(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
01 April 2021 (01.04.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/062245 A1

(51) International Patent Classification:
C07D 401/12 (2006.01) *A61P 35/00* (2006.01)
C07D 471/04 (2006.01) *A61K 31/4375* (2006.01)

(21) International Application Number:
PCT/US2020/052850

(22) International Filing Date:
25 September 2020 (25.09.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/906,647 26 September 2019 (26.09.2019) US
63/053,530 17 July 2020 (17.07.2020) US

(71) Applicant: **EXELIXIS, INC.** [US/US]; 1851 Harbor Bay Parkway, Alameda, California 94502 (US).

(72) Inventors: **BANNEN, Lynne**; c/o Exelixis, Inc., 1851 Harbor Bay Parkway, Alameda, California 94502 (US). **BUI, Minna**; c/o Exelixis, Inc., 1851 Harbor Bay Parkway, Alameda, California 94502 (US). **JIANG, Faming**; c/o Exelixis, Inc., 1851 Harbor Bay Parkway, Alameda, California 94502 (US). **MAUNG, Jack**; c/o Exelixis, Inc., 1851 Harbor Bay Parkway, Alameda, California 94502 (US). **RAUB, Andrew**; c/o Exelixis, Inc., 1851 Harbor Bay Parkway, Alameda, California 94502 (US). **SALVANT, Justin**; c/o Exelixis, Inc., 1851 Harbor Bay Parkway, Alameda, California 94502 (US). **SPANGLER, Benjamin**; c/o Exelixis, Inc., 1851 Harbor Bay Parkway, Alameda, California 94502 (US). **TSO, Kin**; c/o Exelixis, Inc., 1851 Harbor Bay Parkway, Alameda, California 94502 (US). **WANG, Yong**; c/o Exelixis, Inc., 1851 Harbor Bay Parkway, Alameda, Califonia 94502 (US). **XU, Wei**; c/o Exelixis, Inc., 1851 Harbor Bay Parkway, Alameda, California 94502 (US).

(74) Agent: **TANNER, Lorna L.** et al.; Sheppard Mullin Richter & Hampton LLP, 650 Town Center Drive, 10th Floor, Costa Mesa, California 92626-1993 (US).

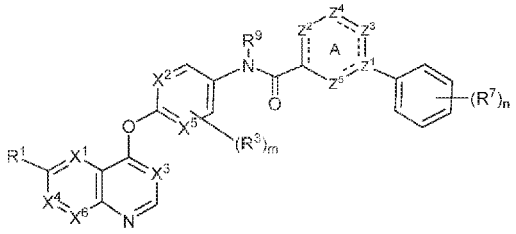
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*

(54) Title: PYRIDONE COMPOUNDS AND METHODS OF USE IN THE MODULATION OF A PROTEIN KINASE



(I''')

(57) Abstract: The present disclosure relates generally to compounds and pharmaceutical compositions suitable as modulators of protein kinases, and methods for their use in treating disorders mediated, at least in part by, protein kinases.

WO 2021/062245 A1

PYRIDONE COMPOUNDS AND METHODS OF USE IN THE MODULATION OF A PROTEIN KINASE

[0001] This application claims the benefit under 35 U.S.C. §119(e) of United States Provisional Application No. 62/906,647, filed September 26, 2019, and United States Provisional Application No. 63/053,530, filed July 17, 2020, each of which is hereby incorporated by reference in its entirety.

FIELD

[0002] Provided herein are compounds and pharmaceutical compositions suitable as modulators of protein kinases, and methods for their use in treating disorders mediated, at least in part by, protein kinases.

BACKGROUND

[0003] Human Axl belongs to the TAM subfamily of receptor tyrosine kinases that includes Mer. TAM kinases are characterized by an extracellular ligand binding domain consisting of two immunoglobulin-like domains and two fibronectin type III domains. Axl is overexpressed in a number of tumor cell types and was initially cloned from patients with chronic myelogenous leukemia. When overexpressed, Axl exhibits transforming potential. Axl signaling is believed to cause tumor growth through activation of proliferative and anti-apoptotic signaling pathways. Axl has been associated with cancers including, but not limiting to lung cancer, myeloid leukemia, uterine cancer, ovarian cancer, gliomas, melanoma, thyroid cancer, renal cell carcinoma, osteosarcoma, gastric cancer, prostate cancer, and breast cancer. The over-expression of Axl results in a poor prognosis for patients with the indicated cancers.

[0004] Activation of Mer, like Axl, conveys downstream signaling pathways that cause tumor growth and activation. Mer binds ligands such as the soluble protein Gas-6. Gas-6 binding to Mer induces autophosphorylation of Mer on its intracellular domain, resulting in downstream signal activation. Over-expression of Mer in cancer cells leads to increased metastasis, most likely by generation of soluble Mer extracellular domain protein as a decoy receptor. Tumor cells secrete a soluble form of the extracellular Mer receptor which reduces the ability of soluble Gas-6 ligand to activate Mer on endothelial cells, leading to cancer progression.

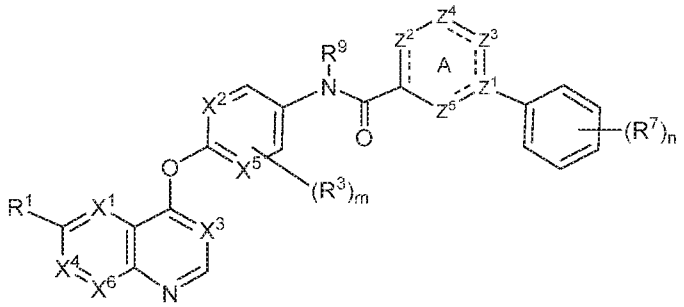
[0005] c-Met, is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. Expression of c-Met occurs in a wide variety of cell types including epithelial, endothelial and mesenchymal cells where activation of the receptor induces cell migration, invasion, proliferation and other biological activities associated with invasive cell growth. Signal transduction through c-Met receptor activation is responsible for many of the characteristics of tumor cells.

[0006] KDR is a tyrosine kinase receptor that binds vascular endothelial growth factor (VEGF). The binding of VEGF to the KDR receptor leads to angiogenesis. High levels of VEGF are found in various cancers causing tumor angiogenesis and permitting the rapid growth of cancerous cells.

[0007] Therefore, a need exists for new compounds that modulate Axl, Mer, c-Met, and/or KDR kinases for the treatment of cancers.

SUMMARY

[0008] Provided herein are compounds that inhibit c-Met, Axl, Mer and/or KDR. In certain embodiments, the compounds are of formula (I'''):



(I''')

or a pharmaceutically acceptable salt, a stereoisomer, tautomer or a mixture of stereoisomers thereof.

[0009] Some embodiments provide for a compound, or a pharmaceutically acceptable salt, stereoisomer, or a mixture of stereoisomers thereof, selected from Table 1, Table 2, or Table 3.

[0010] Also provided herein are pharmaceutical compositions comprising a compound as described herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or mixture of stereoisomers thereof, and a pharmaceutically acceptable carrier or excipient.

[0011] Some embodiments provide for methods of modulating in vivo activity of a protein kinase in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or mixture of stereoisomers thereof, or a pharmaceutical composition as described herein.

[0012] Some embodiments provide for methods of treating a disease, disorder, or syndrome in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or mixture of stereoisomers thereof, or a pharmaceutical composition as described herein, wherein the disease, disorder, or syndrome is mediated at least in part by modulating in vivo activity of a protein kinase.

[0013] Some embodiments provide for methods of treating a disease, disorder, or syndrome in a subject, the method comprising: administering to the subject in need thereof a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or mixture of stereoisomers thereof, or a pharmaceutical composition as described herein, in combination with a therapeutic agent or therapy.

[0014] The disclosure also provides compositions, including pharmaceutical compositions, kits that include the compounds, and method of using (or administering) and making the compounds. The disclosure further provides compounds or compositions for use in a method of treating a disease, disorder, or condition that is mediated, at least in part, by c-Met, Axl, Mer and/or KDR activity. Moreover, the disclosure provides uses of the compounds or compositions thereof in the manufacture of a

medicament for the treatment of a disease, disorder, or condition that is mediated, at least in part, by c-Met, Axl, Mer and/or KDR.

DETAILED DESCRIPTION

Definitions

[0015] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0016] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-C(O)NH_2$ is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line or a dashed line drawn through or perpendicular across the end of a line in a structure indicates a specified point of attachment of a group. Unless chemically or structurally required, no directionality or stereochemistry is indicated or implied by the order in which a chemical group is written or named.

[0017] The prefix "C_{u-v}" indicates that the following group has from u to v carbon atoms. For example, "C_{1-6} alkyl" indicates that the alkyl group has from 1 to 6 carbon atoms.

[0018] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. In certain embodiments, the term "about" includes the indicated amount ± 10%. In other embodiments, the term "about" includes the indicated amount ± 5%. In certain other embodiments, the term "about" includes the indicated amount ± 1%. Also, to the term "about X" includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0019] "Alkyl" refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (i.e., C_{1-20} alkyl), 1 to 12 carbon atoms (i.e., C_{1-12} alkyl), 1 to 8 carbon atoms (i.e., C_{1-8} alkyl), 1 to 6 carbon atoms (i.e., C_{1-6} alkyl) or 1 to 4 carbon atoms (i.e., C_{1-4} alkyl). Examples of alkyl groups include, e.g., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, "butyl" includes n-butyl (i.e., $-(CH_2)_3CH_3$), sec-butyl (i.e., $-CH(CH_3)CH_2CH_3$), isobutyl (i.e., $-CH_2CH(CH_3)_2$) and tert-butyl (i.e., $-C(CH_3)_3$); and "propyl" includes n-propyl (i.e., $-(CH_2)_2CH_3$) and isopropyl (i.e., $-CH(CH_3)_2$).

[0020] Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent "alkyl" group, a divalent "aryl" group, etc., may also be referred to as an "alkylene" group or an "alkylenyl" group, an "arylene" group or an "arylenyl" group, respectively. Also,

unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, e.g., arylalkyl or aralkyl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

[0021] "Alkenyl" refers to an alkyl group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkenyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkenyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkenyl) or 2 to 4 carbon atoms (i.e., C_{2-4} alkenyl). Examples of alkenyl groups include, e.g., ethenyl, propenyl, butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

[0022] "Alkynyl" refers to an alkyl group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkynyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkynyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkynyl) or 2 to 4 carbon atoms (i.e., C_{2-4} alkynyl). The term "alkynyl" also includes those groups having one triple bond and one double bond.

[0023] "Alkoxy" refers to the group "alkyl-O-". Examples of alkoxy groups include, e.g., methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy and 1,2-dimethylbutoxy.

[0024] "Alkylthio" refers to the group "alkyl-S-". "Alkylsulfinyl" refers to the group "alkyl-S(O)-". "Alkylsulfonyl" refers to the group "alkyl-$S(O)_2$-". "Alkylsulfonylalkyl" refers to -alkyl-$S(O)_2$-alkyl.

[0025] "Acyl" refers to a group $-C(O)R^y$, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include, e.g., formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethyl-carbonyl and benzoyl.

[0026] "Amido" refers to both a "C-amido" group which refers to the group $-C(O)NR^yR^z$ and an "N-amido" group which refers to the group $-NR^yC(O)R^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein, or R^y and R^z are taken together to form a cycloalkyl or heterocycloalkyl; each of which may be optionally substituted, as defined herein.

[0027] "Amino" refers to the group $-NR^yR^z$ wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[0028] "Amidino" refers to $-C(NR^y)(NR^z{}_2)$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[0029] "Aryl" refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (i.e., C_{6-20} aryl), 6 to 12 carbon ring atoms (i.e., C_{6-12} aryl), or 6 to 10 carbon ring atoms (i.e., C_{6-10} aryl). Examples of aryl groups include, e.g., phenyl, naphthyl, fluorenyl and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl

groups are fused with a heteroaryl, the resulting ring system is heteroaryl. If one or more aryl groups are fused with a heterocycloalkyl, the resulting ring system is heterocycloalkyl.

[0030] "Arylalkyl" or "Aralkyl" refers to the group "aryl-alkyl-".

[0031] "Carbamoyl" refers to $-C(O)NR^yR^z$. "O-carbamoyl" refers to $-O-C(O)NR^yR^z$ and "N-carbamoyl" refers to $-NR^yC(O)OR^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[0032] "Carboxyl ester" or "ester" refer to both $-OC(O)R^x$ and $-C(O)OR^x$, wherein R^x is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[0033] "Cycloalkyl" refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond) and carbocyclic fused ring systems having at least one sp^3 carbon atom (i.e., at least one non-aromatic ring). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl). Monocyclic groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Polycyclic groups include, for example, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl and the like. In some embodiments, one or more ring carbons of "cycloalkyl" can be optionally replaced by a carbonyl group. Examples of such cycloalkyl include cyclohexanone-4-yl, and the like. Further, the term cycloalkyl is intended to encompass moieties that have one or more aromatic ring fused (i.e., having a bond in common with) to the cycloalkyl ring, e.g., benzo or thienyl derivatives of cyclopentane, cyclohexane, and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Still further, cycloalkyl also includes "spirocycloalkyl" when there are two positions for substitution on the same carbon atom, for example spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl.

[0034] "Cycloalkylalkyl" refers to the group "cycloalkyl-alkyl-".

[0035] "Guanidino" refers to $-NR^yC(=NR^z)(NR^yR^z)$, wherein each R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[0036] "Hydrazino" refers to $-NHNH_2$.

[0037] "Imino" refers to a group $-C(NR^y)R^z$, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[0038] "Imido" refers to a group $-C(O)NR^yC(O)R^z$, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[0039] "Halogen" or "halo" refers to atoms occupying group VIIA of the periodic table, such as fluoro, chloro, bromo or iodo.

[0040] "Haloalkyl" refers to an unbranched or branched alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two ("di") or three ("tri") halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl and the like.

[0041] "Haloalkoxy" refers to an alkoxy group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen.

[0042] "Hydroxyalkyl" refers to an alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a hydroxy group.

[0043] "Heteroalkyl" refers to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group, provided the point of attachment to the remainder of the molecule is through a carbon atom. The term "heteroalkyl" includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, $-NR^y-$, -O-, -S-, -S(O)-, $-S(O)_2-$, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkyl groups include, e.g., ethers (e.g., $-CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_2OCH_3$, etc.), thioethers (e.g., $-CH_2SCH_3$, $-CH(CH_3)SCH_3$, $-CH_2CH_2SCH_3$, $-CH_2CH_2SCH_2CH_2SCH_3$, etc.), sulfones (e.g., $-CH_2S(O)_2CH_3$, $-CH(CH_3)S(O)_2CH_3$, $-CH_2CH_2S(O)_2CH_3$, $-CH_2CH_2S(O)_2CH_2CH_2OCH_3$, etc.) and amines (e.g., $-CH_2NR^yCH_3$, $-CH(CH_3)NR^yCH_3$, $-CH_2CH_2NR^yCH_3$, $-CH_2CH_2NR^yCH_2CH_2NR^yCH_3$, etc., where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). As used herein, heteroalkyl includes 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

[0044] "Heteroaryl" refers to an aromatic group having a single ring, multiple rings or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, boron, phosphorus and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (i.e., C_{1-20} heteroaryl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heteroaryl), or 3 to 8 carbon ring atoms (i.e., C_{3-8}

heteroaryl), and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. In certain instances, heteroaryl includes 5-10 membered ring systems, 5-7 membered ring systems, or 5-6 membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. In some embodiments, the heteroaryl has 5-14 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-14, or 5-10 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-6 ring atoms and 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl is a five-membered or six-membered heteroaryl ring. In other embodiments, the heteroaryl is an eight-membered, nine-membered or ten-membered fused bicyclic heteroaryl ring. Examples of heteroaryl groups include, e.g., acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl and triazinyl. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide.

[0045] In certain instances, a fused heteroaryl refers to a heteroaryl ring fused to another heteroaryl ring. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinolinyl, isoquinolinyl, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl and imidazo[1,5-a]pyridinyl, where the heteroaryl can be bound *via* either ring of the fused system. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

[0046] "Heteroarylalkyl" refers to the group "heteroaryl-alkyl-".

[0047] "Heterocycloalkyl" or "heterocyclyl" refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from boron, phosphorus, nitrogen, oxygen and sulfur. The term "heterocycloalkyl" includes heterocycloalkenyl groups (i.e., the heterocycloalkyl group having at least one double bond), bridged-heterocycloalkyl groups, fused-heterocycloalkyl groups and spiro-heterocycloalkyl groups. A heterocycloalkyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged or spiro. One or more ring carbon atoms and ring heteroatoms of a heterocycloalkyl group can be optionally oxidized to form an oxo or sulfido

group or other oxidized linkage (*e.g.*, C(O), S(O), C(S) or $S(O)_2$, *N*-oxide *etc.*) or a nitrogen atom can be quaternized. The heterocycloalkyl group can be attached through a ring carbon atom or a ring heteroatom. Any non-aromatic ring containing at least one heteroatom is considered a heterocycloalkyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). As used herein, heterocycloalkyl has 2 to 20 ring carbon atoms (i.e., C_{2-20} heterocycloalkyl), 2 to 12 ring carbon atoms (i.e., C_{2-12} heterocycloalkyl), 2 to 10 ring carbon atoms (i.e., C_{2-10} heterocycloalkyl), 2 to 8 ring carbon atoms (i.e., C_{2-8} heterocycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heterocycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} heterocyclyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} heterocycloalkyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur or oxygen. Examples of heterocycloalkyl groups include, e.g., azetidinyl, azepinyl, benzodioxolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzopyranyl, benzodioxinyl, benzopyranonyl, benzofuranonyl, dioxolanyl, dihydropyranyl, hydropyranyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, furanonyl, imidazolinyl, imidazolidinyl, indolinyl, indolizinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, oxiranyl, oxetanyl, phenothiazinyl, phenoxazinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, tetrahydropyranyl, trithianyl, tetrahydroquinolinyl, thiophenyl (i.e., thienyl), tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl and 1,1-dioxo-thiomorpholinyl. The term "heterocycloalkyl" also includes "spiroheterocycloalkyl" when there are two positions for substitution on the same carbon atom. Examples of the spiro-heterocycloalkyl rings include, e.g., bicyclic and tricyclic ring systems, such as 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.4]octanyl and 6-oxa-1-azaspiro[3.3]heptanyl.

[0048] Further, the term heterocycloalkyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring is fused to one or more aryl or heteroaryl rings, regardless of the attachment to the remainder of the molecule (i.e., a heterocycloalkyl group containing a fused aromatic ring can be attached through any ring atom including a ring atom of the fused aromatic ring). Examples of the fused-heterocycloalkyl rings include, but are not limited to, 1,2,3,4-tetrahydroisoquinolinyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridinyl, indolinyl and isoindolinyl, where the heterocycloalkyl can be bound *via* either ring of the fused system.

[0049] "Heterocycloalkylalkyl" refers to the group "heterocycloalkyl-alkyl-."

[0050] "Oxime" refers to the group $-CR^y(=NOH)$ wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[0051] "Sulfonyl" refers to the group $-S(O)_2R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl and toluenesulfonyl.

[0052] "Sulfinyl" refers to the group $-S(O)R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfinyl are methylsulfinyl, ethylsulfinyl, phenylsulfinyl and toluenesulfinyl.

[0053] "Sulfonamido" refers to the groups $-SO_2NR^yR^z$ and $-NR^ySO_2R^z$, where R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[0054] The terms "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term "optionally substituted" refers to any one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[0055] The term "substituted" used herein means any of the above groups (i.e., alkyl, alkenyl, alkynyl, alkylene, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, and/or heteroalkyl) wherein at least one (e.g., 1 to 5 or 1 to 3) hydrogen atom is replaced by a bond to a non-hydrogen atom such as, but not limited to alkyl, alkenyl, alkynyl, alkoxy, alkylthio, acyl, amido, amino, amidino, aryl, aralkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkylalkyl, guanidino, halo, haloalkyl, haloalkoxy, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, $-NHNH_2$, $=NNH_2$, imino, imido, hydroxy, oxo, oxime, nitro, sulfonyl, sulfinyl, alkylsulfonyl, alkylsulfinyl, thiocyanate, $-S(O)OH$, $-S(O)_2OH$, sulfonamido, thiol, thioxo, N-oxide or $-Si(R^y)_3$, wherein each R^y is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heteroaryl or heterocycloalkyl.

[0056] In certain embodiments, "substituted" includes any of the above alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl groups in which one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms are independently replaced with deuterium, halo, cyano, nitro, azido, oxo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-NR^qR^h$, $-NR^qC(=O)R^h$, $-NR^qC(=O)NR^qR^h$, $-NR^qC(=O)OR^h$, $-NR^qS(=O)_{1-2}R^h$, $-C(=O)R^q$, $-C(=O)OR^q$, $-OC(=O)OR^q$, $-OC(=O)R^q$, $-C(=O)NR^qR^h$, $-OC(=O)NR^qR^h$, $-OR^q$, $-SR^q$, $-S(=O)R^q$, $-S(=O)_2R^q$, $-OS(=O)_{1-2}R^q$, $-S(=O)_{1-2}OR^q$, $-NR^qS(=O)_{1-2}NR^qR^h$, $=NSO_2R^q$, $=NOR^q$, $-S(=O)_{1-2}NR^qR^h$, $-SF_5$, $-SCF_3$ or $-OCF_3$. In certain embodiments, "substituted" also means any of the above groups in which one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms are replaced with $-C(=O)R^q$, $-C(=O)OR^q$, $-C(=O)NR^qR^h$, $-CH_2SO_2R^q$, or $-CH_2SO_2NR^qR^h$. In the foregoing, R^q and R^h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and/or heteroarylalkyl. In certain embodiments, "substituted" also means any of the above groups in which one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl,

heterocycloalkyl, N-heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and/or heteroarylalkyl, or two of R^q and R^h and R^i are taken together with the atoms to which they are attached to form a heterocycloalkyl ring optionally substituted with oxo, halo or alkyl optionally substituted with oxo, halo, amino, hydroxyl, or alkoxy.

[0057] Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to ((substituted aryl)substituted aryl) substituted aryl. Similarly, the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term "substituted" may describe other chemical groups defined herein.

[0058] In certain embodiments, as used herein, the phrase "one or more" refers to one to five. In certain embodiments, as used herein, the phrase "one or more" refers to one to three.

[0059] Any compound or structure given herein, is intended to represent unlabeled forms as well as isotopically labeled forms (isotopologues) of the compounds. These forms of compounds may also be referred to as and include "isotopically enriched analogs." Isotopically labeled compounds have structures depicted herein, except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H, ^{13}C and ^{14}C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

[0060] The term "isotopically enriched analogs" includes "deuterated analogs" of compounds described herein in which one or more hydrogens is/are replaced by deuterium, such as a hydrogen on a carbon atom. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound when administered to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

[0061] Deuterium labelled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and

excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements and/or an improvement in therapeutic index (see e.g., A. Kerekes et.al. J. Med. Chem. 2011, 54, 201-210; R. Xu et.al. J. Label Compd. Radiopharm. 2015, 58, 308-312). An ^{18}F, ^{3}H, ^{11}C labeled compound may be useful for PET or SPECT or other imaging studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in a compound described herein.

[0062] One or more constituent atoms of the compounds presented herein can be replaced or substituted with isotopes of the atoms in natural or non-natural abundance. In some embodiments, the compound includes at least one deuterium atom. For example, one or more hydrogen atoms in a compound presented herein can be replaced or substituted by deuterium (e.g., one or more hydrogen atoms of a C_{1-6} alkyl group can be replaced by deuterium atoms, such as $-CH_3$ being replaced for $-CD_3$). In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 deuterium atoms. In some embodiments, all of the hydrogen atoms in a compound can be replaced or substituted by deuterium atoms. Synthetic methods for including isotopes into organic compounds are known in the art (Deuterium Labeling in Organic Chemistry by Alan F. Thomas (New York, NY., Appleton-Century-Crofts, 1971; The Renaissance of H/D Exchange by Jens Atzrodt, Volker Derdau, Thorsten Fey and Jochen Zimmermann, Angew. Chem. Int. Ed. 2007, 7744-7765; The Organic Chemistry of Isotopic Labelling by James R. Hanson, Royal Society of Chemistry, 2011). Isotopically labeled compounds can be used in various studies such as NMR spectroscopy, metabolism experiments, and/or assays.

[0063] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium. Further, in some embodiments, the corresponding deuterated analog is provided.

[0064] In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0065] Provided also are a pharmaceutically acceptable salt, isotopically enriched analog, deuterated analog, isomer (such as a stereoisomer), mixture of isomers (such as a mixture of stereoisomers), and prodrug of the compounds described herein.

[0066] "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0067] The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from non-toxic inorganic and organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol or butanol) or acetonitrile (MeCN) are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences , 17th Ed., (Mack Publishing Company, Easton, 1985), p. 1418, Berge et al., J. Pharm. Sci., 1977, 66(1), 1-19 and in Stahl et al., Handbook of Pharmaceutical Salts: Properties, Selection, and Use, (Wiley, 2002).

[0068] The term "tautomer" means compounds produced by the phenomenon wherein a proton of one atom of a molecule shifts to another atom of the molecule. The tautomers also refer to one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another. Non-limiting examples include enol-keto, imine-enamine, amide-imidic acid tautomers, the tautomeric forms of heteroaryl groups containing a -N=C(H)-NH- ring atom arrangement, such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles, and the tautomeric forms of hydroxy substituted 6-membered heteroaryl groups (e.g., hydroxy substituted pyridine, pyrimidine, pyrazine or pyridazine) such as 4-hydroxypyridine and puridin-4(1H)-one, and the like. The compounds described herein may have one or more tautomers and therefore include various isomers. A person of ordinary skill in the art would recognize that other tautomeric ring atom arrangements are possible. All such isomeric forms of these compounds are expressly included in the present disclosure.

[0069] Some of the compounds exist as tautomers. Tautomers are in equilibrium with one another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown and regardless of the nature of the equilibrium among tautomers, the

compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

[0070] The compounds of the invention, or their pharmaceutically acceptable salts include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0071] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers," which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

[0072] "Diastereomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0073] Relative centers of the compounds as depicted herein are indicated graphically using the "thick bond" style (bold or parallel lines) and absolute stereochemistry is depicted using wedge bonds (bold or parallel lines).

[0074] "Prodrugs" means any compound which releases an active parent drug according to a structure described herein *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound described herein are prepared by modifying functional groups present in the compound described herein in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds described herein wherein a hydroxy, amino, carboxyl, or sulfhydryl group in a compound described herein is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate and benzoate derivatives), amides, guanidines, carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds described herein and the like. Preparation, selection and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; "Design of Prodrugs," ed. H.

Bundgaard, Elsevier, 1985; and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, each of which are hereby incorporated by reference in their entirety.

[0075] The term "leaving group" refers to an atom or a group of atoms that is displaced in a chemical reaction as stable species taking with it the bonding electrons. The non-limiting examples of a leaving group include, halo, methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy, nonafluorobutanesulfonyloxy, (4-bromo-benzene)sulfonyloxy, (4-nitro-benzene)sulfonyloxy, (2-nitro-benzene)-sulfonyloxy, (4-isopropyl-benzene)sulfonyloxy, (2,4,6-tri-isopropyl-benzene)-sulfonyloxy, (2,4,6-trimethyl-benzene)sulfonyloxy, (4-*tert*-butyl-benzene)sulfonyloxy, benzenesulfonyloxy, (4-methoxy-benzene)sulfonyloxy, and the like.

[0076] The term "amide coupling conditions" refers to the reaction conditions under which an amine and a carboxylic acid couple to form an amide using a coupling reagent in presence of a base. The non-limiting examples of coupling reagents include 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) with hydroxybenzotriazole monohydrate (HOBt), O-(7-Azabenzotriazole-1-yl)-*N,N,N,N'*-tetramethyluronium hexafluorophosphate (HATU), 1-hydroxy-7-azabenzotriazole, and the like. The non-limiting examples of the base include N-methylmorpholine, pyridine, morpholine, imidazole, and the like.

[0077] The term "protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protective group varies widely. One function of a protective group is to serve as an intermediate in the synthesis of the parental drug substance. Chemical protective groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991. Protective groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g., making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

[0078] The non-limiting examples of protective groups for a hydroxy (i.e. a "hydroxy protecting group") include methoxymethyl ether, tetrahydropyranyl ether, t-butyl ether, allyl ether, benzyl ether, t-butyldiphenylsilyl ether, acetate ester, pivalate ester, benzoate ester, benzylidene acetal, acetonide, silyl ether, and the like.

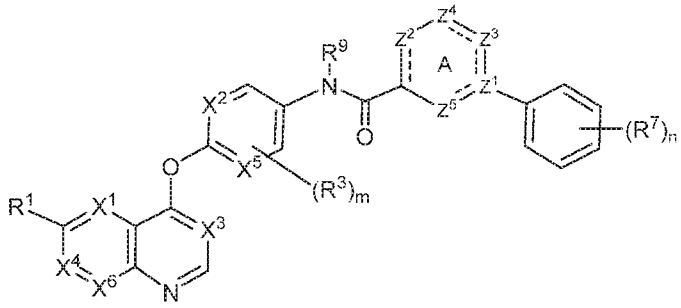
List of Abbreviations and Acronyms

Abbreviation	**Meaning**
ACN	acetonitrile

$Amphos_2PdCl_2$	bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II)
anhyd.	anhydrous
aq.	aqueous
δ	Chemical shift (ppm)
DCC	dicyclohexylcarbodiimide
DCE	dicholoroethane
DCM	dichloromethane
DIEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMSO	dimethylsulfoxide
eq. or equiv.	Equivalent(s)
Et	Ethyl
EtOAc	ethyl acetate
EtOH	ethanol
HATU	N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide
HPLC	High performance liquid chromatography
LC-MS	Liquid chromatography – mass spectrometry
Meldrum's acid	2,2-dimethyl-1,3-dioxane-4,6-dione
MeOH	methanol
MS	Mass spectrometry
m/z	Mass to charge ratio
NBS	N-bromosuccinimide
NMP	N-methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance spectroscopy
Ph	phenyl
$Pd(PPh_3)_4$ or tetrakis	tetrakis(triphenylphosphine)palladium(0)
Prep	preparatory
THF	tetrahydrofuran
TLC	Thin layer chromatography
XPhos Pd G2	chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)

Compounds

[0079] Provided herein is a compound of Formula (I'''):



(I''')

or a pharmaceutically acceptable salt, a stereoisomer, tautomer or a mixture of stereoisomers thereof, wherein:

X^1 is N or CR^{11};

X^2 is N, CR^3, or CH;

X^3 is N or CH;

X^4 is N or CR^2;

X^5 is N, CR^3, or CH;

X^6 is N or CR^{10};

Z^1 is N, CH or C;

Z^2 is N, NR^{40}, -C(=O)-, or CR^{45};

Z^3 is N, NR^{41}, CR^{42}, -C(=O)-, -C(=S)-;

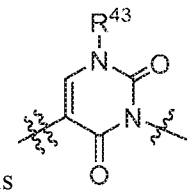
Z^4 is N, NR^{43}, CR^{44}, -C(=O)- or a bond;

Z^5 is N, COR^{46}, -C(=O)- or CR^{18};

⋯ is a single bond or a double bond;

one or two of Z^1, Z^2, Z^3, Z^4, and Z^5 are independently selected from N, NR^{40}, NR^{41}, and NR^{43};

no more than two of Z^2, Z^3, Z^4 and Z^5 are –C(=O)-;

when ring A is  then X^1 is N, wherein the single wavy line indicates the point of attachment to the phenyl ring and the double wavy line indicates the point of attachment to the carbonyl of the amide linkage;

R^1 and R^2 and R^{10} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$,

$C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^1, R^2 and R^{10} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

each R^3 is independently selected from halo, OH, CN, -COOH, -CONH(C_{1-6} alkyl), -SO_2(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, C_1-C_6 alkoxy, -NH(C_1-C_6alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl of R^3 are each optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{40}, R^{41} and R^{43} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $N=C(NR^aR^a)_2$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^{40}, R^{41} and R^{43} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

R^{45}, R^{42} and R^{44} are each independently H, halo, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, C_{2-6} alkenyl, C_{3-14} cycloalkyl, C_{1-6} alkoxy, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -S-C_{1-6} alkyl, -COOH, -COC_{1-4}alkyl, -$COOC_{1-4}$alkyl, -$CONH_2$, -$CONHC_{1-4}$ alkyl, -$NHC(O)OC_{1-4}$alkyl, NH_2, -NHC_{1-4}alkyl, or –N(C_{1-4} alkyl)$_2$;

each R^7 is independently selected from halo, OH, $COOR^a$, $CONR^aR^a$, CN, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $CONR^aR^a$, NR^aCOR^a, $NR^aCONR^aR^a$, SO_2R^a, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4 alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4

alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene- of R^7 are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{46} is H, C_{1-6} alkyl or a hydroxy protecting group;

R^9 is H or C_{1-6} alkyl optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{11} is selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)- C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)- C_1-C_4 alkylene-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^{11} are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{18} is H, halo, CN, C_{1-6} alkyl, NH_2, -NHC_{1-4}alkyl, -$N(C_{1-4}$ alkyl$)_2$, or -S-C_{1-6} alkyl;

or R^{40} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{43} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{44} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or when Z^4 is a bond, R^{40} and R^{42} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{41} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{42} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each

optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or R^{41} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{43} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{44} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl, fused phenyl, or fused heteroaryl, wherein the fused C_{3-7} cycloalkyl, fused phenyl, and fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

each R^a is independently selected from the group consisting of H, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14 membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14 membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^b is independently selected from the group consisting of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $C(O)NR^cS(O)_2R^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NOH)R^c$, $C(=NOH)NR^c$, $C(=NCN)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(=NR^c)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, $S(O)_2NR^cC(O)R^c$, $Si(R^c)_3$, $P(O)R^cR^c$, $P(O)(OR^c)(OR^c)$, $B(OH)_2$, $B(OR^c)_2$, and $S(O)_2NR^cR^c$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-

C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^b are each further optionally substituted with 1, 2, or 3 independently selected R^d substituents;

each R^c is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^d is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^d are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^e is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, C_6-C_{10} aryl, C_6-C_{10} aryl-C_1-C_4 alkylene-, 5- or 6-membered heteroaryl, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, 4-7-membered heterocycloalkyl, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_4 alkenyl, and C_2-C_4 alkynyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, 5 or 6-membered heteroaryl, 4-7-membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_2-C_4 alkenyl, and C_2-C_4 alkynyl of R^e are each optionally substituted with 1, 2, or 3 R^f substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^f is independently selected from the group consisting of halo, OH, CN, COOH, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy,

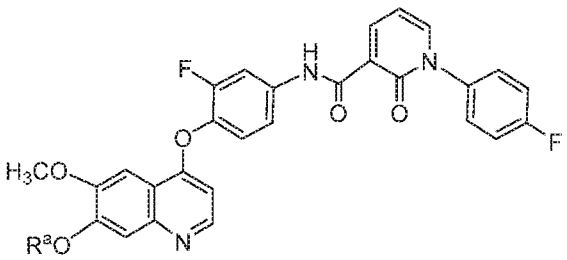
phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, phenyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^f are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, $-NH_2$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, C_3-C_{10} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^g is independently selected from the group consisting of halo, OH, CN, COOH, -COO-C_1-C_4 alkyl, -OC(O)C_1-C_4 alkyl, NH_2, NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl;

the ring nitrogen atom in Formula (I''') is optionally oxidized;

the subscript m is 0, 1, 2, or 3; and

the subscript n is 0, 1, 2, 3, 4 or 5.

[0080] In some embodiments, provided is a compound of Formula (I''') with the proviso that the compound is not  , wherein R^a is H, methyl, benzyl, piperidin-4-yl, (piperidin-4-yl)methyl, (1-methylpiperidin-4-yl)methyl, or (1-t-butoxypiperidin-4-yl)methyl.

[0081] In some embodiments, provided is a compound of Formula (I''') with the proviso that when X^1 is CH, X^2 is CF, X^3 is CH, X^4 is CR^2, X^5 is CH, m is 0, R^9 is H, R^{10} is H, n is 1, R^1 is OCH_3 or CN, R^2 is OCH_3, R^7 is fluoro and is para to ring A, and Z^3 is CR^{42}, then R^{42} cannot be CN, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2OCH_3$, or OH.

[0082] In some embodiments, provided is a compound of Formula (I''') with the proviso that when X^1 is CH, X^3 is CH, X^4 is CR^2, R^1 is OCH_3, R^2 is OCH_3, R^9 is H, n is 1, R^7 is fluoro and is para to ring A, one of X^2 and X^5 is N, or X^2 and X^5 are each N, then R^{43} is not cyclopropyl or isopropyl.

[0083] In some embodiments, provided is a compound of Formula (I''') with the proviso that the compound is not:

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-1-cyclopropyl-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-1-cyclobutyl-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6-cyano-7-methoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-(aminomethyl)-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-methyl-6-((methylamino)methyl)-2-oxo-1,2-dihydropyridine-3-carboxamide;

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-(methoxymethyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-bromo-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-isopropyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-5-(prop-1-en-2-yl)-1,2-dihydropyridine-3-carboxamide;

N-(6-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-3-yl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridazine-3-carboxamide;

N-(2-((6,7-dimethoxyquinolin-4-yl)oxy)pyrimidin-5-yl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridazine-3-carboxamide;

1-cyclopropyl-N-(6-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-3-yl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridazine-3-carboxamide;

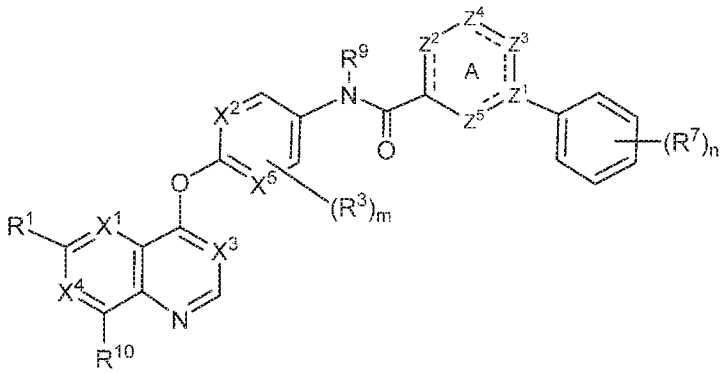
1-cyclopropyl-N-(2-((6,7-dimethoxyquinolin-4-yl)oxy)pyrimidin-5-yl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridazine-3-carboxamide;

N-(2-((6,7-dimethoxyquinolin-4-yl)oxy)pyrimidin-5-yl)-6-(4-fluorophenyl)-2-isopropyl-5-oxo-2,5-dihydropyridazine-4-carboxamide;

2-cyclopropyl-N-(6-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-3-yl)-6-(4-fluorophenyl)-5-oxo-2,5-dihydropyridazine-4-carboxamide; or

2-cyclopropyl-N-(2-((6,7-dimethoxyquinolin-4-yl)oxy)pyrimidin-5-yl)-6-(4-fluorophenyl)-5-oxo-2,5-dihydropyridazine-4-carboxamide.

[0084] Provided herein is a compound of Formula (I'):



(I')

or a pharmaceutically acceptable salt, a stereoisomer, tautomer or a mixture of stereoisomers thereof, wherein:

X^1 is N or CR^{11};

X^2 is N, CR^3, or CH;

X^3 is N or CH;

X^4 is N or CR^2;

X^5 is N, CR^3, or CH;

Z^1 is N, CH or C;

Z^2 is N, NR^{40}, -C(=O)-, or CR^{45};

Z^3 is N, NR^{41}, CR^{42}, -C(=O)-, -C(=S)-;

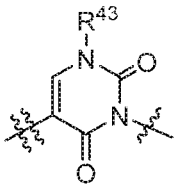
Z^4 is N, NR^{43}, CR^{44}, -C(=O)- or a bond;

Z^5 is COR^{46}, -C(=O)- or CR^{18};

⎓ is a single bond or a double bond;

one or two of Z^1, Z^2, Z^3 and Z^4 are independently selected from N, NR^{40}, NR^{41}, and NR^{43};

no more than two of Z^2, Z^3, Z^4 and Z^5 are –C(=O)-;

when ring A is  then X^1 is N, wherein the single wavy line indicates the point of attachment to the phenyl ring and the double wavy line indicates the point of attachment to the carbonyl of the amide linkage;

R^1 and R^2 and R^{10} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4}

alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^1 and R^2 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

each R^3 is independently selected from halo, OH, CN, -COOH, -CONH(C_{1-6} alkyl), -SO_2(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, C_1-C_6 alkoxy, -NH(C_1-C_6alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl of R^3 are each optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{40}, R^{41} and R^{43} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $N=C(NR^aR^a)_2$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^{40}, R^{41} and R^{43} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

R^{45}, R^{42} and R^{44} are each independently H, halo, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, C_{2-6} alkenyl, C_{1-6} alkoxy, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -S-C_{1-6} alkyl, -COOH, -COC_{1-4}alkyl, -$COOC_{1-4}$alkyl, -$CONH_2$, -$CONHC_{1-4}$ alkyl, -$NHC(O)OC_{1-4}$alkyl, NH_2, -NHC_{1-4}alkyl, or –N(C_{1-4} alkyl)$_2$;

each R^7 is independently selected from halo, OH, $COOR^a$, $CONR^aR^a$, CN, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $CONR^aR^a$, NR^aCOR^a, $NR^aCONR^aR^a$, SO_2R^a, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4 alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4 alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene- of R^7 are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{46} is H, C_{1-6} alkyl or a hydroxy protecting group;

R^9 is H or C_{1-6} alkyl optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{11} is selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)- C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)- C_1-C_4 alkylene-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^{11} are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{18} is H, halo, CN, C_{1-6} alkyl, NH_2, -NHC_{1-4}alkyl, -N(C_{1-4} alkyl)$_2$, or -S-C_{1-6} alkyl;

or R^{40} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{43} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{44} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or when Z^4 is a bond, R^{40} and R^{42} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{41} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{42} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or R^{41} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{43} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{44} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl, fused phenyl, or fused heteroaryl, wherein the fused C_{3-7} cycloalkyl, fused phenyl, and fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

each R^a is independently selected from the group consisting of H, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14 membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered

heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14 membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^b is independently selected from the group consisting of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $C(O)NR^cS(O)_2R^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NOH)R^c$, $C(=NOH)NR^c$, $C(=NCN)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(=NR^c)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, $S(O)_2NR^cC(O)R^c$, $Si(R^c)_3$, $P(O)R^cR^c$, $P(O)(OR^c)(OR^c)$, $B(OH)_2$, $B(OR^c)_2$, and $S(O)_2NR^cR^c$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^b are each further optionally substituted with 1, 2, or 3 independently selected R^d substituents;

each R^c is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^d is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^d are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^e is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, C_6-C_{10} aryl, C_6-C_{10} aryl-C_1-C_4 alkylene-, 5- or 6-membered heteroaryl, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, 4-7-membered heterocycloalkyl, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_4 alkenyl, and C_2-C_4 alkynyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, 5 or 6-membered heteroaryl, 4-7-membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_2-C_4 alkenyl, and C_2-C_4 alkynyl of R^e are each optionally substituted with 1, 2, or 3 R^f substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

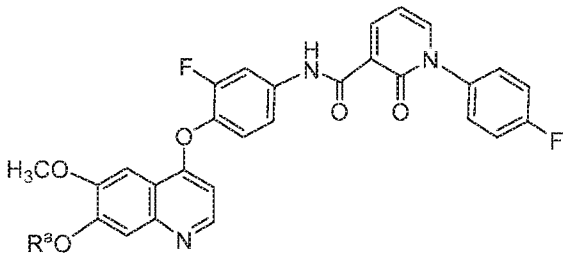
each R^f is independently selected from the group consisting of halo, OH, CN, COOH, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, phenyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^f are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, -NH_2, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, C_3-C_{10} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^g is independently selected from the group consisting of halo, OH, CN, COOH, -COO-C_1-C_4 alkyl, -OC(O)C_1-C_4 alkyl, NH_2, NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl;

the ring nitrogen atom in Formula (I') is optionally oxidized;

the subscript m is 0, 1, 2, or 3; and

the subscript n is 0, 1, 2, 3, 4 or 5.

[0085] In some embodiments, provided is a compound of Formula (I') with the proviso that the compound is not  , wherein R^a is H, methyl, benzyl, piperidin-4-yl, (piperidin-4-yl)methyl, (1-methylpiperidin-4-yl)methyl, or (1-t-butoxypiperidin-4-yl)methyl.

[0086] In some embodiments, provided is a compound of Formula (I') with the proviso that when X^1 is CH, X^2 is CF, X^3 is CH, X^4 is CR^2, X^5 is CH, m is 0, R^9 is H, R^{10} is H, n is 1, R^1 is OCH_3 or CN, R^2 is OCH_3, R^7 is fluoro and is para to ring A, and Z^3 is CR^{42}, then R^{42} cannot be CN, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2OCH_3$, or OH.

[0087] In some embodiments, provided is a compound of Formula (I') with the proviso that when X^1 is CH, X^3 is CH, X^4 is CR^2, R^1 is OCH_3, R^2 is OCH_3, R^9 is H, n is 1, R^7 is fluoro and is para to ring A, one of X^2 and X^5 is N, or X^2 and X^5 are each N, then R^{43} is not cyclopropyl or isopropyl.

[0088] In some embodiments, provided is a compound of Formula (I') with the proviso that the compound is not:

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-1-cyclopropyl-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-1-cyclobutyl-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6-cyano-7-methoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-(aminomethyl)-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-methyl-6-((methylamino)methyl)-2-oxo-1,2-dihydropyridine-3-carboxamide;

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-(methoxymethyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-bromo-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-isopropyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-5-(prop-1-en-2-yl)-1,2-dihydropyridine-3-carboxamide;

N-(6-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-3-yl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridazine-3-carboxamide;

N-(2-((6,7-dimethoxyquinolin-4-yl)oxy)pyrimidin-5-yl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridazine-3-carboxamide;

1-cyclopropyl-N-(6-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-3-yl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridazine-3-carboxamide;

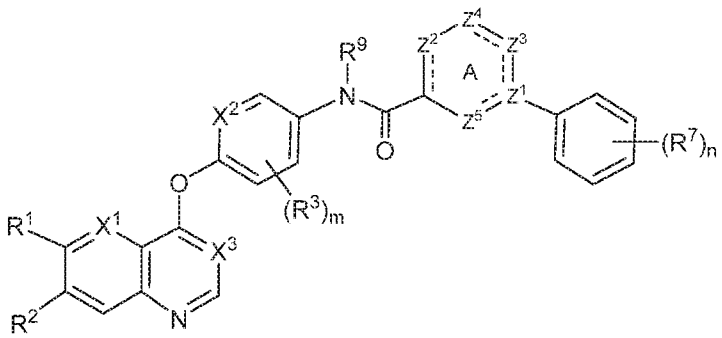
1-cyclopropyl-N-(2-((6,7-dimethoxyquinolin-4-yl)oxy)pyrimidin-5-yl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridazine-3-carboxamide;

N-(2-((6,7-dimethoxyquinolin-4-yl)oxy)pyrimidin-5-yl)-6-(4-fluorophenyl)-2-isopropyl-5-oxo-2,5-dihydropyridazine-4-carboxamide;

2-cyclopropyl-N-(6-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-3-yl)-6-(4-fluorophenyl)-5-oxo-2,5-dihydropyridazine-4-carboxamide; or

2-cyclopropyl-N-(2-((6,7-dimethoxyquinolin-4-yl)oxy)pyrimidin-5-yl)-6-(4-fluorophenyl)-5-oxo-2,5-dihydropyridazine-4-carboxamide.

