of claim 16, wherein the compound is of Formula (B-i):



(B-i)

or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein each of R^{4a} and R^{4b} is independently halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy.

19. A compound of Formula (C):



(C)

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

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_{1-4} alkylene bridge;

n is 0 or an integer from 1 to 3, inclusive as permitted by valence, provided that when ring A is 6-membered monocyclic heterocyclyl with one or two N ring atoms, n is 2 or 3;

X^2 is –C=, –CH–, or N;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

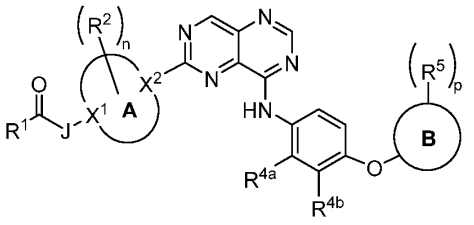
R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

20. A compound of Formula (D):



(D)

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

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted alkyl;

R^2, independently for each occurrence, is optionally substituted alkyl; or taken together two geminal occurrences of R^2 are an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

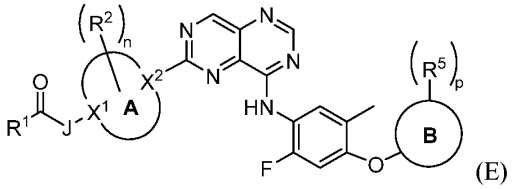
X^2 is –C=, –CH–, or N;

each of R^{4a} and R^{4b} is independently halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

R^5, independently for each occurrence, is halo, optionally substituted alkyl, or optionally substituted alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

21. A compound of Formula (E):



(E)

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

wherein:

ring A is 3- to 10-membered heterocyclyl;

ring B is 6- to 10-membered aryl or 5- to 10-membered heteroaryl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_{1-4} alkylene bridge;

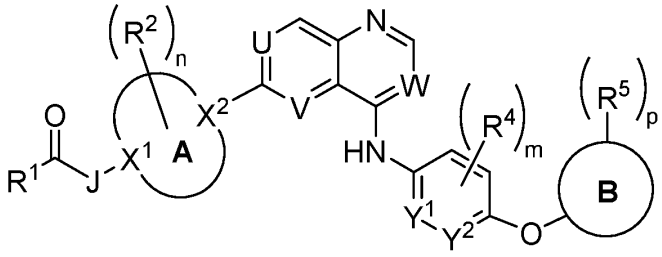
n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

22. A compound of Formula (I):



(I)

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

ring A is partially unsaturated 3- to 8-membered monocyclic heterocyclyl;

R^1 is CN, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or 3- to 6-membered heterocyclyl, wherein the alkenyl, alkynyl, or heterocyclyl is optionally substituted by one or more occurrences of R^a;

R^a, independently for each occurrence, is halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, -O-C_{1-5} alkyl, -O-C_{1-5} alkylene-O-C_{1-5} alkyl, -CO_2-C_{1-5} alkyl, or optionally substituted 3- to 6-membered heterocyclyl, or two R^a taken together form an optionally substituted alkenyl group;

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl;

J is NR^b and X^1 is CH; or J is a bond and X^1 is N;

R^b is hydrogen or optionally substituted C_{1-5} alkyl;

R^2, independently for each occurrence, is optionally substituted C_{1-5} alkyl; or taken together two geminal occurrences of R^2 form an oxo moiety; or two non-geminal occurrences of R^2 taken together form a C_1-C_4 (e.g., C_1-C_2) alkylene bridge;

n is 0 or an integer from 1 to 3, inclusive, as permitted by valence;

X^2 is –C=, –CH–, or N;

U is CR^c or N;

V is CR^d or N; provided that at least one of U and V is N;

R^c is hydrogen, halo, or optionally substituted C_{1-5} alkoxy;

R^d is hydrogen, halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy, or R^d and an occurrence of R^2 taken together with the intervening atoms form a 3- to 6-membered heterocyclic ring;

W is N or CR^e;

R^e is hydrogen, halo (e.g., fluoro), or cyano;

Y^1 and Y^2 are each independently CH, CR^4 or N, provided that at least one of Y^1 and Y^2 is CH or CR^4;

R^4, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy;

m is 0 or an integer from 1 to 4, inclusive, as permitted by valence;

R^5, independently for each occurrence, is halo, optionally substituted C_{1-5} alkyl, or optionally substituted C_{1-5} alkoxy; and

p is 0 or an integer from 1 to 3, inclusive, as permitted by valence.

23. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein ring A is a 4- to 7-membered monocyclic heterocyclyl comprising at least one nitrogen atom.

24. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein ring A is a 6- to 10-membered spiro bicyclic heterocyclyl or fused bicyclic heterocyclyl.

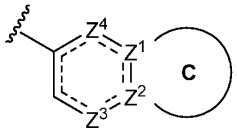
25. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein ring A comprises one and only one double bond.

26. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein ring A is azetidinyl, spirocyclic bis-azetidinyl, pyrrolidinyl, pyrrolinyl, piperidinyl, piperazinyl, tetrahydropyridinyl, azepanyl, or tetrahydroazepinyl.

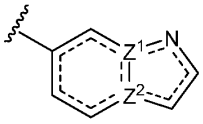
27. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein ring B is 5-membered to 10-membered heteroaryl.

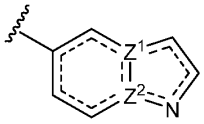
28. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein ring B is a 9-membered bicyclic heteroaryl.

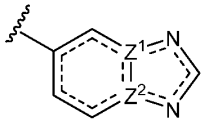
29. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein ring B is



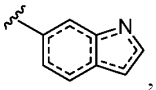
, C (including Z^1 and Z^2) is 5- or 6-membered heteroaryl; Z^1, Z^2, Z^3, and Z^4 are each independently C or N as permitted by valence; and any atom of ring B may be substituted by R^5 as permitted by valence.

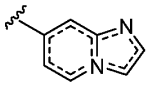
30. The compound of claim 28, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein ring B is 

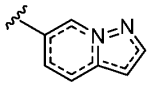
, 

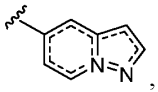
, or 

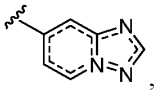
, and any atom of ring B may be substituted by R^5 as permitted by valence.

31. The compound of claim 28, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein ring B is 

, 

, 

, 

, or 

, and any atom of ring B may be substituted by R^5 as permitted by valence.

32. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^1 is $C_{1\text{-}5}$ alkyl optionally substituted by one or more occurrences of R^a.

33. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^1 is $C_{2\text{-}5}$ alkenyl optionally substituted by one or more occurrences of R^a.

34. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^1 is C_{2-5} alkynyl optionally substituted by one or more occurrences of R^a.

35. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^1 is ethenyl, ethynyl, methyl, ethyl, or oxiranyl.

36. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^1 is substituted by at least one R^a that is CN, F, Cl, $-CH_3$, $-CH_2OCH_3$, $-CH_2O(CH_2)_2OCH_3$, $-CO_2CH_3$, $-N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-(CH_2)_2N(CH_3)_2$, morpholinomethyl, or pyrrolidinyl.

37. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^1 is unsubstituted.

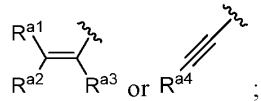
38. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein J is NR^b; and X^1 is CH.

39. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein J is a bond and X^1 is N.

40. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein K is SO_2.

41. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein J is a bond; K is a bond; and R1 is CN.

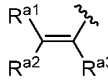
42. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein

R^1 is  ;

R^{a1}, R^{a2}, R^{a3}, and R^{a4} are each independently hydrogen, halo, CN, $N(R^{n1})_2$, optionally substituted C_{1-5} alkyl, optionally substituted $-CH_2O-C_{1-5}$ alkyl, optionally substituted $-CH_2O-(CH_2)_{1-2}-O-C_{1-5}$ alkyl, optionally substituted $-CO_2-C_{1-5}$ alkyl, or optionally substituted 3- to 6-membered heterocyclyl; and

each instance of R^{n1} is independently hydrogen or C_{1-5} alkyl.

43. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^2, independently for each occurrence, is $-CH_3$ or CH_2F, or taken together two geminal occurrences of R^2 form an oxo moiety, or two non-geminal occurrences of R^2 taken together form a methylene or ethylene bridge, or R^d and an occurrence of R^2 taken together with the intervening atoms form a heterocyclic ring.

44. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^1 is  or  ; and R^{a1}, R^{a2}, R^{a3}, and R^{a4} are hydrogen.

45. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein X^2 is –C=.

46. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein X^2 is N.

47. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein X^2 is –CH–.

48. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein U is CR^c.

49. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^c is hydrogen or fluoro.

50. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein U is N.

51. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein V is CR^d.

52. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^d is hydrogen, fluoro, methyl, or methoxy.

53. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein V is N.

54. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein W is N.

55. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein W is CR^e.

56. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein W is CH or CF.

57. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein Y^1 and Y^2 are CR^4.

58. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein Y^1 is CR^4; and Y^2 is N.

59. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^4, independently for each occurrence, is fluoro, chloro, methyl, methoxy, or difluoromethyl.

60. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein n is 0.

61. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein n is an integer from 1 to 2.

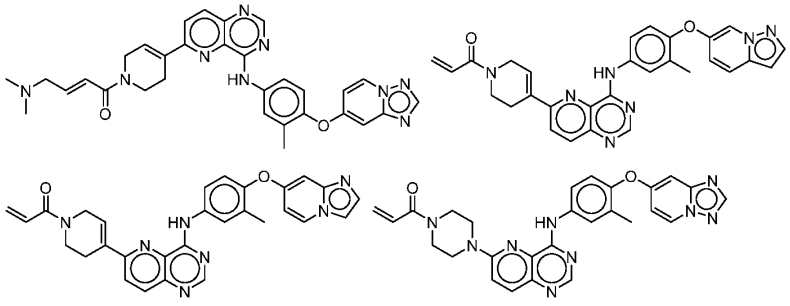
62. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein m is 0, 1, or 2.

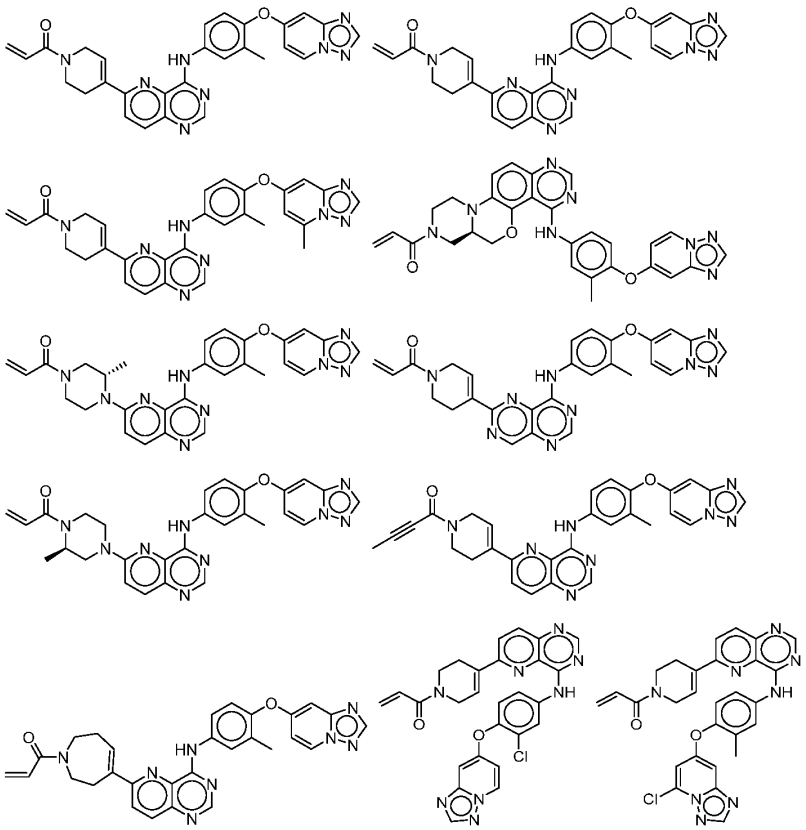
63. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein m is 2.