[0089] Provided herein is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, wherein:

X^1 is N or CR^{11};

X^2 is N, CR^3, or CH;

X^3 is N or CH;

Z^1 is N, CH or C;

Z^2 is N, NR^{40}, -C(=O)-, or CR^{45};

Z^3 is N, NR^{41}, CR^{42}, -C(=O)-, -C(=S)-;

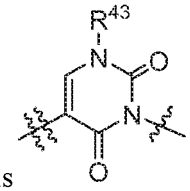
Z^4 is N, NR^{43}, CR^{44}, -C(=O)- or a bond;

Z^5 is COR^{46}, -C(=O)- or CR^{18};

⎓ is a single bond or a double bond;

one or two of Z^1, Z^2, Z^3 and Z^4 are independently selected from N, NR^{40}, NR^{41}, and NR^{43};

no more than two of Z^2, Z^3, Z^4 and Z^5 are –C(=O)-;

when ring A is  then X^1 is N, wherein the single wavy line indicates the point of attachment to the phenyl ring and the double wavy line indicates the point of attachment to the carbonyl of the amide linkage;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^1 and R^2 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

each R^3 is independently selected from halo, OH, CN, -COOH, -CONH(C_{1-6} alkyl), -SO_2(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, C_1-C_6 alkoxy, -NH(C_1-C_6alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl of R^3 are each optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{40}, R^{41} and R^{43} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a,

$NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $N=C(NR^aR^a)_2$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^{40}, R^{41} and R^{43} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

R^{45}, R^{42} and R^{44} are each independently H, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, C_{1-6} alkoxy, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -COC_{1-4}alkyl, -$COOC_{1-4}$alkyl, -$CONC_{1-4}$ alkyl, NH_2, -NHC_{1-4}alkyl, or –$N(C_{1-4}$ alkyl$)_2$;

each R^7 is independently selected from halo, OH, $COOR^a$, $CONR^aR^a$, CN, NH_2, -$NH(C_1$-C_6 alkyl), -$N(C_1$-C_6 alkyl$)_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $CONR^aR^a$, NR^aCOR^a, $NR^aCONR^aR^a$, SO_2R^a, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4 alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4 alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene- of R^7 are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{46} is H, C_{1-6} alkyl or a hydroxy protecting group;

R^9 is H or C_{1-6} alkyl optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{11} is selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)- C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)- C_1-C_4 alkylene-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^{11} are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{18} is H, halo, CN, or C_{1-6} alkyl;

or R^{40} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused

heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{43} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{44} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or when Z^4 is a bond, R^{40} and R^{42} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{41} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{42} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or R^{41} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{43} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{44} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl, fused phenyl, or fused heteroaryl, wherein the fused C_{3-7} cycloalkyl, fused phenyl, and fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

each R^a is independently selected from the group consisting of H, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14

membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14 membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^b is independently selected from the group consisting of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, OH, NH_2, NO_2, NHOR^c, OR^c, SR^c, C(O)R^c, C(O)NR^{c}R^c, C(O)OR^c, C(O)NR^{c}S(O)$_2$R^c, OC(O)R^c, OC(O)NR^{c}R^c, C(=NOH)R^c, C(=NOH)NR^c, C(=NCN)NR^{c}R^c, NR^{c}C(=NCN)NR^{c}R^c, C(=NR^c)NR^{c}R^c, NR^{c}C(=NR^c)NR^{c}R^c, NHR^c, NR^{c}R^c, NR^{c}C(O)R^c, NR^{c}C(=NR^c)R^c, NR^{c}C(O)OR^c, NR^{c}C(O)NR^{c}R^c, NR^{c}S(O)R^c, NR^{c}S(O)$_2$R^c, NR^{c}S(O)$_2$NR^{c}R^c, S(O)R^c, S(O)NR^{c}R^c, S(O)$_2$R^c, S(O)$_2$NR^{c}C(O)R^c, Si(R^c)$_3$, P(O)R^{c}R^c, P(O)(OR^c)(OR^c), B(OH)$_2$, B(OR^c)$_2$, and S(O)$_2$NR^{c}R^c; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^b are each further optionally substituted with 1, 2, or 3 independently selected R^d substituents;

each R^c is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^d is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10

membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^d are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^e is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, C_6-C_{10} aryl, C_6-C_{10} aryl-C_1-C_4 alkylene-, 5- or 6-membered heteroaryl, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, 4-7-membered heterocycloalkyl, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_4 alkenyl, and C_2-C_4 alkynyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, 5 or 6-membered heteroaryl, 4-7-membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_2-C_4 alkenyl, and C_2-C_4 alkynyl of R^e are each optionally substituted with 1, 2, or 3 R^f substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

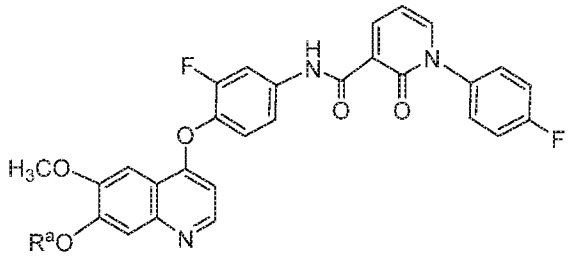
each R^f is independently selected from the group consisting of halo, OH, CN, COOH, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, phenyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^f are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, $-NH_2$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, C_3-C_{10} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^g is independently selected from the group consisting of halo, OH, CN, COOH, -COO-C_1-C_4 alkyl, NH_2, NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl;

the ring nitrogen atom in Formula (I) is optionally oxidized;

the subscript m is 0, 1, 2, or 3; and

the subscript n is 0, 1, 2, 3, 4 or 5;

with the proviso that the compound is not  ,

wherein R^a is H, methyl, benzyl, piperidin-4-yl, (piperidin-4-yl)methyl, (1-methylpiperidin-4-yl)methyl, or (1-t-butoxypiperidin-4-yl)methyl.

[0090] In some embodiments, provided is a compound of Formula (I) with the proviso that when X^1 is CH, X^2 is CF, X^3 is CH, m is 0, R^9 is H, n is 1, R^1 is OCH_3 or CN, R^2 is OCH_3, R^7 is fluoro and is para to ring A, and Z^3 is CR^{42}, then R^{42} cannot be CN, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2OCH_3$, or OH.

[0091] In some embodiments, provided is a compound of Formula (I) with the proviso that when X^1 is CH, X^3 is CH, R^1 is OCH_3, R^2 is OCH_3, R^9 is H, n is 1, R^7 is fluoro and is para to ring A, and X^2 is N, then R^{43} is not cyclopropyl or isopropyl.

[0092] In some embodiments, provided is a compound of Formula (I) with the proviso that the compound is not:

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-1-cyclopropyl-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-1-cyclobutyl-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6-cyano-7-methoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxamide;

6-(aminomethyl)-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-methyl-6-((methylamino)methyl)-2-oxo-1,2-dihydropyridine-3-carboxamide;

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-(methoxymethyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-bromo-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxamide;

6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-isopropyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

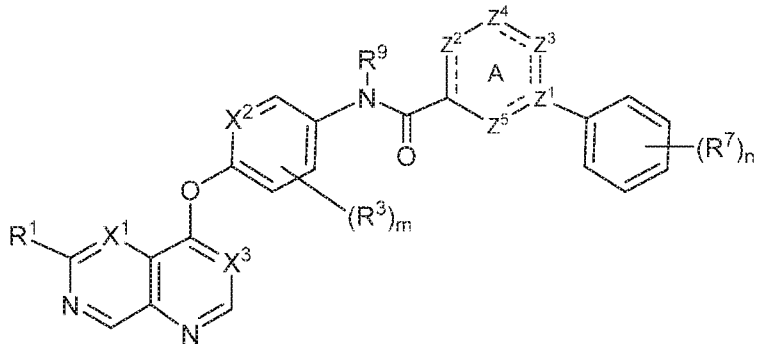
6-cyano-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-5-(prop-1-en-2-yl)-1,2-dihydropyridine-3-carboxamide;

N-(6-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-3-yl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridazine-3-carboxamide;

1-cyclopropyl-N-(6-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-3-yl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridazine-3-carboxamide; or

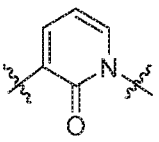
2-cyclopropyl-N-(6-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-3-yl)-6-(4-fluorophenyl)-5-oxo-2,5-dihydropyridazine-4-carboxamide.

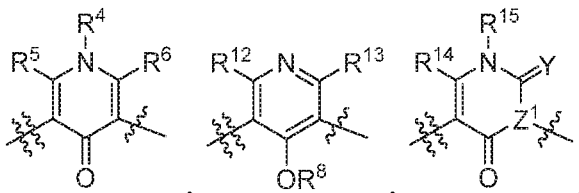
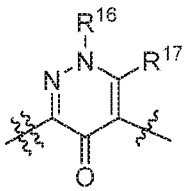
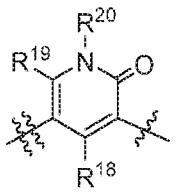
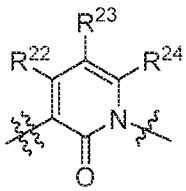
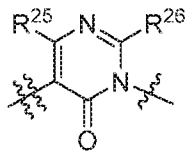
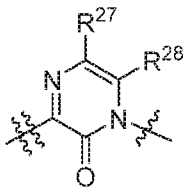
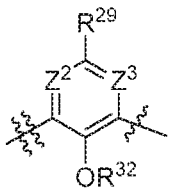
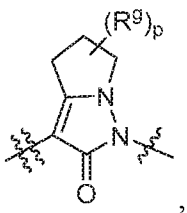
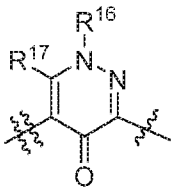
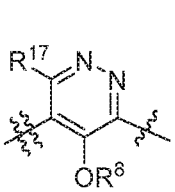
[0093] Also provided herein is a compound of Formula (I''):



(I'')

or a pharmaceutically acceptable salt, a stereoisomer, or a mixture of stereoisomers thereof.

[0094] In some embodiments, when ring A is  , then X^1 is N.

[0095] In some embodiments, ring A is  , , ,  ,  ,  ,  ,  ,  ,  ,  ,  , wherein the single wavy line indicates the point of attachment to the phenyl ring and the double wavy line indicates the point of attachment to the carbonyl of the amide linkage;

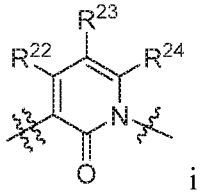
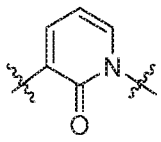
Y is O or S;

Z^1 is N or CH;

Z^2 is N or CR^{45};

Z^3 is N or CR^{42};

when Y is O and Z^1 is N, then X^1 is N;

alternatively, when  is  , then X^1 is N;

R^4, R^{15}, R^{16} and R^{20} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $N=C(NR^aR^a)_2$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$ and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^4, R^{15}, R^{16} and R^{20} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

R^5, R^{12}, R^{14}, R^{19}, R^{22}, R^{25}, R^{27}, R^{28}, and R^{45} are each independently H, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -$COOC_{1-4}$alkyl, -$CONC_{1-4}$alkyl, NH_2, -NHC_{1-4}alkyl, or –$N(C_{1-4}$ alkyl$)_2$;

R^6, R^{13}, R^{17}, R^{23}, R^{24}, R^{26}, R^{29} and R^{42} are each independently H, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -$COOC_{1-4}$alkyl, -$CONC_{1-4}$alkyl, NH_2, -NHC_{1-4}alkyl, or –$N(C_{1-4}$ alkyl$)_2$;

or R^4 and R^5 taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^4 and R^6 taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-

membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{14} and R^{15} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{16} and R^{17} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{19} and R^{20} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{22} and R^{23} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{23} and R^{24} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl, fused phenyl, or fused heteroaryl, wherein the fused C_{3-7} cycloalkyl, fused phenyl, and fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{27} and R^{28} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{29} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

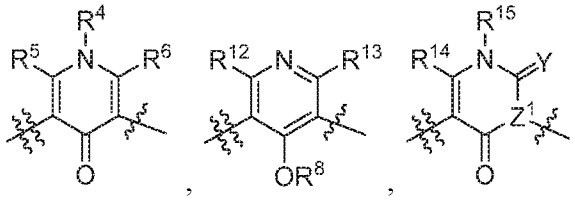
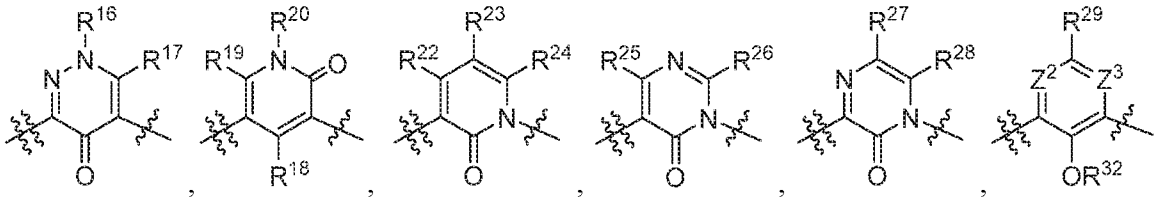
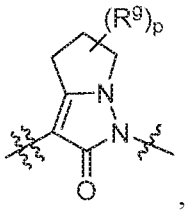
or R^{42} and R^{29} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

R^8 and R^{32} are each independently H, C_{1-6} alkyl or a hydroxy protecting group;

R^{12} is H or C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents;

R^{13} is H or C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents; and

the subscript p is 0, 1, or 2.

[0096] In some embodiments, ring A is  ,  , or  , wherein the single wavy line indicates the point of attachment to the phenyl ring and the double wavy line indicates the point of attachment to the carbonyl of the amide linkage;

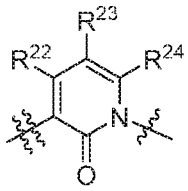
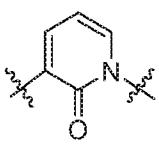
Y is O or S;

Z^1 is N or CH;

Z^2 is N or CR^{45};

Z^3 is N or CR^{42};

when Y is O and Z^1 is N, then X^1 is N;

alternatively, when  is  , then X^1 is N;

R^4, R^{15}, R^{16} and R^{20} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $N=C(NR^aR^a)_2$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$ and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered

heterocycloalkyl)-C_{1-4} alkylene- of R^4, R^{15}, R^{16} and R^{20} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

R^5, R^{12}, R^{14}, R^{19}, R^{22}, R^{25}, R^{27}, R^{28}, and R^{45} are each independently H, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -$COOC_{1-4}$alkyl, -$CONC_{1-4}$alkyl, NH_2, -NHC_{1-4}alkyl, or –$N(C_{1-4}$ alkyl$)_2$;

R^6, R^{13}, R^{17}, R^{23}, R^{24}, R^{26}, R^{29} and R^{42} are each independently H, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -$COOC_{1-4}$alkyl, -$CONC_{1-4}$alkyl, NH_2, -NHC_{1-4}alkyl, or –$N(C_{1-4}$ alkyl$)_2$;

or R^4 and R^5 taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^4 and R^6 taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{14} and R^{15} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{16} and R^{17} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{19} and R^{20} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{22} and R^{23} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{23} and R^{24} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl, fused phenyl, or fused heteroaryl, wherein the fused C_{3-7} cycloalkyl, fused phenyl, and fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{27} and R^{28} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{29} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{29} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

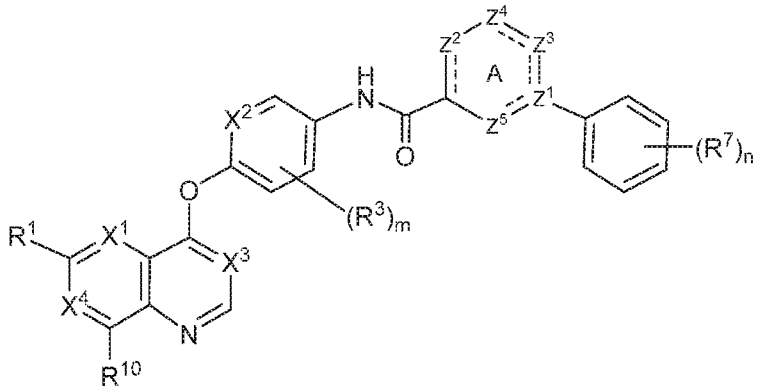
R^8 and R^{32} are each independently H, C_{1-6} alkyl or a hydroxy protecting group;

R^{12} is H or C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents;

R^{13} is H or C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents; and

the subscript p is 1 or 2.

[0097] Some embodiments provide for a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt, a stereoisomer, or a mixture of stereoisomers thereof, wherein:

X^1 is N or CR^{11};

X^2 is CR^3 or CH, and R^3 is halo;

X^3 is N or CH;

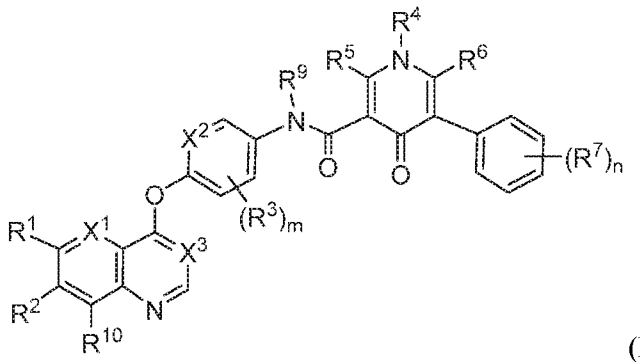
X^4 is N or CR^2;

m is 0, 1 ,or 2;

n is 0, 1, 2, or 3;

and the remaining variables are as defined herein.

[0098] Some embodiments provide for a compound of formula (Ia):

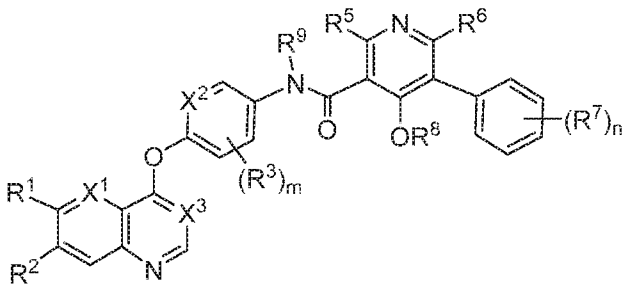


(Ia)

or pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof.

[0099] In some embodiments, R^{10} is H.

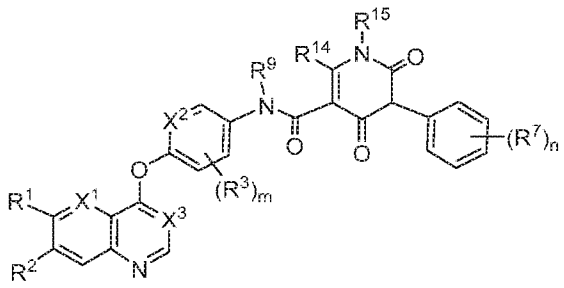
[0100] Some embodiments provide for a compound of formula (Ib):



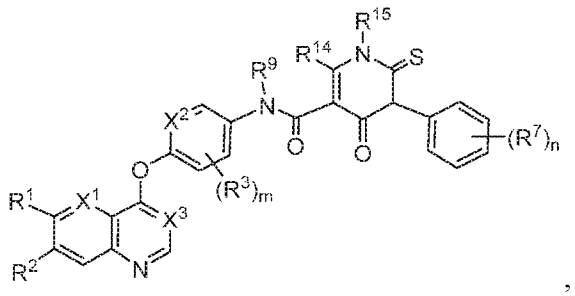
(Ib)

or pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof.

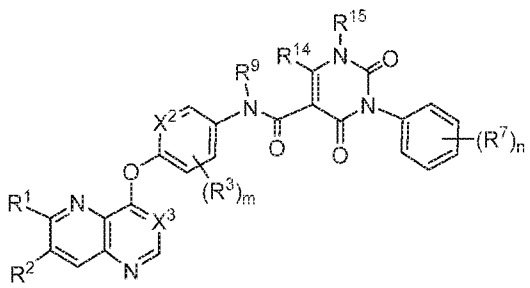
[0101] Some embodiments provide for a compound of formula (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), or (It):



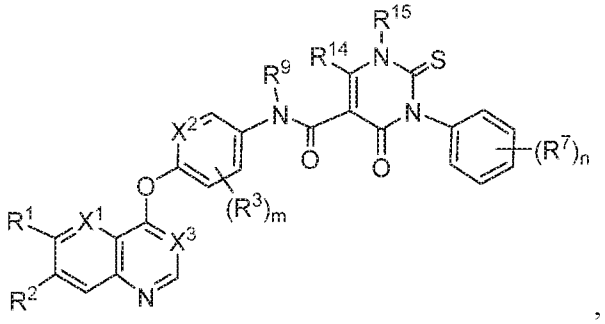
(Ic)



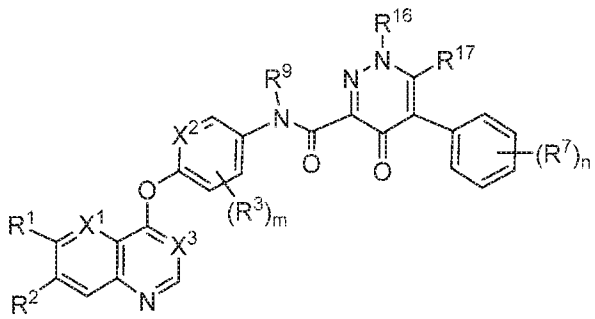
(Id)



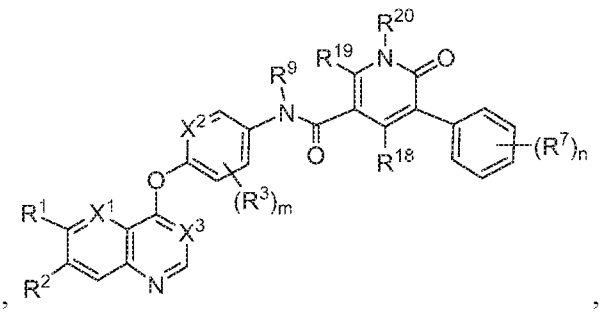
(Ie)



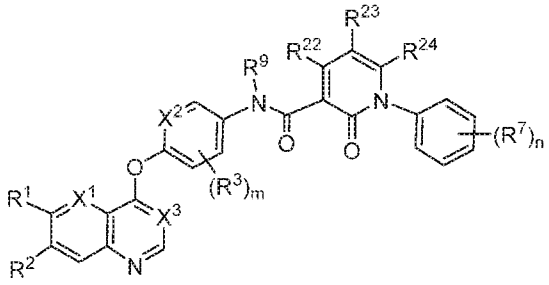
(If)



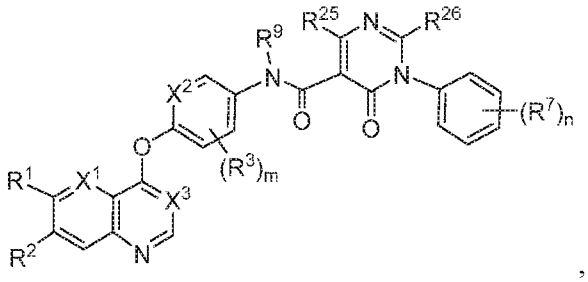
(Ig)



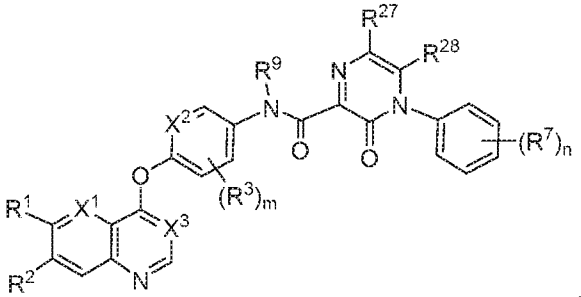
(Ih)



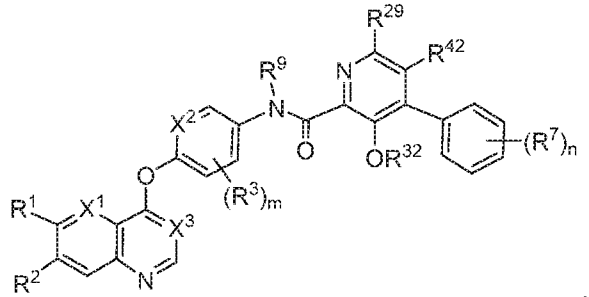
(Ij)



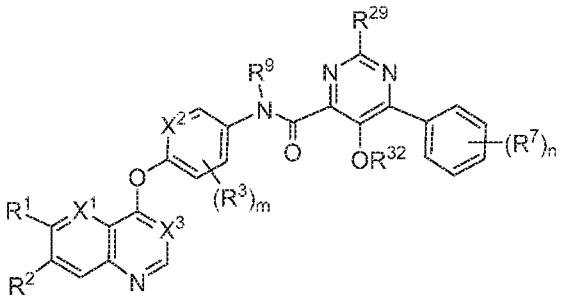
(Ik)



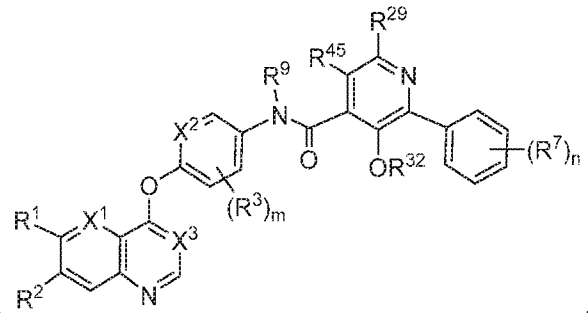
(Im)



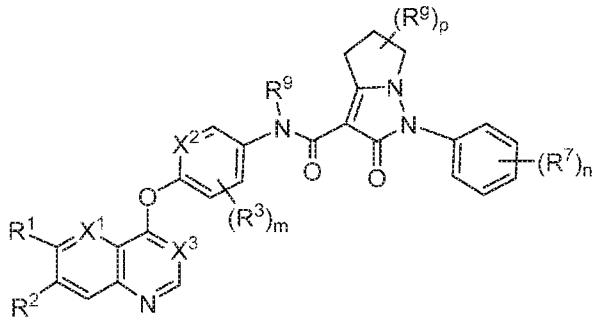
(In)



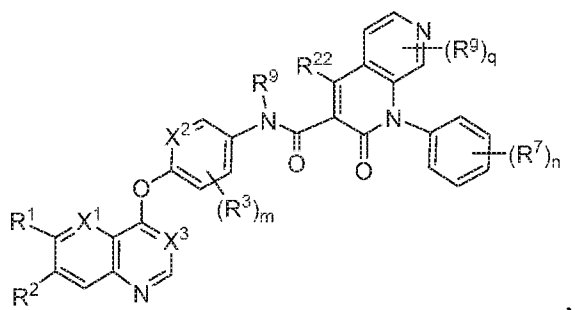
(Io)



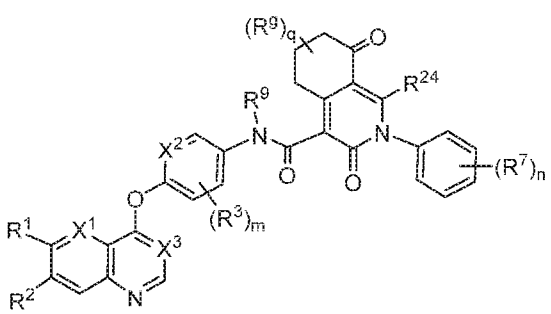
(Ip)



(Iq)

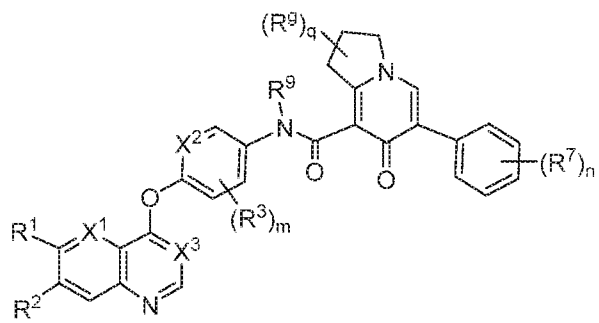


(Ir)



(Is)

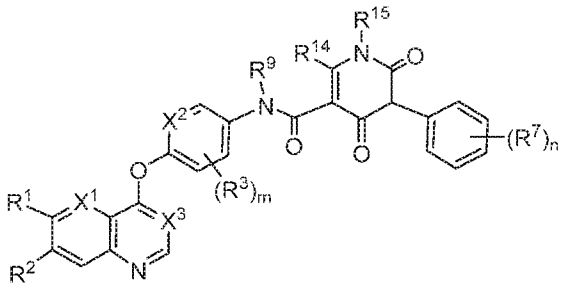
, or



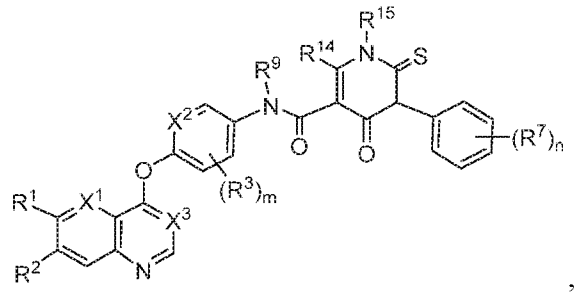
(It)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, wherein each subscript q is independently 0, 1, or 2.

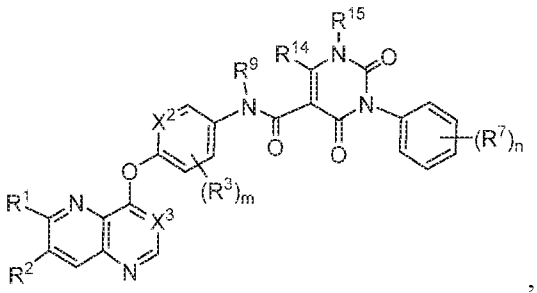
[0102] Some embodiments provide for a compound of formula (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Ix), (Iy), (Iz), (Iaa), or (Ibb):



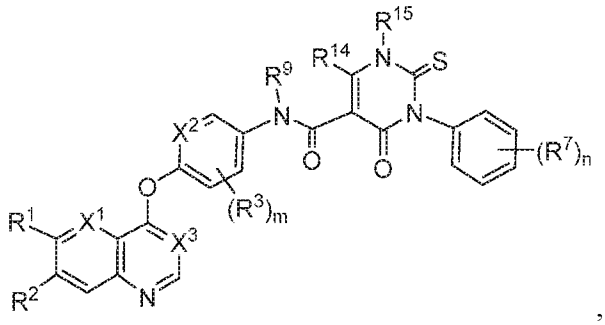
(Ic)



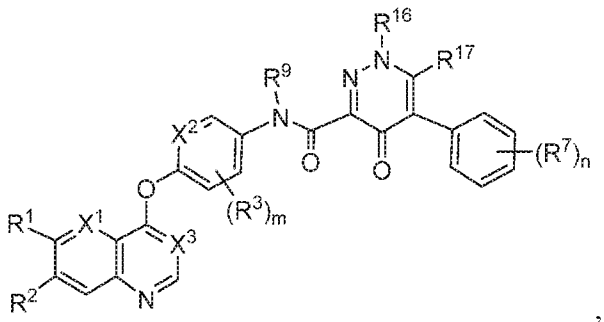
(Id)



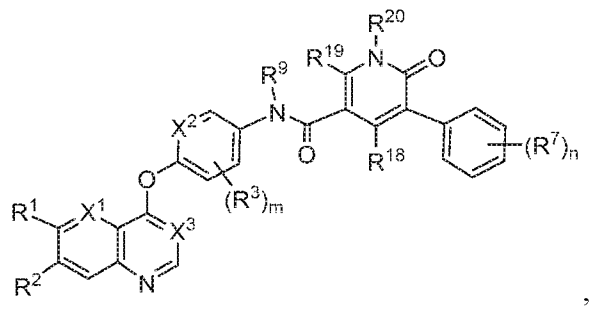
(Ie)



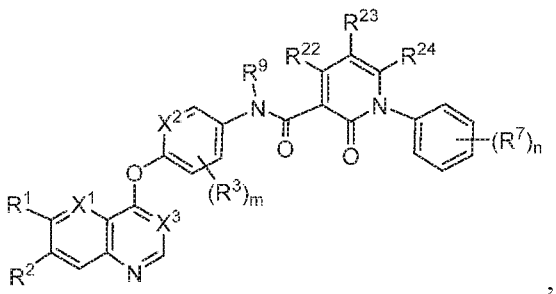
(If)



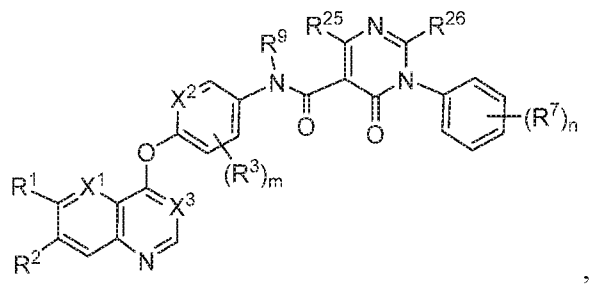
(Ig)



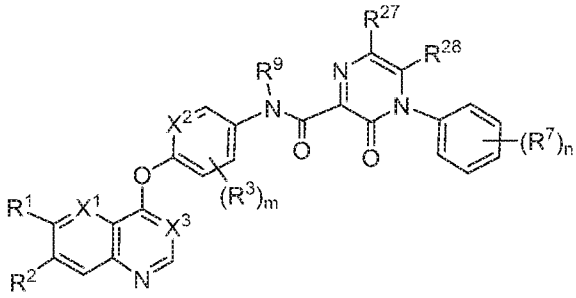
(Ih)



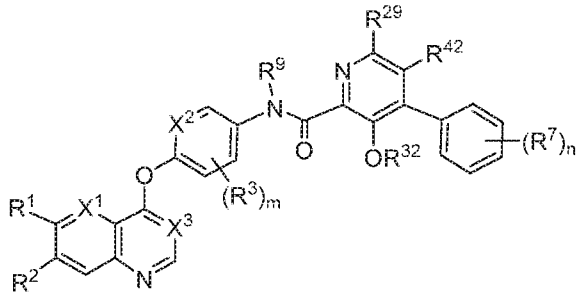
(Ij)



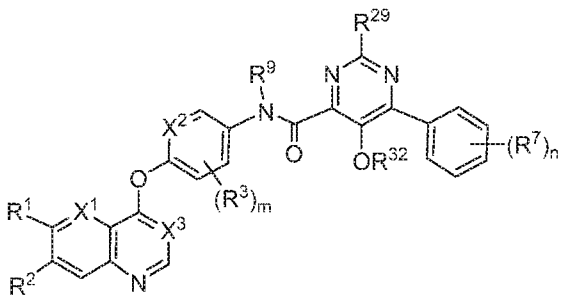
(Ik)



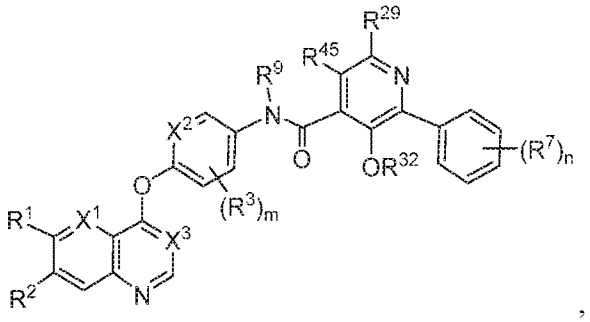
(Im)



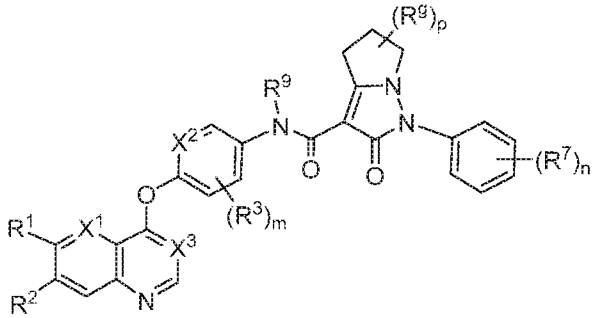
(In)



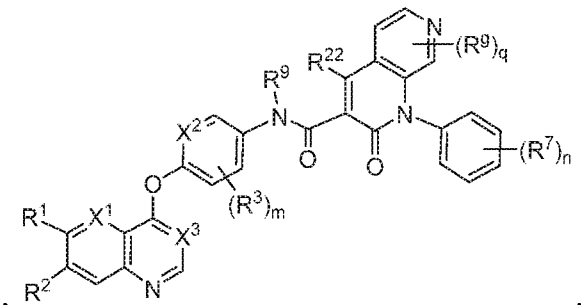
(Io)



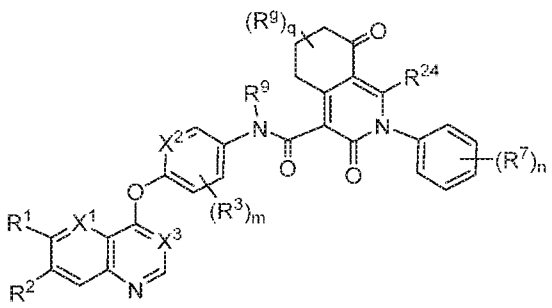
(Ip)



(Iq)

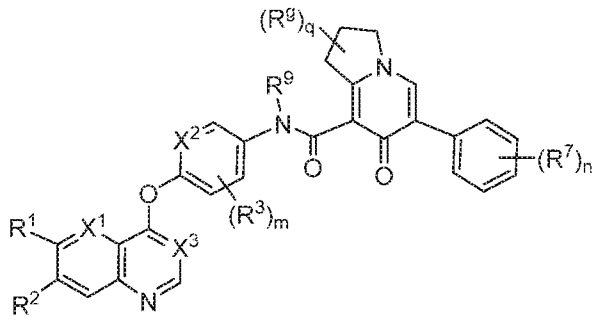


(Ir)

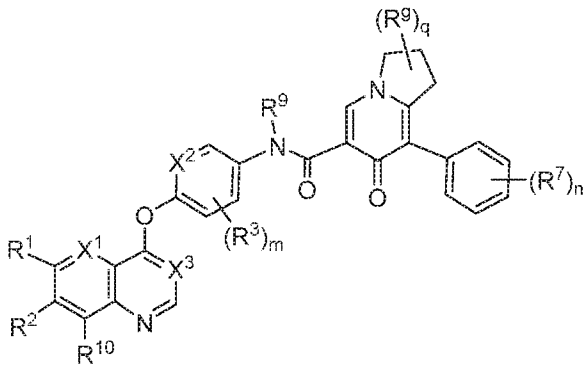


(Is)

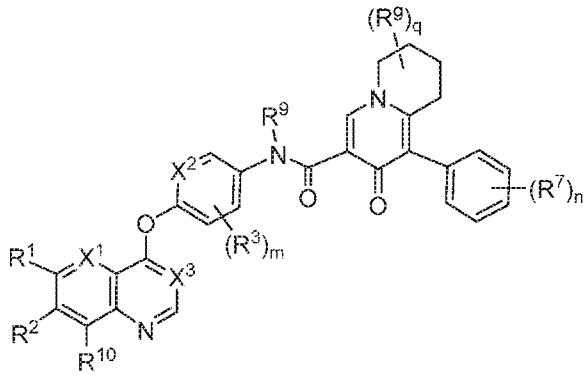
, or



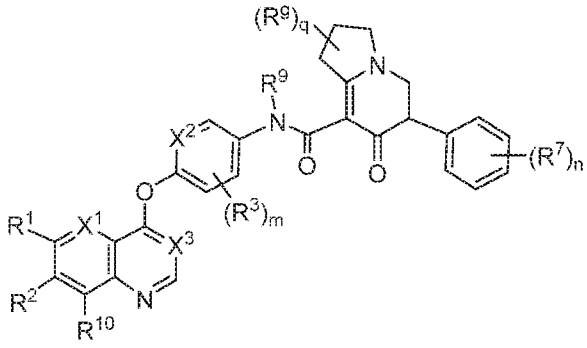
(It)



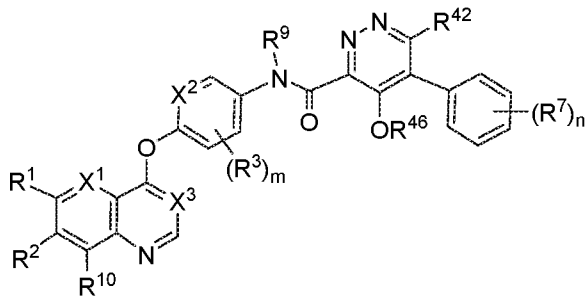
(Iu)



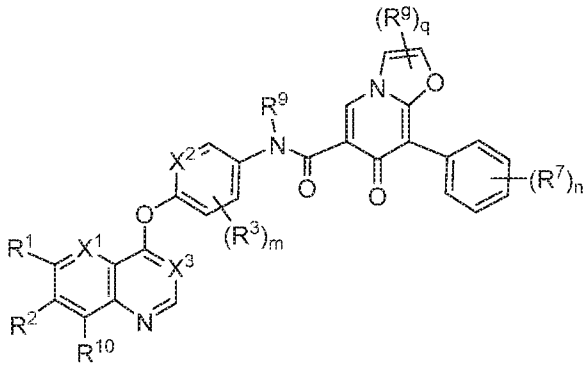
(Iv)



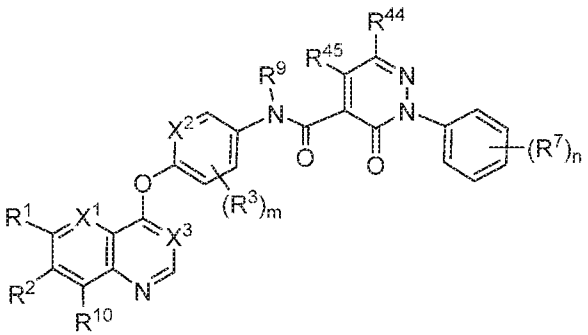
(Iw)



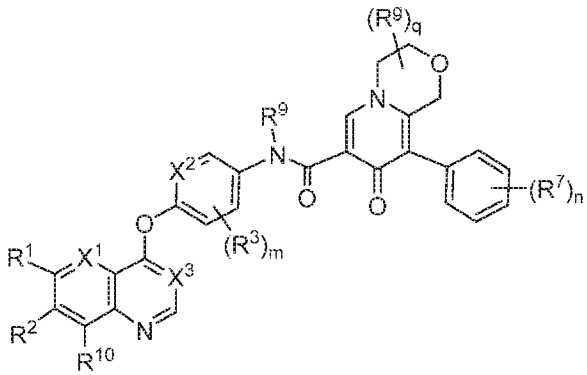
(Ix)



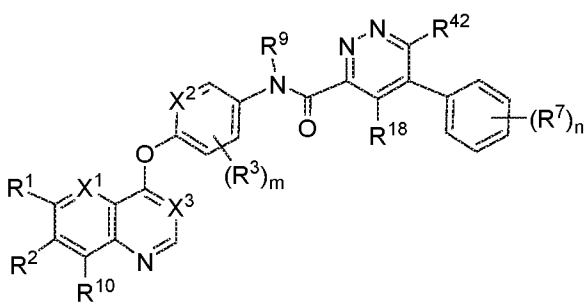
(Iy)



(Iz)



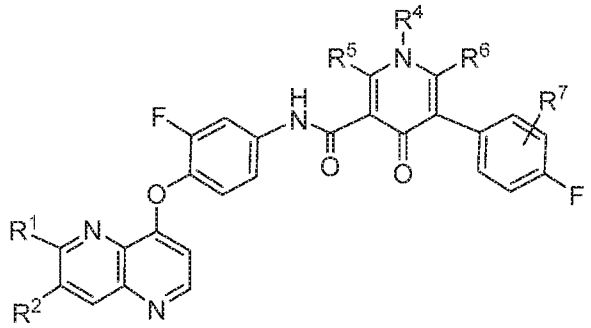
(Iaa)



(Ibb)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, wherein each subscript q is independently 0, 1, or 2.

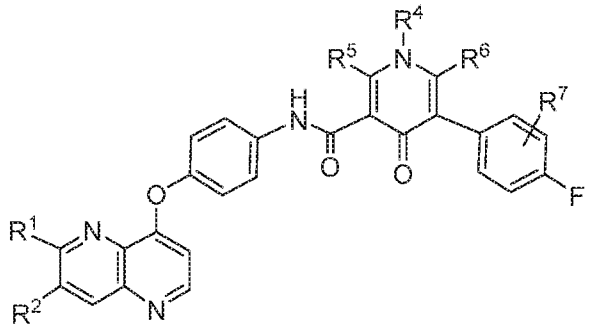
[0103] Some embodiments provide for a compound of formula (Ia-1):



(Ia-1)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof.

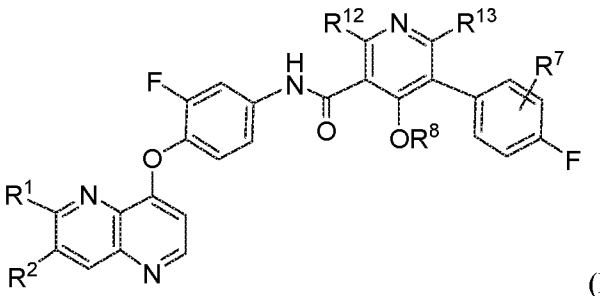
[0104] Some embodiments provide for a compound of formula (Ia-2):



(Ia-2)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof.

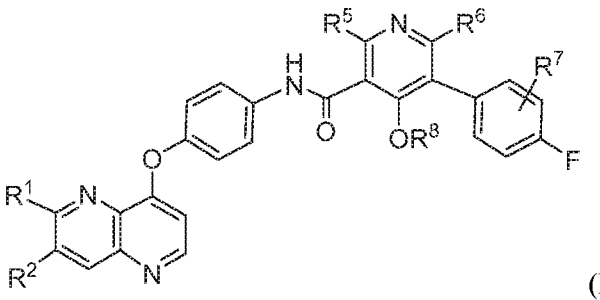
[0105] Some embodiments provide for a compound of formula (III-1):



(III-1)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof.

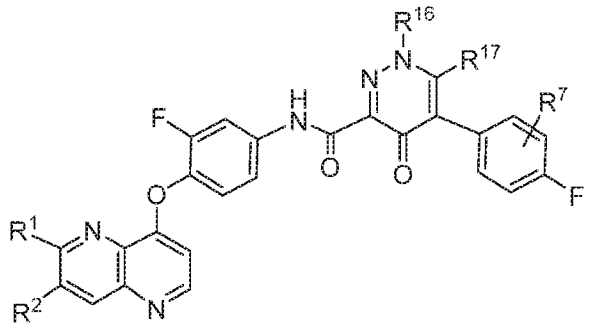
[0106] Some embodiments provide for a compound of formula (III-2):



(III-2)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof.

[0107] Some embodiments provide for a compound of formula (IV-1):

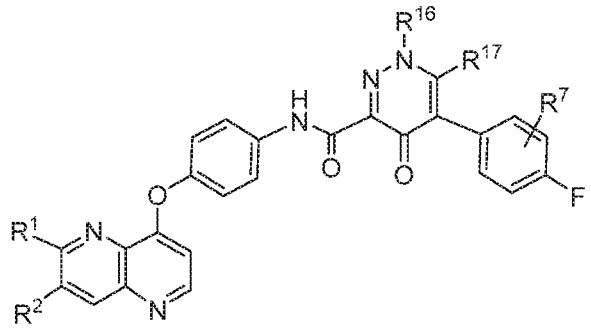


(IV-1)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof.

[0108] Some embodiments provide for a compound of formula (IV-1), or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, wherein R^{16} is H, C_{1-6} alkyl, or C_{1-6} haloalkyl; and R^{17} is H or C_{1-6} alkyl.

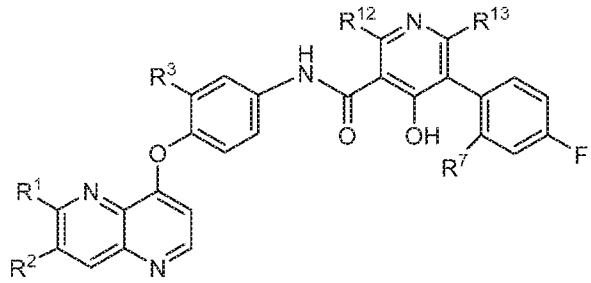
[0109] Some embodiments provide for a compound of formula (IV-2):



(IV-2)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof.

[0110] Some embodiments provide for a compound having formula (III-3):



(III-3)

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

R^1 is H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH

R^2 is C_{1-6} alkoxy;

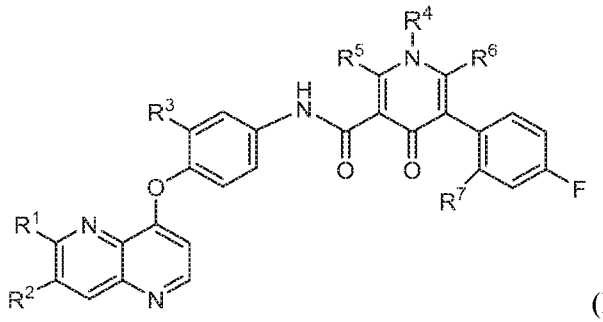
R^3 is H or halo;

R^{12} is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH;

R^{13} is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH; and

R^7 is H or C_{1-6} alkyl.

[0111] Some embodiments provide for a compound having formula (Ia-3):



(Ia-3)

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

R^1 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH

R^2 is C_{1-6} alkoxy;

R^3 is H or halo;

R^4 is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH;

R^5 is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH;

R^6 is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH and

R^7 is H or C_{1-6} alkyl.

[0112] Some embodiments provide for a compound having formula (Ia-3), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

R^1 is H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH;

R^2 is C_{1-6} alkoxy;

R^3 is H or halo;

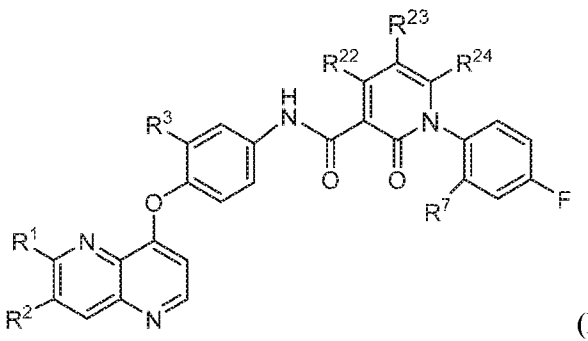
R^4 is H, C_{1-6} haloalkyl, or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH;

R^5 is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH;

R^6 is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH and

R^7 is H or C_{1-6} alkyl.

[0113] Some embodiments provide for a compound having formula (Ij-1):



(Ij-1)

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

R^1 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 is optionally substituted with C_{1-6} alkoxy or OH

R^2 is C_{1-6} alkoxy;

R^3 is H or halo;

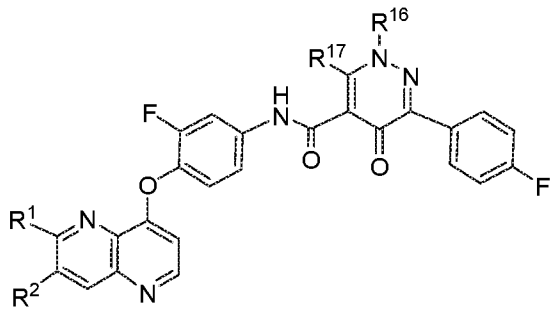
R^{22} is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH;

R^{23} is H, C_{1-6} alkyl or C_{1-6} alkyl-C(O)-, wherein the C_{1-6} alkyl and C_{1-6} alkyl-C(O)- of R^{23} are each optionally substituted with C_{1-6} alkoxy or OH;

R^{24} is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH and

R^7 is H or C_{1-6} alkyl.

[0114] Some embodiments provide for a compound of formula (V):



(V)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, wherein:

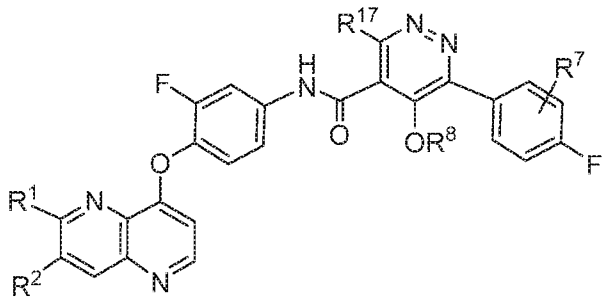
R^1 is H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH;

R^2 is C_{1-6} alkoxy;

R^{16} is H, C_{1-6} alkyl, or C_{1-6} haloalkyl; and

R^{17} is H or C_{1-6} alkyl.

[0115] Some embodiments provide for a compound of formula (VI):



(VI)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, wherein:

R^1 is H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH;

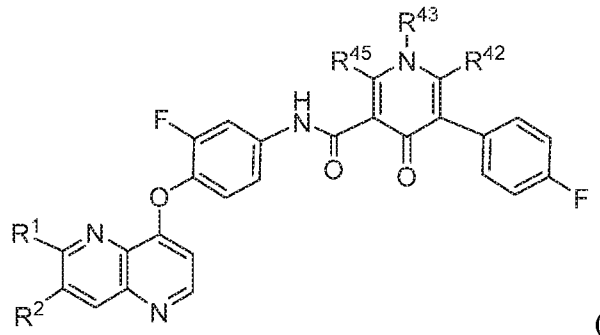
R^2 is C_{1-6} alkoxy;

R^7 is H or C_{1-6} alkyl.

R^8 is H or C_{1-6} alkyl; and

R^{17} is H or C_{1-6} alkyl.

[0116] Some embodiments provide for a compound of formula (VII):



(VII)

or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, wherein:

R^1 is H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH;

R^2 is C_{1-6} alkoxy;

R^{42} and R^{43} taken together with the atoms to which they are attached form 5- to 6-membered fused heterocycloalkyl having 0-1 additional ring heteroatoms selected from O and N; and

R^{45} is H or C_{1-6} alkyl.

[0117] Some embodiments provide for a compound of formula (VII), or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, wherein:

R^1 is H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH;

R^2 is C_{1-6} alkoxy;

R^{43} and R^{45} taken together with the atoms to which they are attached form 5- to 6-membered fused heterocycloalkyl having 0-1 additional ring heteroatoms selected from O and N; and

R^{42} is H or C_{1-6} alkyl.

[0118] In some embodiments, R^1 is H, C_{1-6} alkyl, C_{1-6} alkoxy, halo, NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, C_{1-6} alkylNHC(O)-, or C_{1-6}alkylSO_2NH-.

[0119] In some embodiments, R^2 is H, C_{1-6} alkyl, C_{1-6} alkoxy, halo, OH, NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -C_{1-6} alkylNHC(O)-, CF_3, C_{1-6} alkylOC(O)-, pyridyl, C_{1-6}alkylSO_2NH- or 1H-pyrazol-4-yl optionally substituted with R^g.

[0120] In some embodiments, R^3 is H or halo.

[0121] In some embodiments, R^7 is H, halo, C_{1-6} alkyl or C_{1-6} alkoxy.

[0122] In some embodiments, R^7 is H, CH_3, F, Cl or OCH_3.

[0123] In some embodiments, R^9 is H.

[0124] In some embodiments, R^{43}, R^4, R^{15}, R^{16}, R^{20}, R^{23}, R^{27} and R^{29} are each independently selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, OH, NH_2, -NHC_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkylene-, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-4} alkylene-, 5-6 membered heteroaryl, (5-6 membered heteroaryl)-C_{1-4} alkylene-, and N=C[N(C_{1-6} alkyl)(C_{1-6} alkyl)]$_2$, wherein the C_{1-6} alkyl, C_{1-6} alkoxy, -NHC_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkylene-, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-4} alkylene-, 5-6 membered heteroaryl, (5-6 membered heteroaryl)-C_{1-4} alkylene-, and N=C[N(C_{1-6} alkyl)(C_{1-6} alkyl)]$_2$ of R^{43}, R^4, R^{15}, R^{16}, R^{20}, R^{23}, R^{27} and R^{29} are each optionally substituted with 1 or 2 independently selected R^b or R^g substituents.

[0125] In some embodiments, R^{43}, R^4, R^{15}, R^{16}, R^{20}, R^{23}, R^{27} and R^{29} are each independently selected from H, methyl, isopropyl, t-butyl, ethyl, OH, methoxy, NH_2, methylamino, dimethylamino, -$N=C(N(CH_3)_2)_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopropyl, 1-(trifluoromethyl)cyclopropyl, oxetan-3-yl, 3-methyloxetan-3-yl, 2,2,2-trifluoroethyl, azetidin-3-yl, 1-methylazetidin-3-yl, 1-t-butoxycarbonylazetidin-3-yl, morpholino, 2-morpholinoethyl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1-methylpyrazol-4-yl, 1-(difluoromethyl)pyrazol-4-yl, 2-hydroxyethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-(imidazol-1-yl)ethyl, 2-(benzotriazol-1-yloxy)ethyl, and 2-hydroxy-1,1-dimethyl-ethyl, each of which when applicable is optionally substituted with 1 or 2 independently selected R^g substituents.

[0126] In some embodiments, R^{45}, R^{42}, R^{44}, R^5, R^{17} and R^6 are each independently selected from H, OH, halo, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl-C(O)- and C_{1-6} alkylamino, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl-C(O)- and C_{1-6} alkylamino of R^{45}, R^{42}, R^{44}, R^5, R^{17} and R^6 are each optionally substituted with 1 or 2 independently selected R^g substituents.

[0127] In some embodiments, R^{45}, R^{42}, R^{44}, R^5 and R^6 are each independently selected from H, CH_3, propen-2-yl, Br, Cl, CN, methoxy, 2-fluoroethyl, isopropyl, $CH_3C(O)$-, OH, t-butyl, ethyl, hydroxymethyl, isopropylthio, and methoxymethyl.

[0128] In some embodiments, R^{45}, R^{42}, and R^{44} are each independently selected from H and C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents.

[0129] some embodiments, R^{40}, R^{41} and R^{43} are each independently selected from H, halo, and C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents.

[0130] In some embodiments, R^{46}, R^8 and R^{32} are each independently H or C_{1-6} alkyl.

[0131] In some embodiments, R^{18} is H or halo.

[0132] In some embodiments, X^1 is N.

[0133] In some embodiments, X^2 is CH. In some embodiments, X^2 is CR^3. In some embodiments, X^2 is CR^3, and R^3 is halo.

[0134] In some embodiments, X^3 is CH.

[0135] In some embodiments, X^1 is N and X^3 is CH.

[0136] In some embodiments, X^4 is CR^2. In some embodiments, X^4 is N.

[0137] In some embodiments, X^1 is N, X^3 is CH, and X^4 is CR^2.

[0138] In some embodiments, X^1 is CH, X^3 is CH, and X^4 is N.

[0139] In some embodiments, X^5 is CH. In some embodiments, X^5 is CR^3.

[0140] In some embodiments, X^2 is CR^3, X^5 is CH, and R^3 is halo.

[0141] In some embodiments, the subscript m is 0. In other embodiments, m is 1 and R^3 is F or H. In other embodiments, m is 1 and R^3 is F.

[0142] In some embodiments, the subscript n is 0.

[0143] In some embodiments, the subscript n is 1 and R^7 is F. In other embodiments, the n is 2 and R^7 is independently selected from CH_3, F, Cl and OCH_3.

[0144] In some embodiment, the subscript p is 1.

[0145] In some embodiment, the subscript q is 1.

[0146] Some embodiments provide for a compound selected from:

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

5-(3,4-dichlorophenyl)-N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

5-(3-chloro-4-fluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

5-(3,4-dichlorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

1-cyclopentyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide;

5-(3-chloro-4-fluorophenyl)-1-cyclopentyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-5-phenyl-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-methoxyphenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-methoxyphenyl)-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1,6-dimethyl-4-oxo-5-phenylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide;

5-(4-chlorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide;

1-cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide;

N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide;

1-cyclopentyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(oxetan-3-yl)-4-oxopyridine-3-carboxamide;

1-tert-butyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide;

1-cyclobutyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylazetidin-3-yl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-3-yl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(3-methyloxetan-3-yl)-4-oxopyridine-3-carboxamide;

N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-1-(3-methyloxetan-3-yl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-hydroxy-2-methylpropan-2-yl)-4-oxopyridine-3-carboxamide;

N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-hydroxy-2-methylpropan-2-yl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-[1-(trifluoromethyl)cyclopropyl]pyridine-3-carboxamide;

1-[1-(difluoromethyl)pyrazol-4-yl]-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(1H-pyrazol-3-yl)pyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(1H-pyrazol-4-yl)pyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide;

N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide;

N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide;

N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(hydroxymethyl)pyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-6-(methylamino)-4-oxopyridine-3-carboxamide;

6-cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methoxy-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(trifluoromethyl)pyridine-3-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide;

N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide;

N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxopyridine-3-carboxamide;

5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide;

5-cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide;

N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-5,6-dimethyl-3-oxopyrazine-2-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-5-hydroxypyrimidine-4-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methyl-6-oxopyrimidine-5-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-(methylamino)-6-oxopyrimidine-5-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(dimethylamino)-1-(4-fluorophenyl)-6-oxopyrimidine-5-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyrimidine-5-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-2,4-dioxo-1H-pyrimidine-5-carboxamide;

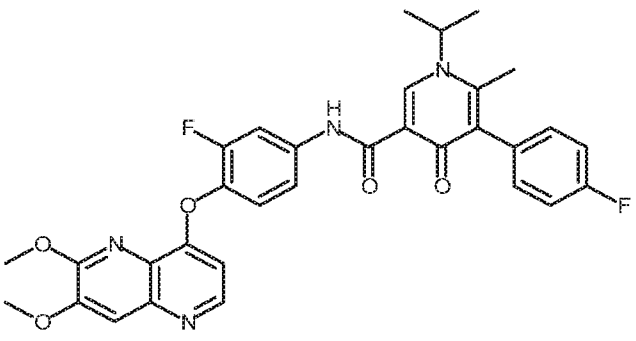
N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-3-(4-fluorophenyl)-2,4-dioxo-1H-pyrimidine-5-carboxamide; and

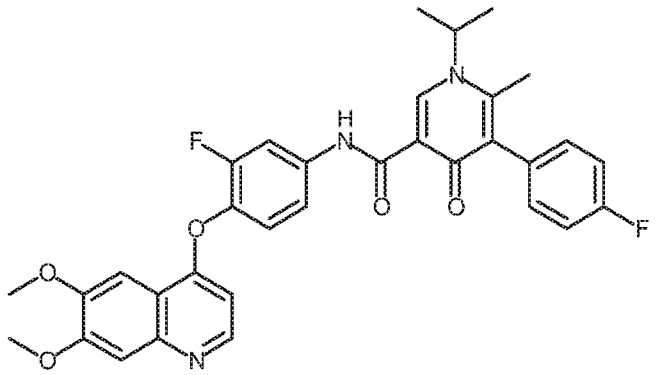
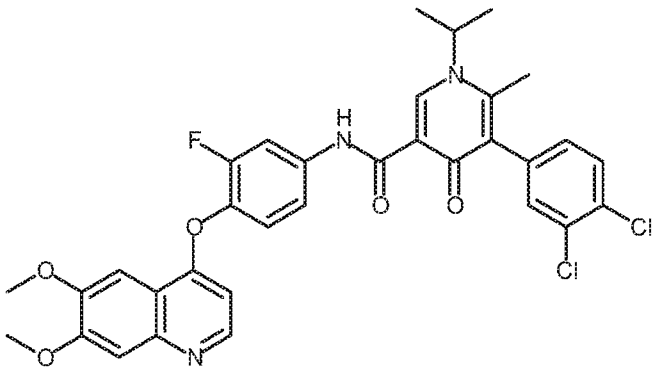
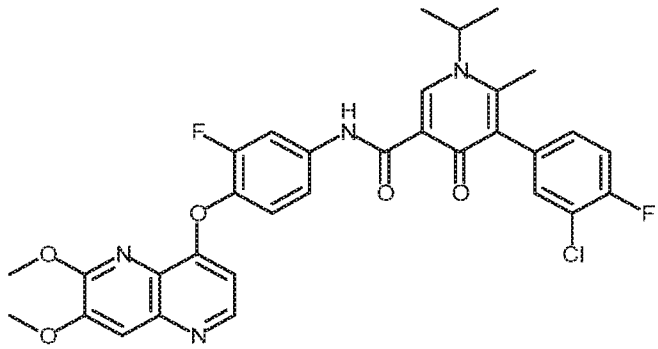
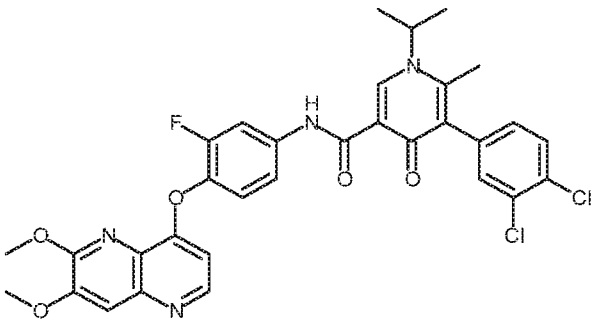
N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-4-oxo-2-sulfanylidene-1H-pyrimidine-5-carboxamide;

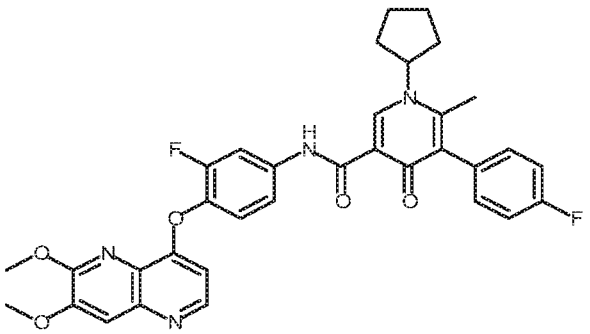
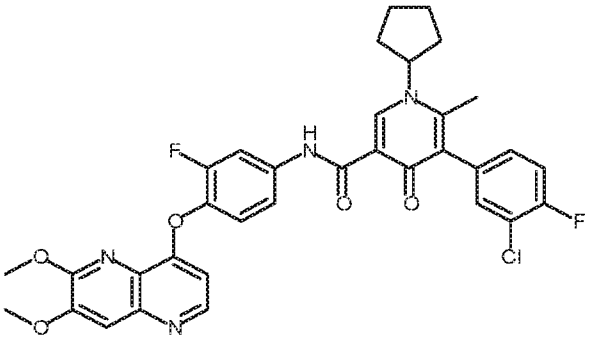
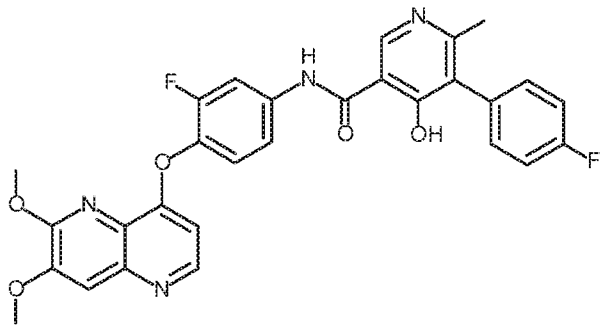
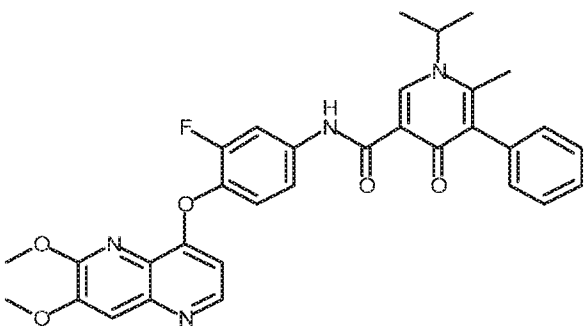
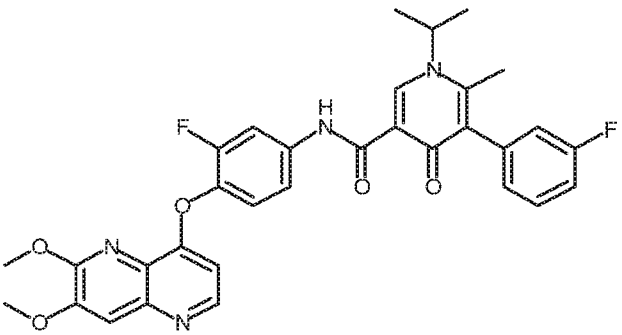
or a pharmaceutically acceptable salt or stereoisomer thereof.

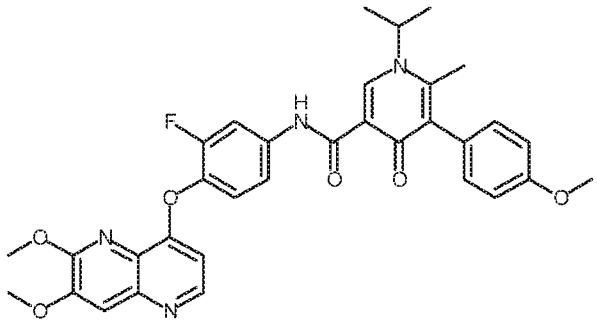
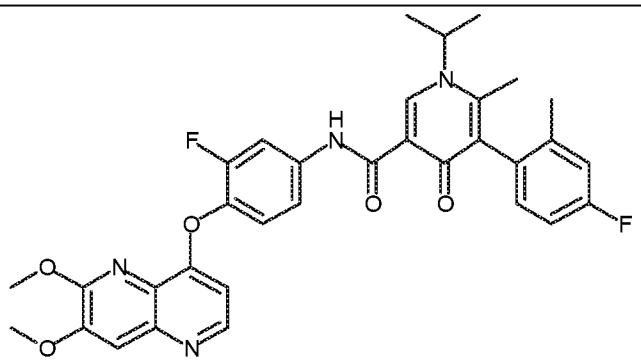
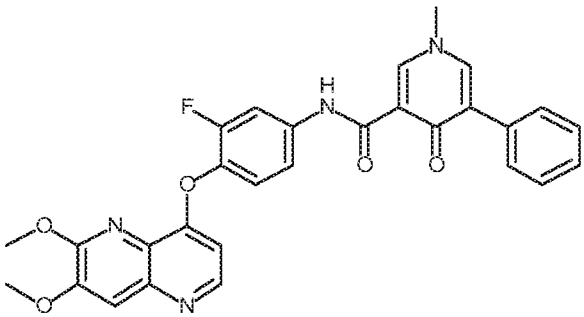
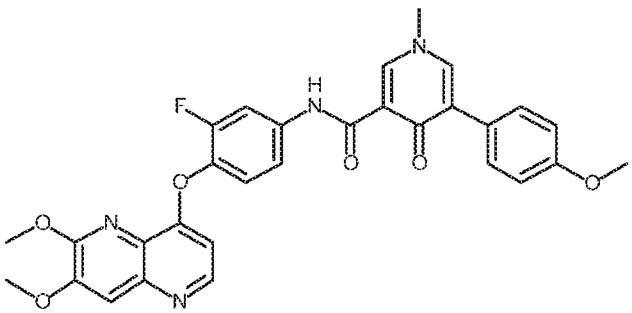
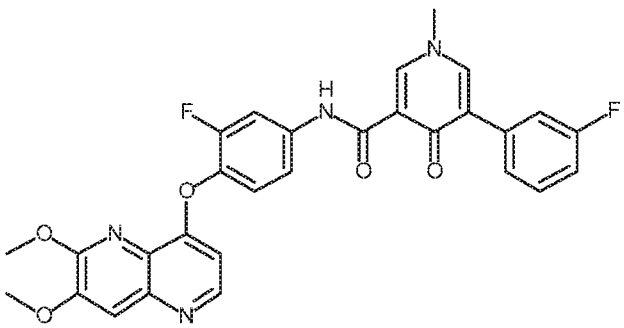
[0147] In some embodiments, provided is a compound, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from Table 1:

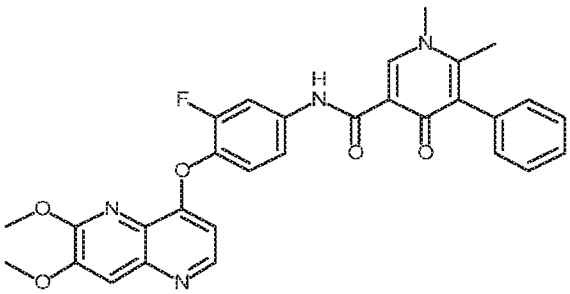
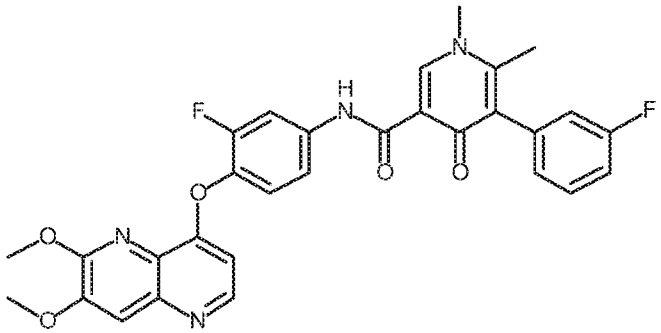
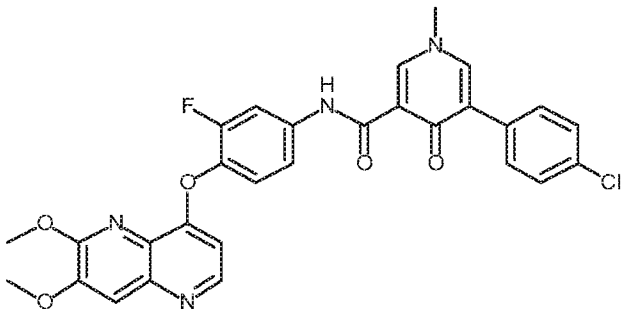
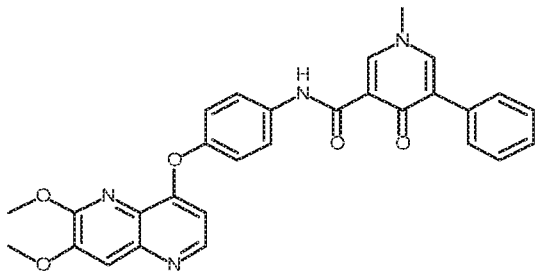
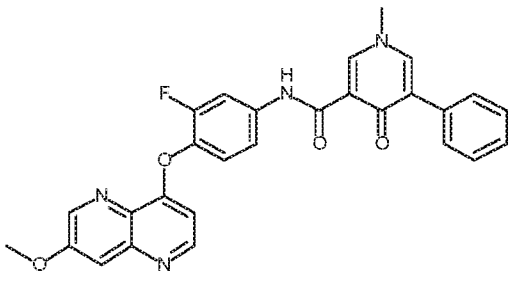
Table 1

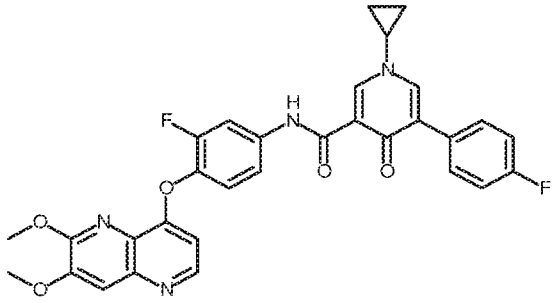
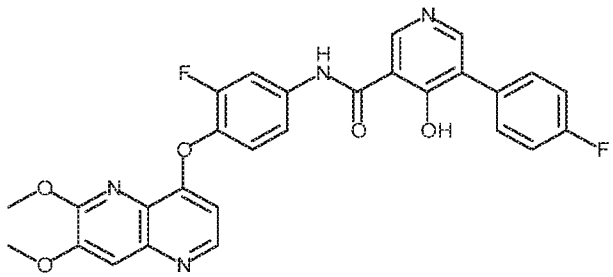
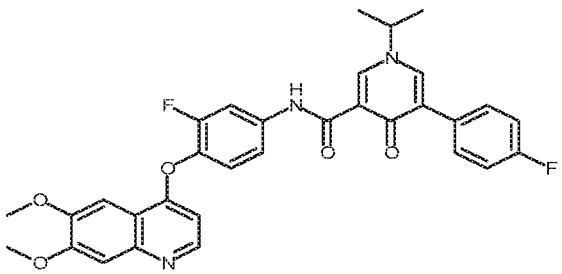
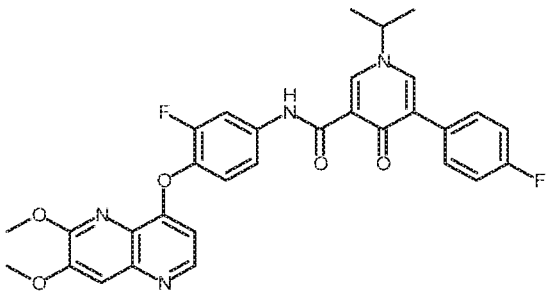
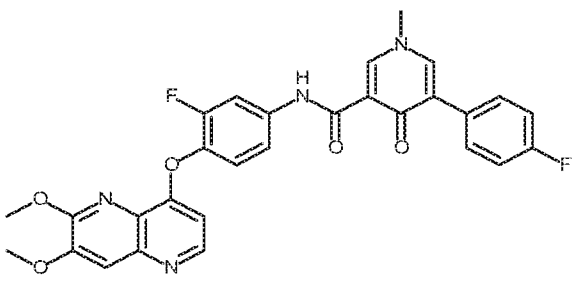
Cpd #	Structure	IUPAC Name
21		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide

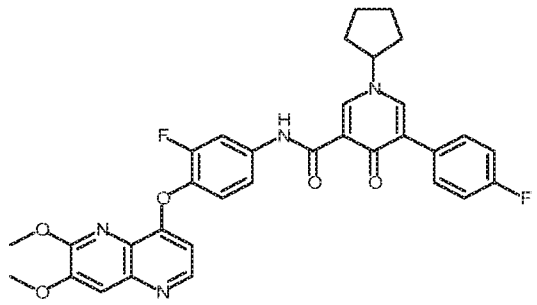
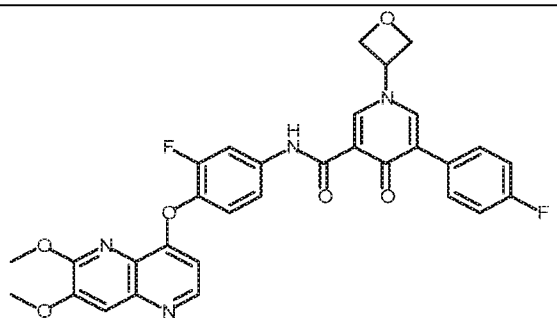
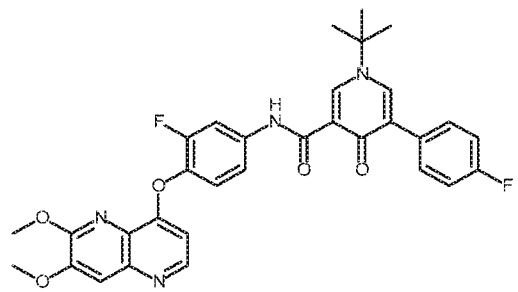
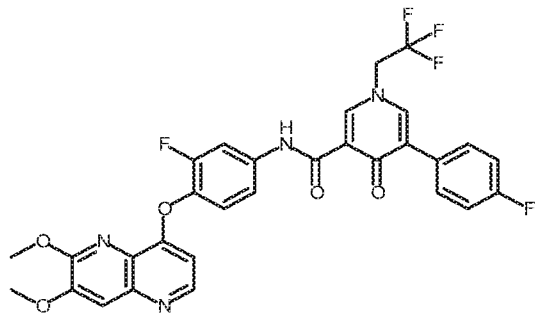
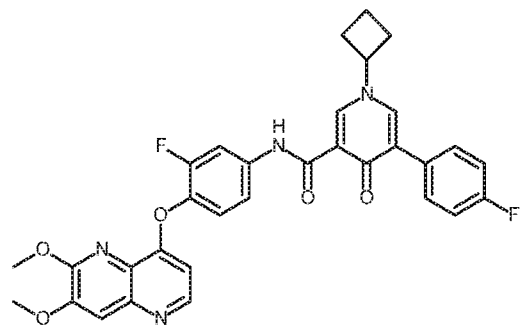
22		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
23		5-(3,4-dichlorophenyl)-N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
24		5-(3-chloro-4-fluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
25		5-(3,4-dichlorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide

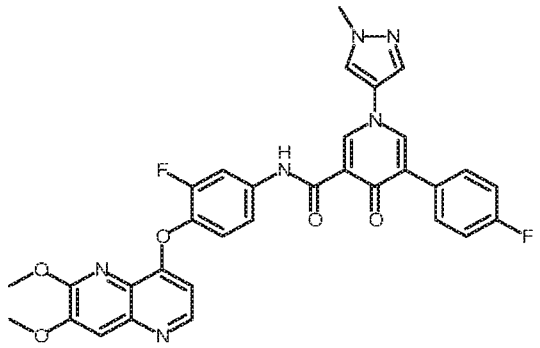
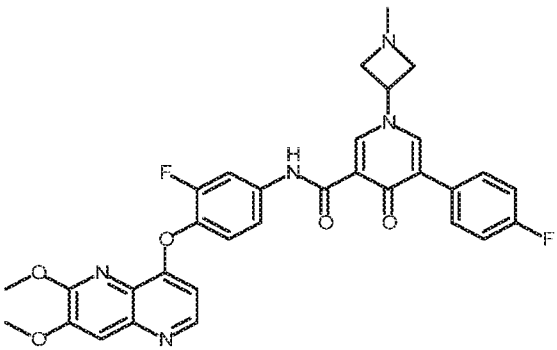
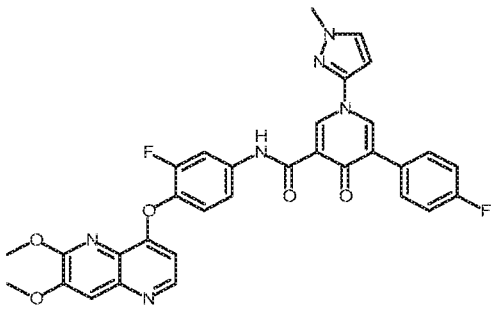
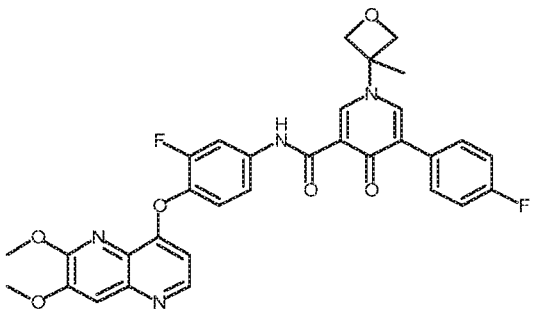
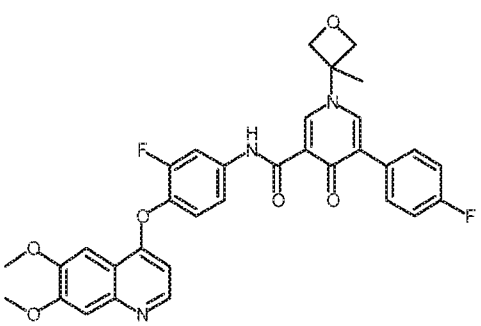
26		1-cyclopentyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
27		5-(3-chloro-4-fluorophenyl)-1-cyclopentyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxopyridine-3-carboxamide
28		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
29		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-5-phenyl-1-propan-2-ylpyridine-3-carboxamide
30		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide

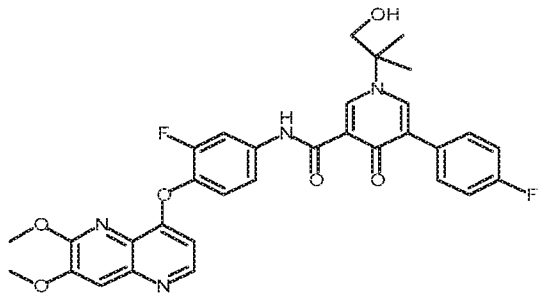
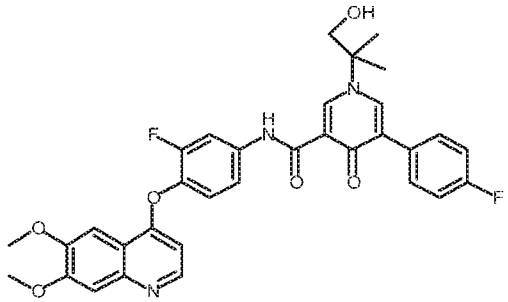
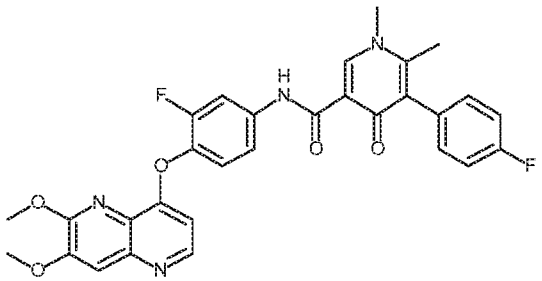
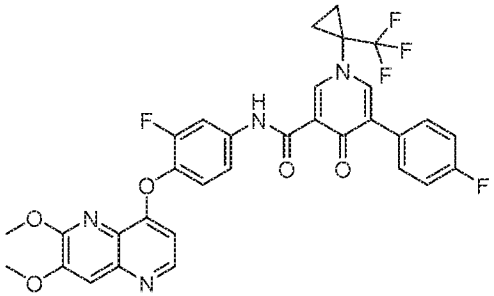
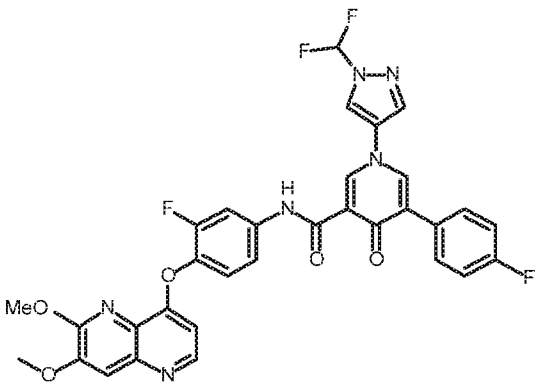
31		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-methoxyphenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
32		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
33		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide
34		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-methoxyphenyl)-1-methyl-4-oxopyridine-3-carboxamide
35		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide

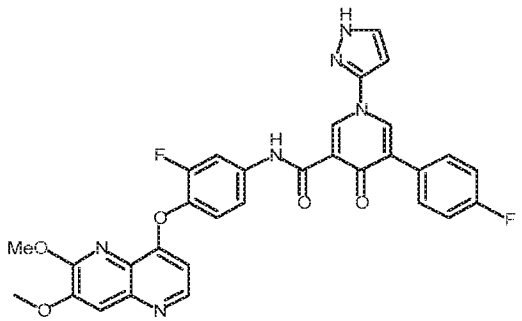
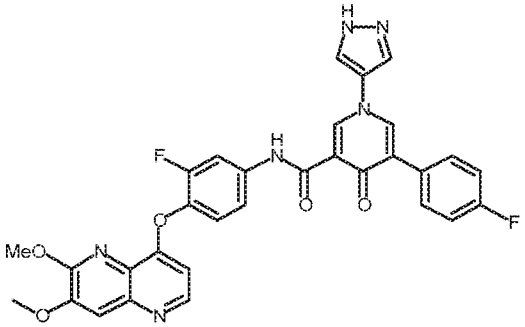
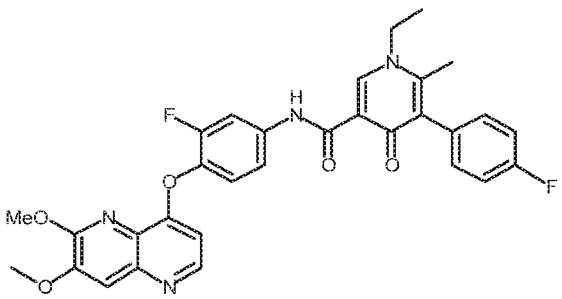
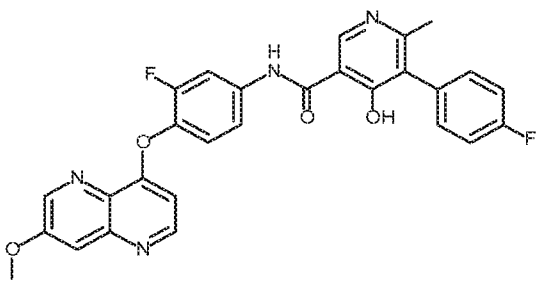
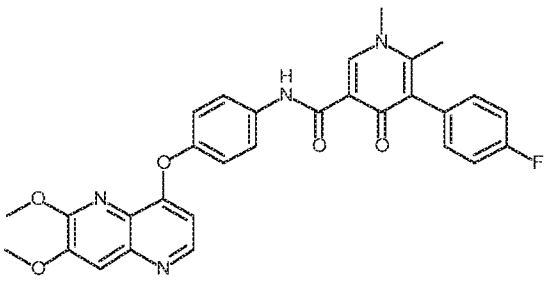
36		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1,6-dimethyl-4-oxo-5-phenylpyridine-3-carboxamide
37		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
38		5-(4-chlorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-methyl-4-oxopyridine-3-carboxamide
39		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide
40		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide

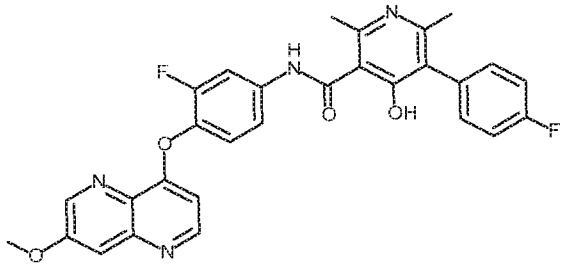
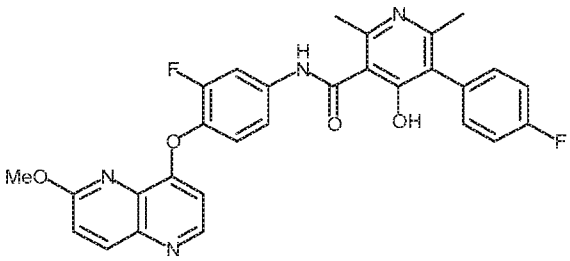
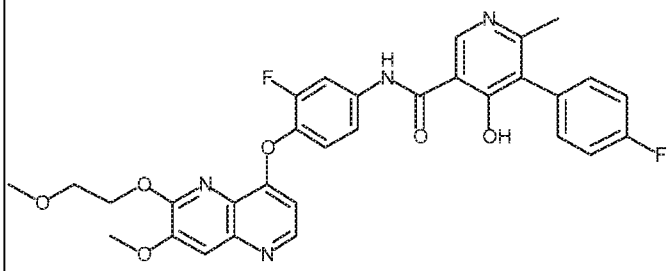
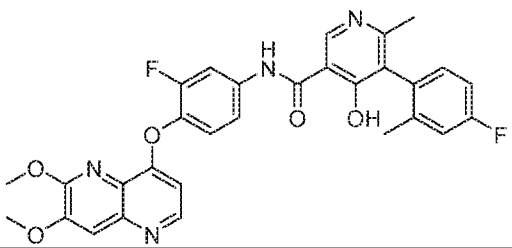
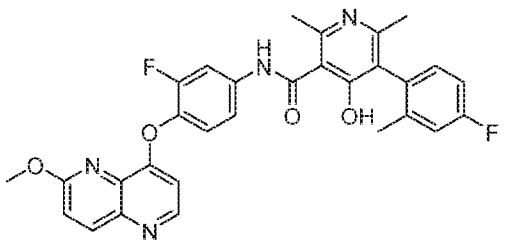
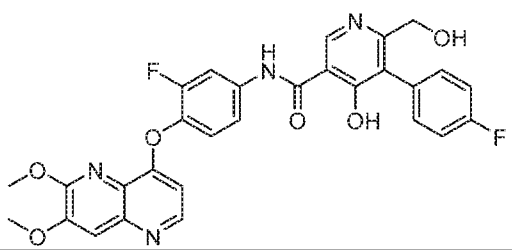
41		1-cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide
42		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide
43		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide
44		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide
45		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide

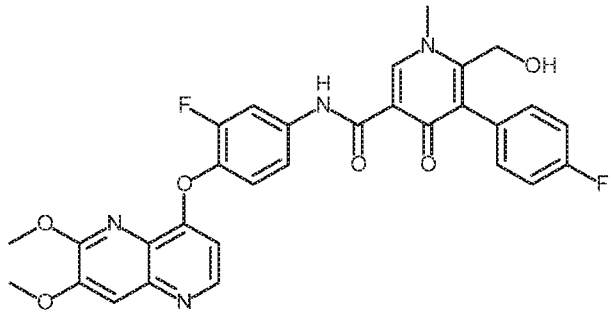
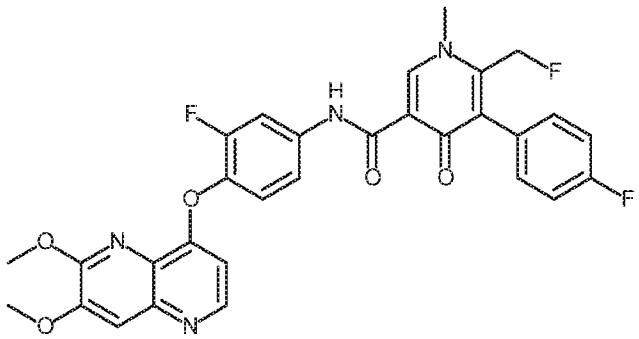
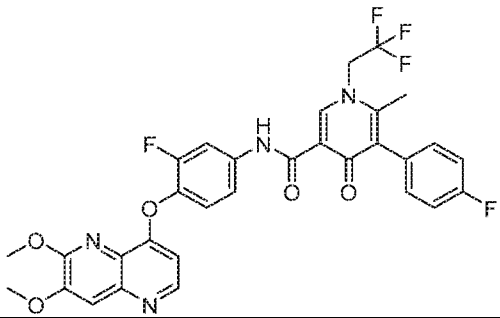
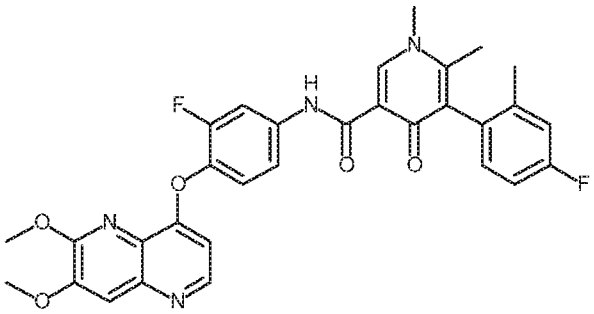
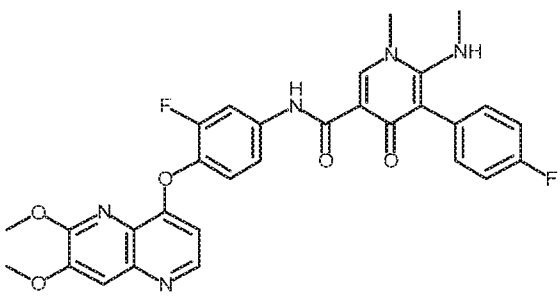
46		1-cyclopentyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide
47		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(oxetan-3-yl)-4-oxopyridine-3-carboxamide
48		1-tert-butyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide
49		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide
50		1-cyclobutyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide

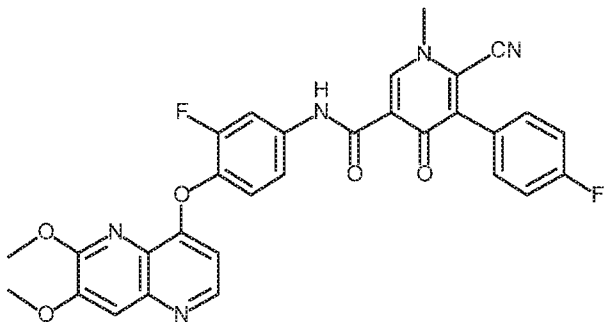
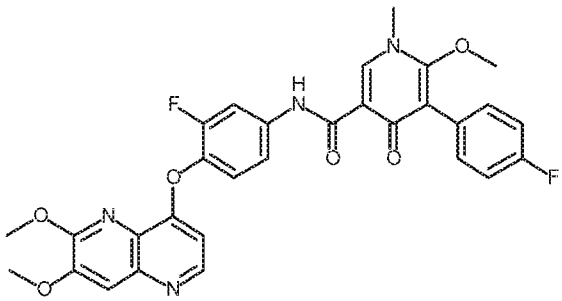
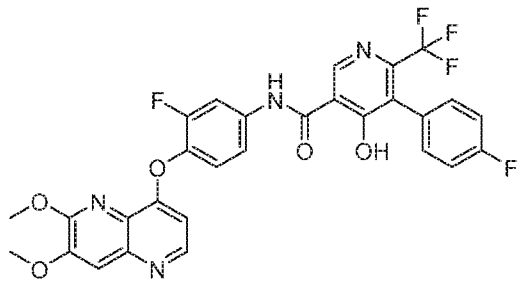
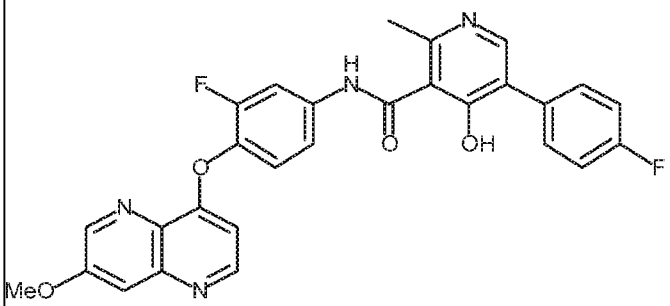
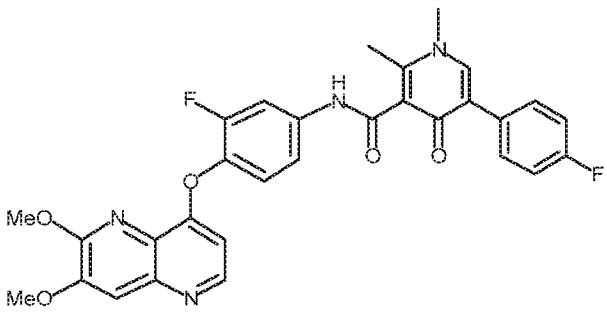
51		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide
52		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylazetidin-3-yl)-4-oxopyridine-3-carboxamide
53		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-3-yl)-4-oxopyridine-3-carboxamide
54		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(3-methyloxetan-3-yl)-4-oxopyridine-3-carboxamide
55		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-1-(3-methyloxetan-3-yl)-4-oxopyridine-3-carboxamide