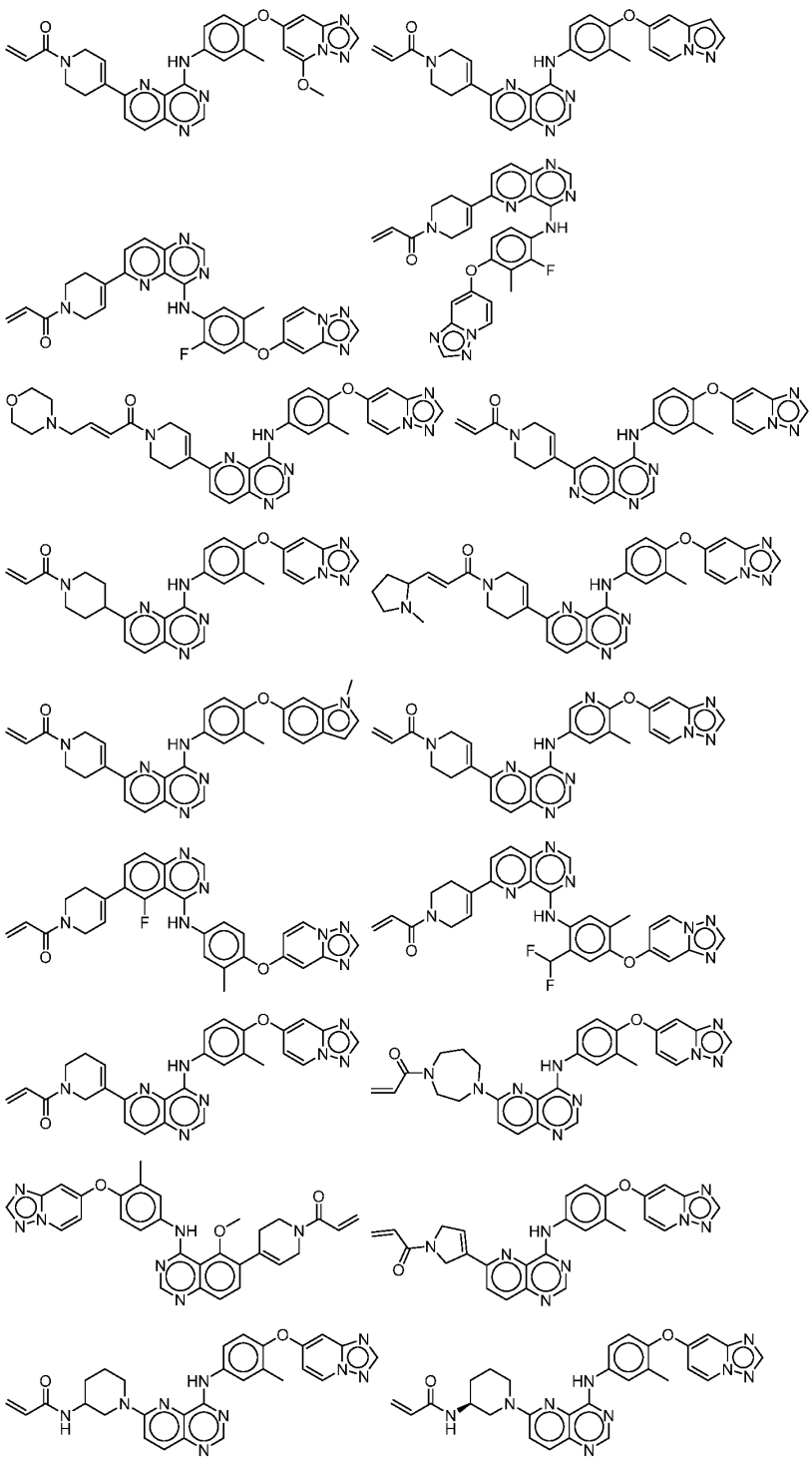
64. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein R^5, independently for each occurrence, is fluoro, chloro, methyl, ethyl, or methoxy.