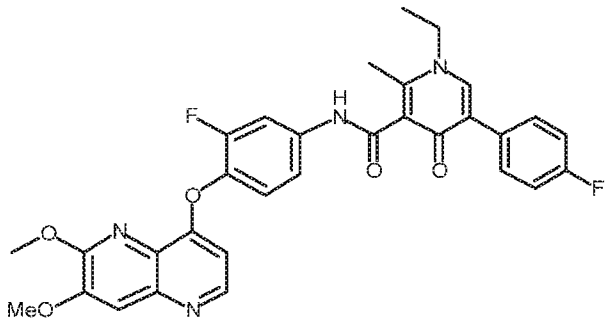
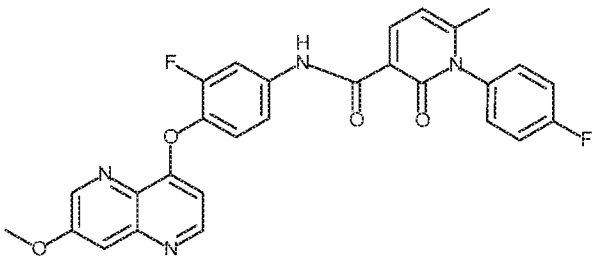
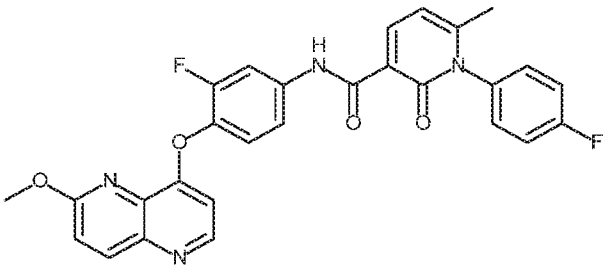
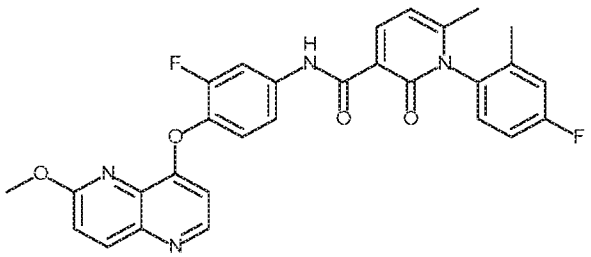
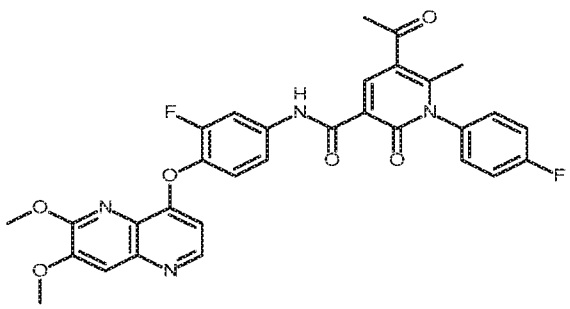
56		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-hydroxy-2-methylpropan-2-yl)-4-oxopyridine-3-carboxamide
57		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-hydroxy-2-methylpropan-2-yl)-4-oxopyridine-3-carboxamide
58		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
59		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-[1-(trifluoromethyl)cyclopropyl]pyridine-3-carboxamide
60		1-[1-(difluoromethyl)pyrazol-4-yl]-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide

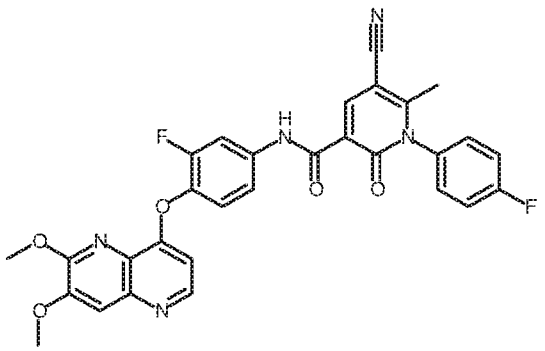
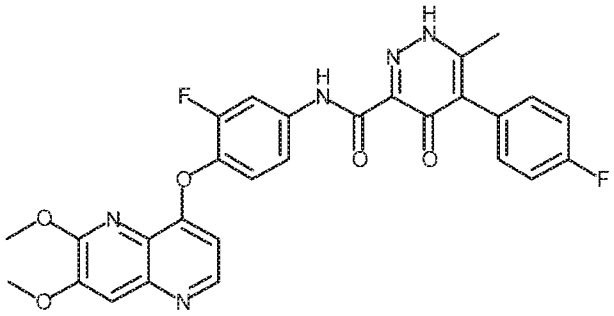
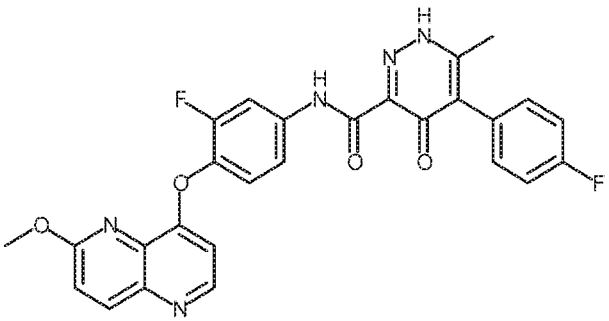
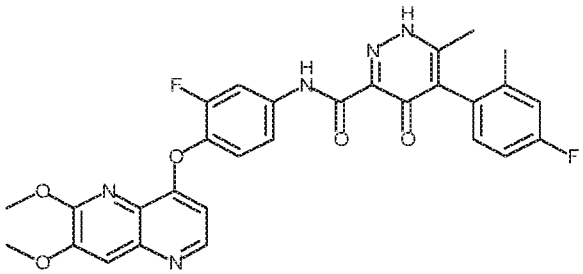
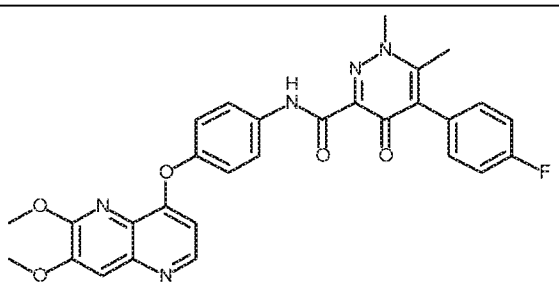
61		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(1H-pyrazol-3-yl)pyridine-3-carboxamide
62		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(1H-pyrazol-4-yl)pyridine-3-carboxamide
63		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
64		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
65		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide

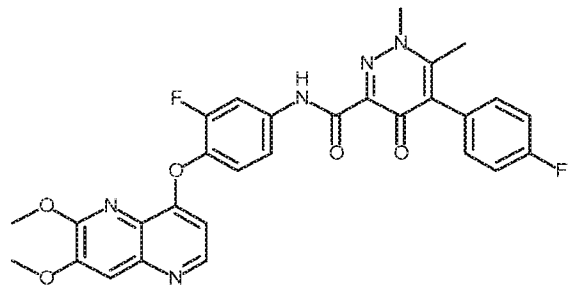
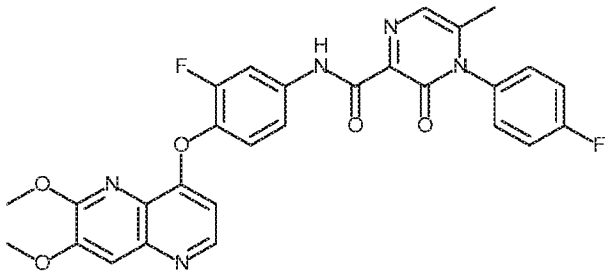
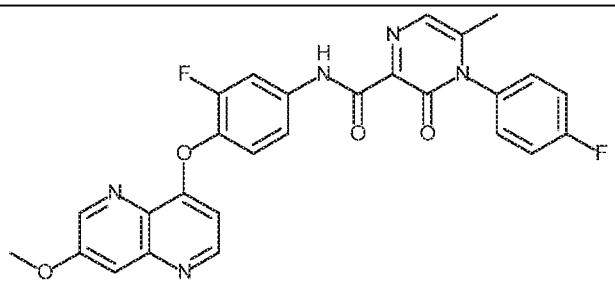
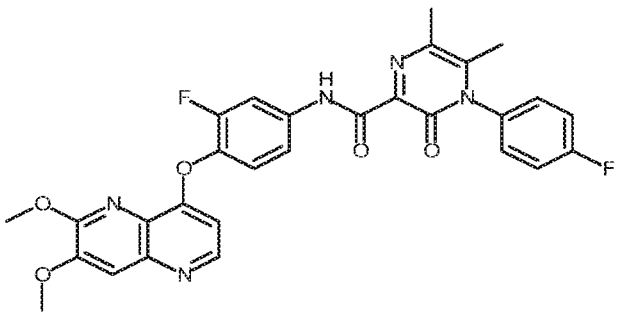
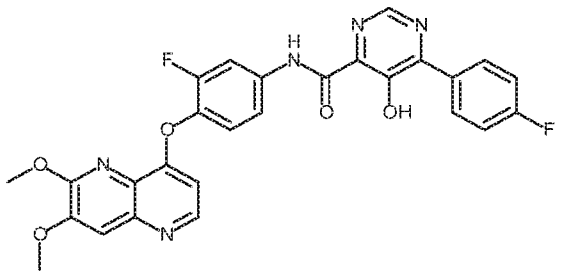
66		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
67		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
68		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
69		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
70		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
71		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(hydroxymethyl)pyridine-3-carboxamide

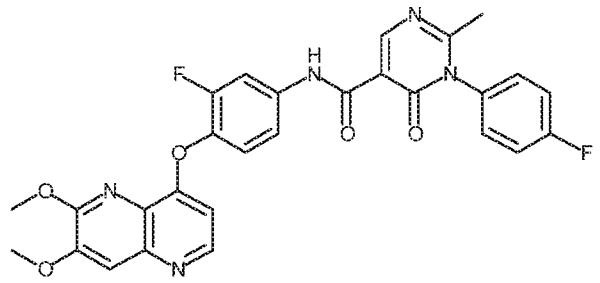
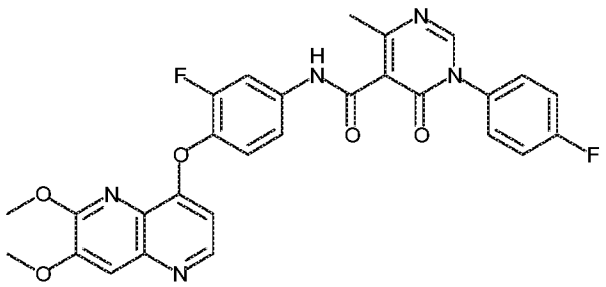
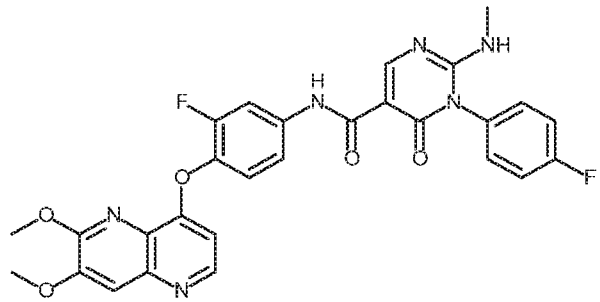
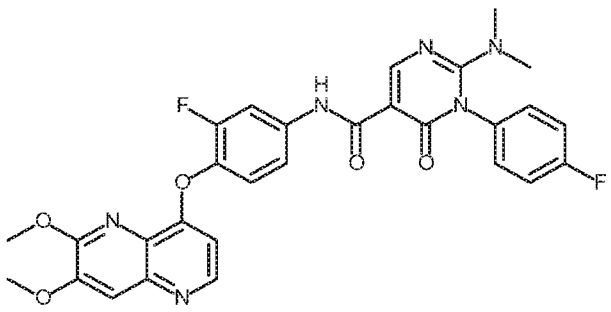
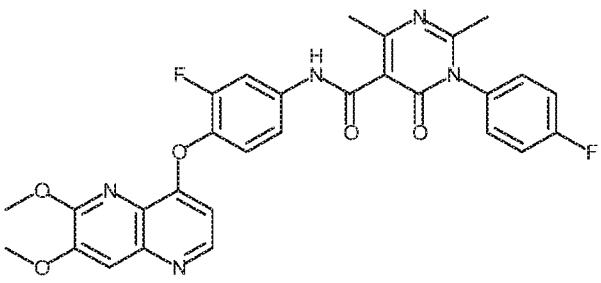
72		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide
73		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide
74		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide
75		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
76		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-6-(methylamino)-4-oxopyridine-3-carboxamide

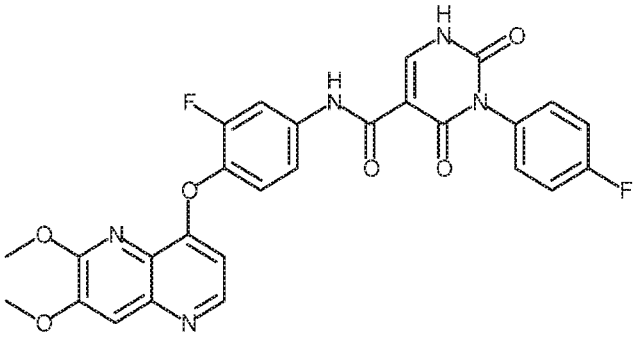
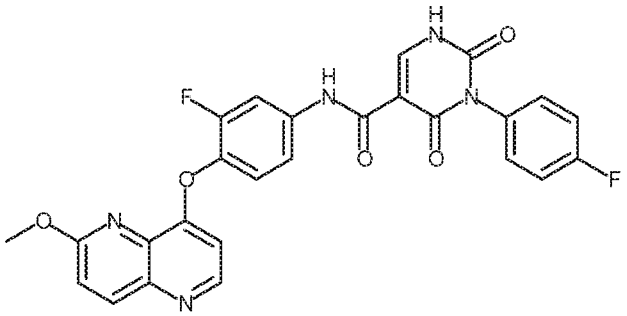
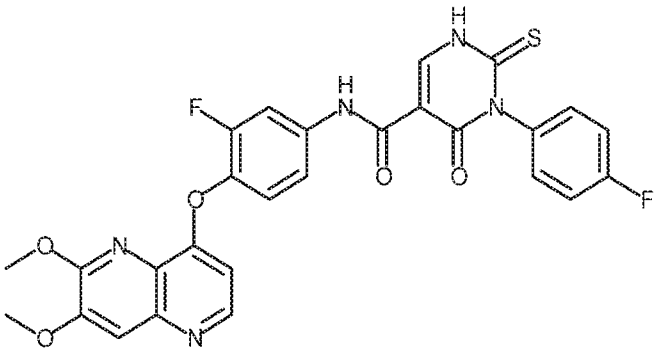
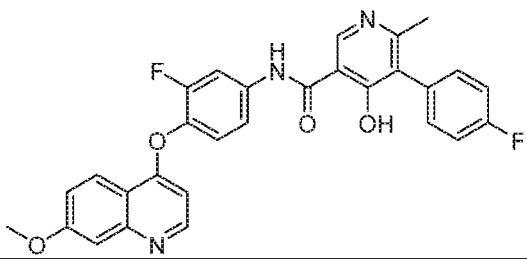
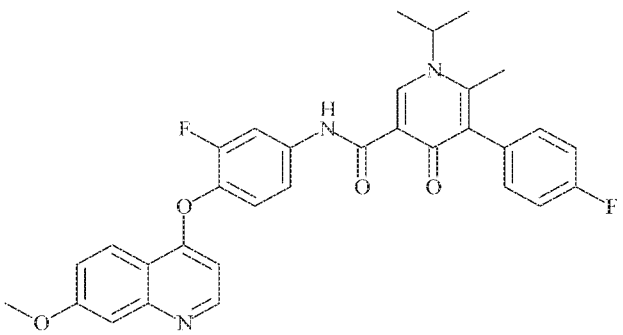
77		6-cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide
78		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methoxy-1-methyl-4-oxopyridine-3-carboxamide
79		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(trifluoromethyl)pyridine-3-carboxamide
80		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide
81		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide

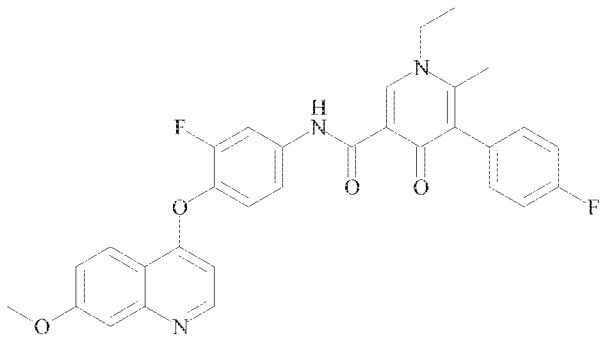
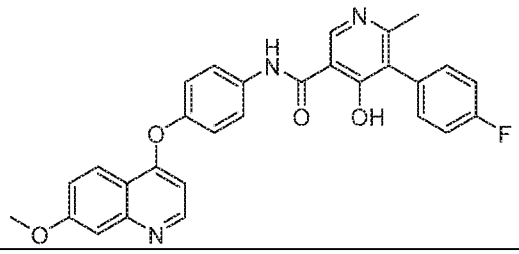
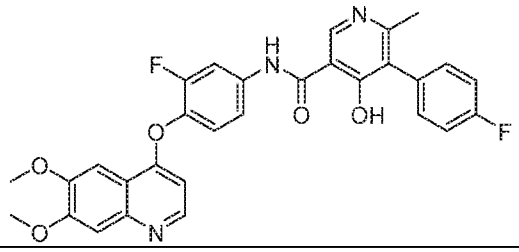
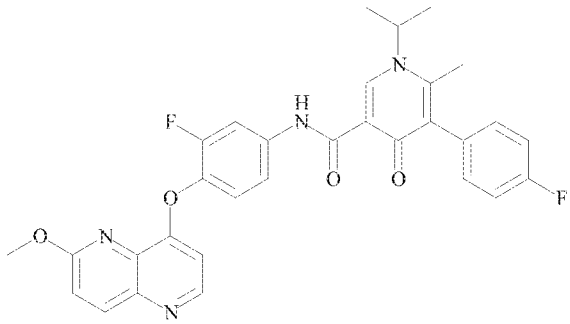
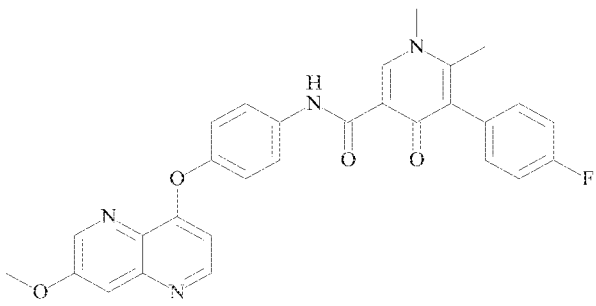
82		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide
83		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
84		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
85		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxopyridine-3-carboxamide
86		5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide

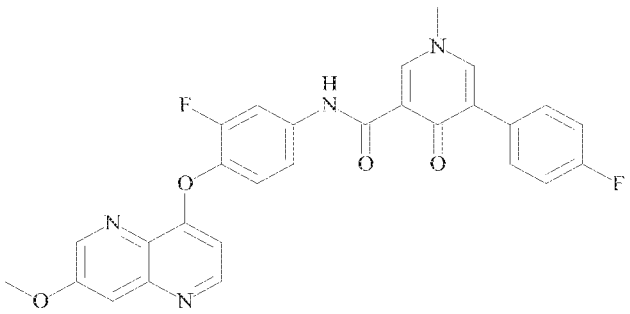
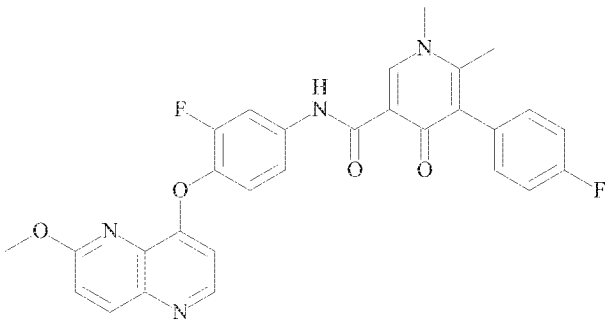
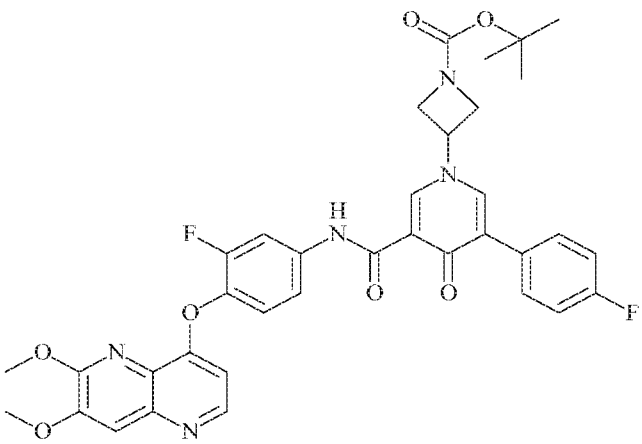
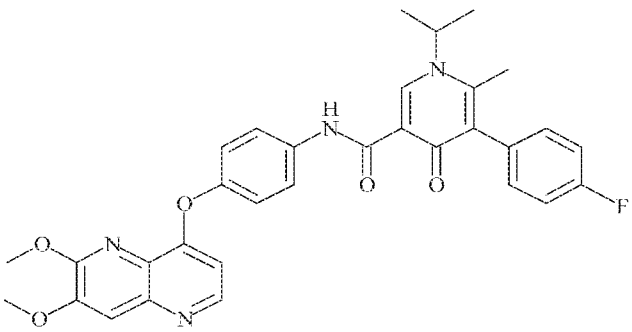
87		5-cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
88		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
89		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
90		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
91		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide

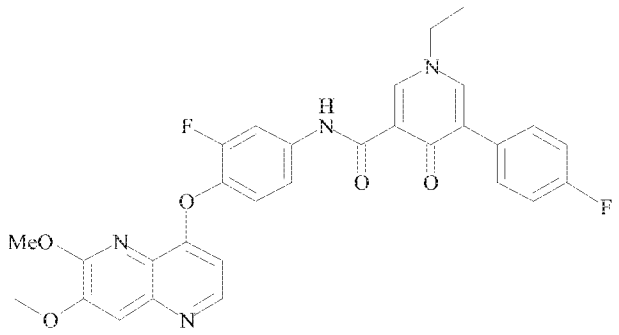
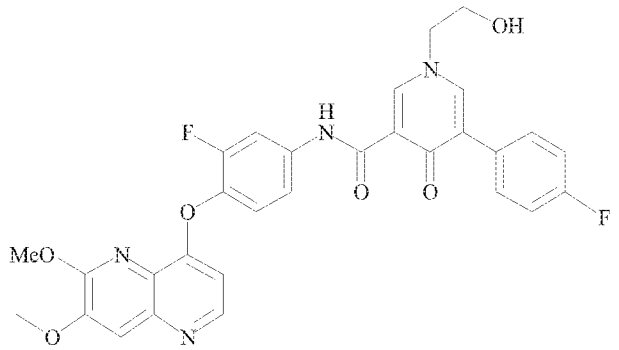
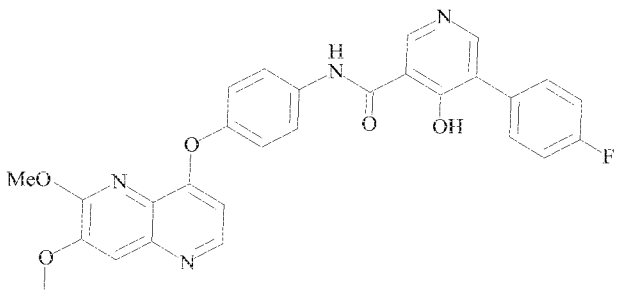
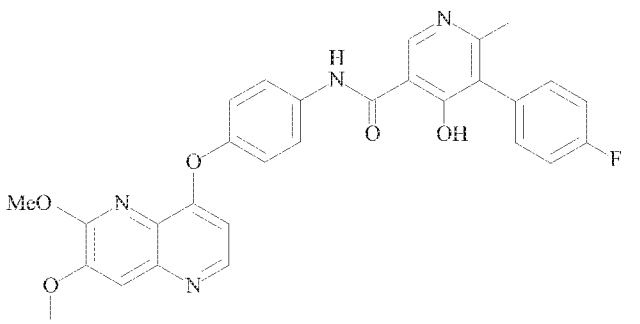
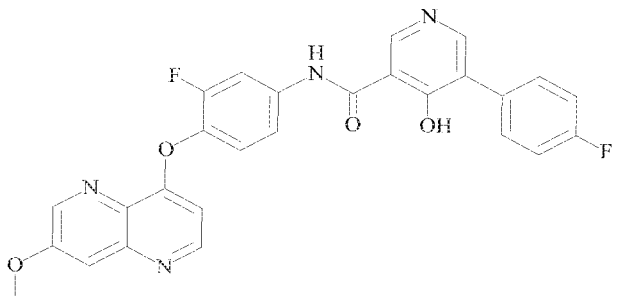
92		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide
93		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide
94		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide
95		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-5,6-dimethyl-3-oxopyrazine-2-carboxamide
96		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-5-hydroxypyrimidine-4-carboxamide

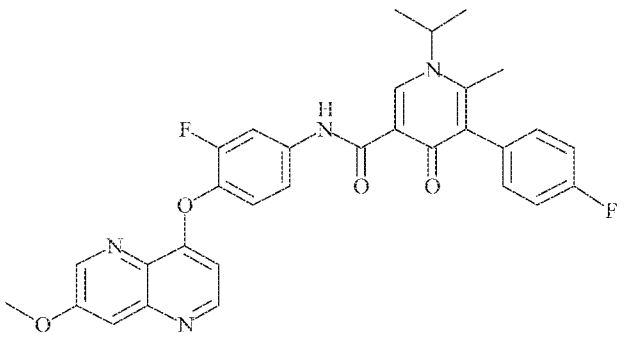
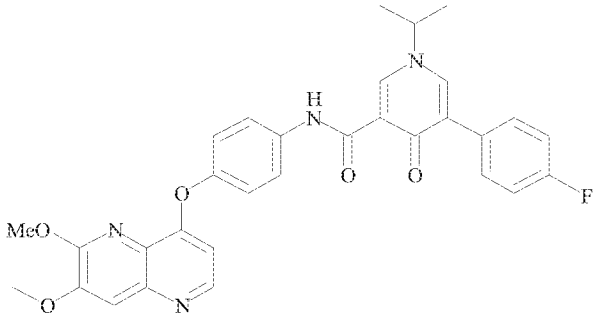
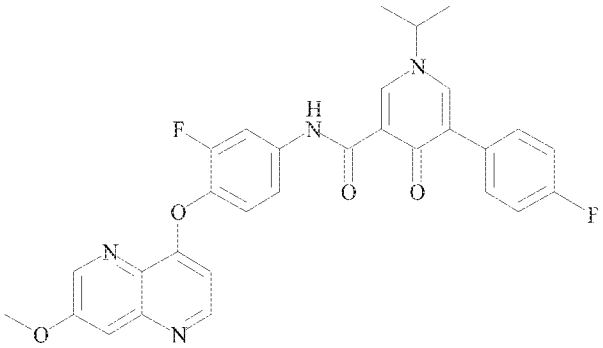
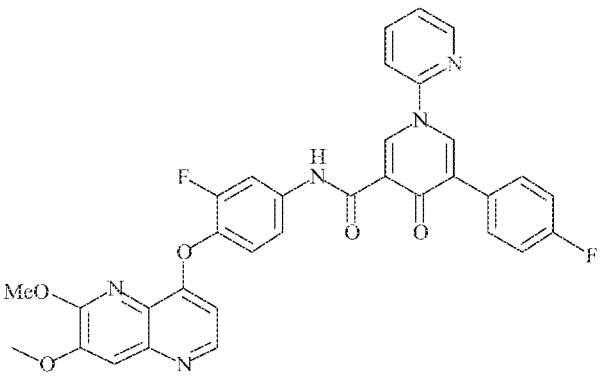
97		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide
98		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methyl-6-oxopyrimidine-5-carboxamide
99		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-(methylamino)-6-oxopyrimidine-5-carboxamide
100		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(dimethylamino)-1-(4-fluorophenyl)-6-oxopyrimidine-5-carboxamide
101		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyrimidine-5-carboxamide

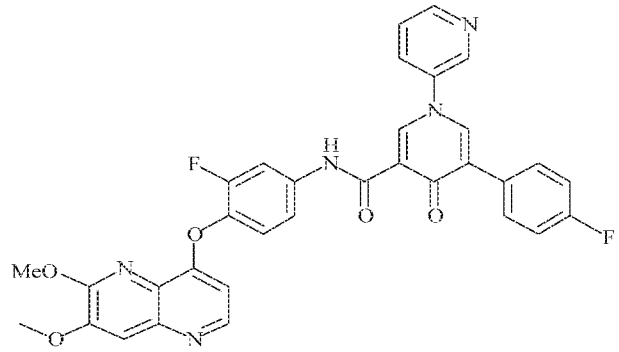
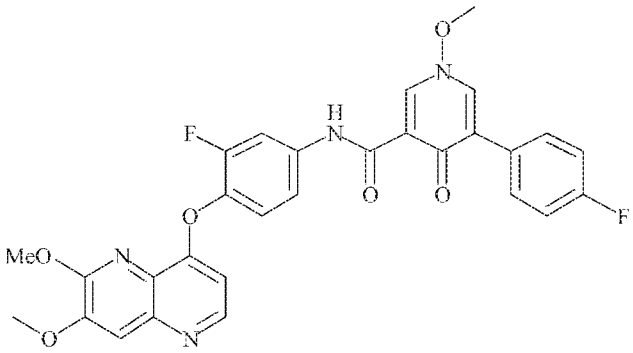
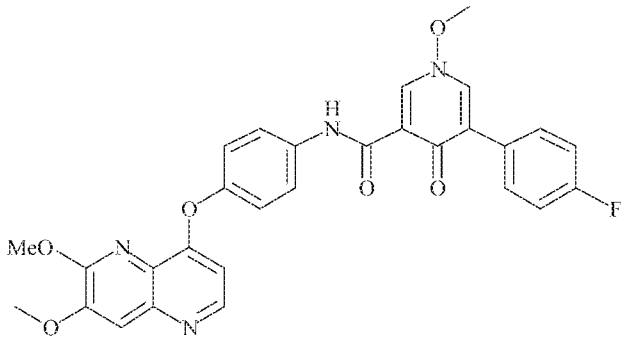
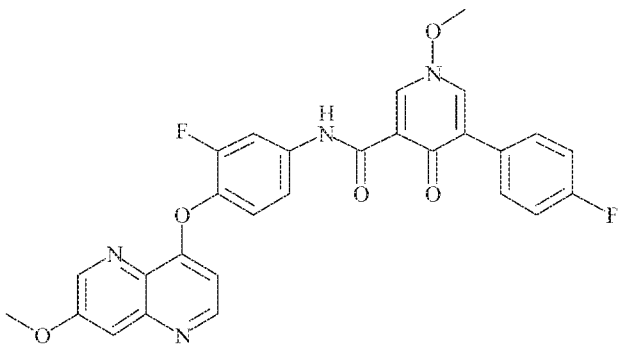
102		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-2,4-dioxo-1H-pyrimidine-5-carboxamide
103		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-3-(4-fluorophenyl)-2,4-dioxo-1H-pyrimidine-5-carboxamide
104		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-4-oxo-2-sulfanylidene-1H-pyrimidine-5-carboxamide
105		N-[3-fluoro-4-(7-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
106		N-[3-fluoro-4-(7-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide

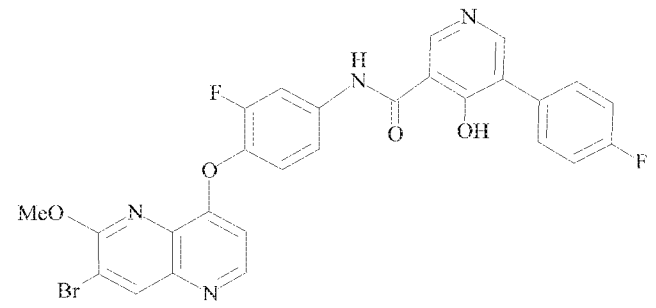
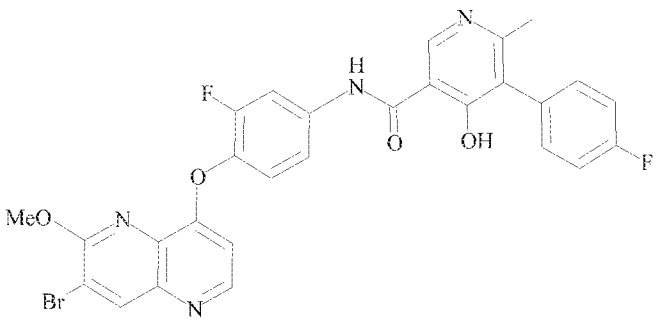
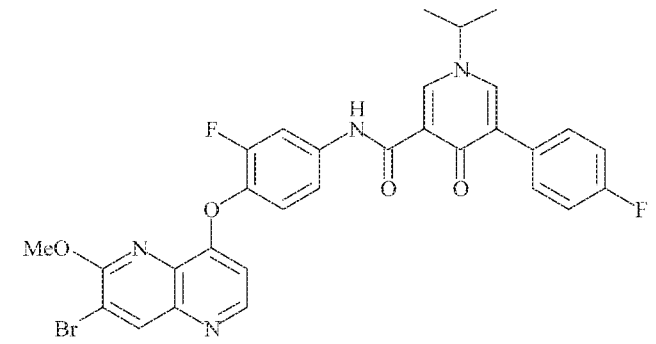
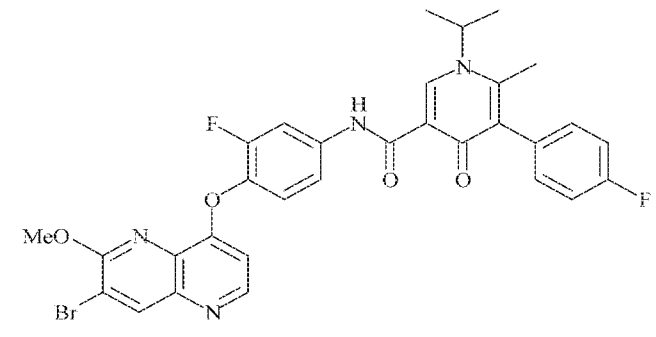
107		1-ethyl-N-[3-fluoro-4-(7-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
108		5-(4-fluorophenyl)-4-hydroxy-N-[4-(7-methoxyquinolin-4-yl)oxyphenyl]-6-methylpyridine-3-carboxamide
109		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
110		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
111		5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridine-3-carboxamide

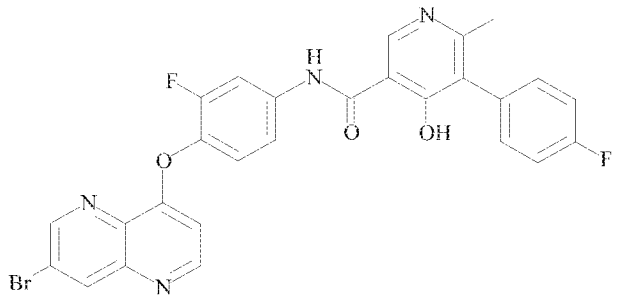
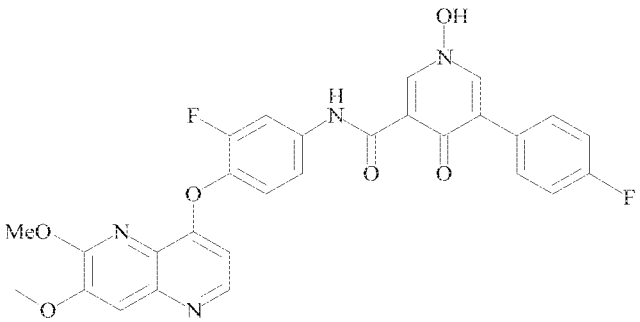
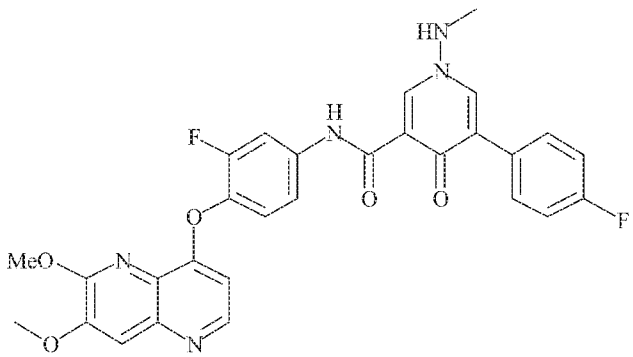
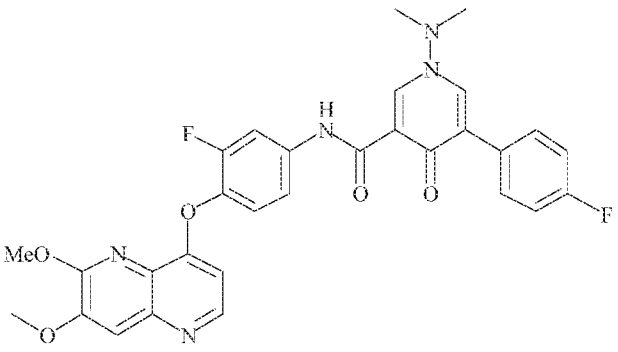
112		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide
113		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
114		tert-butyl 3-[3-[[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]carbamoyl]-5-(4-fluorophenyl)-4-oxopyridin-1-yl]azetidine-1-carboxylate
115		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide

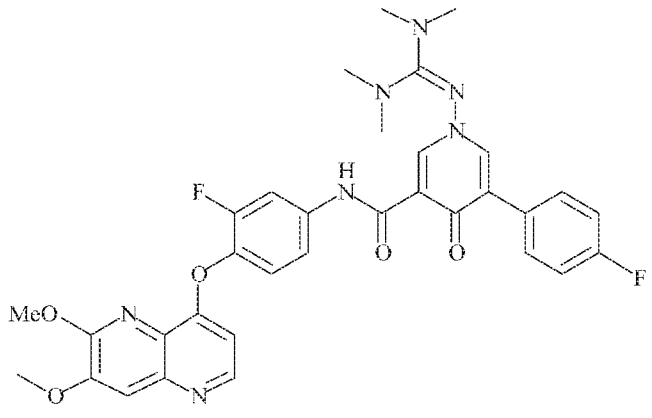
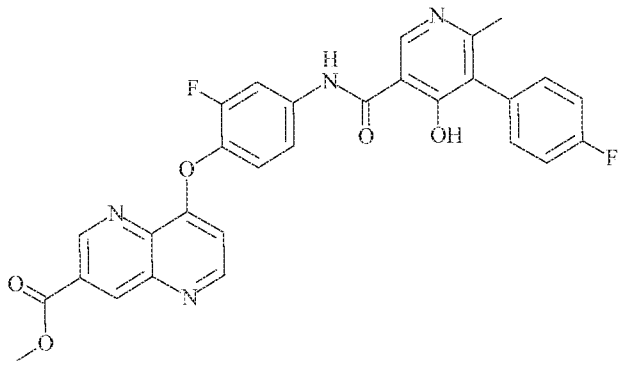
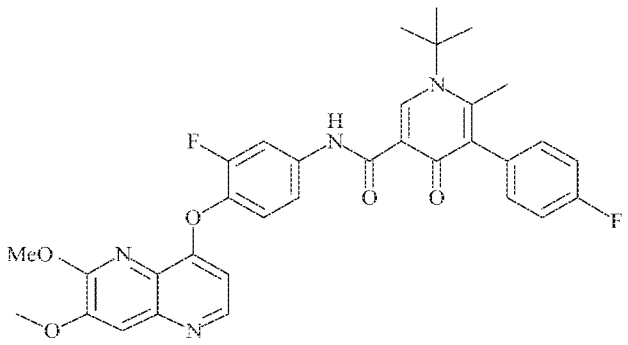
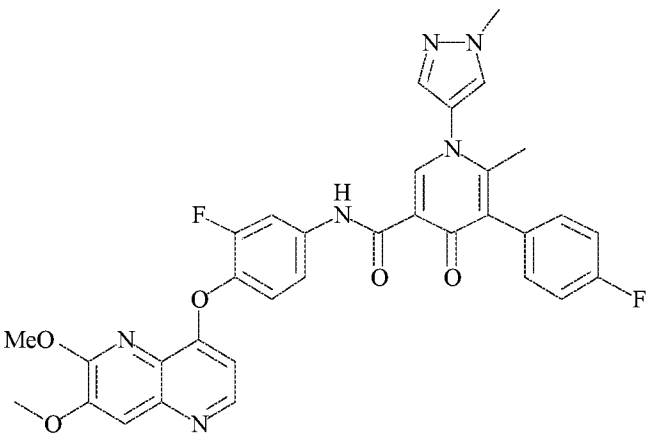
116		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide
117		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-oxopyridine-3-carboxamide
118		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide
119		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
120		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide

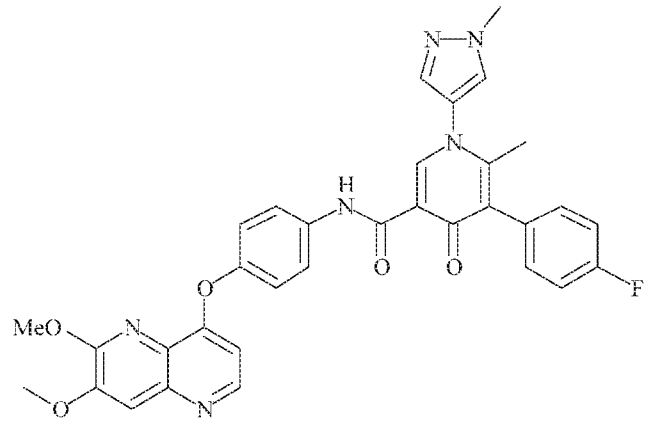
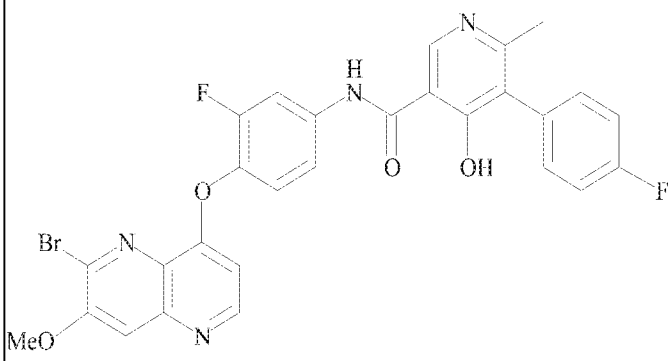
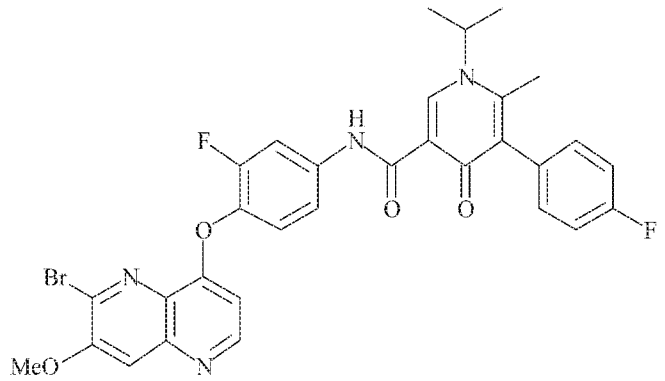
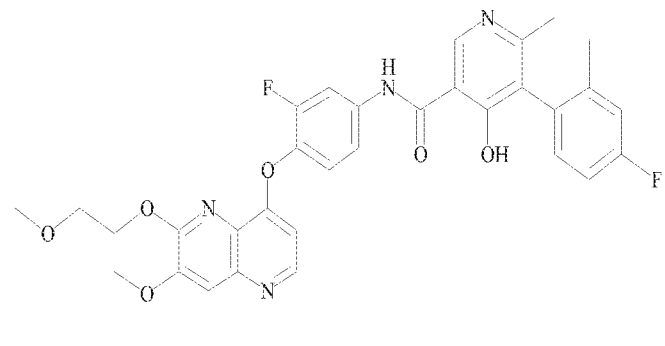
121		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
122		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide
123		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide
124		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-pyridin-2-ylpyridine-3-carboxamide

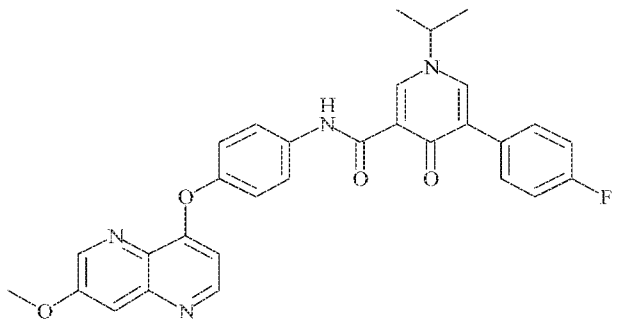
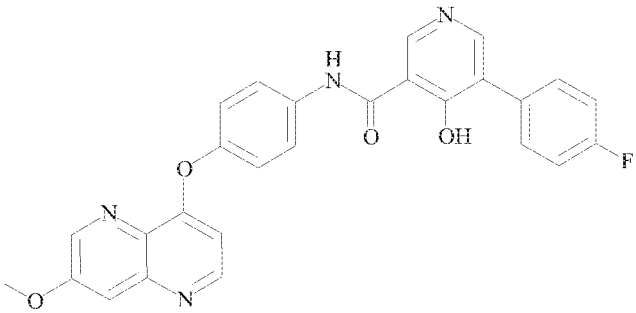
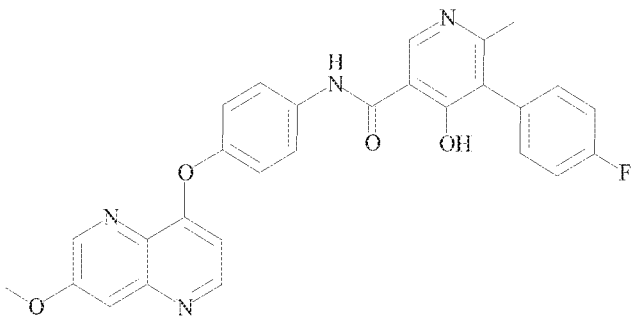
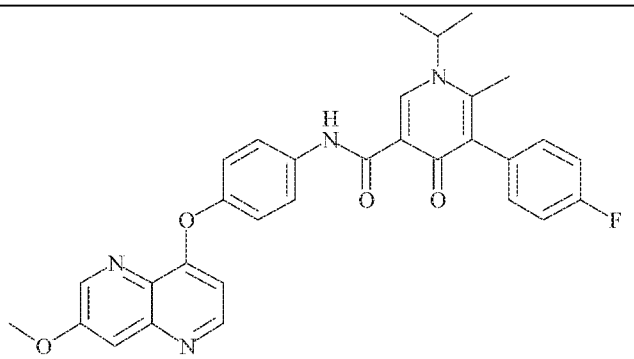
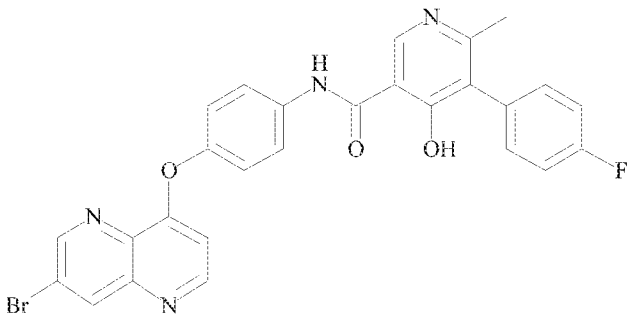
125		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-pyridin-3-ylpyridine-3-carboxamide
126		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methoxy-4-oxopyridine-3-carboxamide
127		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methoxy-4-oxopyridine-3-carboxamide
128		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methoxy-4-oxopyridine-3-carboxamide

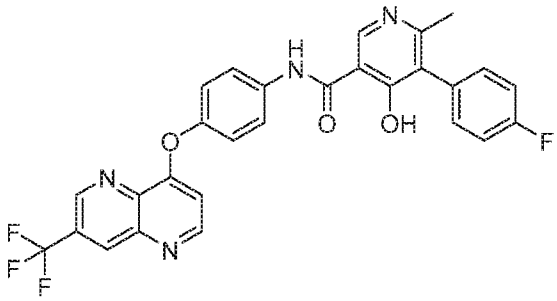
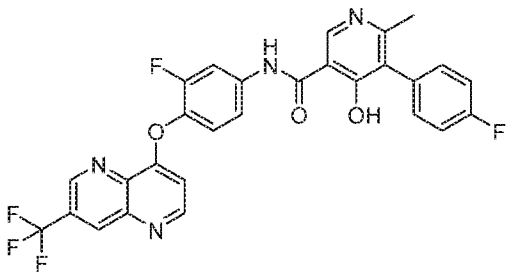
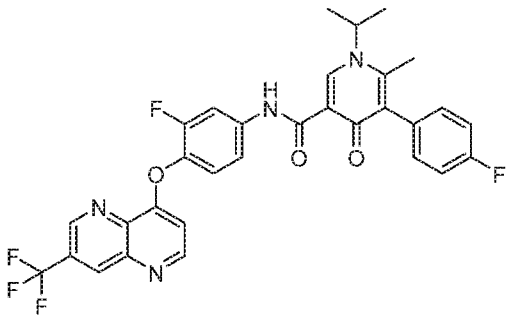
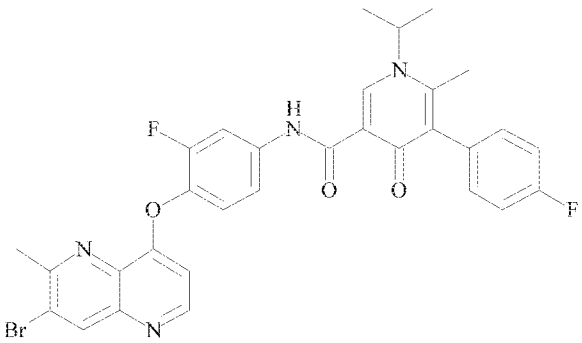
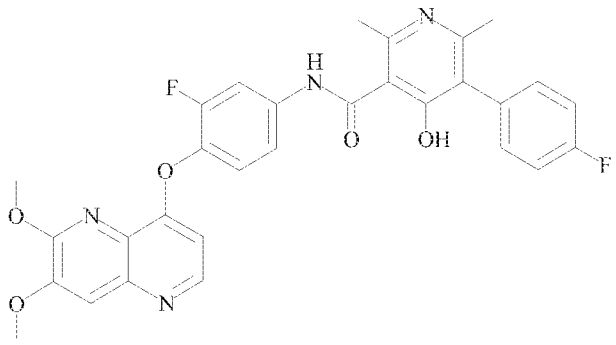
129		N-[4-[(7-bromo-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide
130		N-[4-[(7-bromo-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
131		N-[4-[(7-bromo-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide
132		N-[4-[(7-bromo-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide