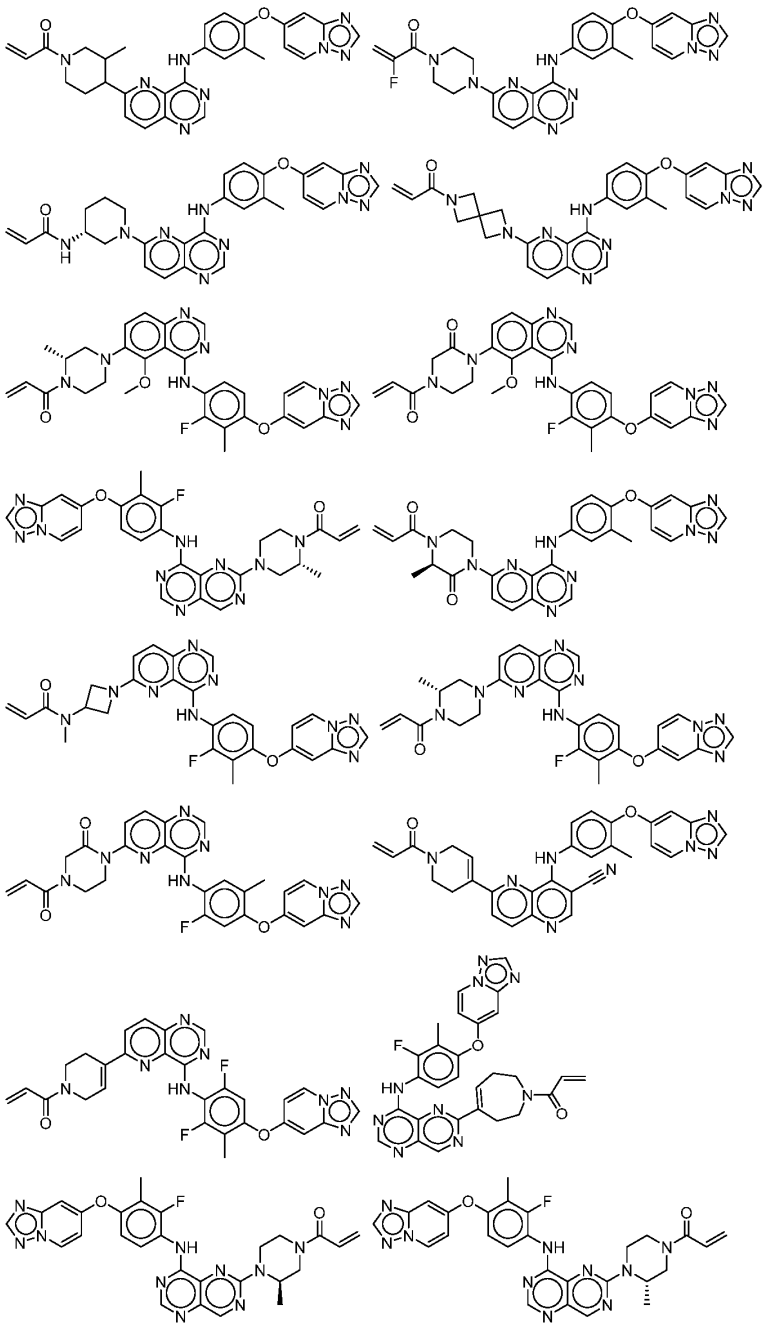
65. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, wherein p is 0.

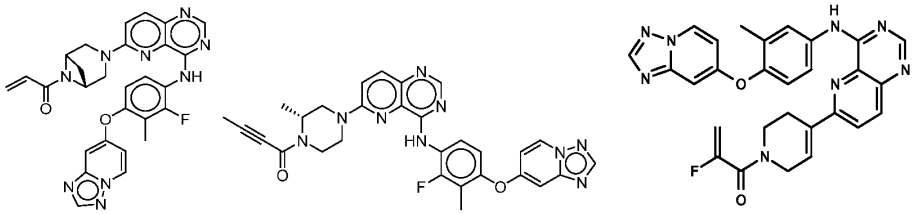
66. A compound selected from the group consisting of:

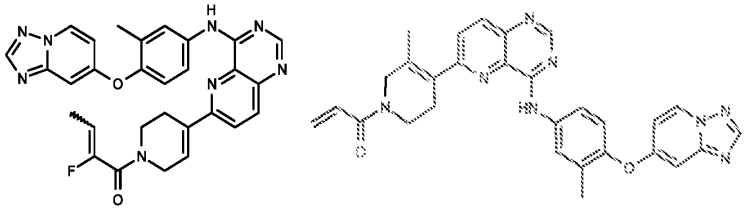


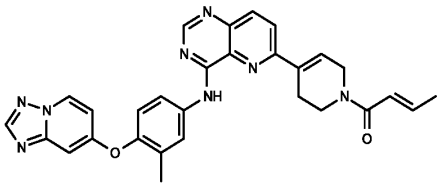


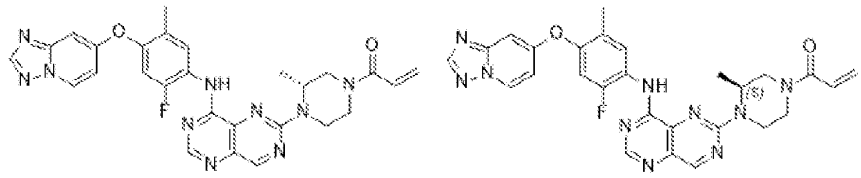


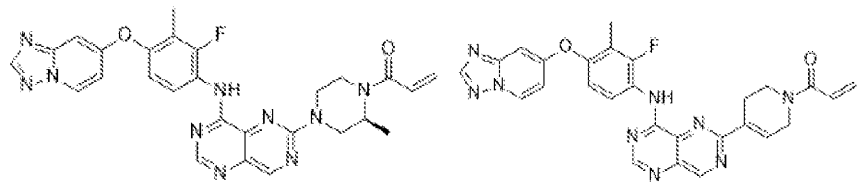


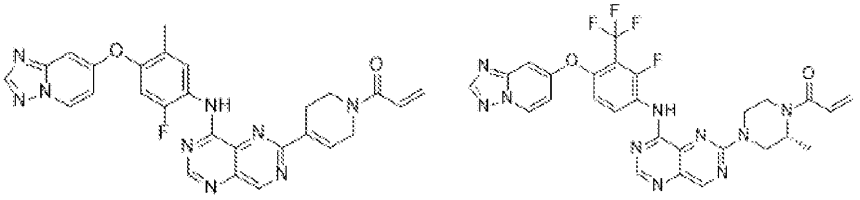


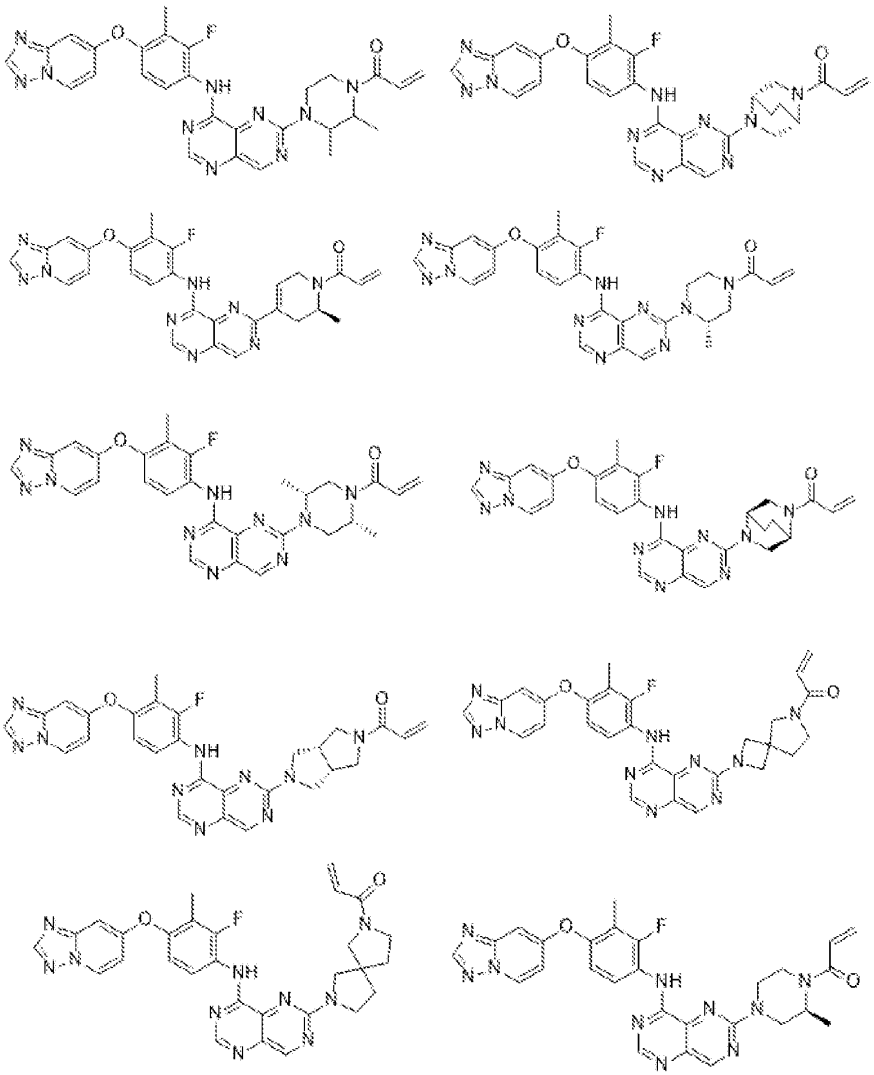


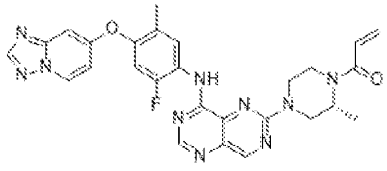
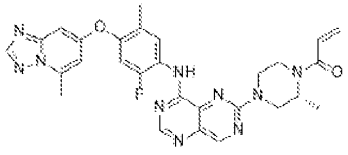
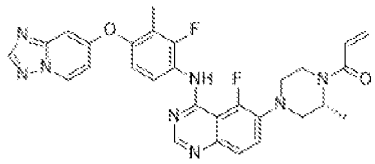
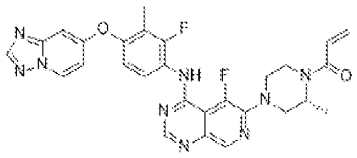
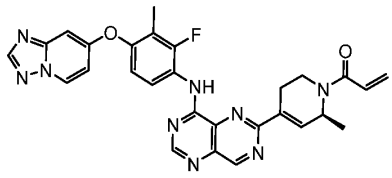