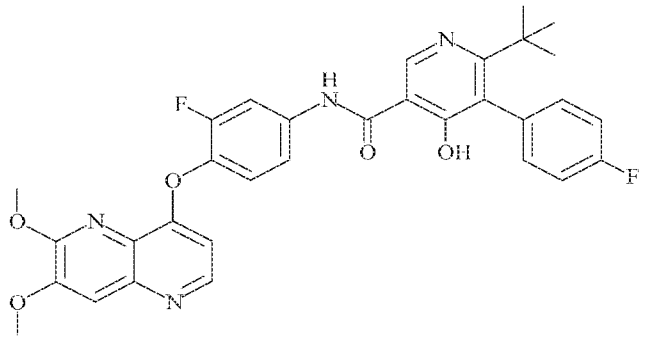
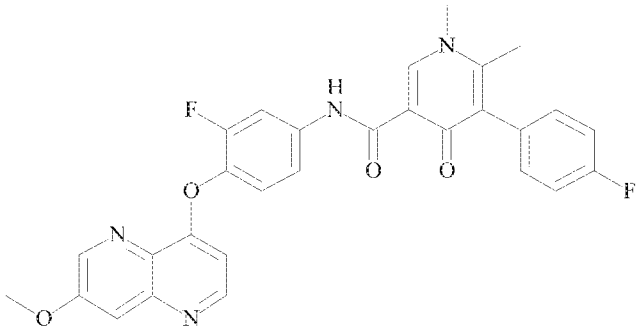
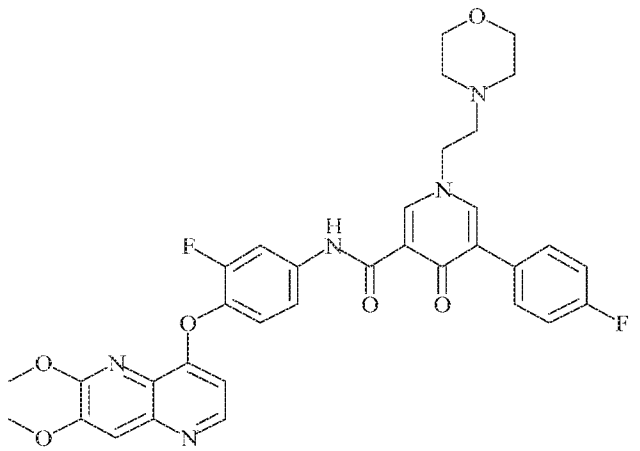
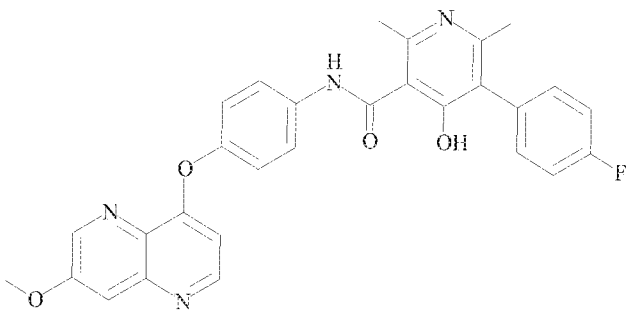
133		N-[4-[(7-bromo-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
134		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-hydroxy-4-oxopyridine-3-carboxamide
135		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(methylamino)-4-oxopyridine-3-carboxamide
136		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(dimethylamino)-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide

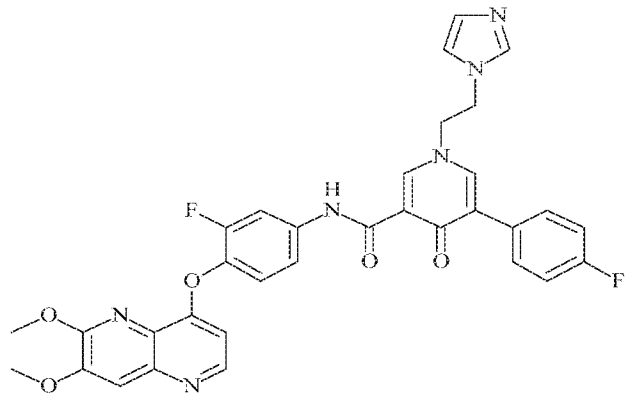
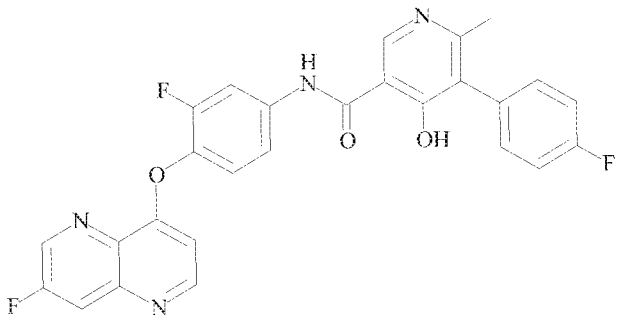
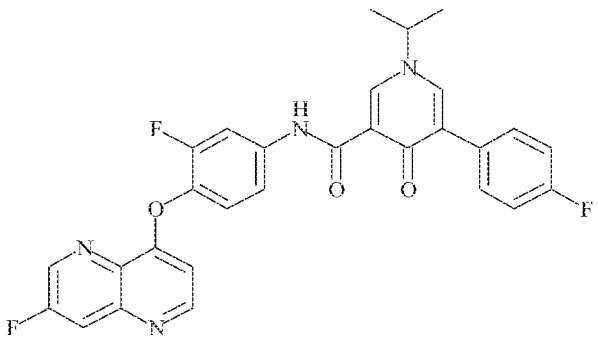
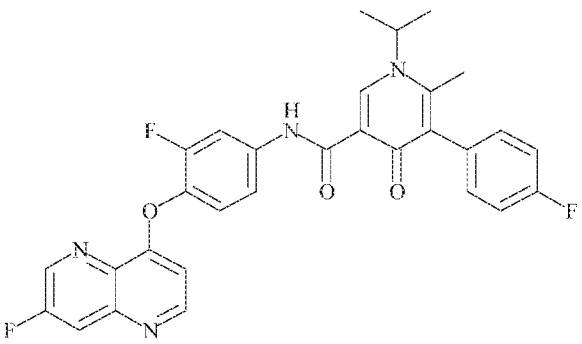
137		1-[bis(dimethylamino)methylideneamino]-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide
138		methyl 8-[2-fluoro-4-[[5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carbonyl]amino]phenoxy]-1,5-naphthyridine-3-carboxylate
139		1-tert-butyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
140		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide

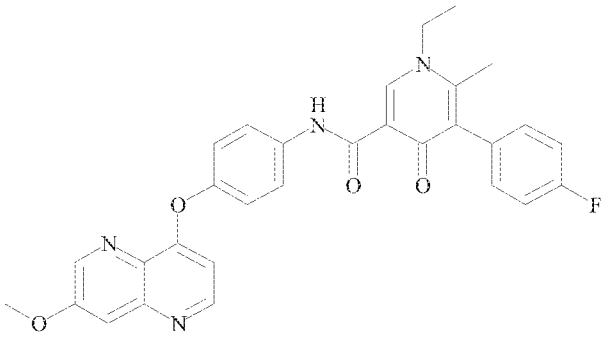
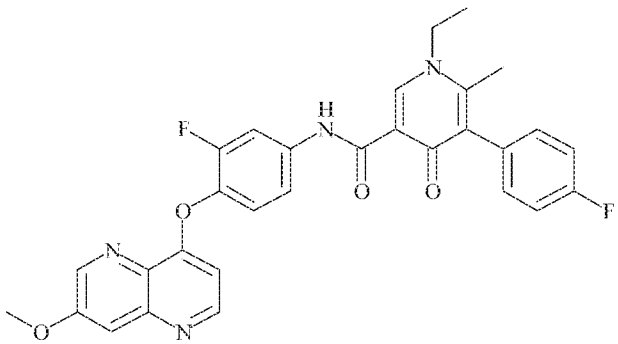
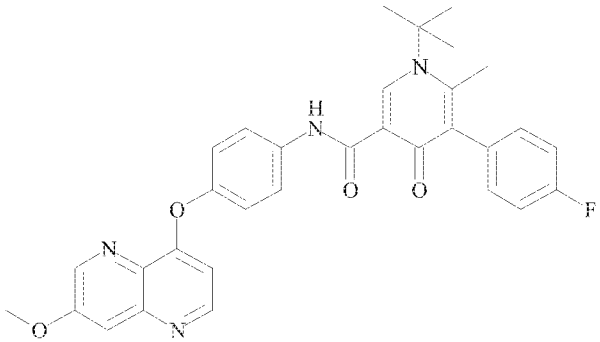
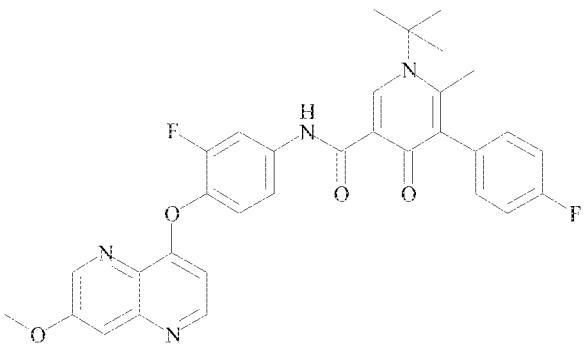
141		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide
142		N-[4-[(6-bromo-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
143		N-[4-[(6-bromo-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
144		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

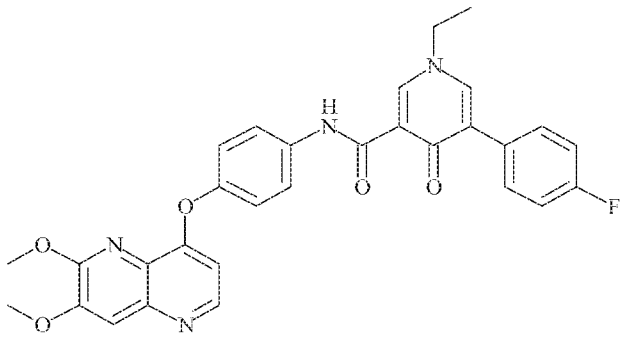
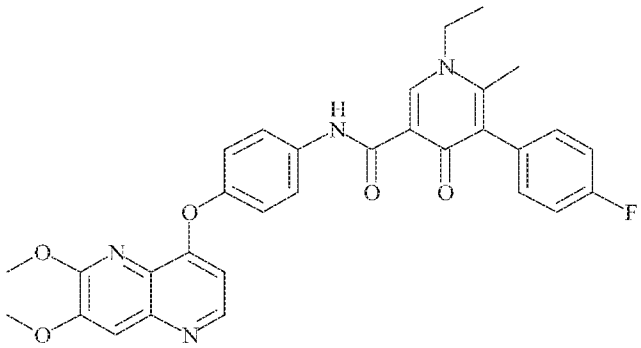
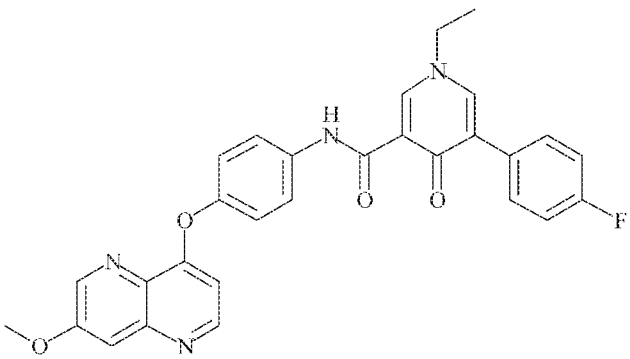
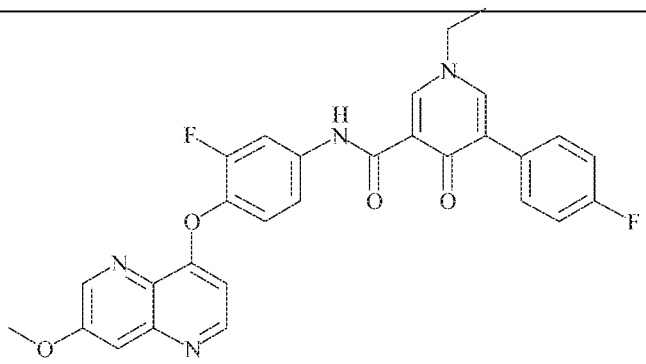
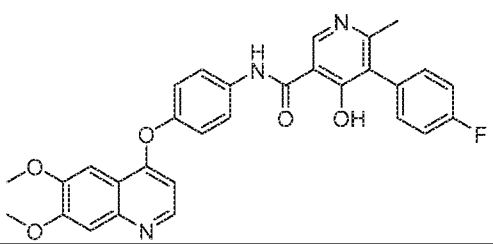
145		5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-oxo-1-propan-2-ylpyridine-3-carboxamide
146		5-(4-fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide
147		5-(4-fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
148		5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
149		N-[4-[(7-bromo-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

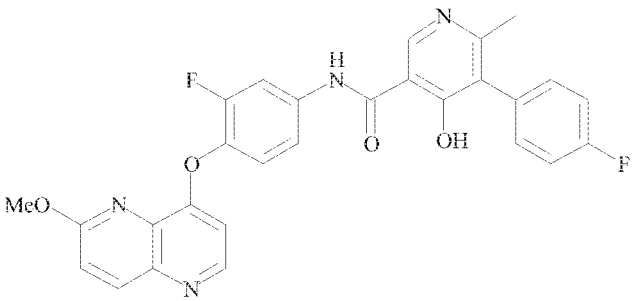
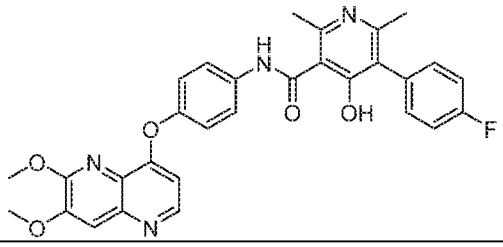
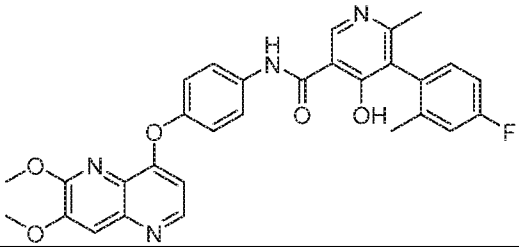
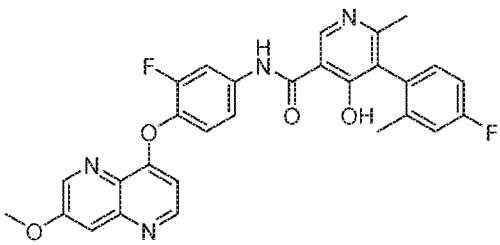
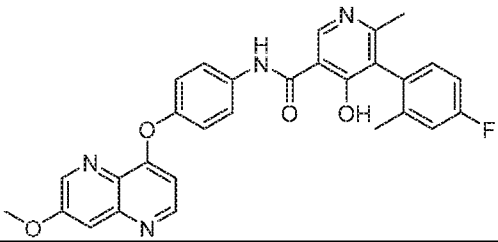
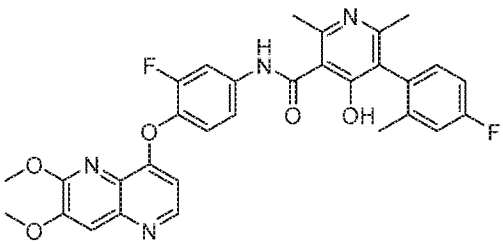
150		5-(4-fluorophenyl)-4-hydroxy-6-methyl-N-[4-[[7-(trifluoromethyl)-1,5-naphthyridin-4-yl]oxy]phenyl]pyridine-3-carboxamide
151		5-(4-fluorophenyl)-N-[3-fluoro-4-[[7-(trifluoromethyl)-1,5-naphthyridin-4-yl]oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide
152		5-(4-fluorophenyl)-N-[3-fluoro-4-[[7-(trifluoromethyl)-1,5-naphthyridin-4-yl]oxy]phenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
153		N-[4-[(7-bromo-6-methyl-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
154		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

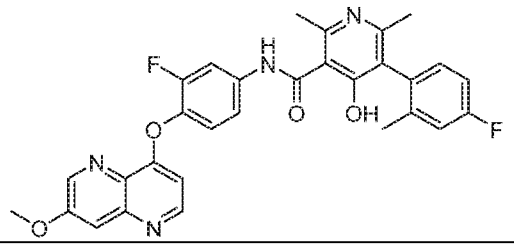
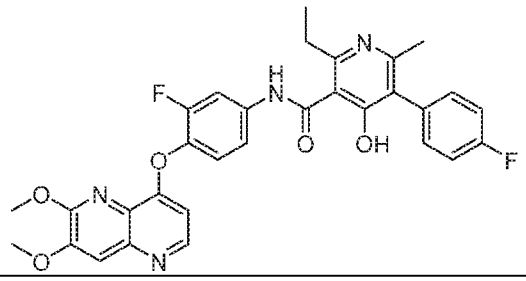
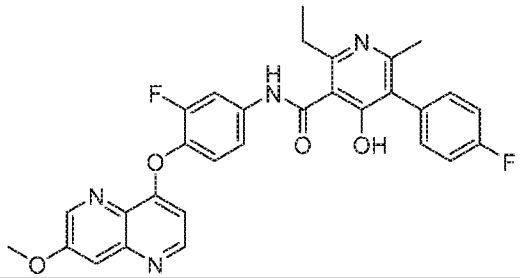
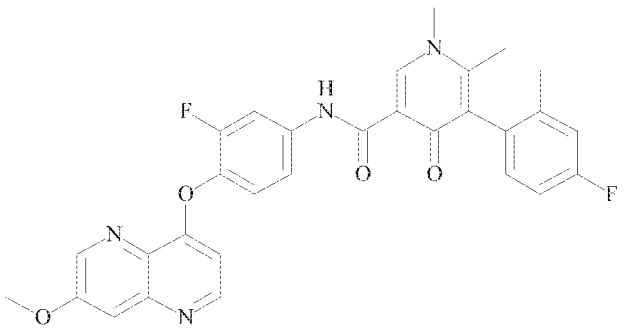
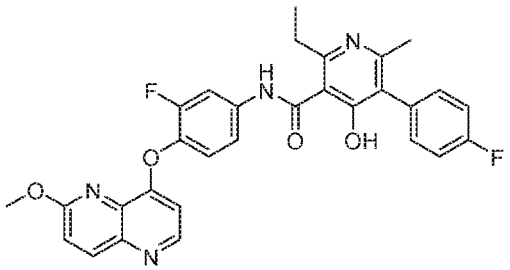
155		6-tert-butyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide
156		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
157		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(2-morpholin-4-ylethyl)-4-oxopyridine-3-carboxamide
158		5-(4-fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2,6-dimethylpyridine-3-carboxamide

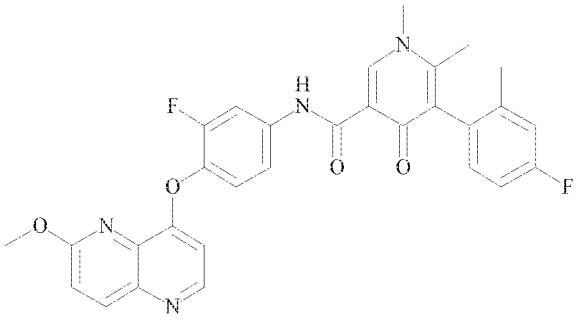
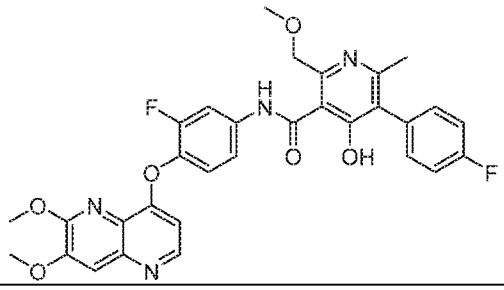
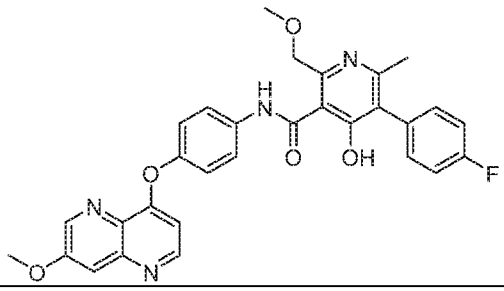
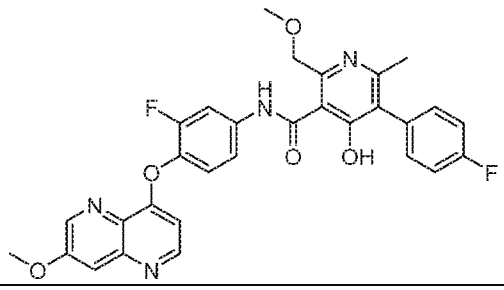
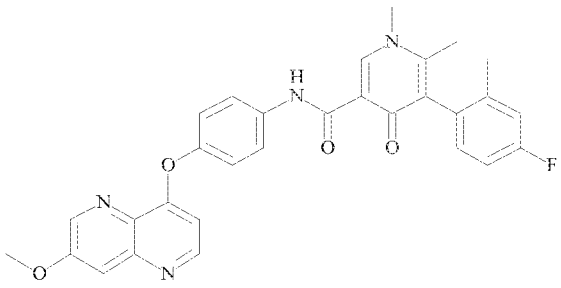
159		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(2-imidazol-1-ylethyl)-4-oxopyridine-3-carboxamide
160		N-[3-fluoro-4-[(7-fluoro-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
161		N-[3-fluoro-4-[(7-fluoro-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide
162		N-[3-fluoro-4-[(7-fluoro-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide

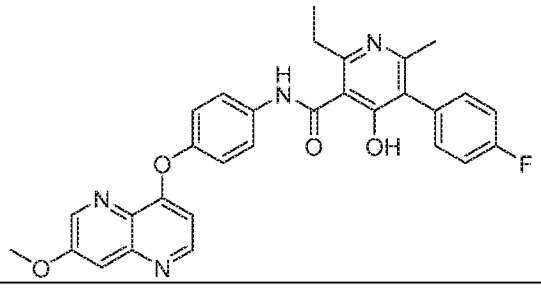
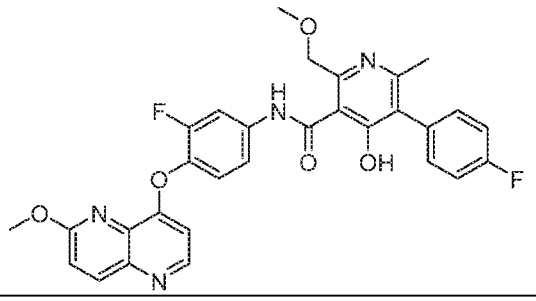
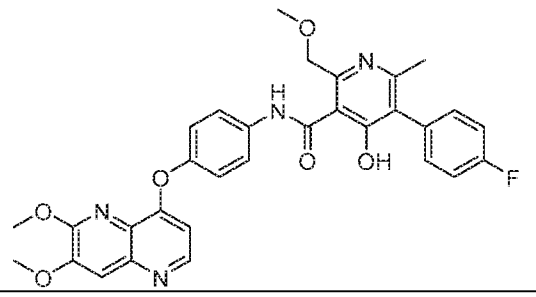
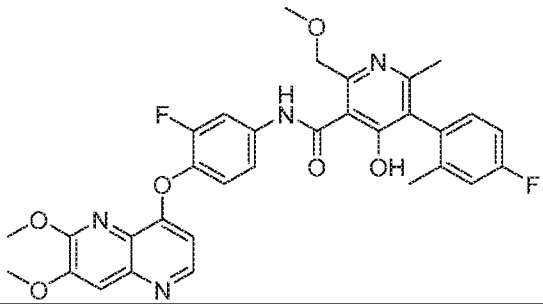
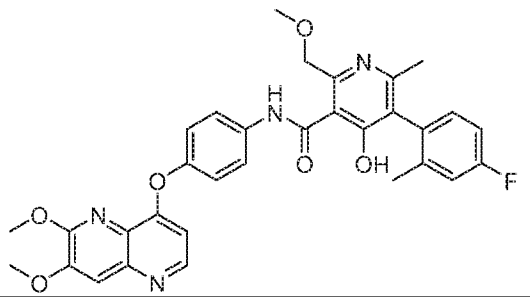
163		1-ethyl-5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide
164		1-ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
165		1-tert-butyl-5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide
166		1-tert-butyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide

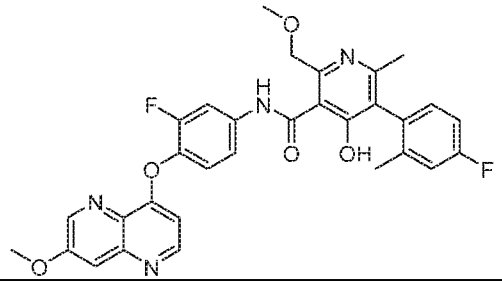
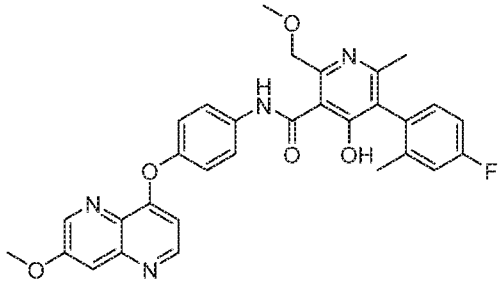
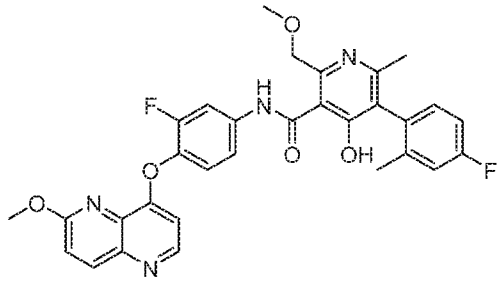
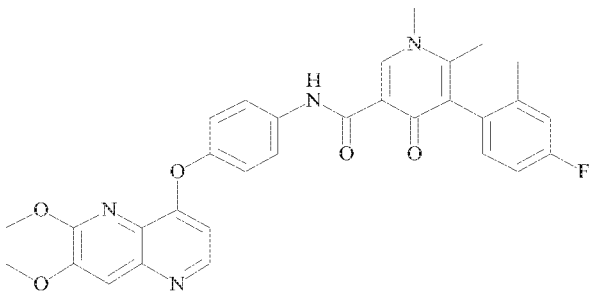
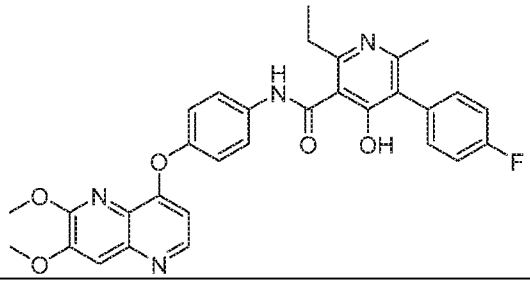
167		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide
168		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
169		1-ethyl-5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-oxopyridine-3-carboxamide
170		1-ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide
171		N-[4-(6,7-dimethoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

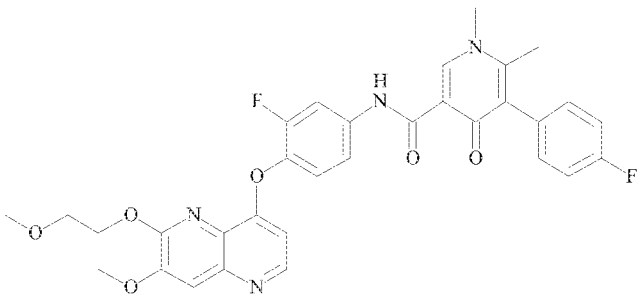
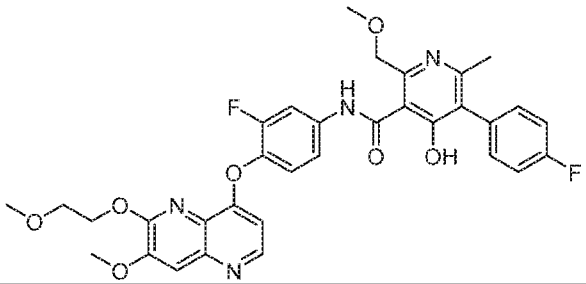
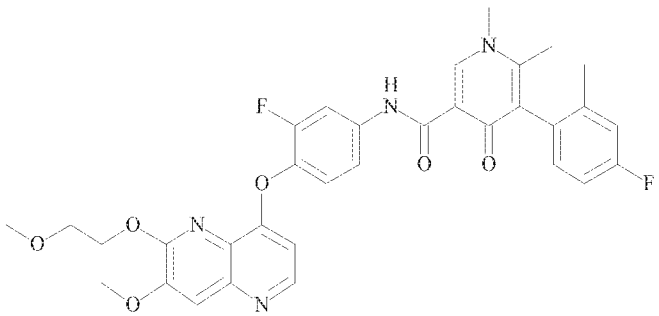
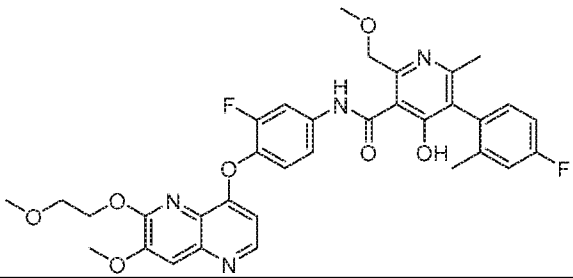
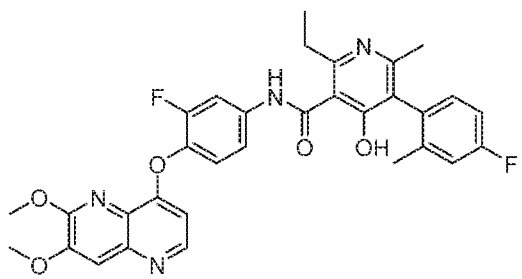
172		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
173		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
174		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
175		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
176		5-(4-fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
177		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

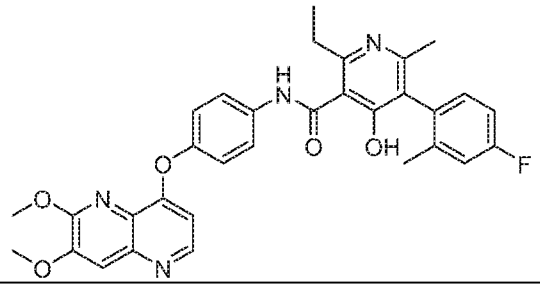
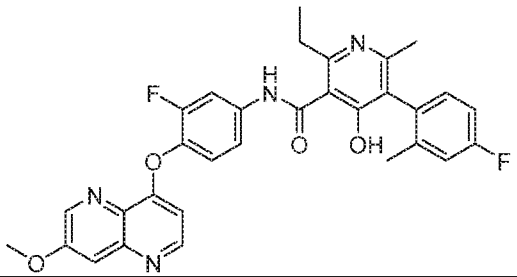
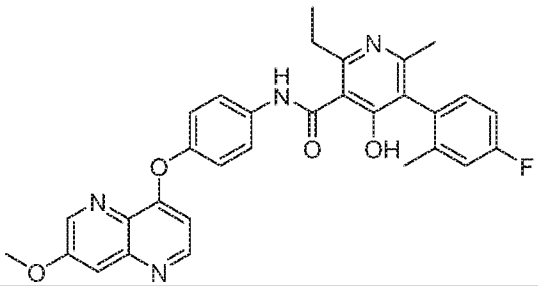
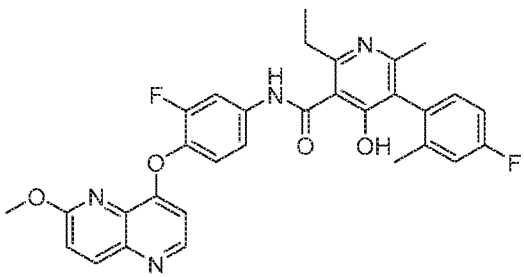
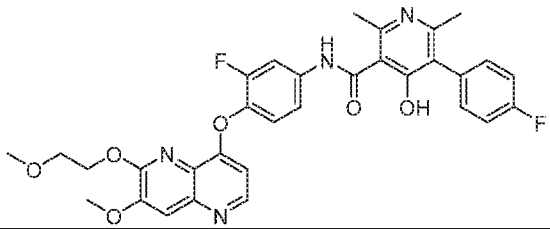
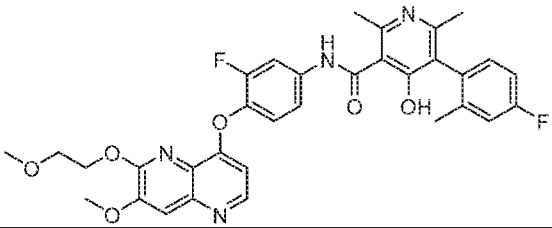
178		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
179		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-ethyl-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
180		2-ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
181		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
182		2-ethyl-N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

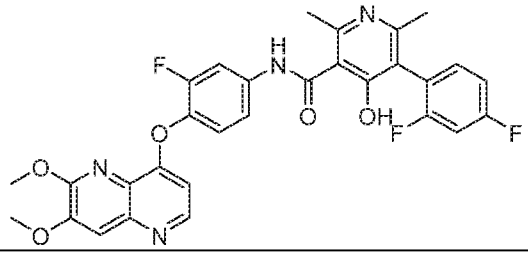
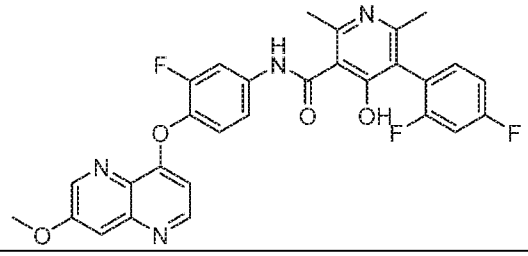
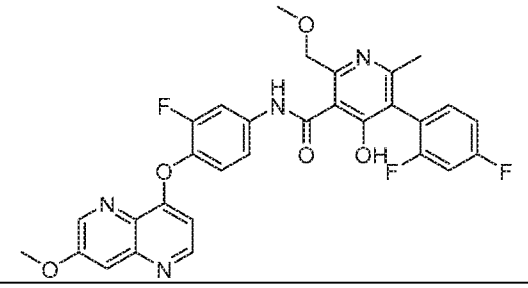
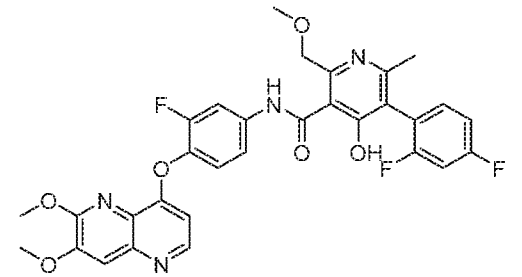
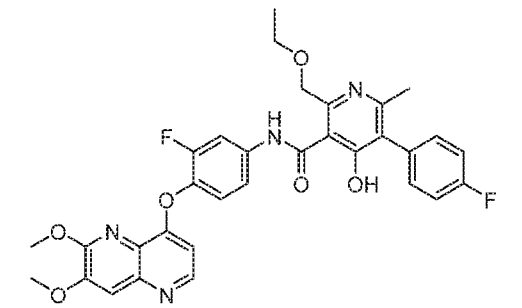
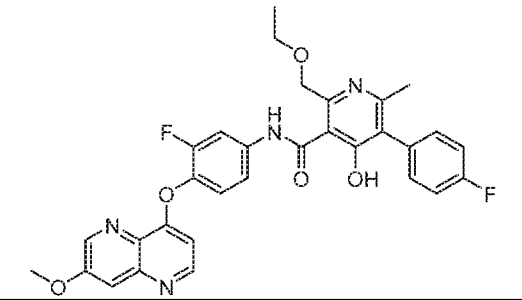
183		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
184		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
185		5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
186		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
187		5-(4-fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridine-3-carboxamide

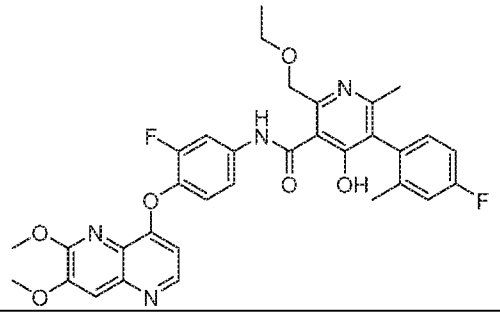
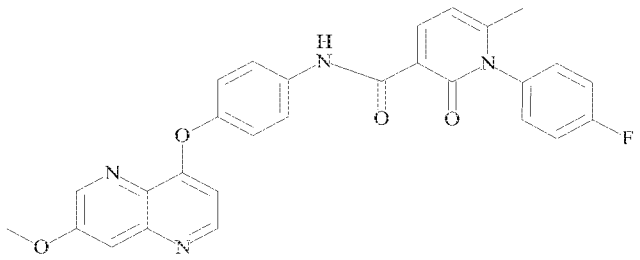
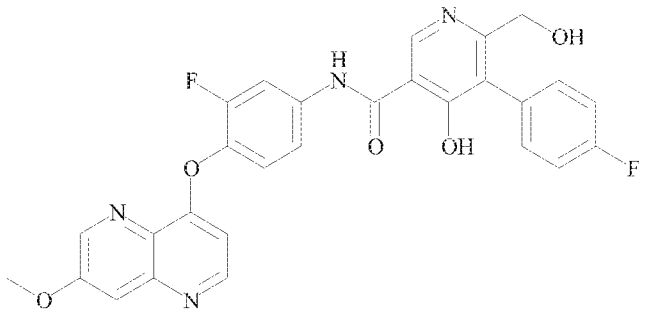
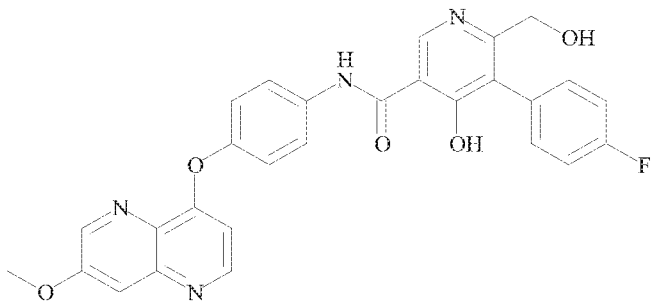
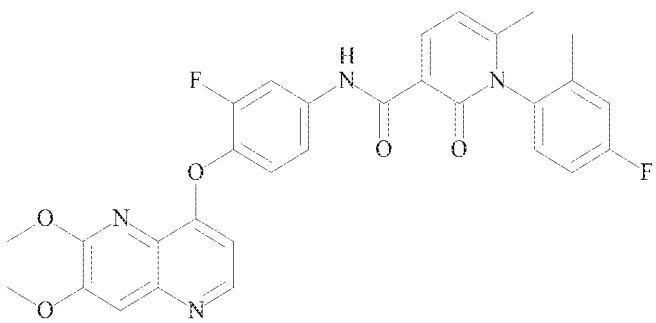
188		2-ethyl-5-(4-fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
189		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
190		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
191		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
192		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide

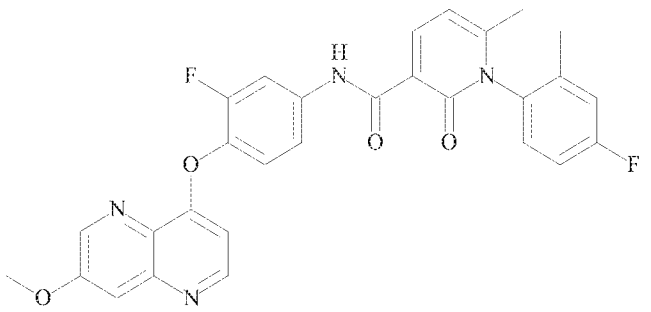
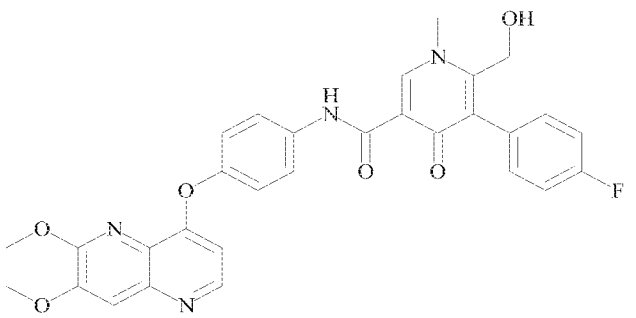
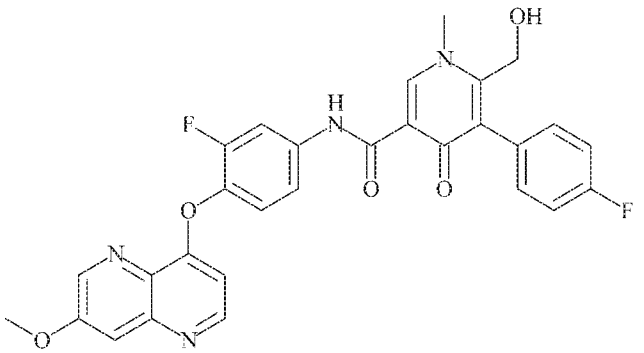
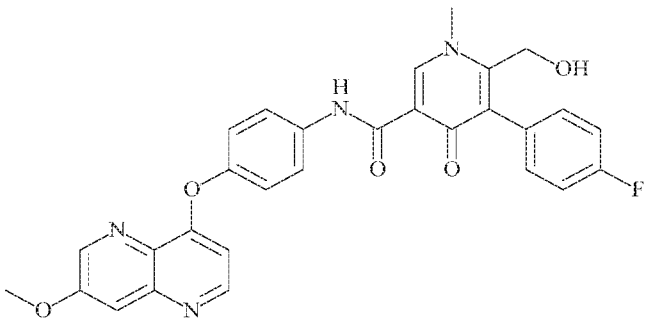
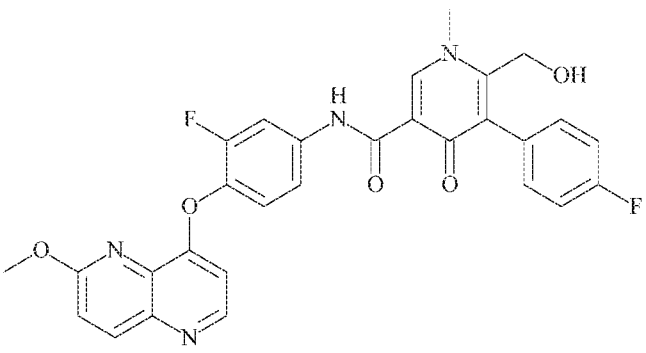
193		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
194		5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
195		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
196		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
197		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-ethyl-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

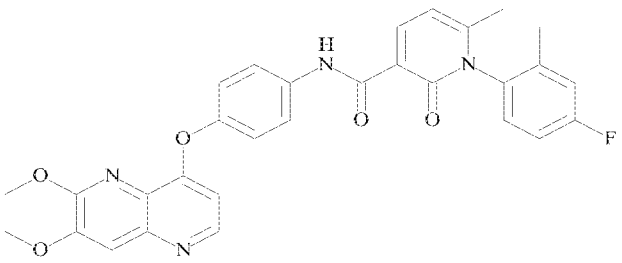
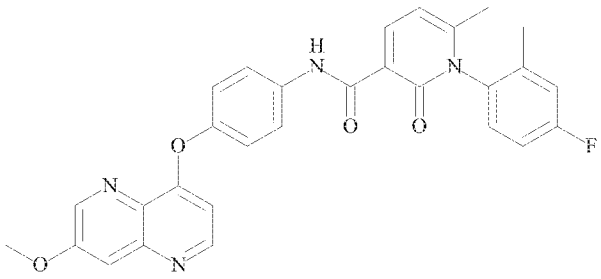
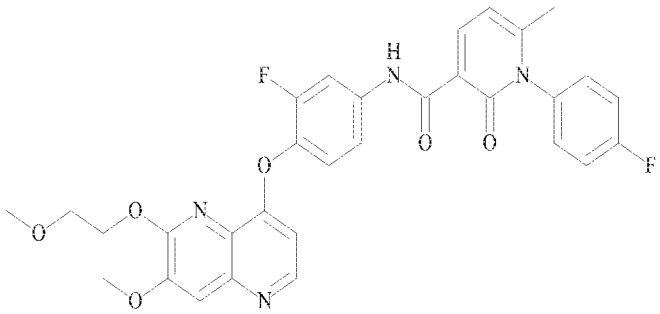
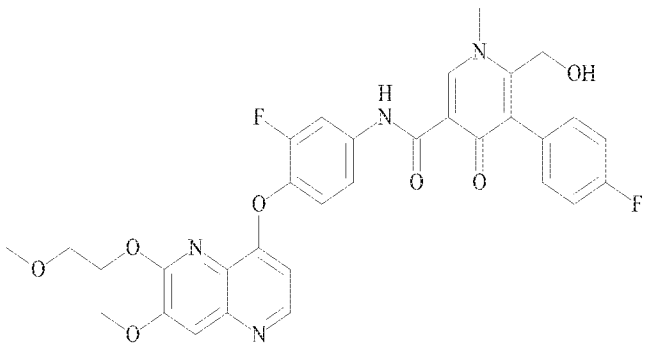
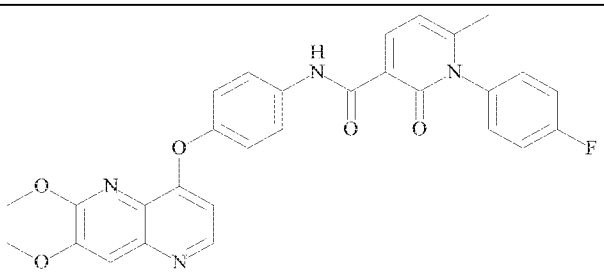
198		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
199		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
200		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
201		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
202		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-ethyl-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

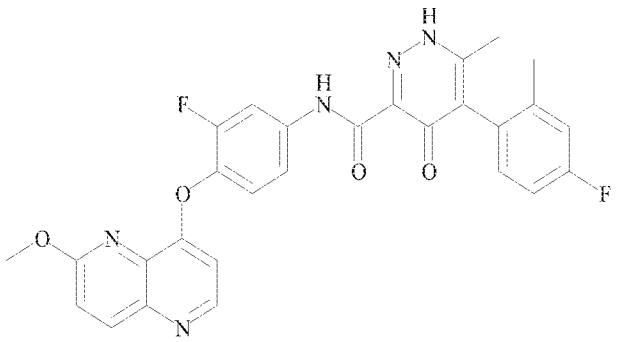
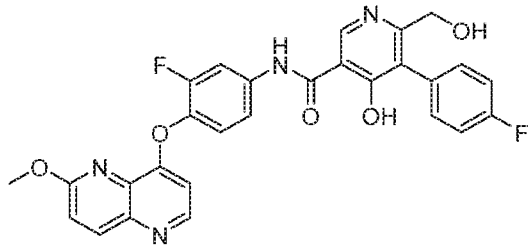
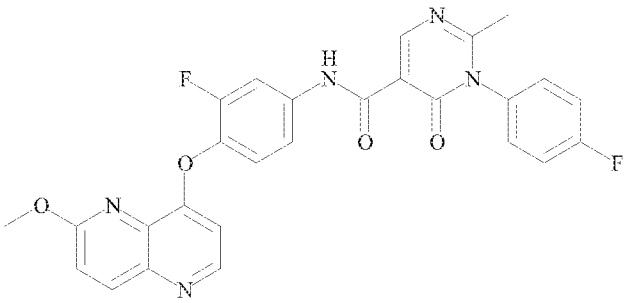
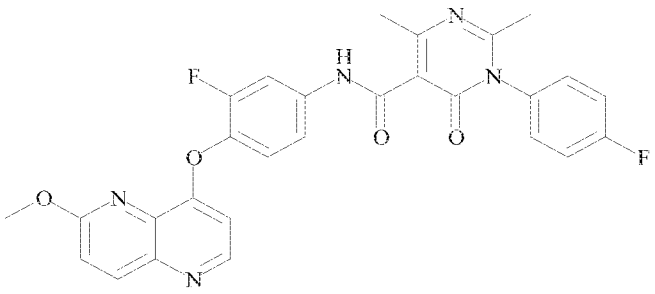
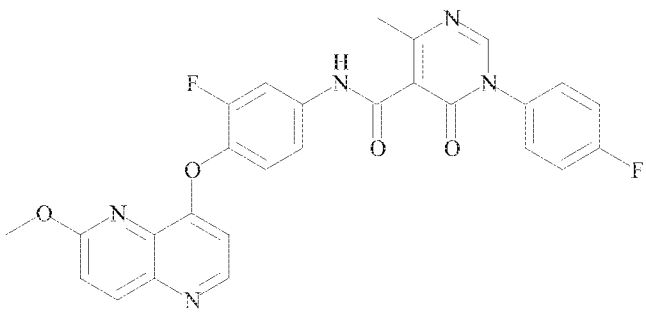
203		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-ethyl-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
204		2-ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
205		2-ethyl-5-(4-fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
206		2-ethyl-N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
207		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
208		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

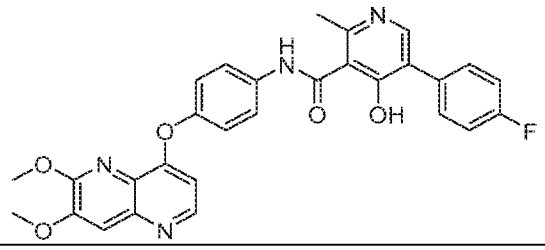
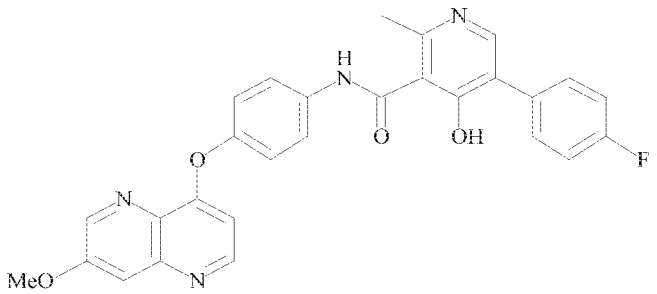
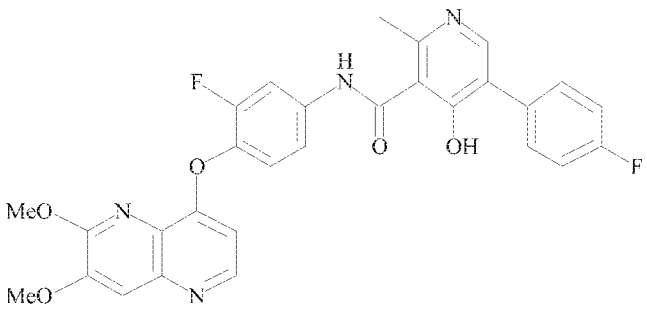
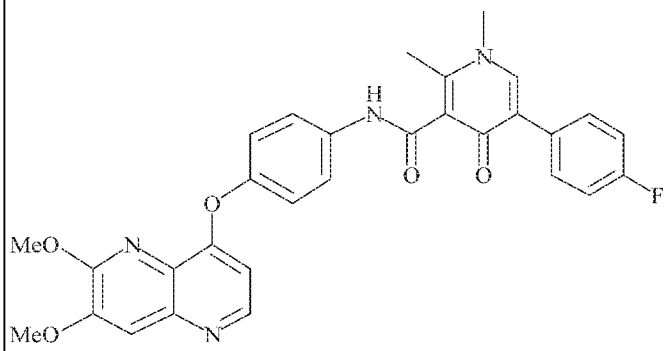
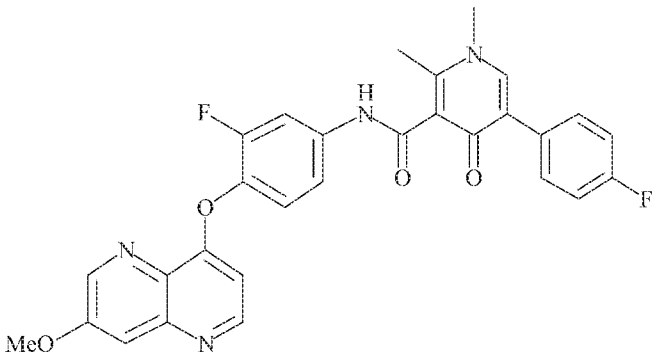
209		5-(2,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
210		5-(2,4-difluorophenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
211		5-(2,4-difluorophenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
212		5-(2,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
213		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(ethoxymethyl)-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
214		2-(ethoxymethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

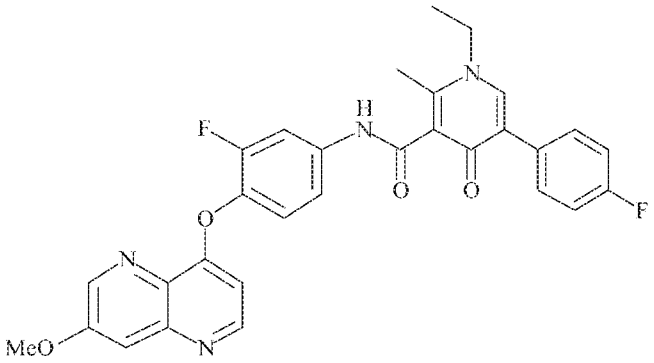
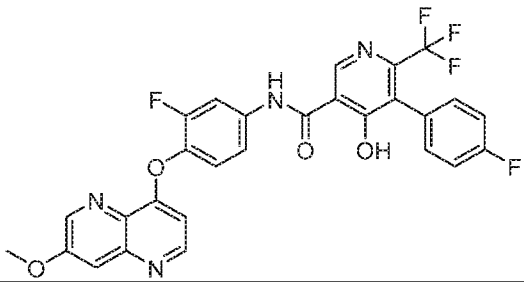
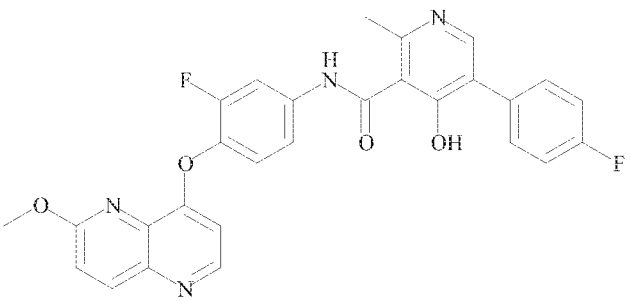
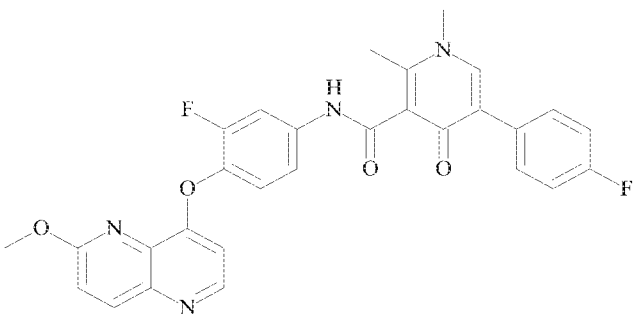
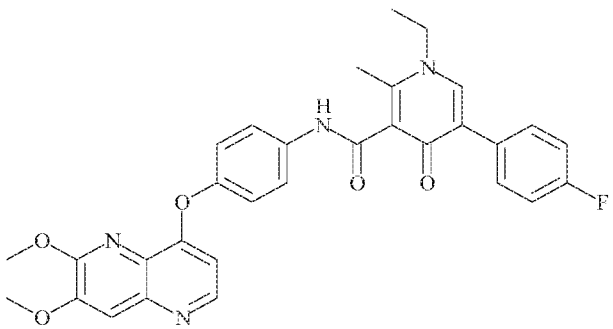
215		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(ethoxymethyl)-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
216		1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-2-oxopyridine-3-carboxamide
217		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(hydroxymethyl)pyridine-3-carboxamide
218		5-(4-fluorophenyl)-4-hydroxy-6-(hydroxymethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide
219		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxopyridine-3-carboxamide

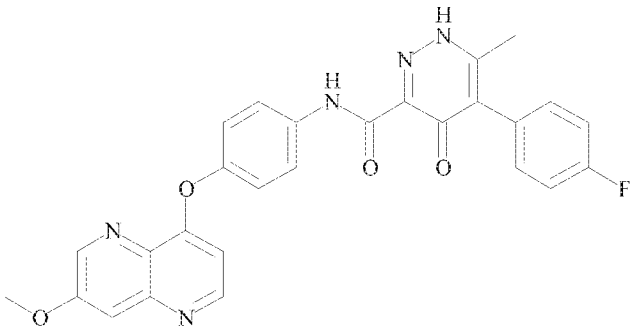
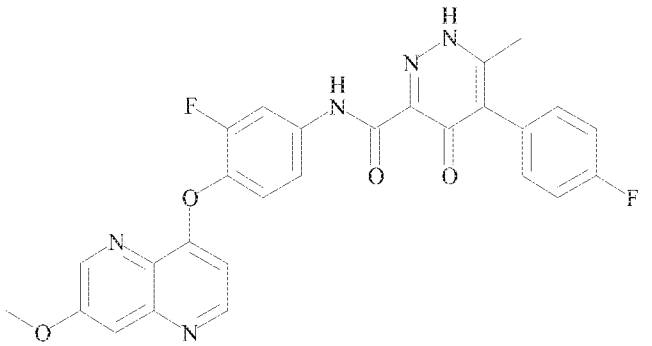
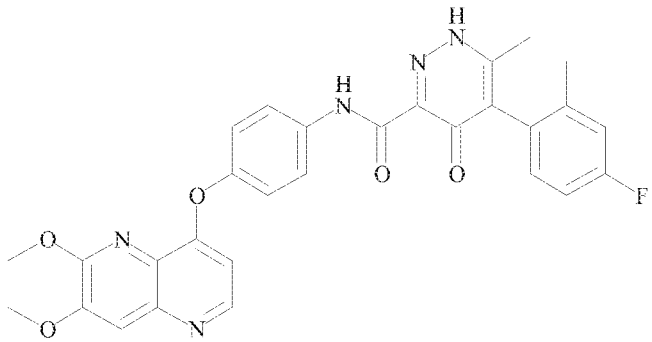
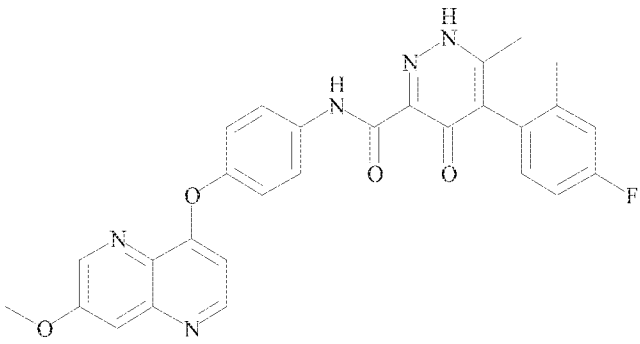
220		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxopyridine-3-carboxamide
221		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide
222		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide
223		5-(4-fluorophenyl)-6-(hydroxymethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-methyl-4-oxopyridine-3-carboxamide
224		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide

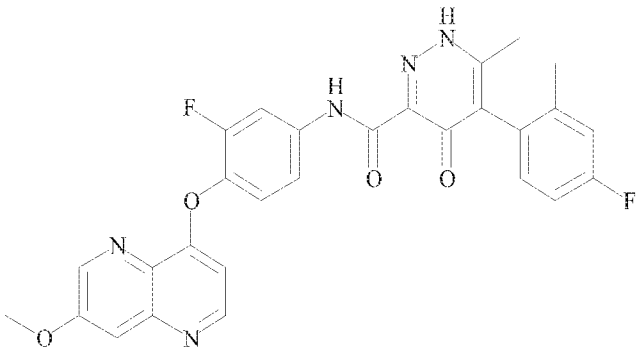
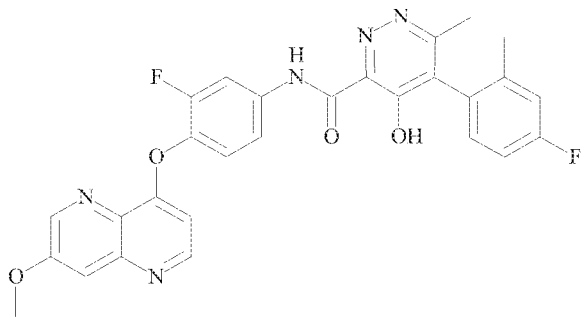
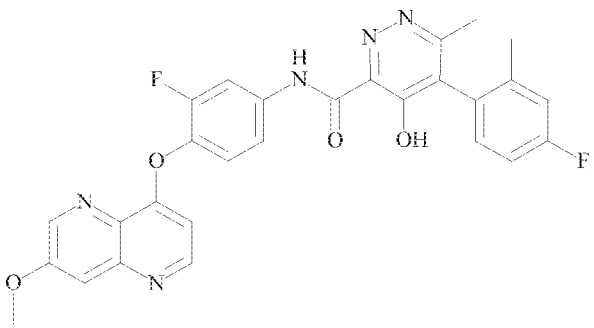
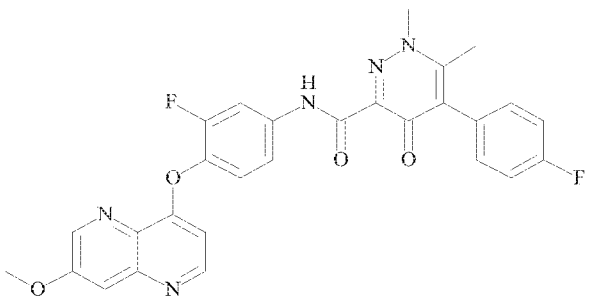
225		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxopyridine-3-carboxamide
226		1-(4-fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-2-oxopyridine-3-carboxamide
227		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
228		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide
229		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide

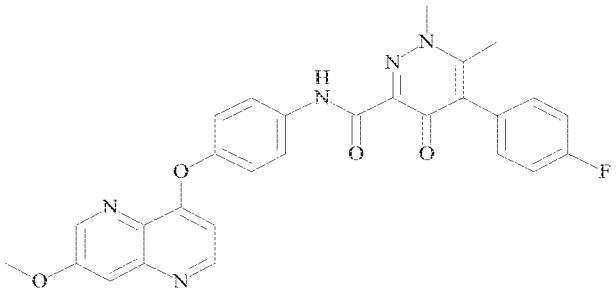
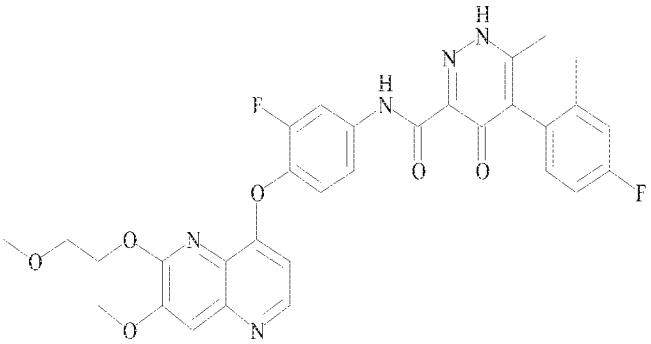
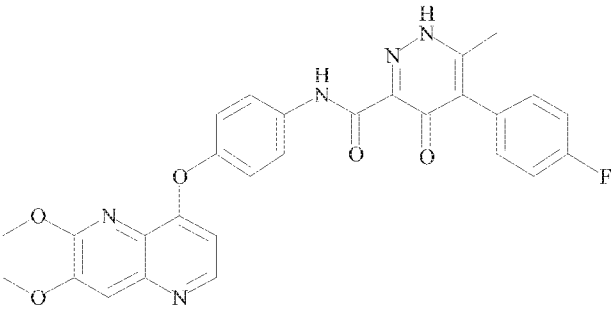
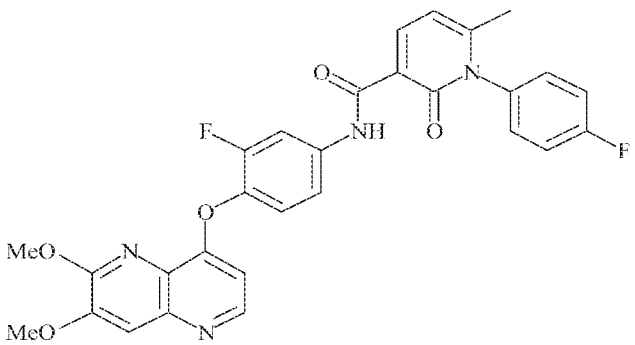
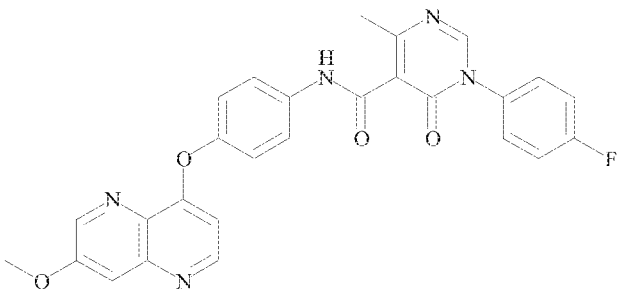
230		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
231		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(hydroxymethyl)pyridine-3-carboxamide
232		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide
233		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyrimidine-5-carboxamide
234		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4-methyl-6-oxopyrimidine-5-carboxamide

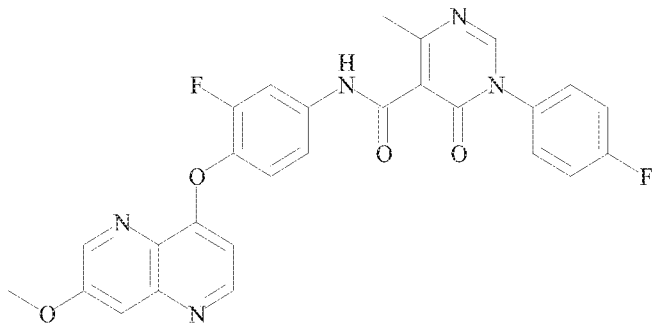
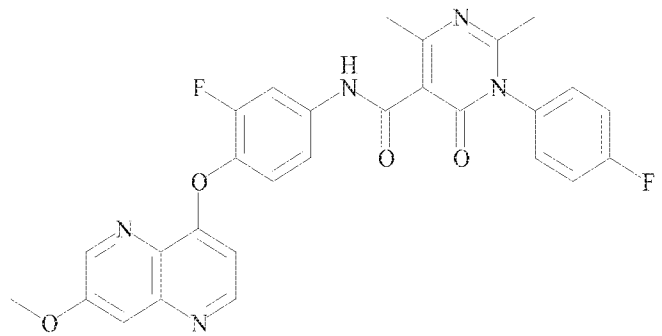
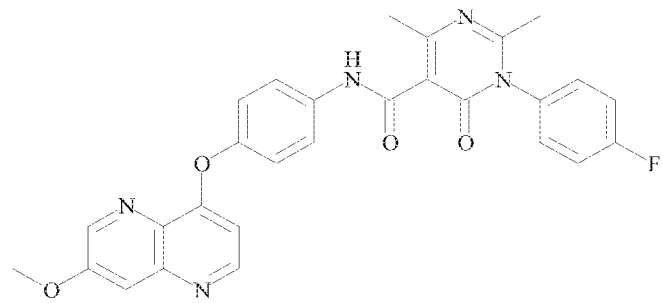
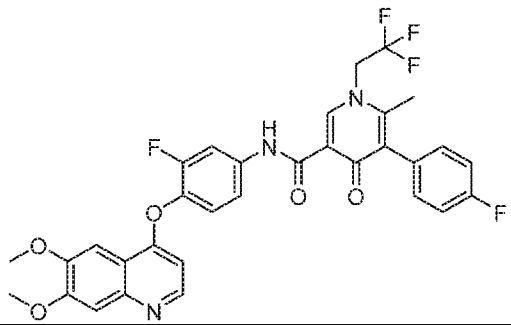
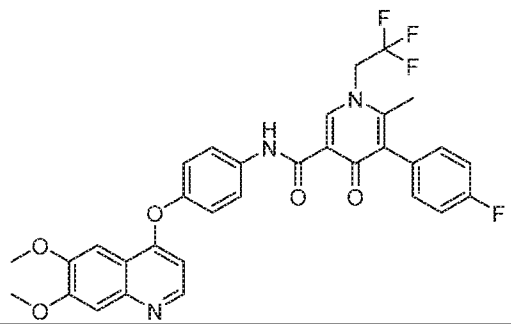
235		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide
236		5-(4-fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methylpyridine-3-carboxamide
237		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide
238		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide
239		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide

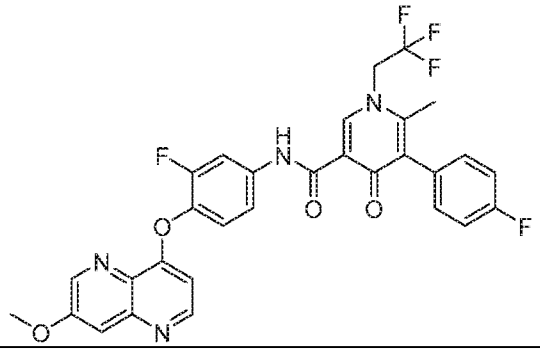
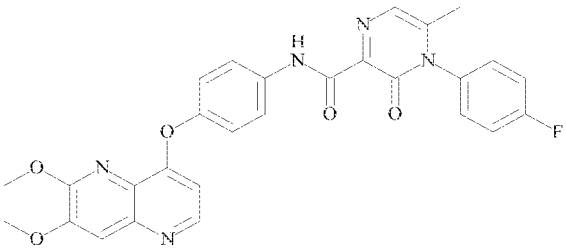
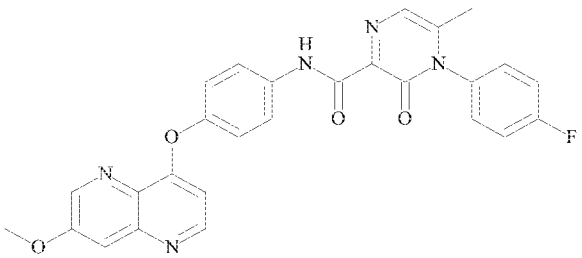
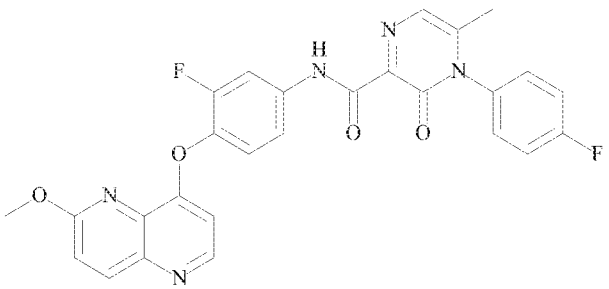
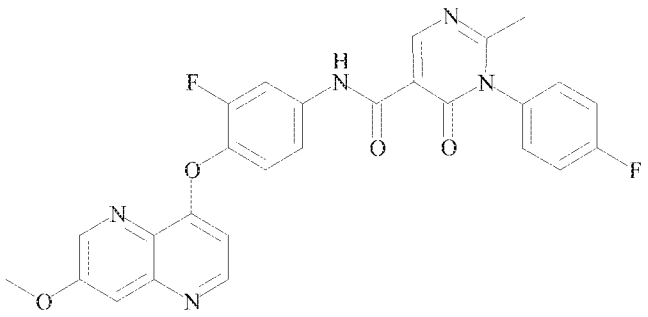
240		1-ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide
241		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(trifluoromethyl)pyridine-3-carboxamide
242		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide
243		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide
244		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide

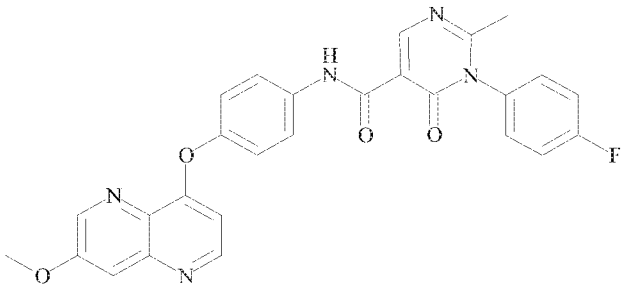
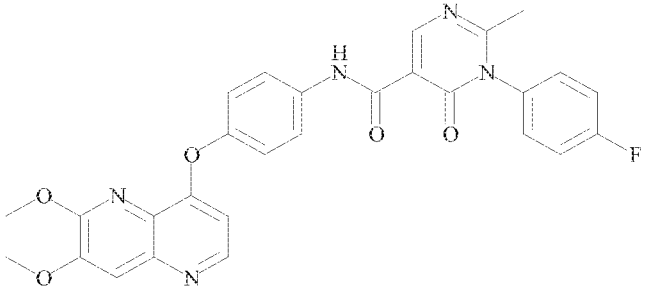
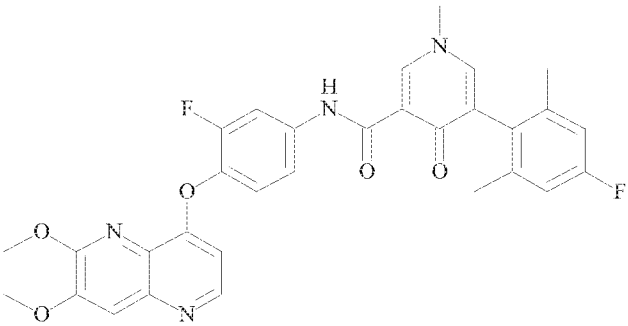
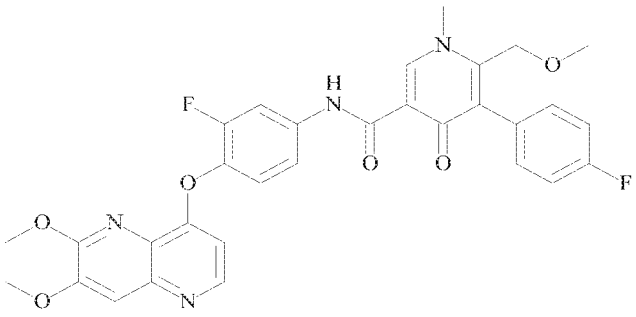
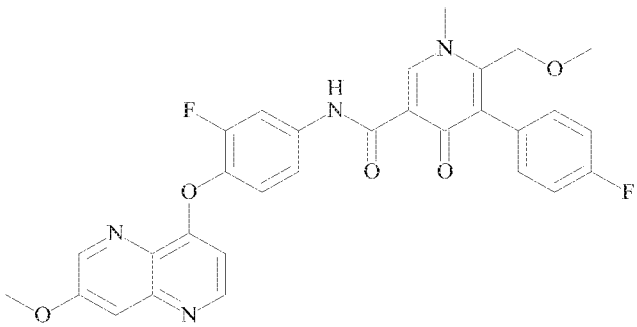
245		5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
246		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
247		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
248		5-(4-fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1H-pyridazine-3-carboxamide

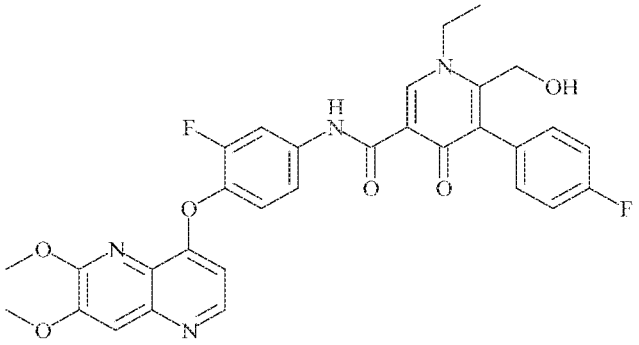
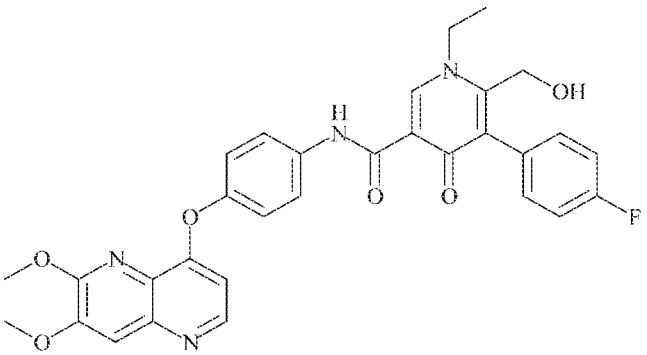
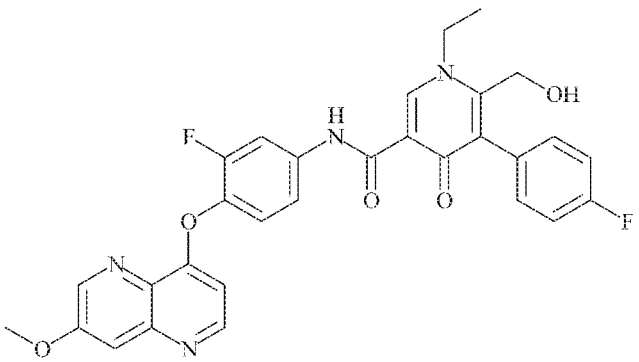
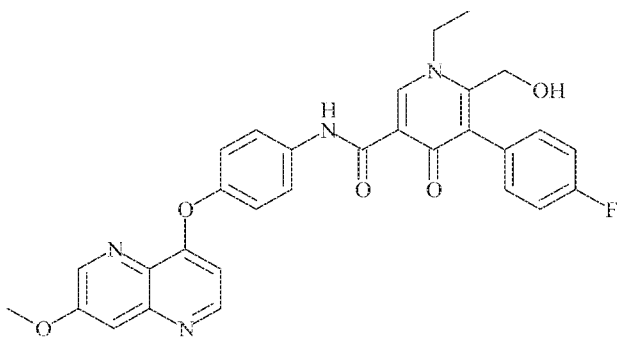
249A		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
249B		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridazine-3-carboxamide, atropoisomer 1
249C		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridazine-3-carboxamide, atropisomer 2
250		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide

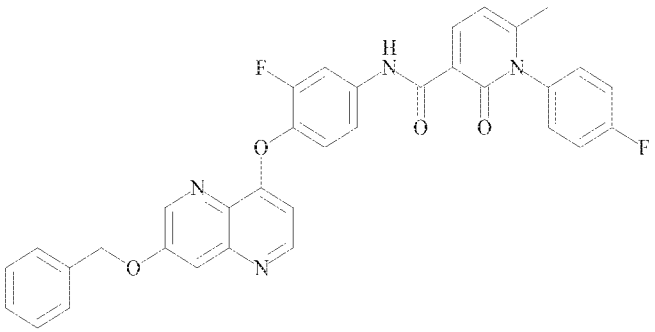
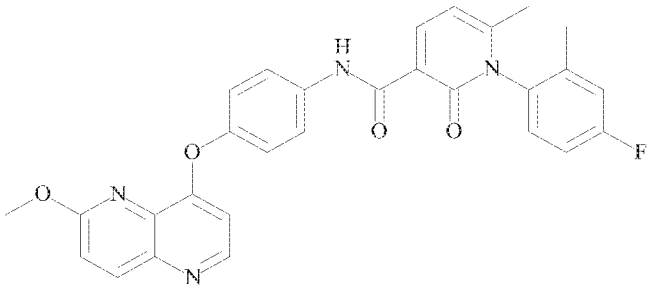
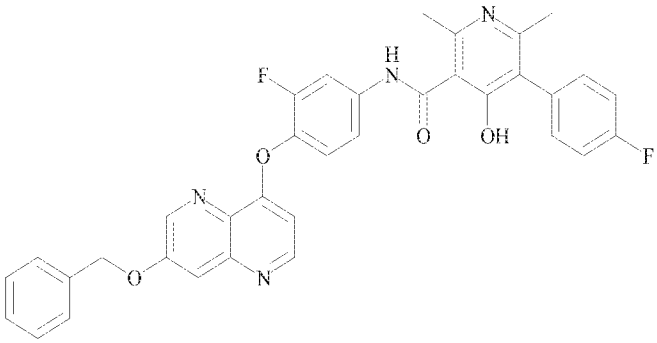
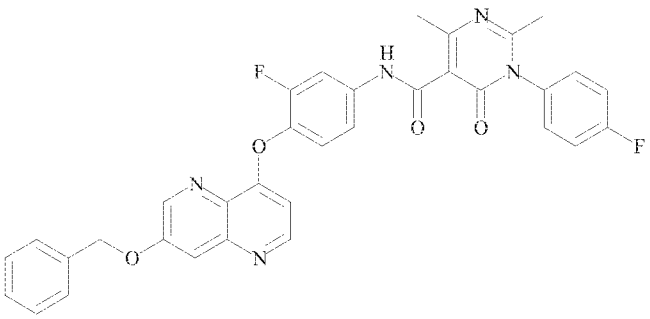
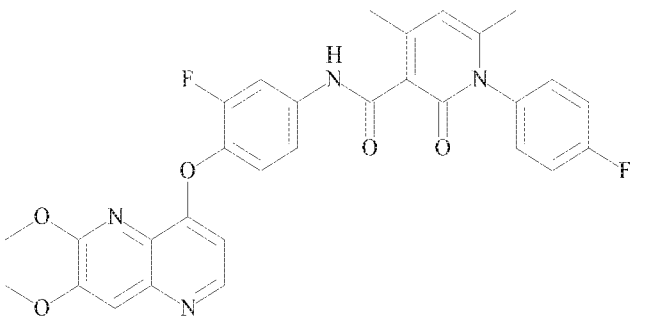
251		5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridazine-3-carboxamide
252		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
253		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
254		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
255		1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-methyl-6-oxopyrimidine-5-carboxamide

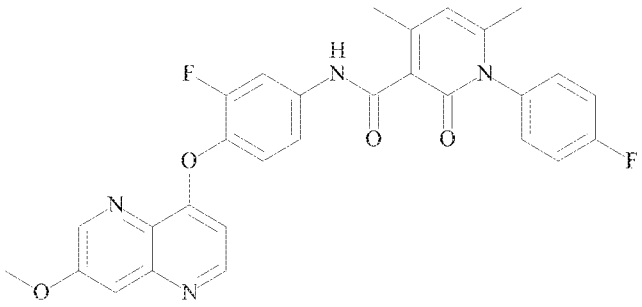
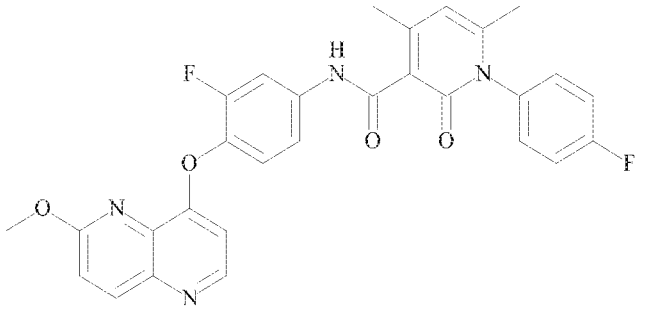
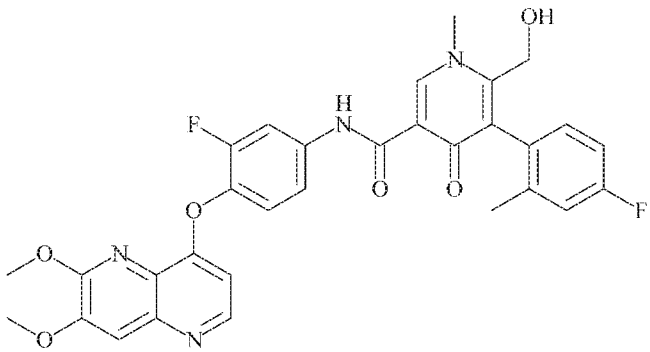
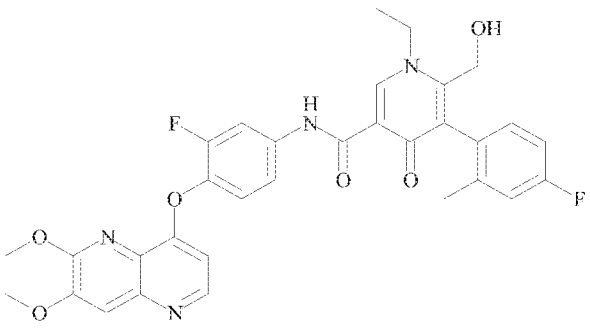
256		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4-methyl-6-oxopyrimidine-5-carboxamide
257		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyrimidine-5-carboxamide
258		1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2,4-dimethyl-6-oxopyrimidine-5-carboxamide
259		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide
260		N-[4-(6,7-dimethoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide

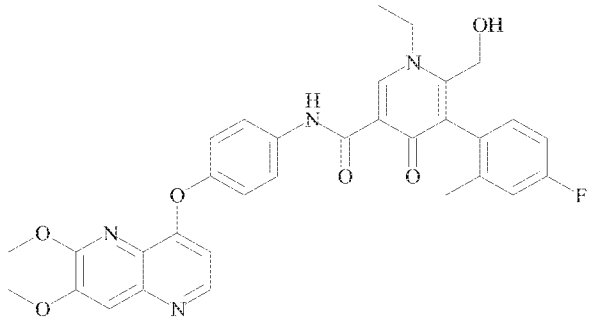
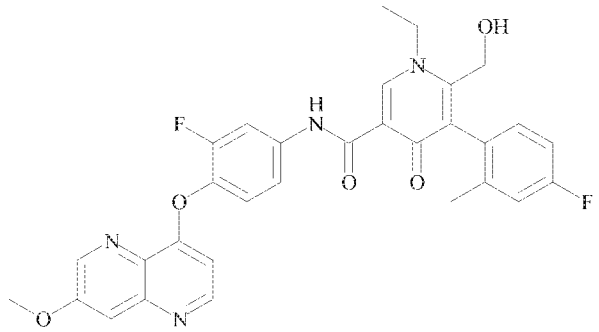
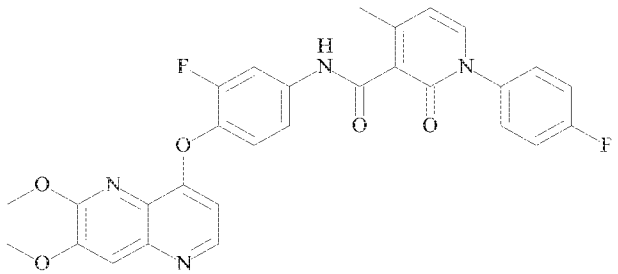
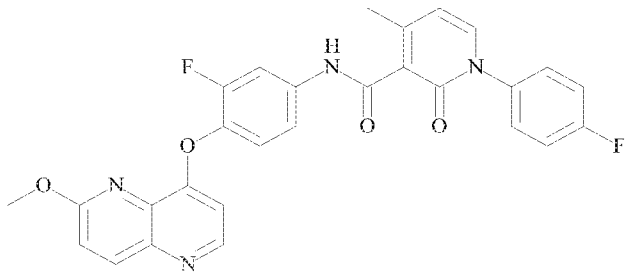
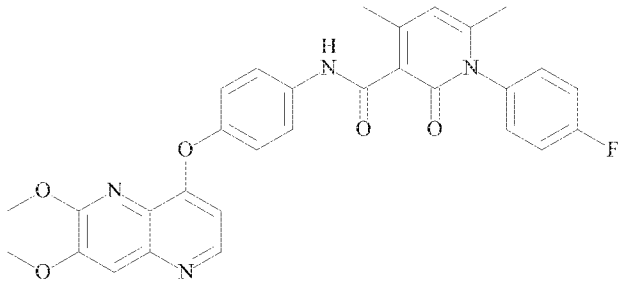
261		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide
262		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide
263		4-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-methyl-3-oxopyrazine-2-carboxamide
264		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide
265		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide

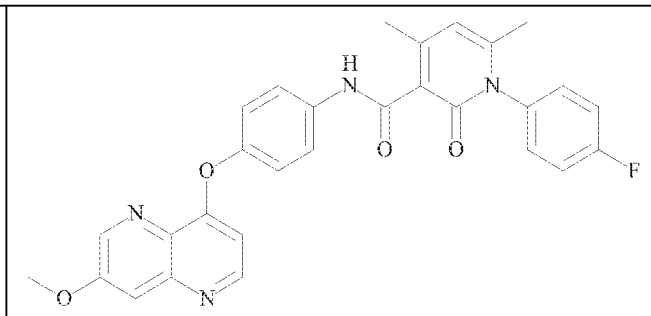
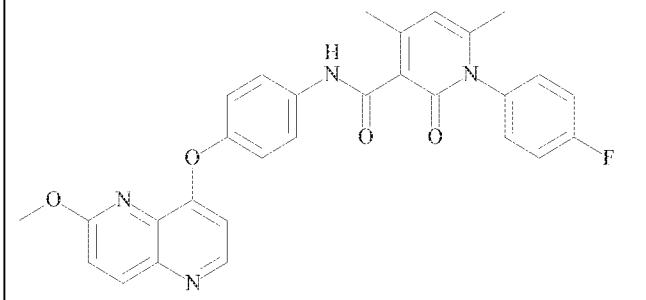
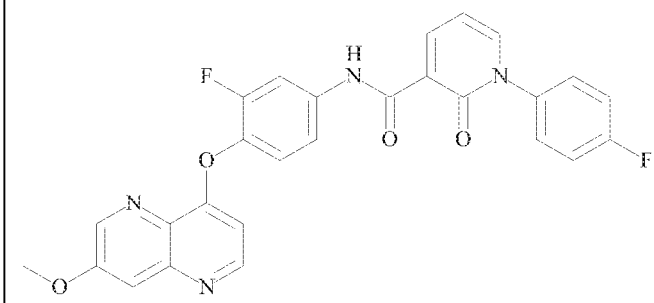
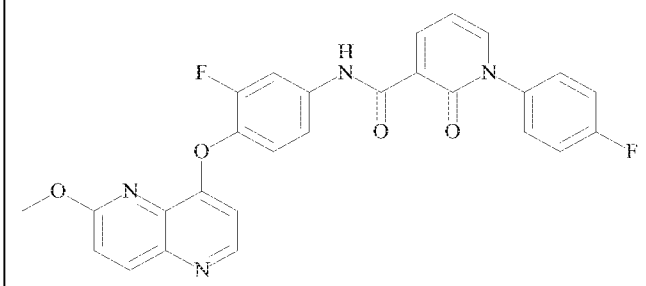
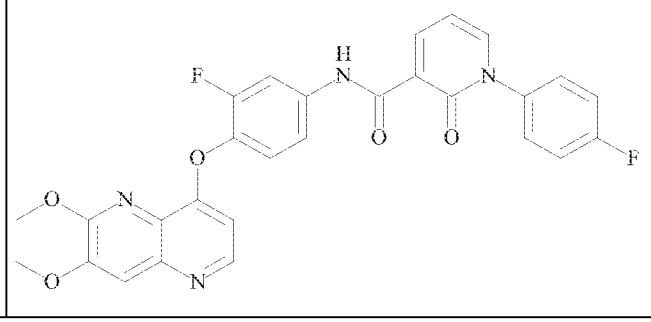
266		1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methyl-6-oxopyrimidine-5-carboxamide
267		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide
268		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2,6-dimethylphenyl)-1-methyl-4-oxopyridine-3-carboxamide
269		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-(methoxymethyl)-1-methyl-4-oxopyridine-3-carboxamide
270		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-(methoxymethyl)-1-methyl-4-oxopyridine-3-carboxamide

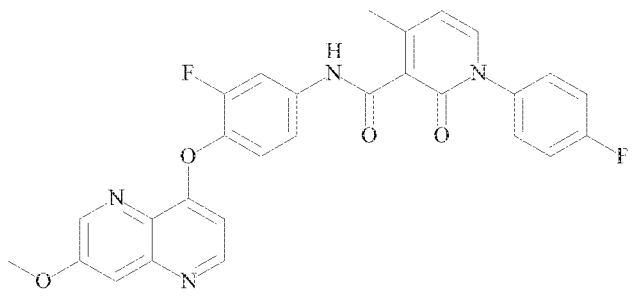
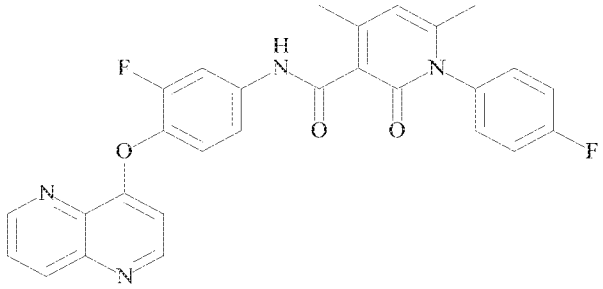
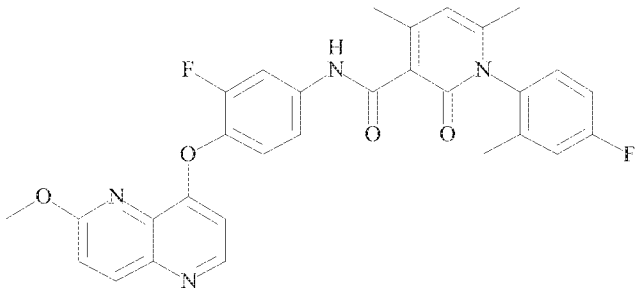
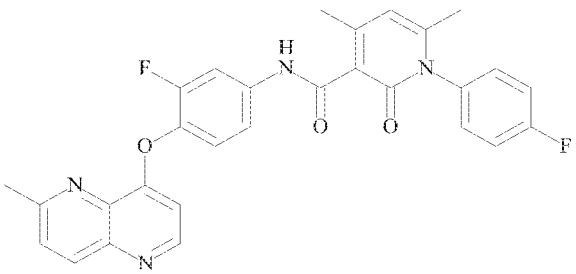
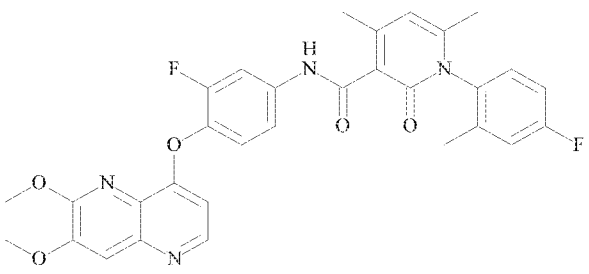
271		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide
272		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-5-(4-fluorophenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide
273		1-ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide
274		1-ethyl-5-(4-fluorophenyl)-6-(hydroxymethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-oxopyridine-3-carboxamide

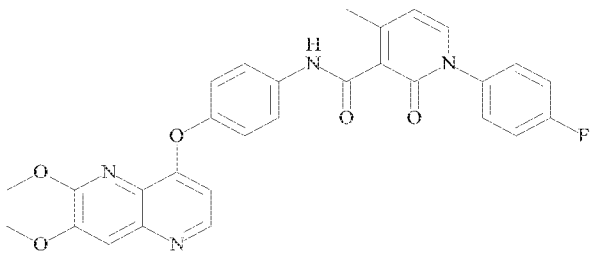
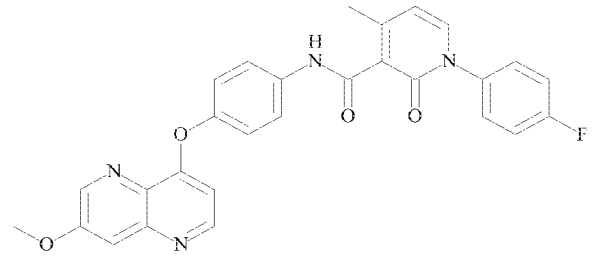
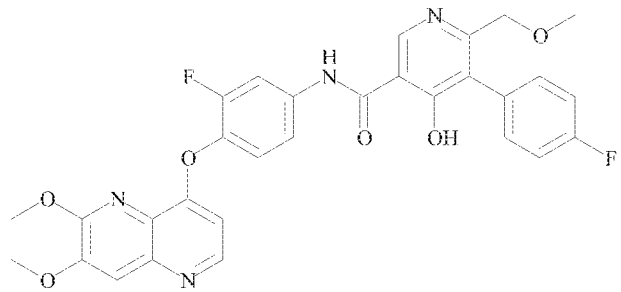
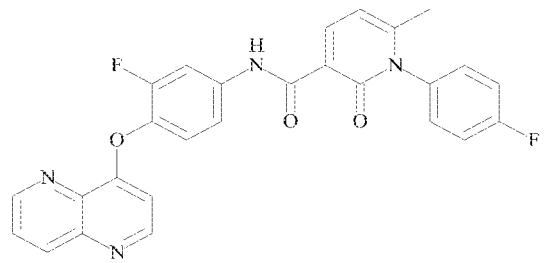
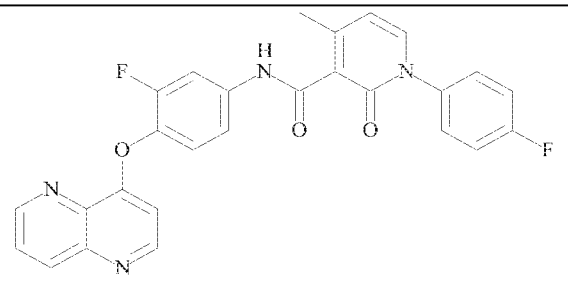
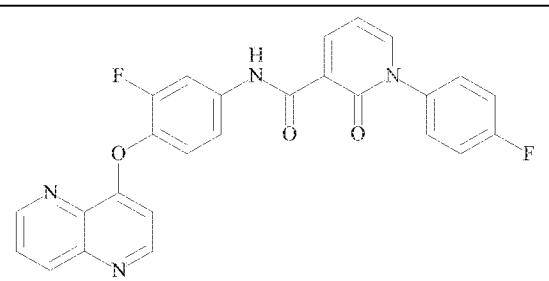
275		1-(4-fluorophenyl)-N-[3-fluoro-4-[(7-phenylmethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-2-oxopyridine-3-carboxamide
276		1-(4-fluoro-2-methylphenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-2-oxopyridine-3-carboxamide
277		5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-phenylmethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
278		1-(4-fluorophenyl)-N-[3-fluoro-4-[(7-phenylmethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2,4-dimethyl-6-oxopyrimidine-5-carboxamide
279		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide