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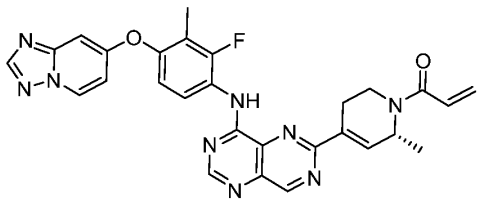
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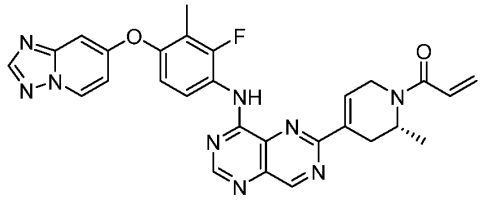
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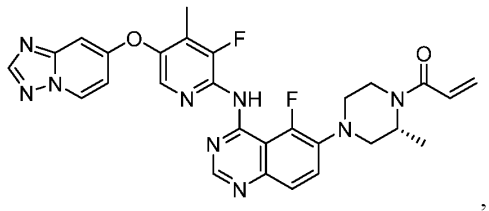
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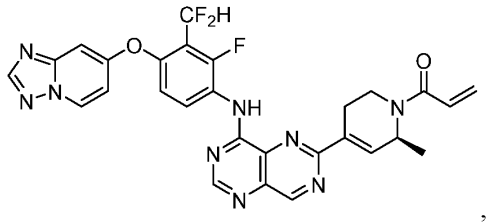
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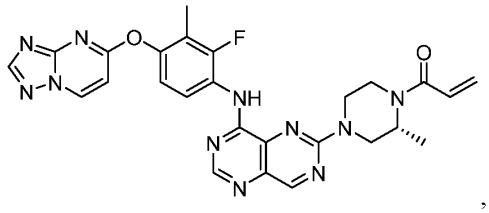
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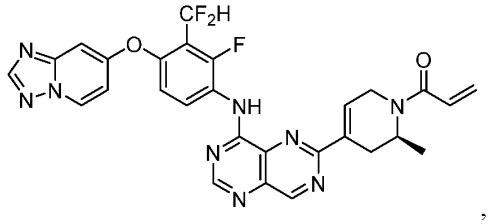
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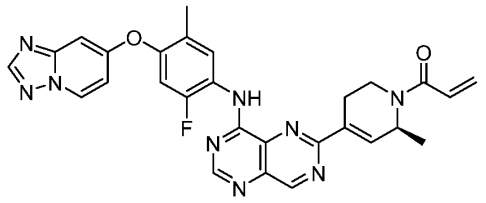
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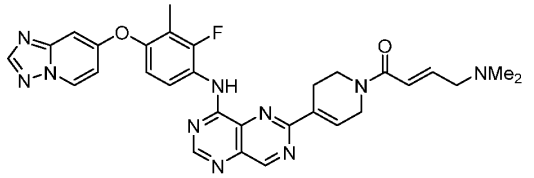
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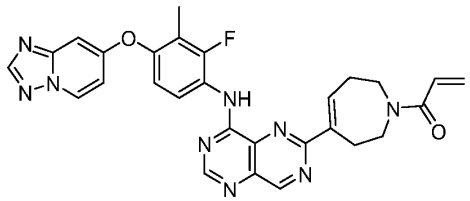
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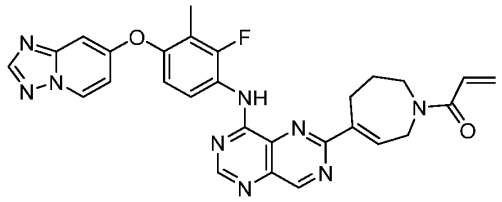
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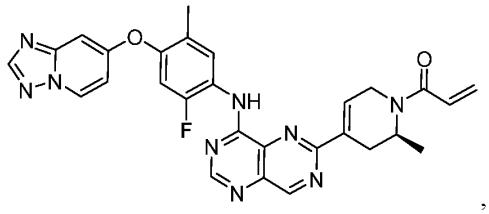
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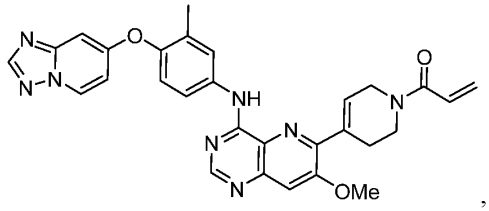
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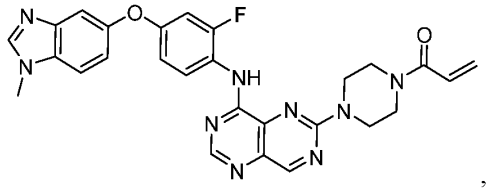
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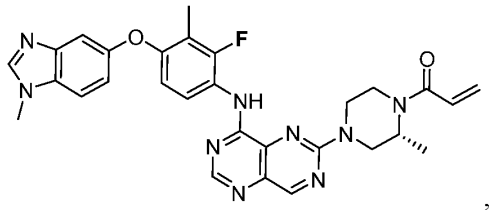
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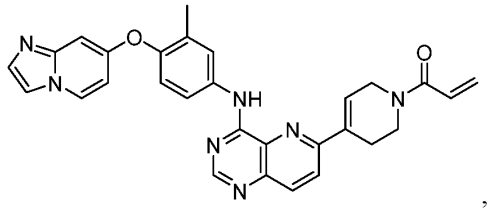
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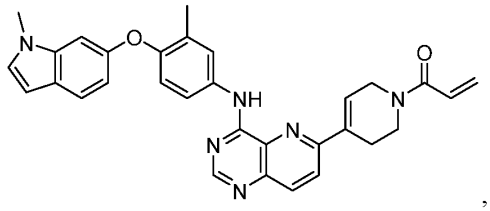
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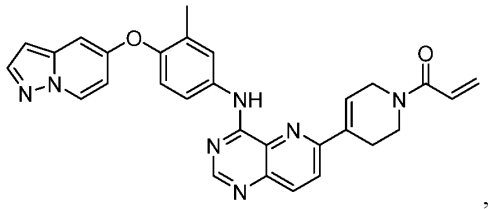
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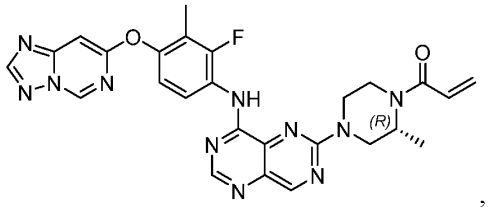
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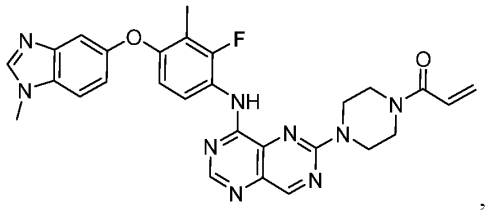
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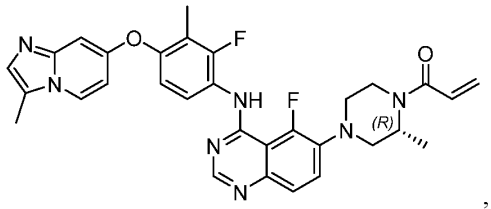
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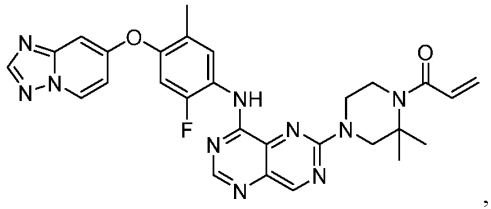
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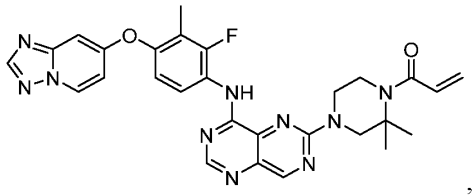
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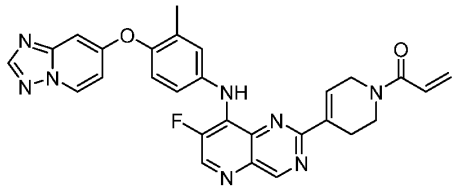