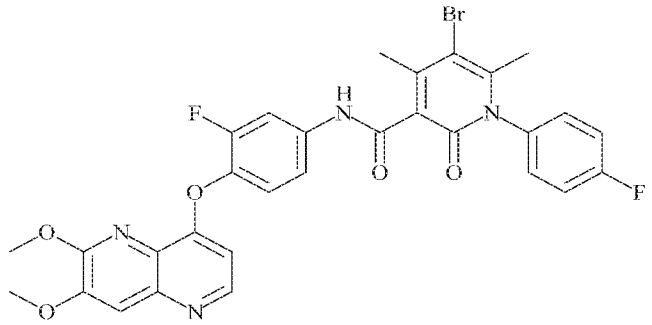
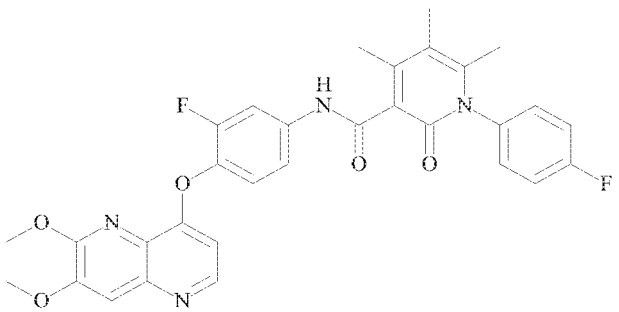
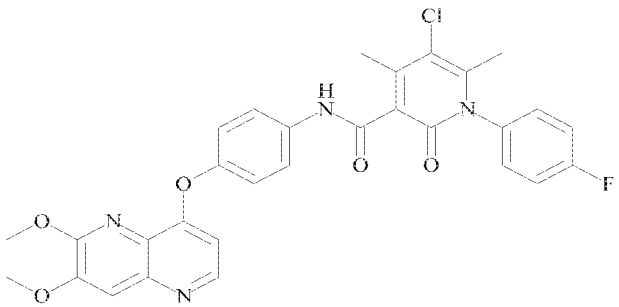
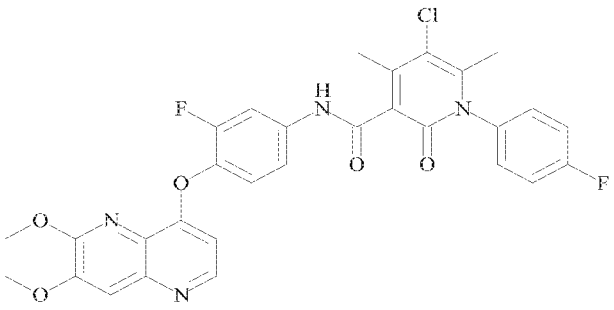
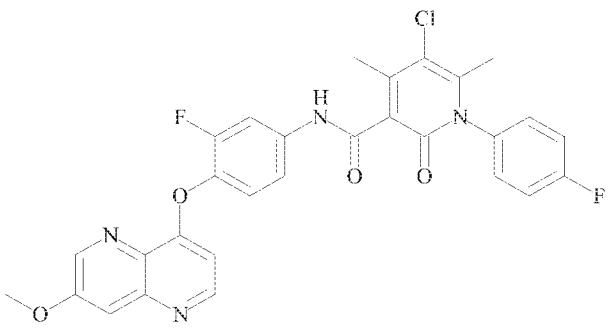
280		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
281		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
282		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide
283		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluoro-2-methylphenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide

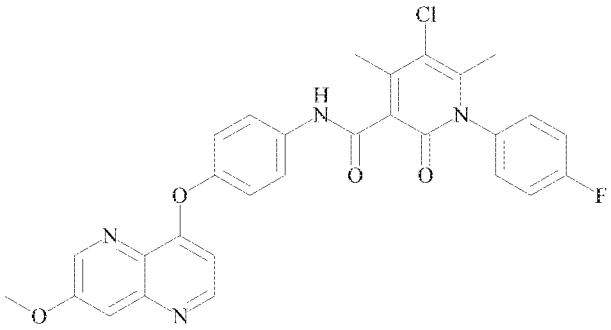
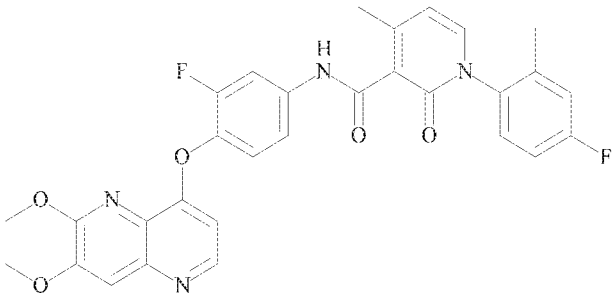
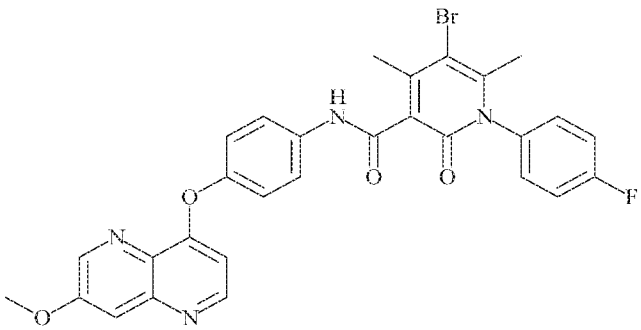
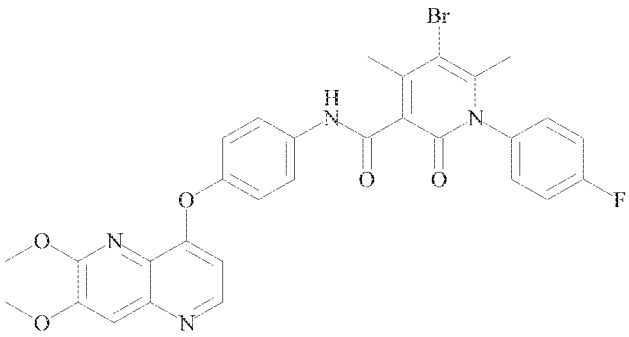
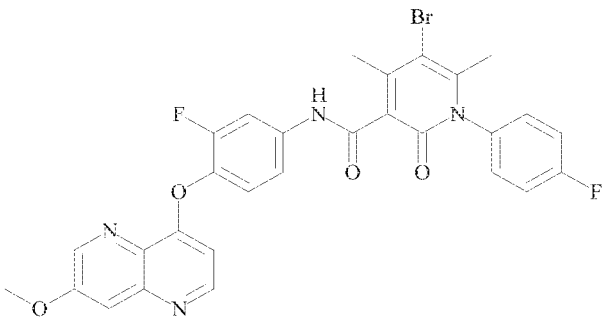
284		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-5-(4-fluoro-2-methylphenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide
285		1-ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide
286		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide
287		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide
288		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide

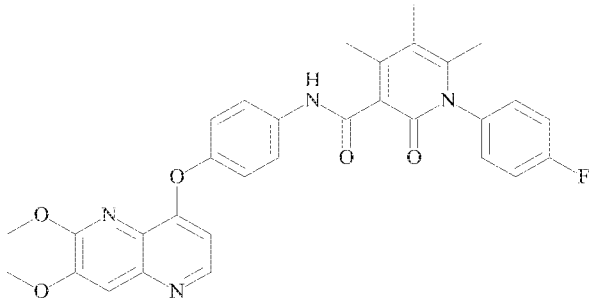
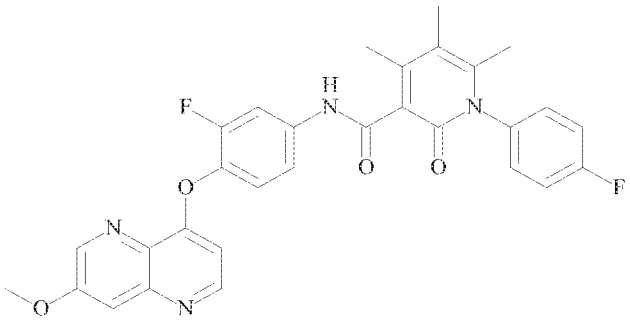
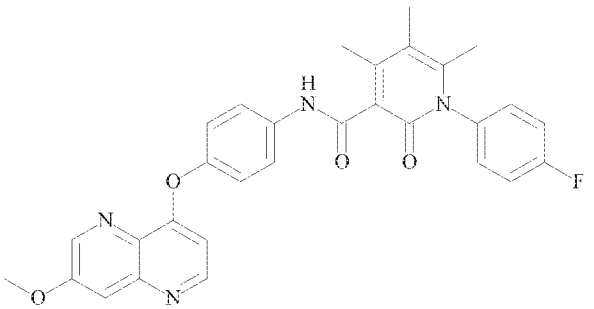
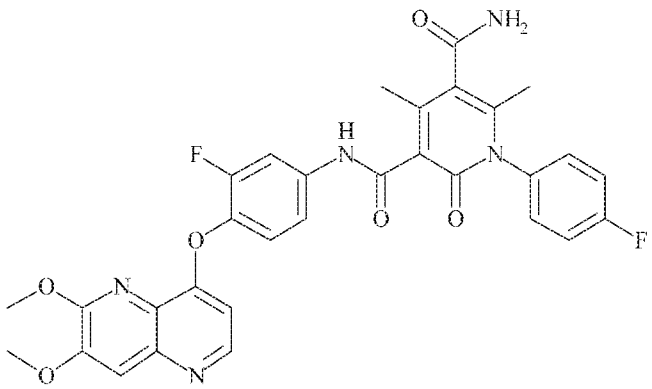
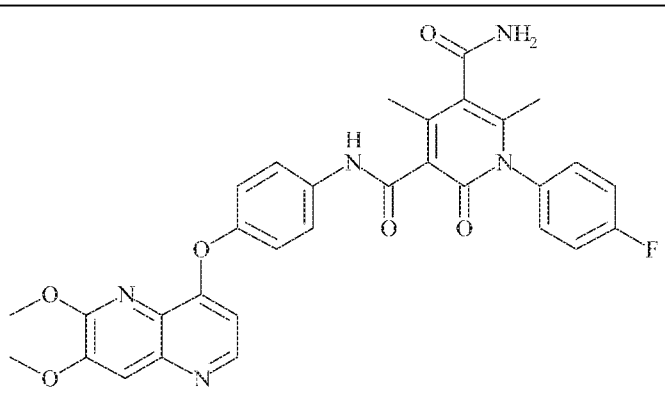
289		1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4,6-dimethyl-2-oxopyridine-3-carboxamide
290		1-(4-fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4,6-dimethyl-2-oxopyridine-3-carboxamide
291		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide
292		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide
293		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide

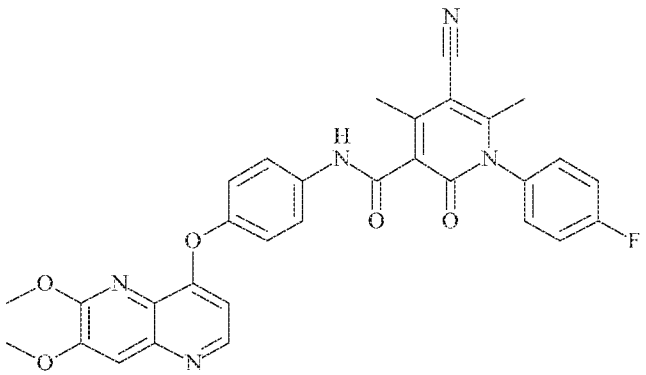
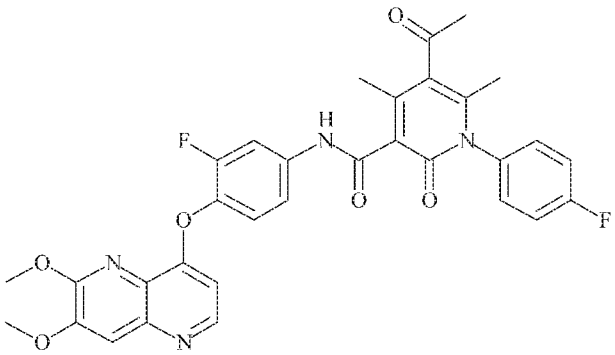
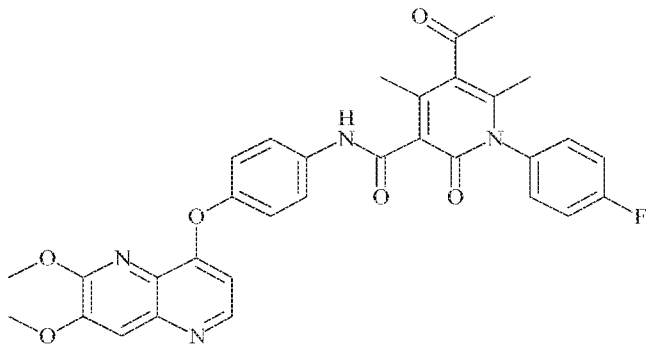
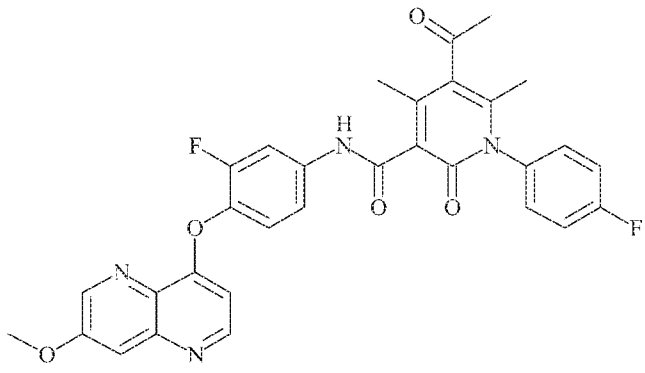
294		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide
295		N-[3-fluoro-4-(1,5-naphthyridin-4-yloxy)phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
296		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
297		N-[3-fluoro-4-[(6-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
298		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide

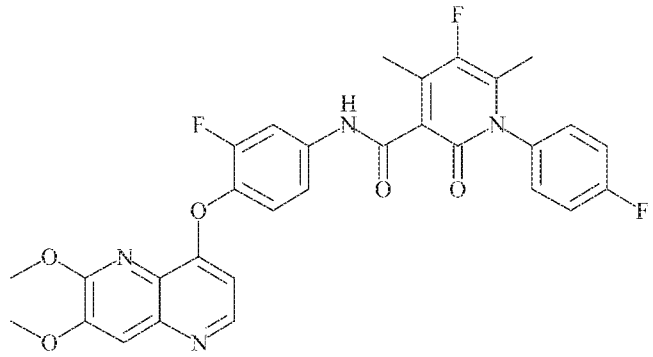
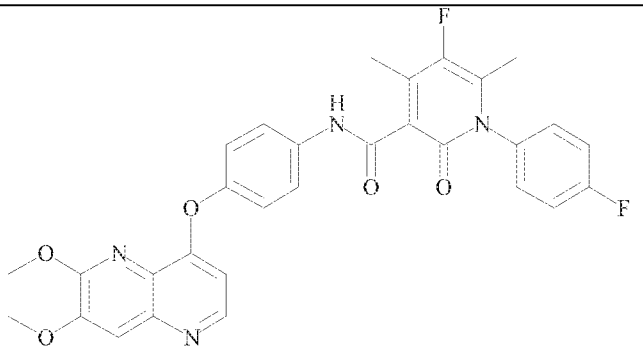
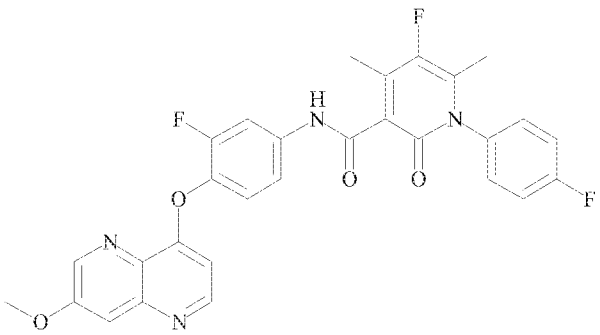
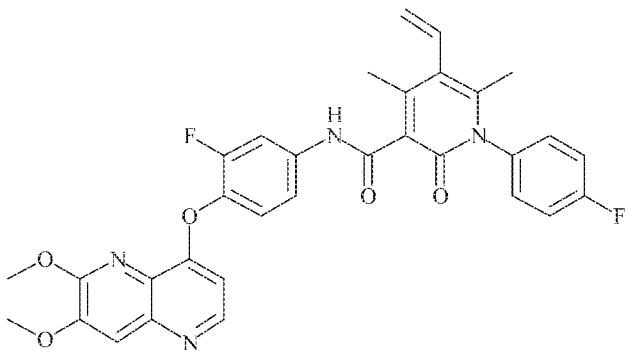
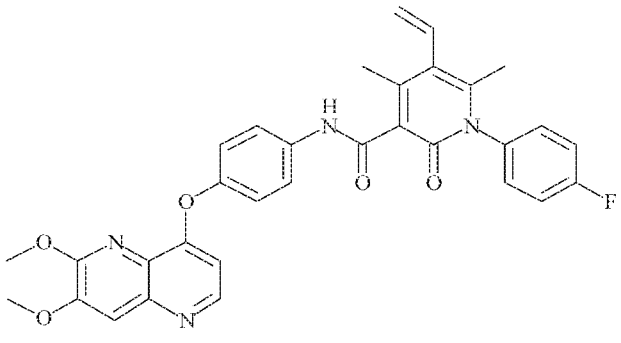
299		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide
300		1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-methyl-2-oxopyridine-3-carboxamide
301		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(methoxymethyl)pyridine-3-carboxamide
302		N-[3-fluoro-4-(1,5-naphthyridin-4-yloxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
303		N-[3-fluoro-4-(1,5-naphthyridin-4-yloxy)phenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide
304		N-[3-fluoro-4-(1,5-naphthyridin-4-yloxy)phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide

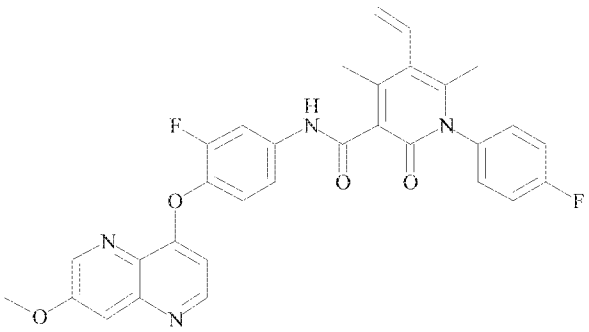
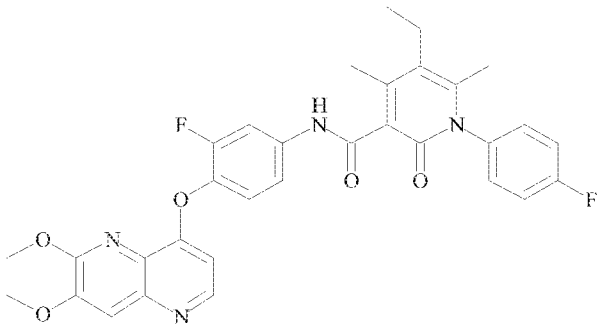
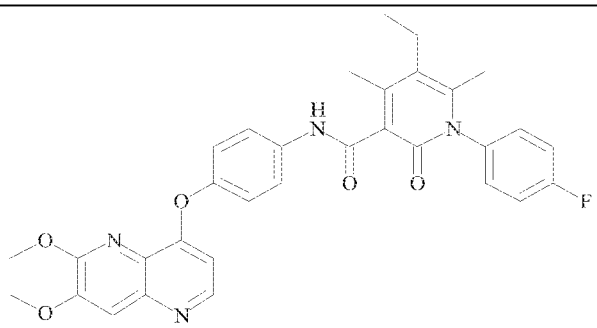
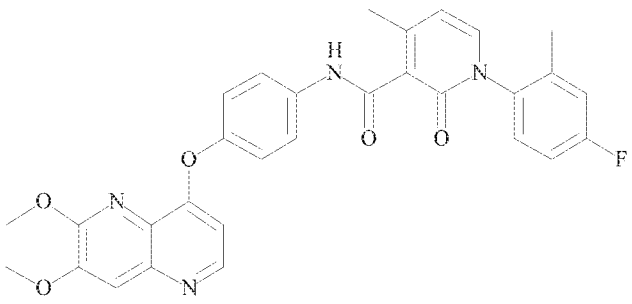
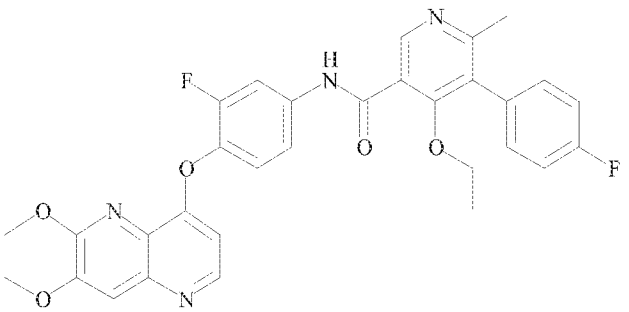
305		5-bromo-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
306		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4,5,6-trimethyl-2-oxopyridine-3-carboxamide
307		5-chloro-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
308		5-chloro-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
309		5-chloro-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide

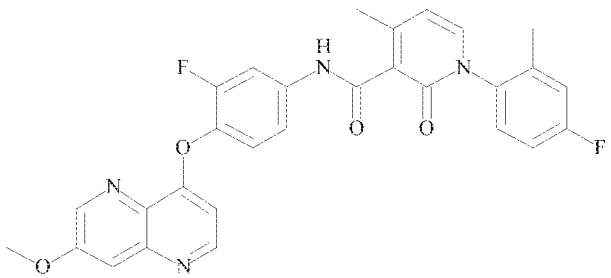
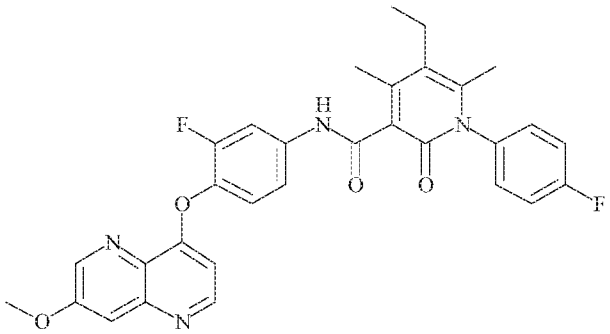
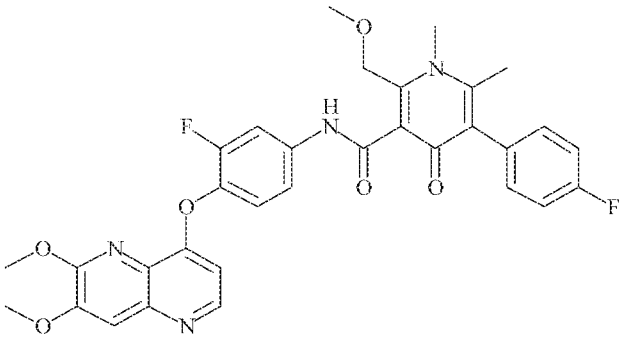
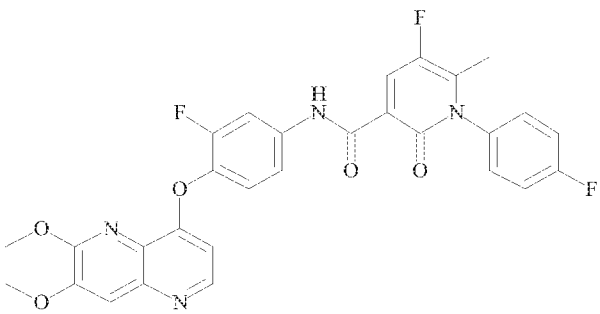
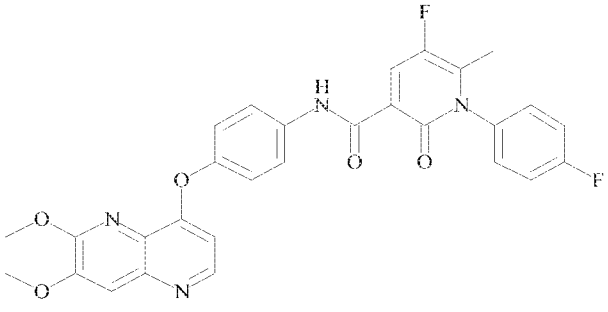
310		5-chloro-1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4,6-dimethyl-2-oxopyridine-3-carboxamide
311		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-4-methyl-2-oxopyridine-3-carboxamide
312		5-bromo-1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4,6-dimethyl-2-oxopyridine-3-carboxamide
313		5-bromo-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
314		5-bromo-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide

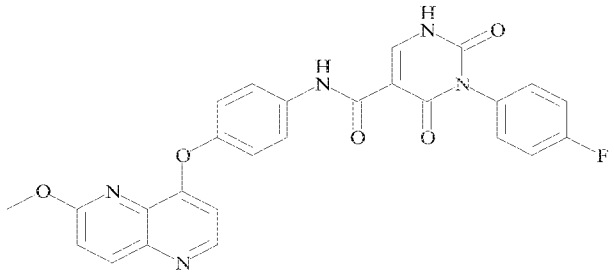
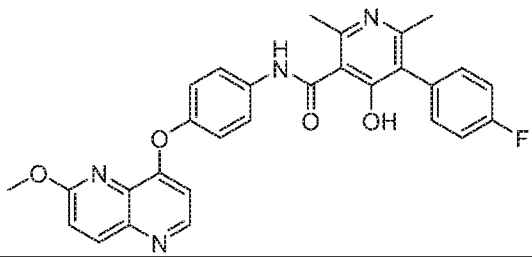
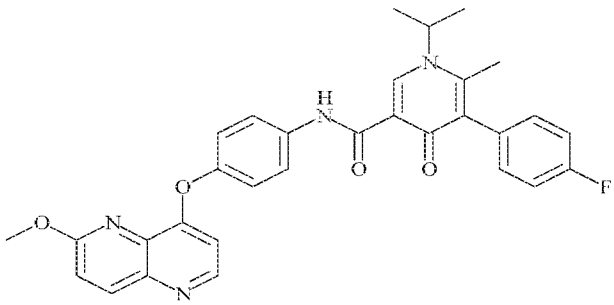
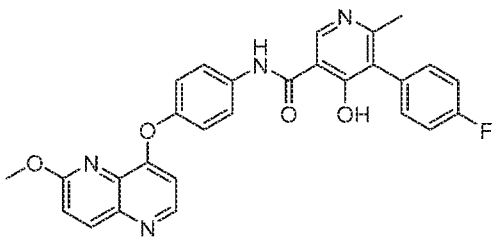
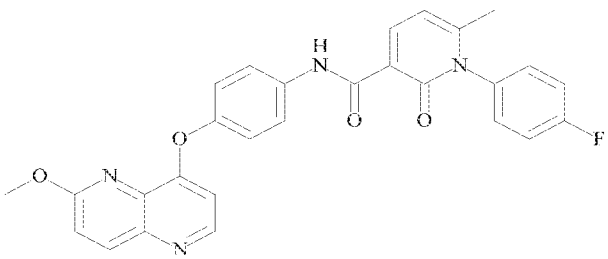
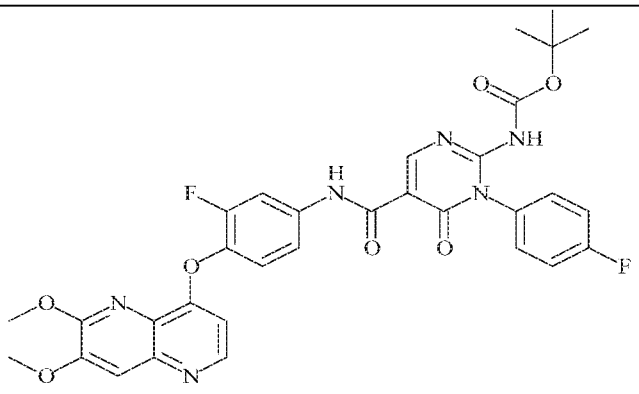
315		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,5,6-trimethyl-2-oxopyridine-3-carboxamide
316		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,5,6-trimethyl-2-oxopyridine-3-carboxamide
317		1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4,5,6-trimethyl-2-oxopyridine-3-carboxamide
318		5-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyridine-3,5-dicarboxamide
319		5-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyridine-3,5-dicarboxamide

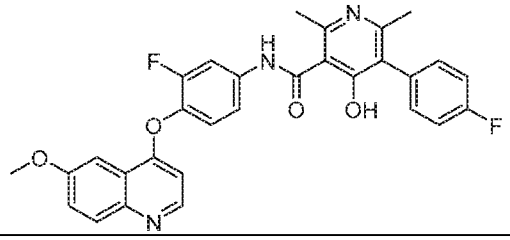
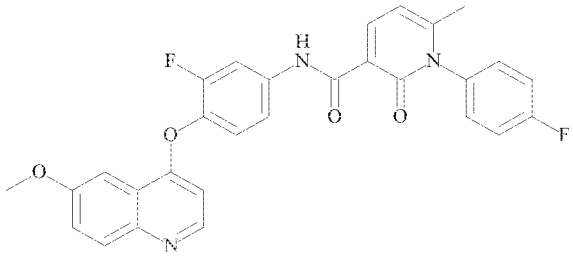
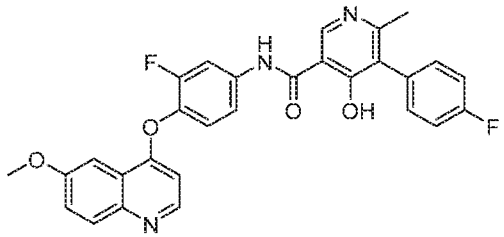
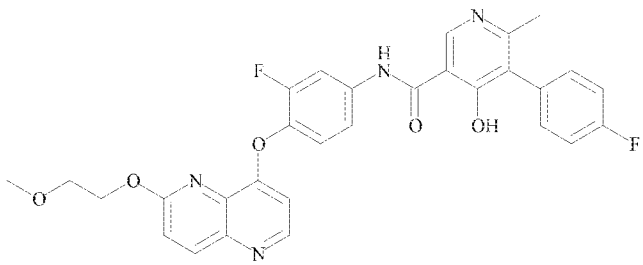
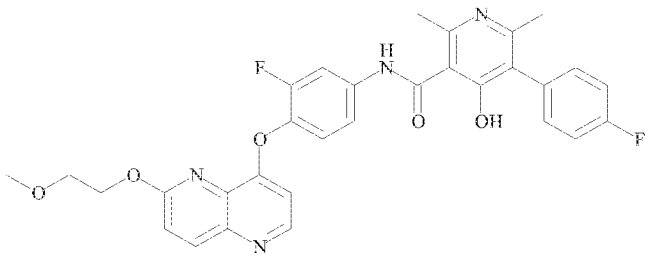
320		5-cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
321		5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
322		5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
323		5-acetyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide

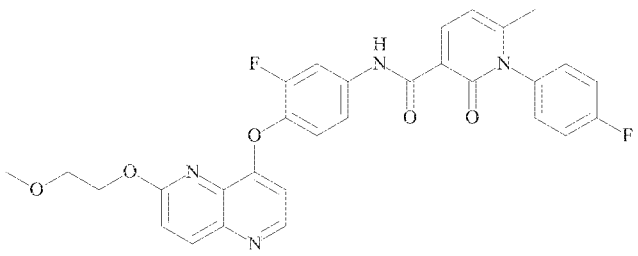
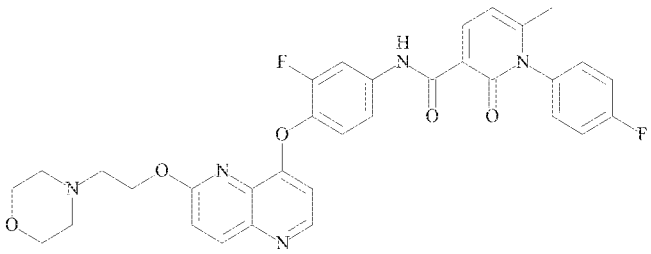
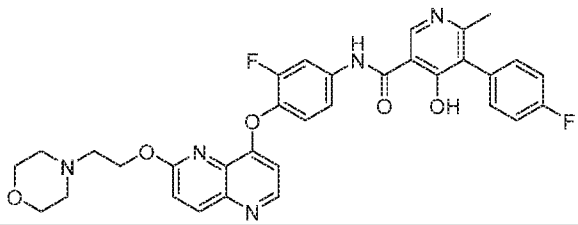
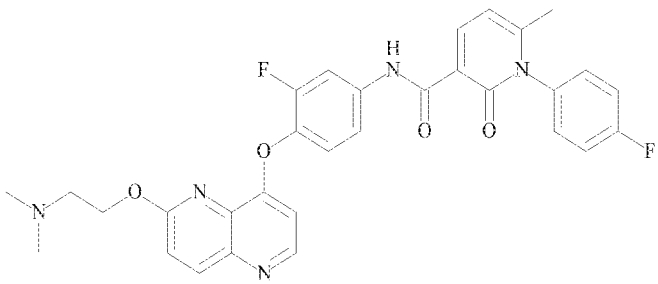
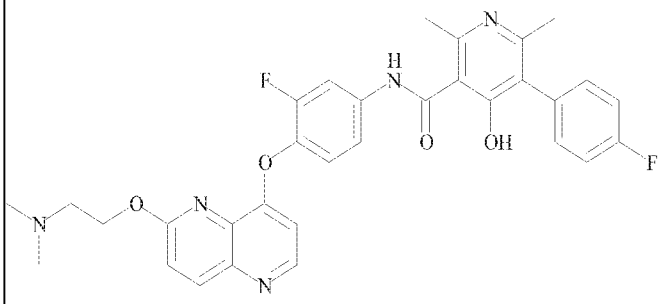
324		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-fluoro-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
325		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-fluoro-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
326		5-fluoro-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
327		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-ethenyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
328		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-ethenyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide

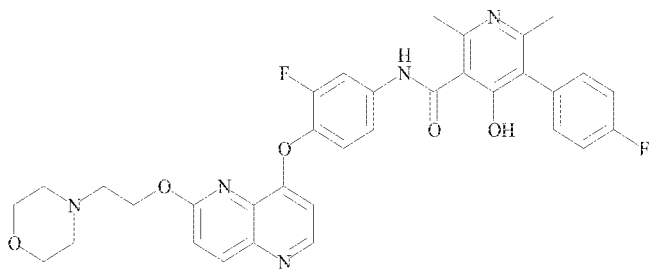
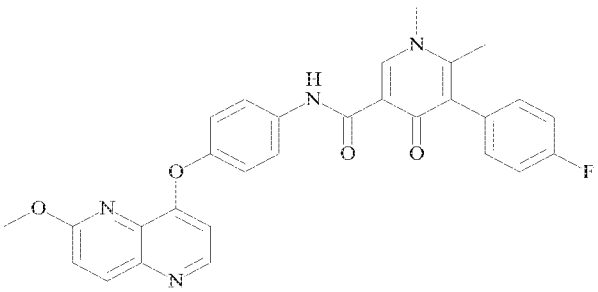
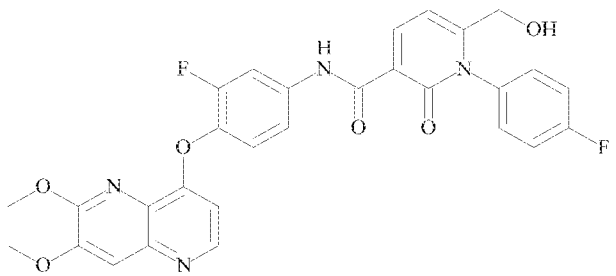
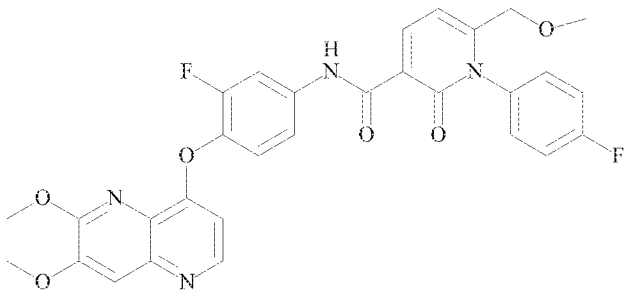
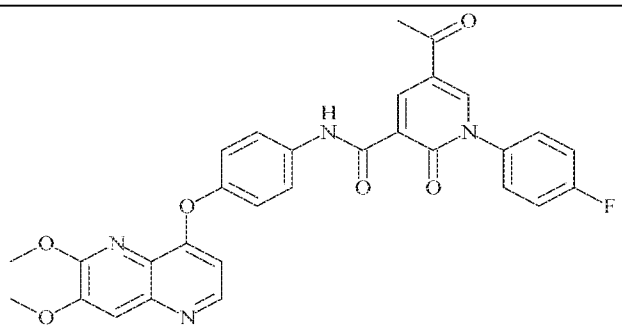
329		5-ethenyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
330		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-ethyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
331		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-ethyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
332		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-4-methyl-2-oxopyridine-3-carboxamide
333		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-ethoxy-5-(4-fluorophenyl)-6-methylpyridine-3-carboxamide

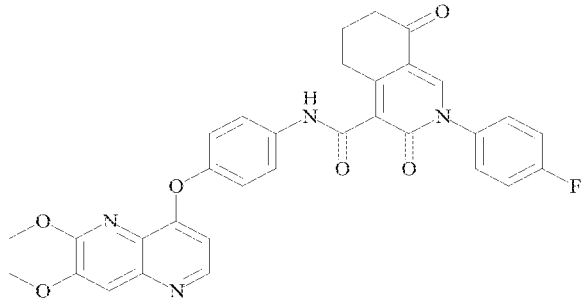
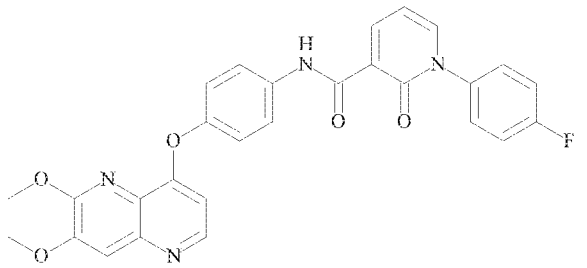
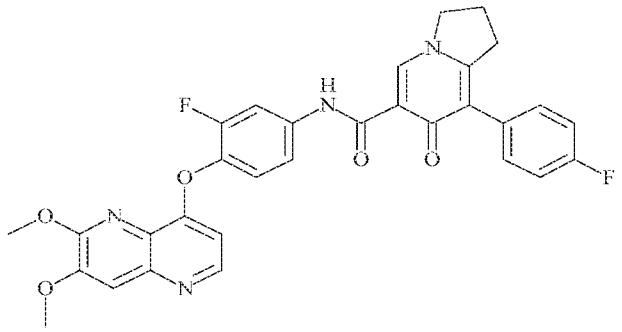
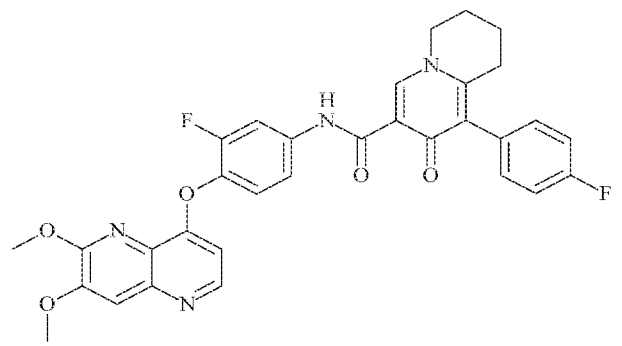
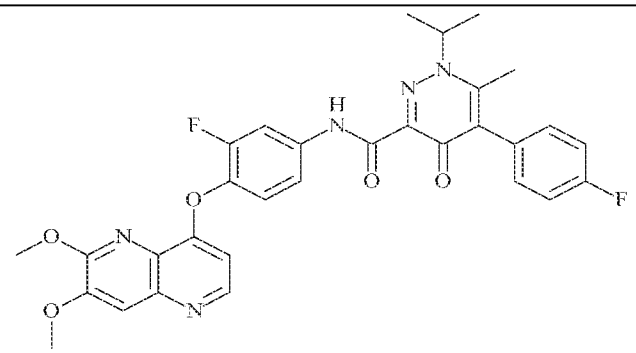
334		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-4-methyl-2-oxopyridine-3-carboxamide
335		5-ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
336		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-2-(methoxymethyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
337		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-fluoro-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
338		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-fluoro-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide

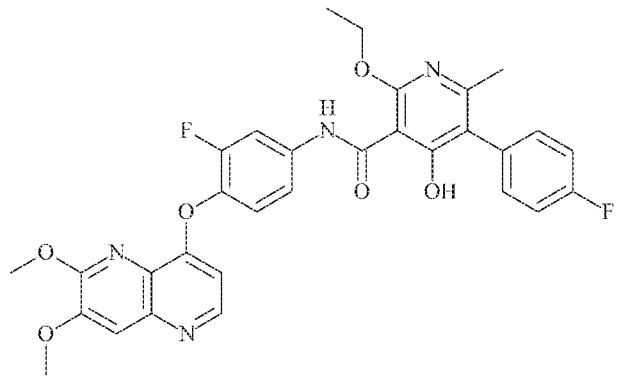
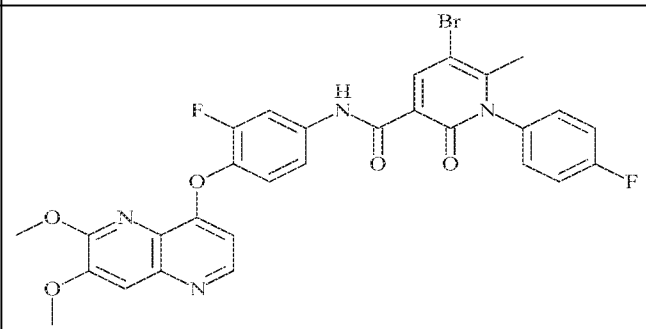
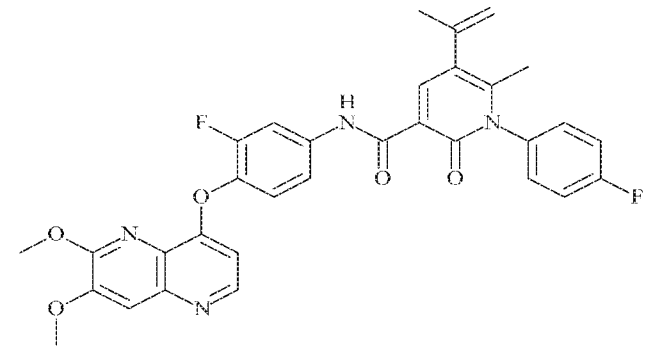
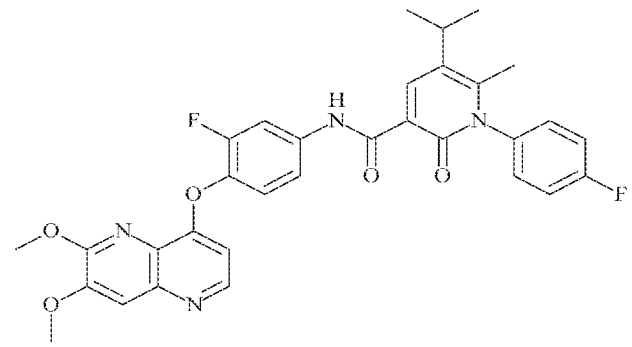
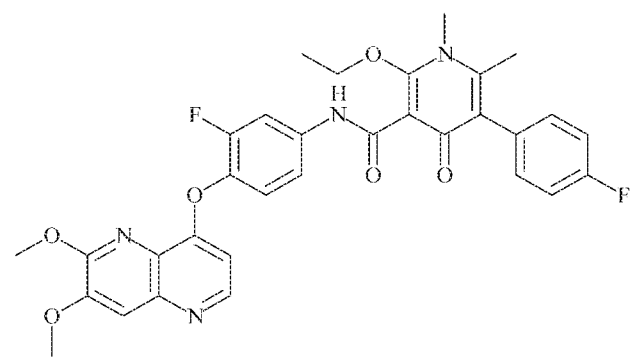
339		3-(4-fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2,4-dioxo-1H-pyrimidine-5-carboxamide
340		5-(4-fluorophenyl)-4-hydroxy-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2,6-dimethylpyridine-3-carboxamide
341		5-(4-fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
342		5-(4-fluorophenyl)-4-hydroxy-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
343		1-(4-fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-2-oxopyridine-3-carboxamide
344		tert-butyl N-[5-[[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]carbamoyl]-1-(4-fluorophenyl)-6-oxopyrimidin-2-yl]carbamate

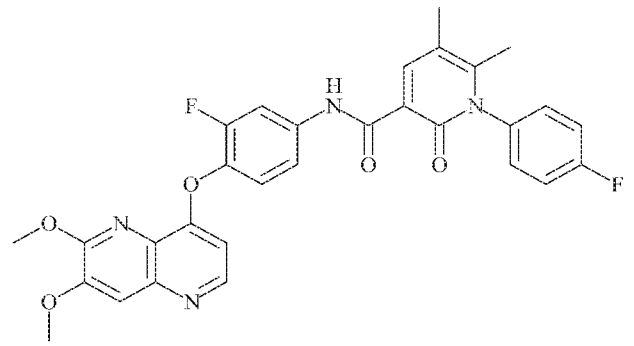
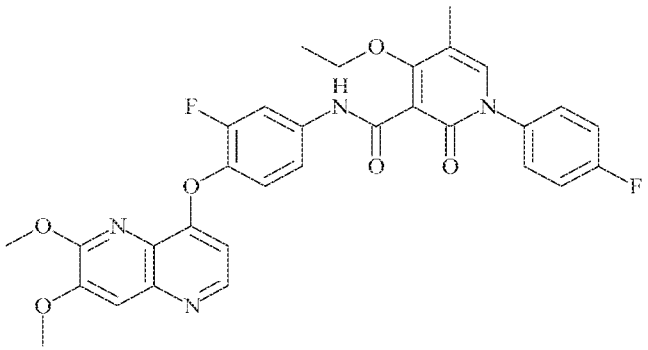
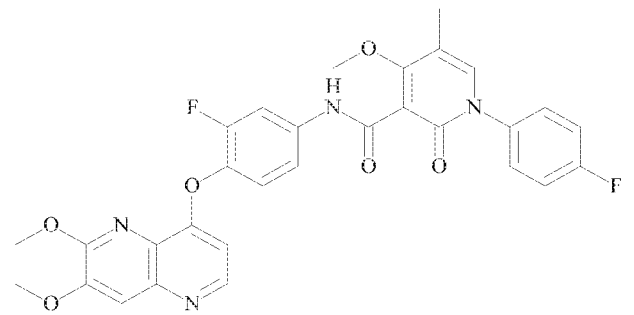
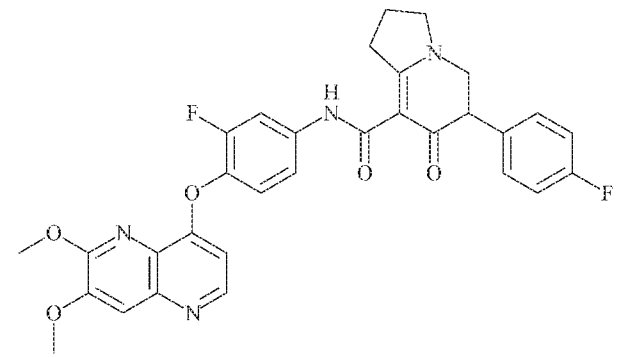
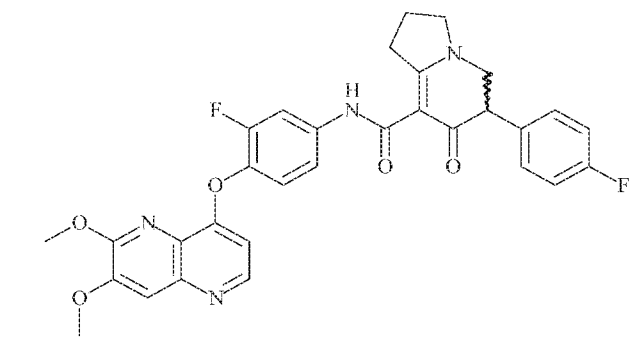
345		N-[3-fluoro-4-(6-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
346		N-[3-fluoro-4-(6-methoxyquinolin-4-yl)oxyphenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
347		N-[3-fluoro-4-(6-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
348		N-[3-fluoro-4-[[6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
349		N-[3-fluoro-4-[[6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