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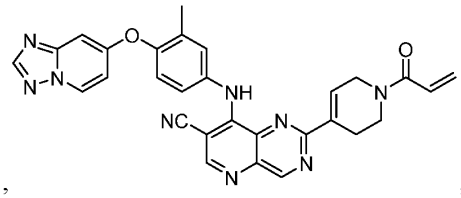
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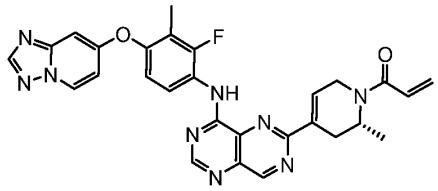
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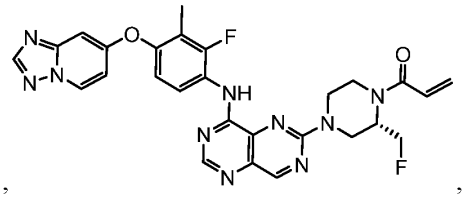
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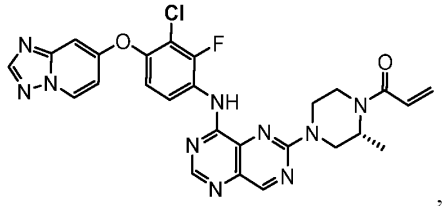
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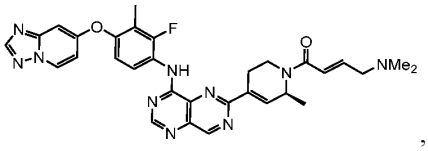
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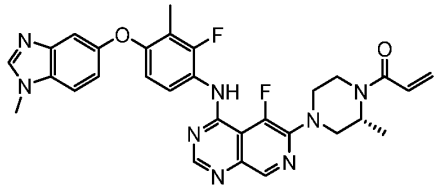
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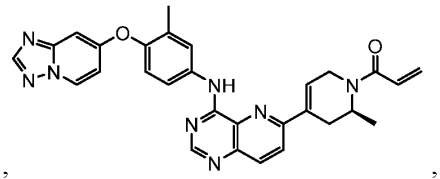
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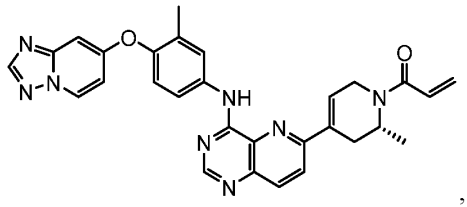
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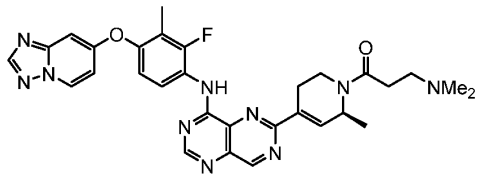
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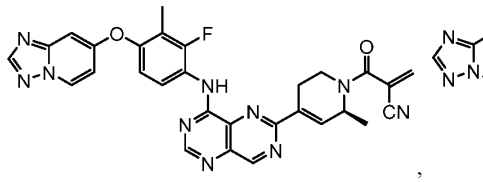
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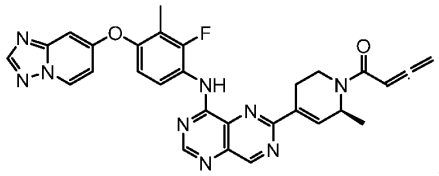
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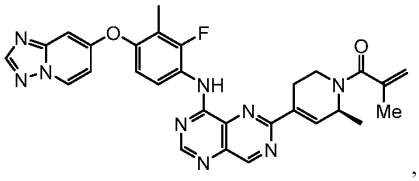
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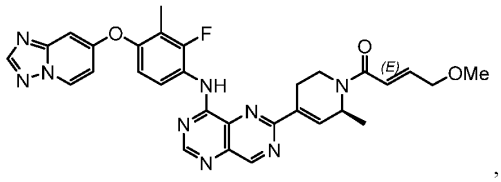
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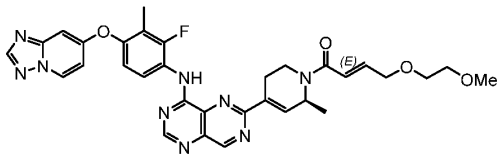
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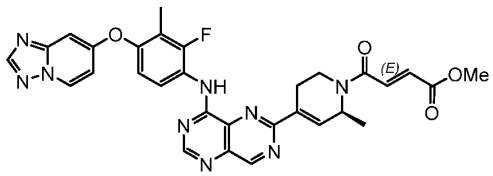
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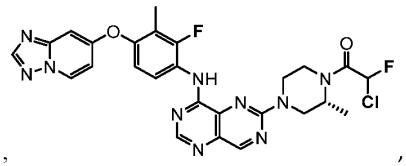
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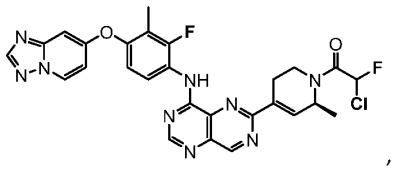
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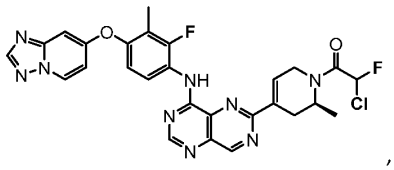
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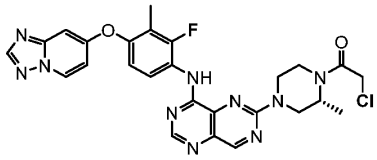
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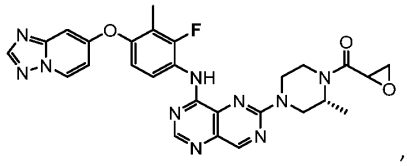
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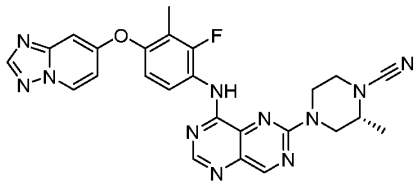
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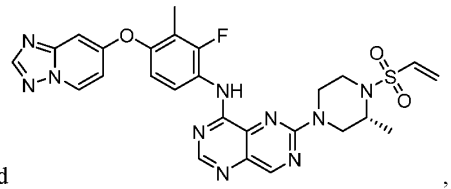
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or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof.

67. A pharmaceutical composition, comprising a compound of any one of claims 1-66, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof; and a pharmaceutically acceptable excipient.

68. A method of treating cancer, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of any one of claims 1-66, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, or the pharmaceutical composition of claim 67.

69. A method of treating human epidermal growth factor receptor 2 (HER2)-associated cancer, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of any one of claims 1-66, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, or the pharmaceutical composition of claim 67.

70. The method of claim 68 or claim 69 wherein the caner is associated with HER2 overexpression, and/or HER2 amplification, and/or HER2 mutation(s).

71. The method of claim 70, wherein the cancer is associated with HER2 exon 20 mutation(s).

72. The method of any one of claims 68-71, wherein the cancer is non-small cell lung cancer or squamous head and neck cancer.

73. The method of claim 72, wherein the cancer is non-small cell lung cancer.

74. The method of claim 73, wherein the non-small cell lung cancer has one or more ErbB mutations.

75. The method of claim 73, wherein the non-small cell lung cancer has one or more EGFR exon 20 insertion mutations.

76. The method of claim 73, wherein the non-small cell lung cancer has one or more HER2 exon 20 insertion mutations.

77. A method for selectively inhibiting wild type HER2 over wild type EGFR and/or EGFR mutant in a mammal (e.g., human subject) having cancer, comprising administering an effective amount of the compound of any one of claims 1-66, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, or the pharmaceutical composition of claim 67.

78. A method for selectively inhibiting HER2 mutant(s) over wild type EGFR and/or EGFR mutant in a mammal (e.g., human subject) having cancer, comprising administering an effective amount of the compound of any one of claims 1-66, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, or the pharmaceutical composition of claim 67.

79. The method of claim 77 or claim 78, wherein the HER2 mutant has exon 20 mutation.

80. The method of claim 79, wherein the HER2 exon 20 mutation is one or more selected from YVMA insertion, VC insertion, and GSP insertion.

81. The method of claim 80, wherein the HER2 exon 20 insertion mutation is one or more selected from A775_G776insYVMA, P780_Y781insGSP, G776 > VC, G776 > IC, G776 > LC, G778_S779insCPG, and G780_P781dupGSP.

82. The method of claim 77 or claim 78, wherein the HER2 mutant has non-exon 20 mutation.

83. The method of claim 82, wherein the non-exon 20 mutation is one or more selected from L755S, S310F, R678Q, V842I, and V777X.

84. The method of any one of claims 68-83 wherein the mammal is a human subject identified or diagnosed as having a HER2-associated cancer.

85. The method of any one of claims 68-84, further comprising administering a second therapeutic agent.

86. The method of claim 85, wherein the second therapeutic agent is an immunomodulator or a platinum analogue.

87. A method of regulating a level of HER2 in a cell, comprising contacting the cell with the compound of any one of claims 1-66, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, or the pharmaceutical composition of claim 67.

88. A method of increasing a level of HER2 in a cell, comprising contacting the cell with the compound of any one of claims 1-66, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, or the pharmaceutical composition of claim 67.

89. A method of decreasing phosphorylation of HER2 in a cell, comprising contacting the cell with the compound of any one of claims 1-66, or a pharmaceutically acceptable salt, a stereoisomer, or a tautomer thereof, or the pharmaceutical composition of claim 67.

90. The method of any one of claims 87 to 89, wherein the cell is in a mammal.

91. The method of any one of claims 87 to 89, wherein the cell is in a human subject.