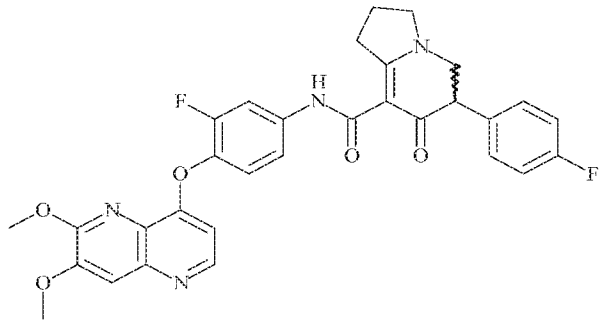
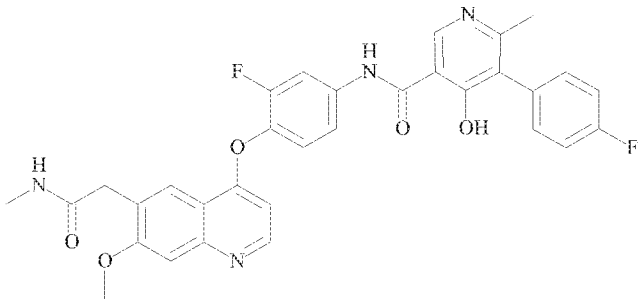
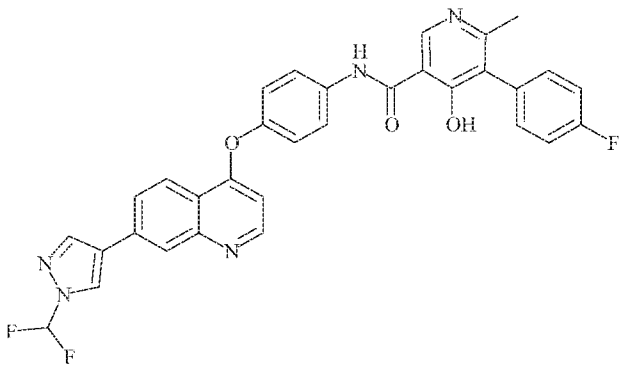
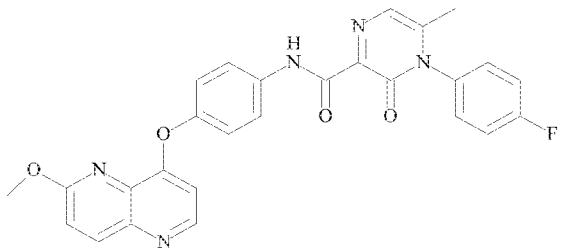
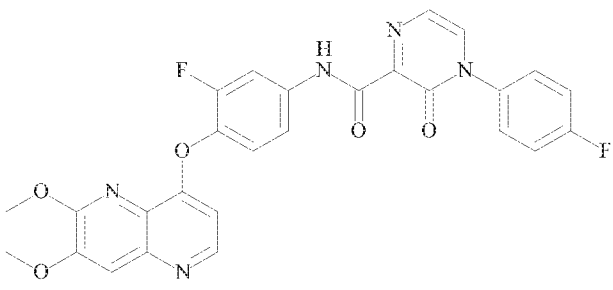
350		N-[3-fluoro-4-[[6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
351		N-[3-fluoro-4-[[6-(2-morpholin-4-ylethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
352		N-[3-fluoro-4-[[6-(2-morpholin-4-ylethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
353		N-[4-[[6-[2-(dimethylamino)ethoxy]-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
354		N-[4-[[6-[2-(dimethylamino)ethoxy]-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

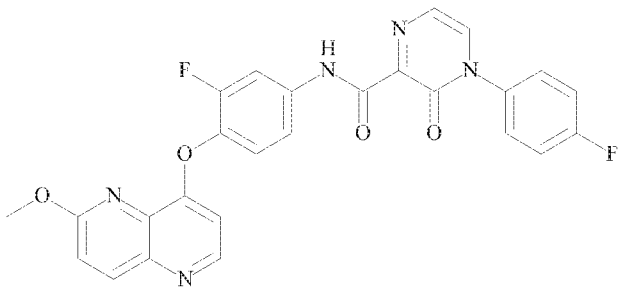
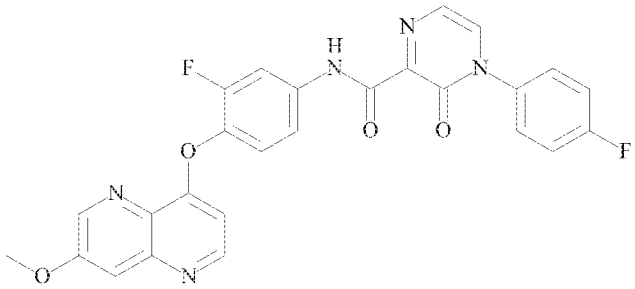
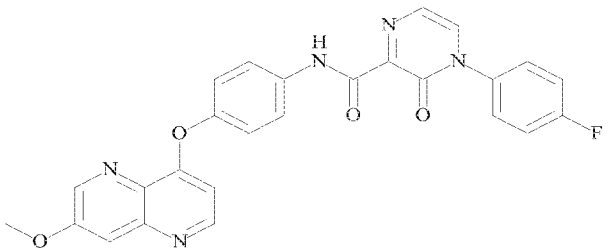
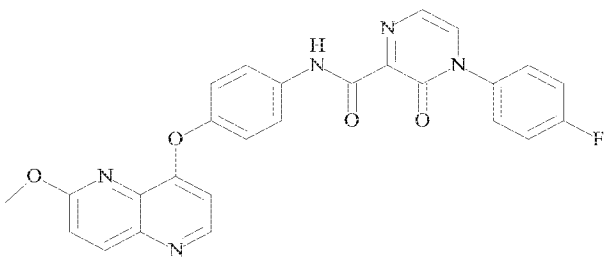
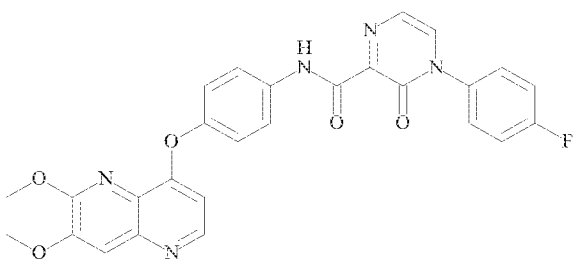
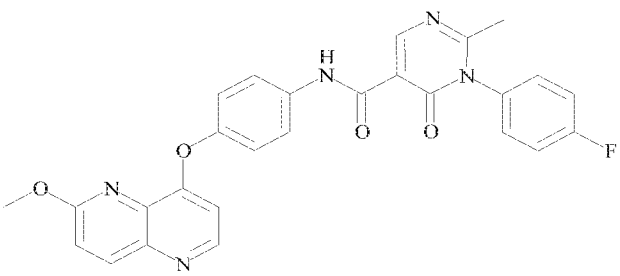
355		N-[3-fluoro-4-[[6-(2-morpholin-4-ylethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
356		5-(4-fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridine-3-carboxamide
357		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-(hydroxymethyl)-2-oxopyridine-3-carboxamide
358		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-(methoxymethyl)-2-oxopyridine-3-carboxamide
359		5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide

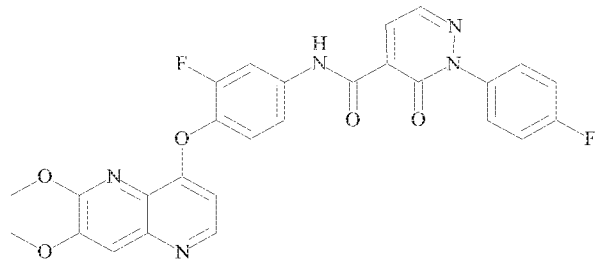
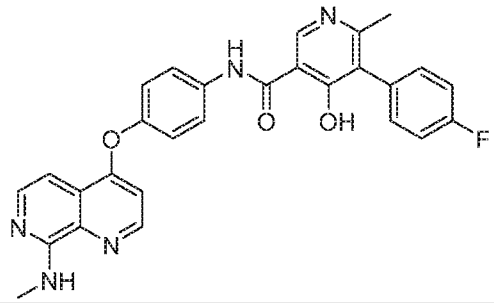
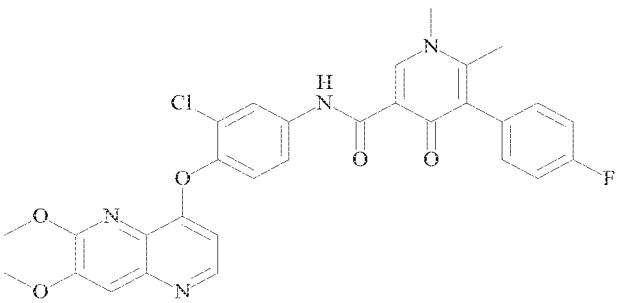
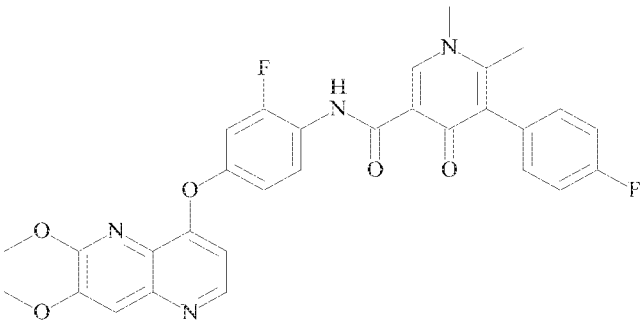
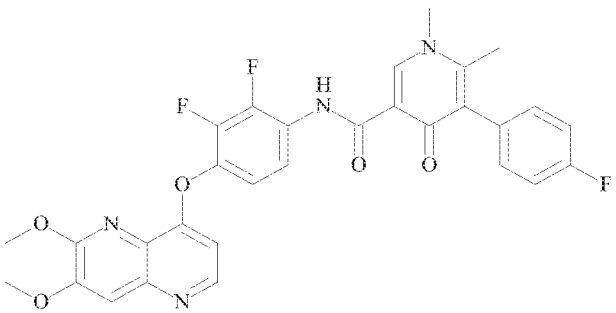
360		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-3,8-dioxo-6,7-dihydro-5H-isoquinoline-4-carboxamide
361		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide
362		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-8-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-6-carboxamide
363		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-oxo-6,7,8,9-tetrahydroquinolizine-3-carboxamide
364		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridazine-3-carboxamide

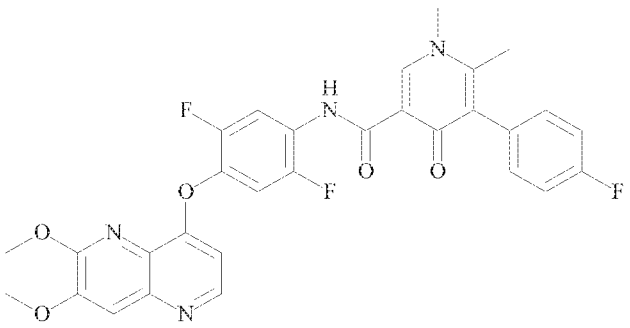
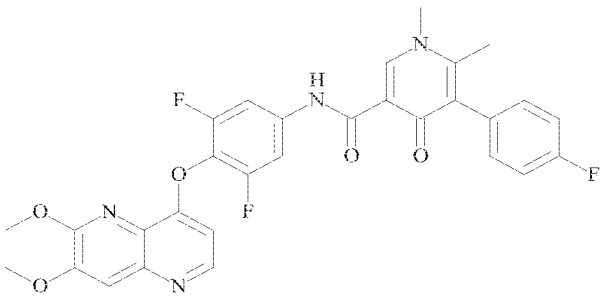
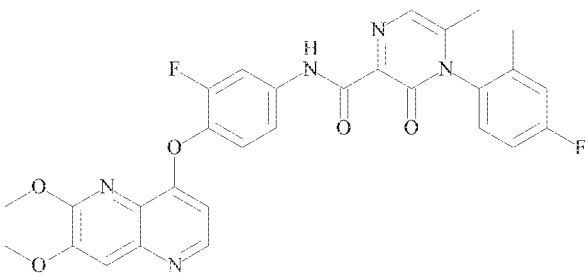
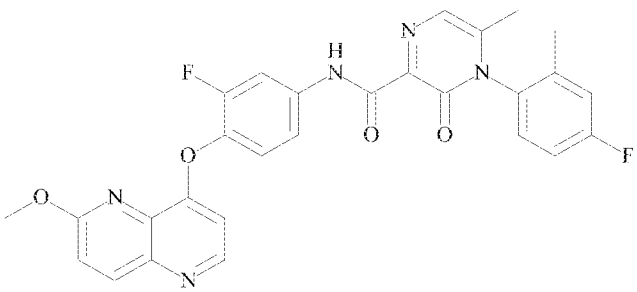
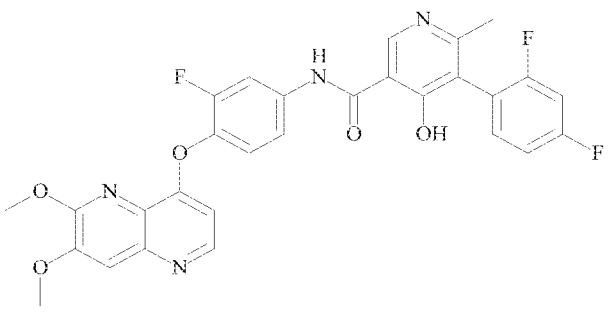
365		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-ethoxy-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
366		5-bromo-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
367		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-5-prop-1-en-2-ylpyridine-3-carboxamide
368		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-5-propan-2-ylpyridine-3-carboxamide
369		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-ethoxy-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide

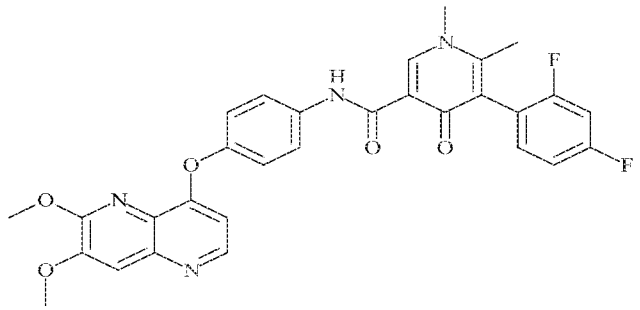
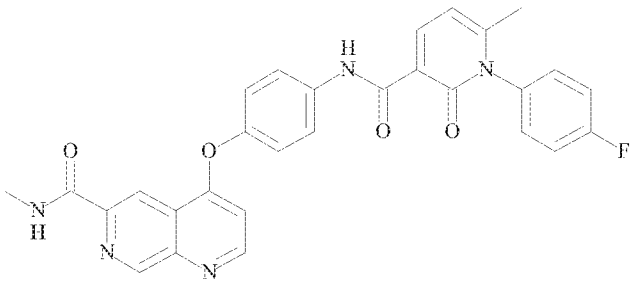
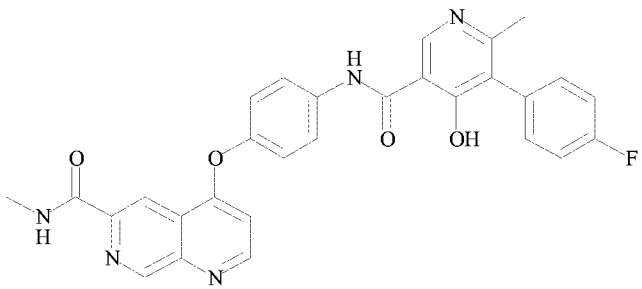
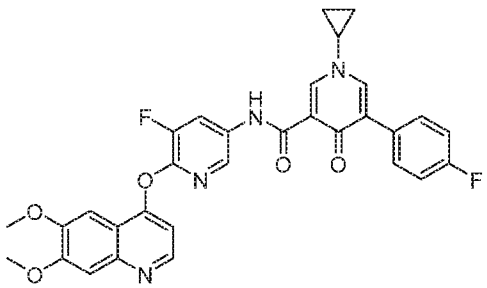
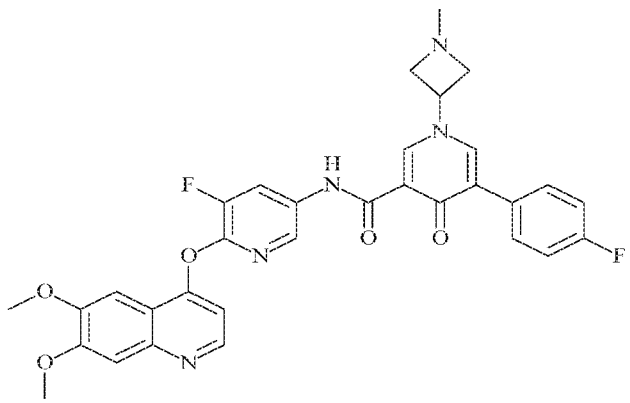
370		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-5,6-dimethyl-2-oxopyridine-3-carboxamide
371		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-ethoxy-1-(4-fluorophenyl)-5-methyl-2-oxopyridine-3-carboxamide
372		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methoxy-5-methyl-2-oxopyridine-3-carboxamide
373		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3,5,6-tetrahydro-1H-indolizine-8-carboxamide
374		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3,5,6-tetrahydro-1H-indolizine-8-carboxamide, enantiomer 1

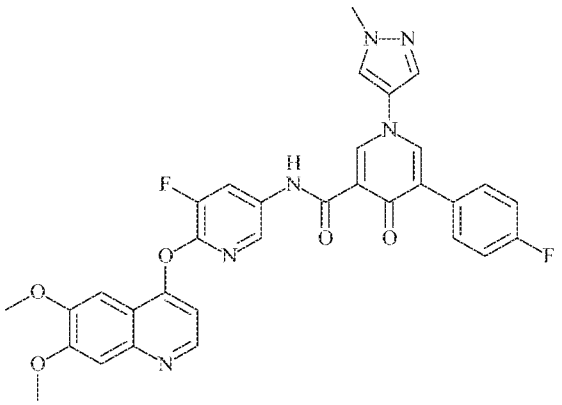
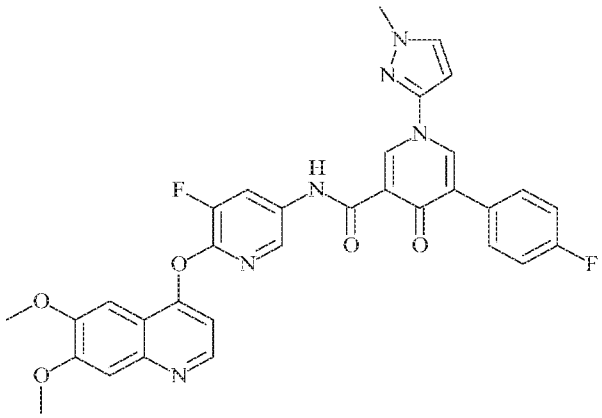
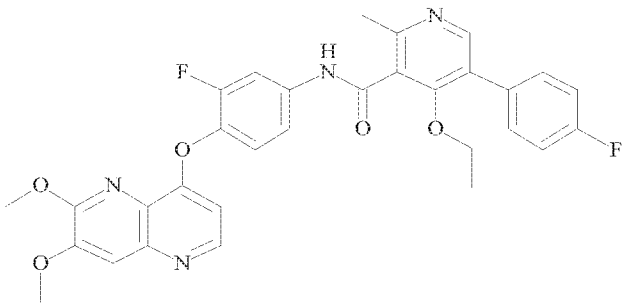
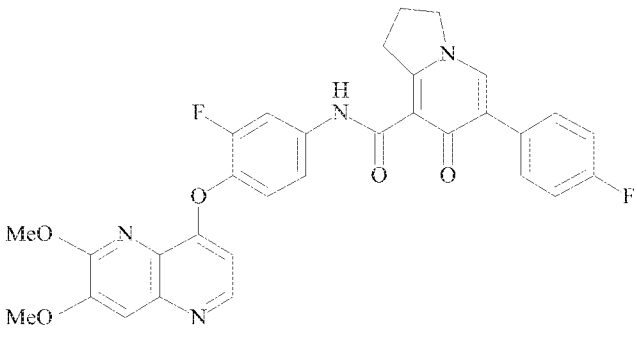
375		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3,5,6-tetrahydro-1H-indolizine-8-carboxamide, enantiomer 2
376		N-[3-fluoro-4-[7-methoxy-6-[2-(methylamino)-2-oxoethyl]quinolin-4-yl]oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
377		N-[4-[7-[1-(difluoromethyl)pyrazol-4-yl]quinolin-4-yl]oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
378		4-(4-fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-methyl-3-oxopyrazine-2-carboxamide
379		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-3-oxopyrazine-2-carboxamide

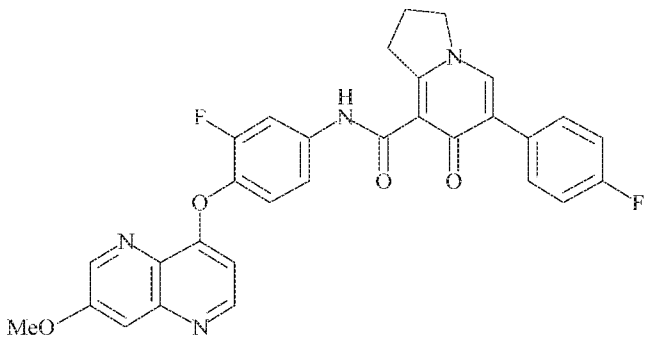
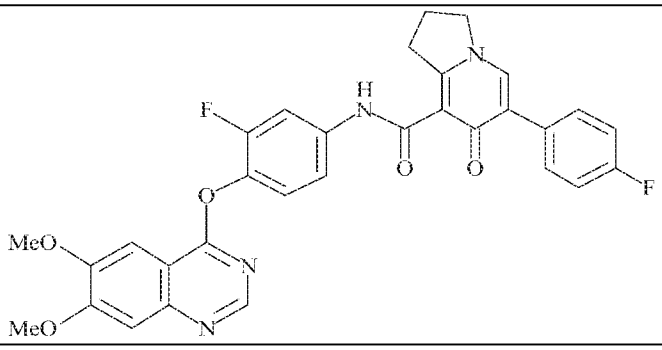
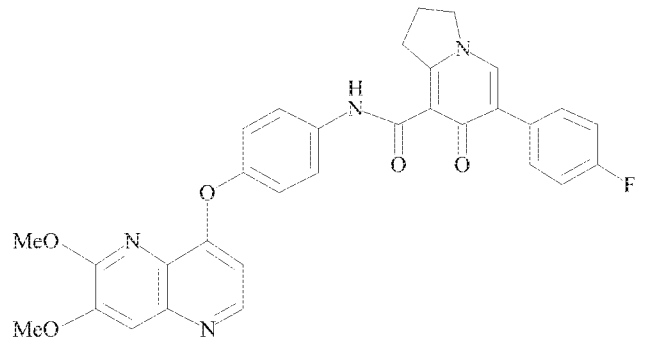
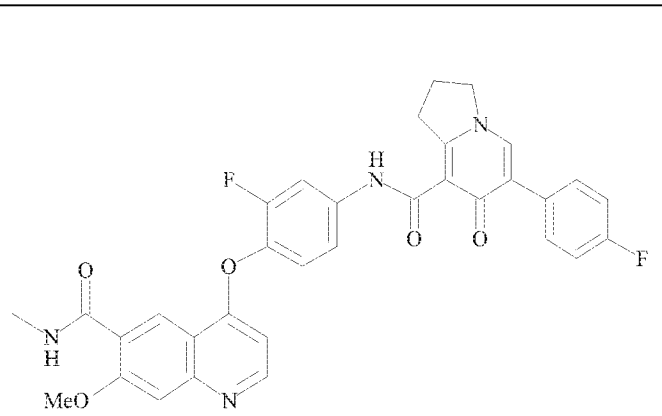
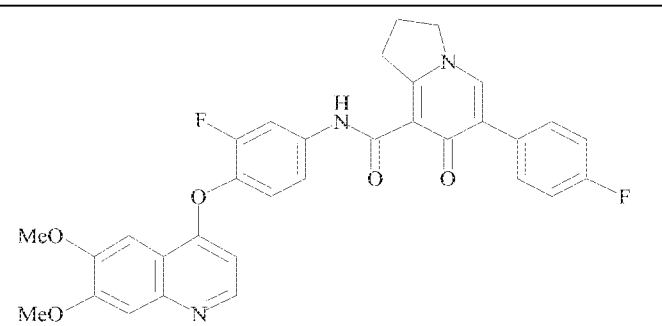
380		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-3-oxopyrazine-2-carboxamide
381		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-3-oxopyrazine-2-carboxamide
382		4-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-3-oxopyrazine-2-carboxamide
383		4-(4-fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-3-oxopyrazine-2-carboxamide
384		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-3-oxopyrazine-2-carboxamide
385		1-(4-fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methyl-6-oxopyrimidine-5-carboxamide

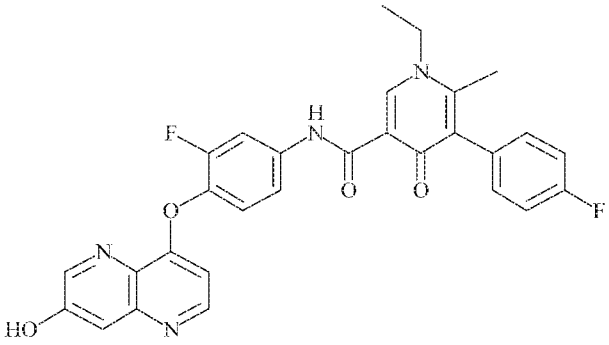
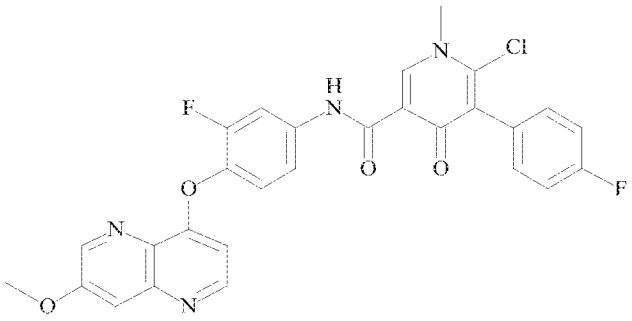
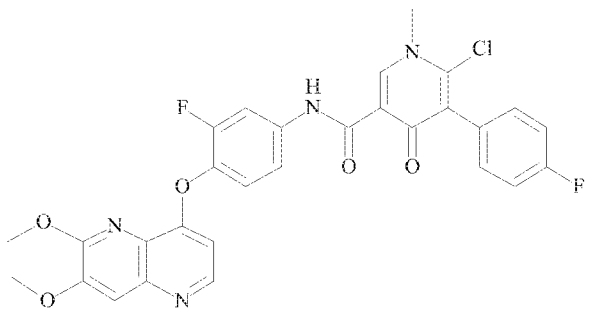
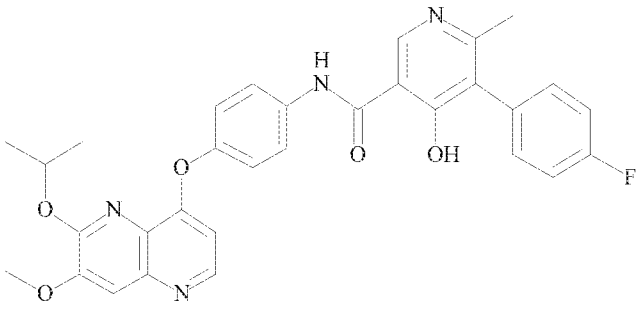
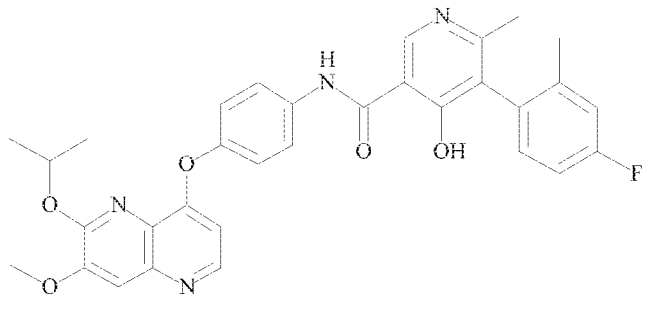
386		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(4-fluorophenyl)-3-oxopyridazine-4-carboxamide
387		5-(4-fluorophenyl)-4-hydroxy-6-methyl-N-[4-[[8-(methylamino)-1,7-naphthyridin-4-yl]oxy]phenyl]pyridine-3-carboxamide
388		N-[3-chloro-4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
389		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-2-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
390		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-2,3-difluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide

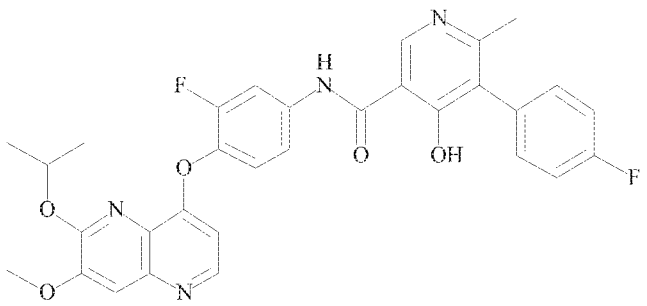
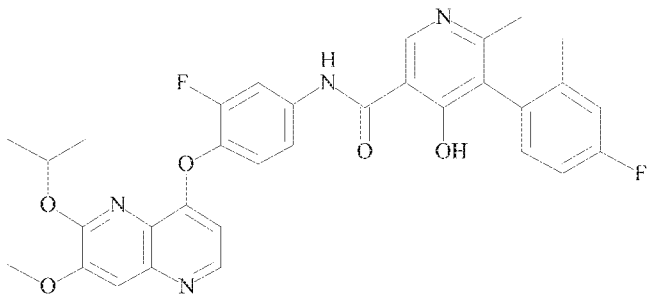
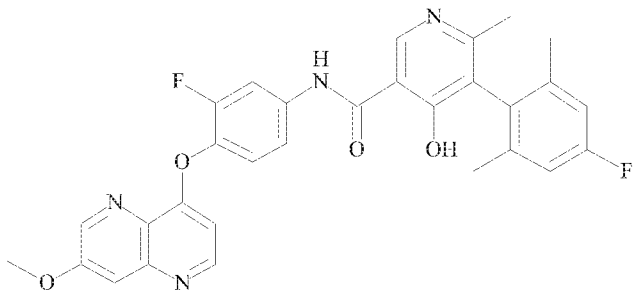
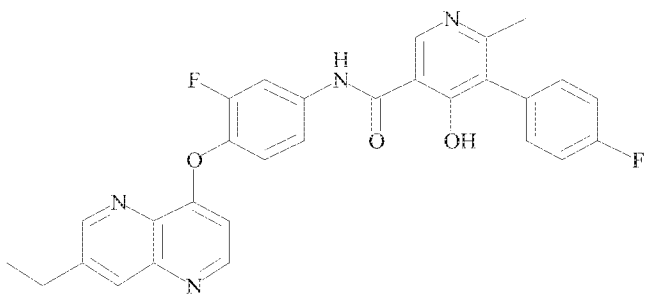
391		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-2,5-difluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
392		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3,5-difluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
393		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluoro-2-methylphenyl)-5-methyl-3-oxopyrazine-2-carboxamide
394		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluoro-2-methylphenyl)-5-methyl-3-oxopyrazine-2-carboxamide
395		5-(2,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-6-methylpyridine-3-carboxamide

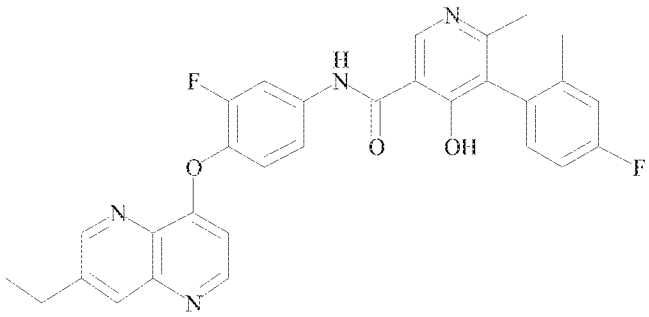
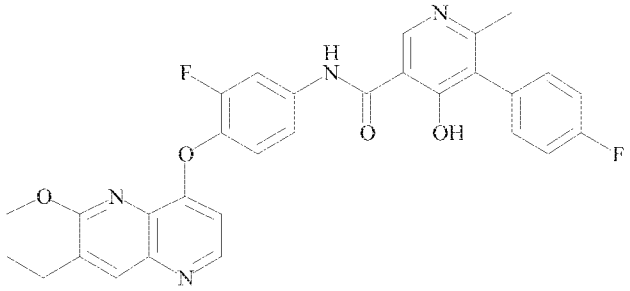
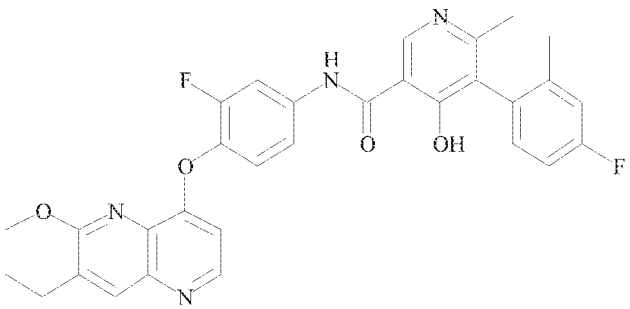
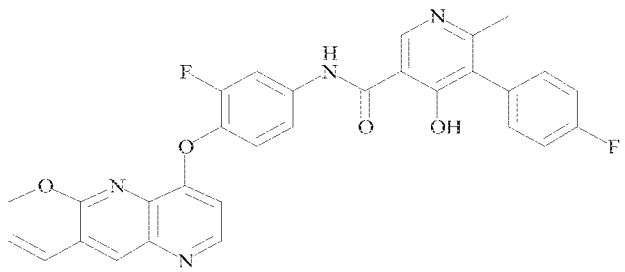
396		5-(2,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridine-3-carboxamide
397		4-[4-[[1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carbonyl]amino]phenoxy]-N-methyl-1,7-naphthyridine-6-carboxamide
398		4-[4-[[5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carbonyl]amino]phenoxy]-N-methyl-1,7-naphthyridine-6-carboxamide
399		1-cyclopropyl-N-[6-(6,7-dimethoxyquinolin-4-yl)oxy-5-fluoropyridin-3-yl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide
400		N-[6-(6,7-dimethoxyquinolin-4-yl)oxy-5-fluoropyridin-3-yl]-5-(4-fluorophenyl)-1-(1-methylazetidin-3-yl)-4-oxopyridine-3-carboxamide

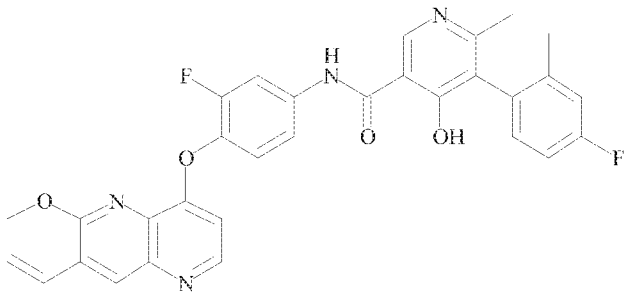
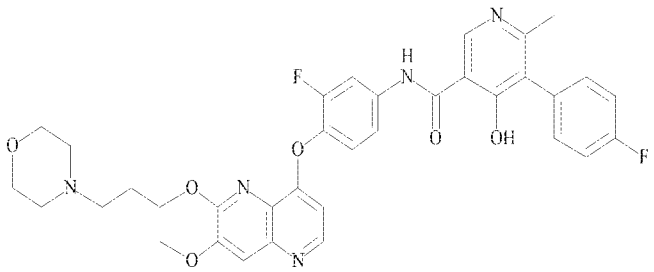
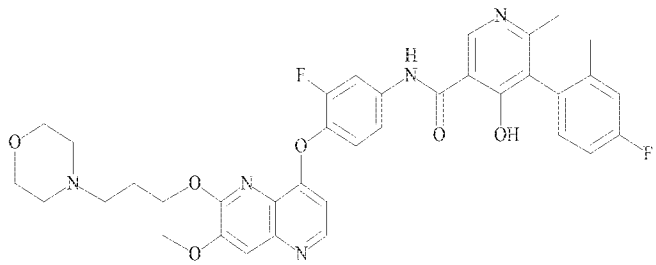
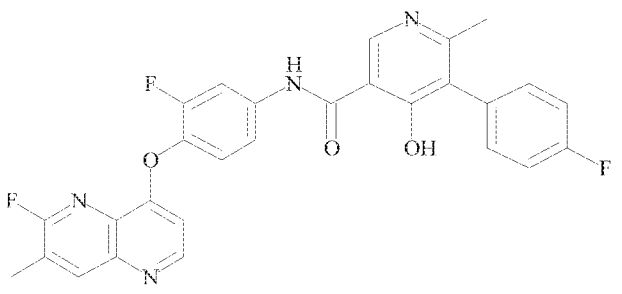
401		N-[6-(6,7-dimethoxyquinolin-4-yl)oxy-5-fluoropyridin-3-yl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide
402		N-[6-(6,7-dimethoxyquinolin-4-yl)oxy-5-fluoropyridin-3-yl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-3-yl)-4-oxopyridine-3-carboxamide
403		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-ethoxy-5-(4-fluorophenyl)-2-methylpyridine-3-carboxamide
404		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carboxamide

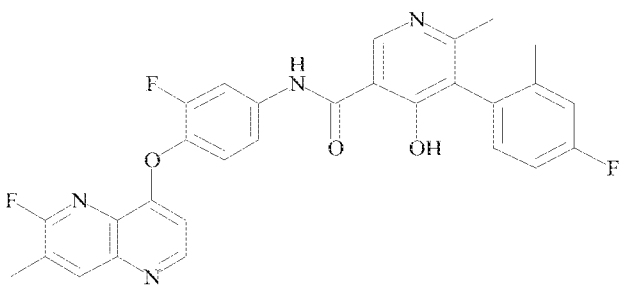
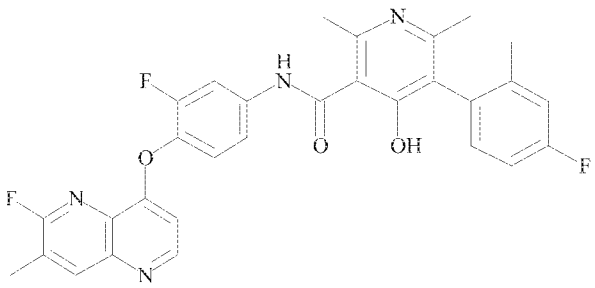
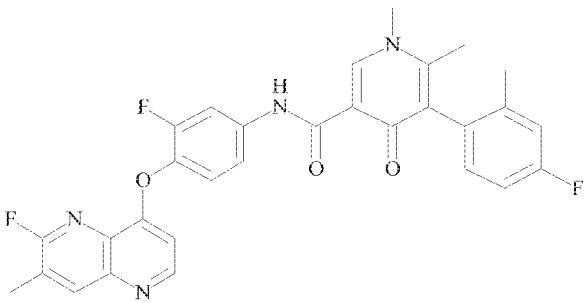
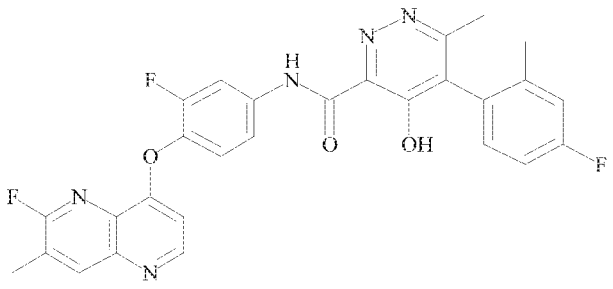
405		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carboxamide
406		N-[4-(6,7-dimethoxyquinazolin-4-yl)oxy-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carboxamide
407		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carboxamide
408		4-[2-fluoro-4-[[6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carbonyl]amino]phenoxy]-7-methoxy-N-methylquinoline-6-carboxamide
409		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carboxamide

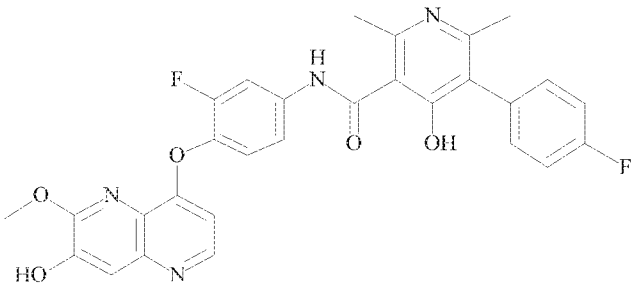
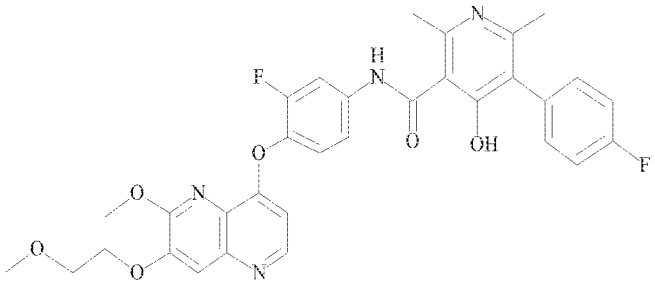
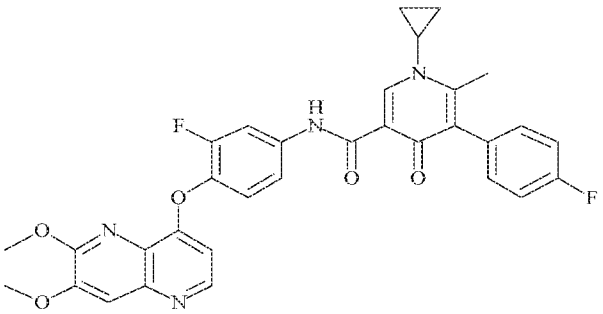
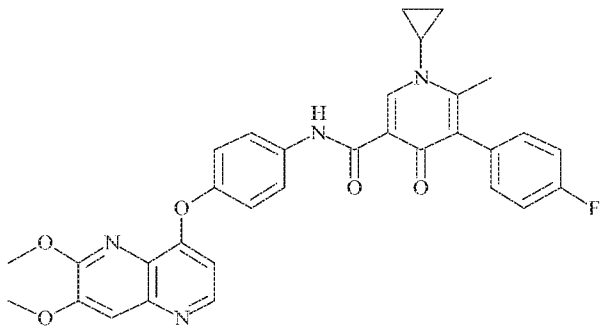
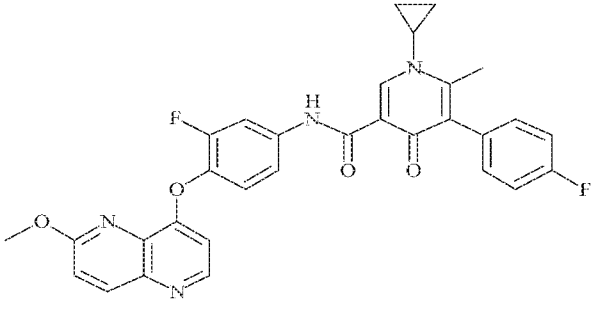
410		1-ethyl-N-[3-fluoro-4-[(7-hydroxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
411		6-chloro-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide
412		6-chloro-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide
413		5-(4-fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-6-propan-2-yloxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
414		5-(4-fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(7-methoxy-6-propan-2-yloxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide

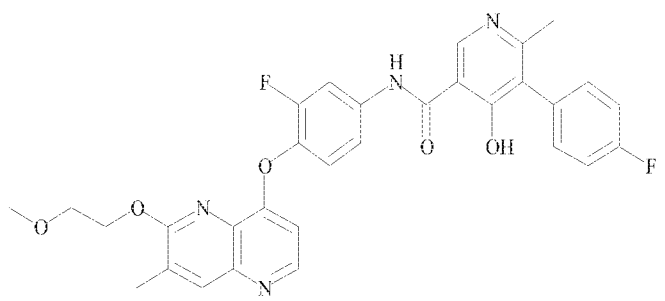
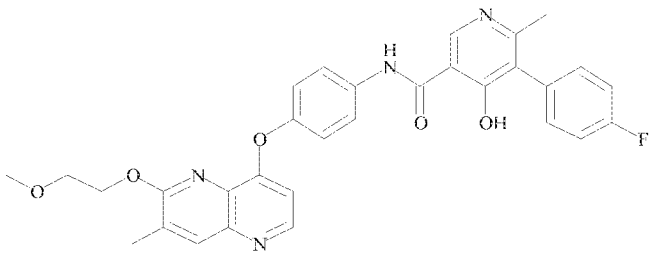
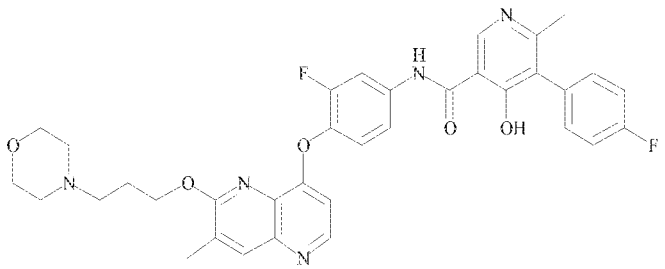
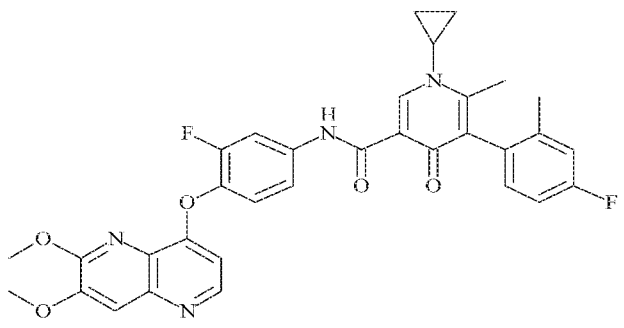
415		N-[3-fluoro-4-[(7-methoxy-6-propan-2-yloxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
416		N-[3-fluoro-4-[(7-methoxy-6-propan-2-yloxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
417		5-(4-fluoro-2,6-dimethylphenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide
418		N-[4-[(7-ethyl-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

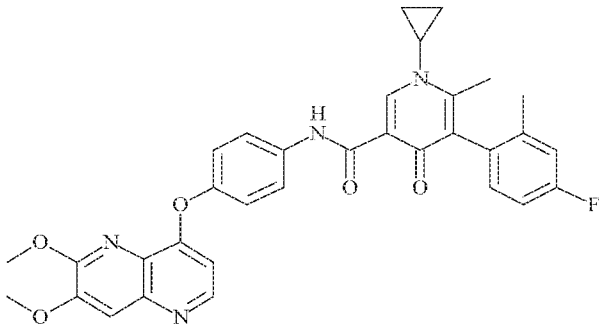
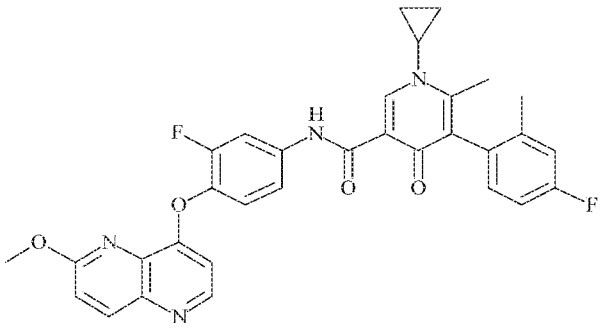
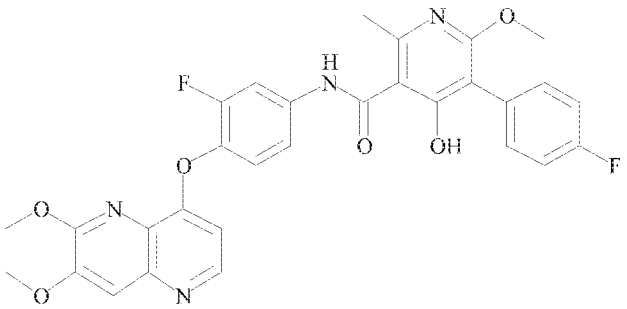
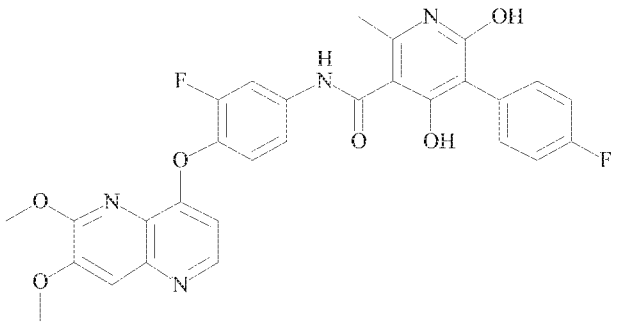
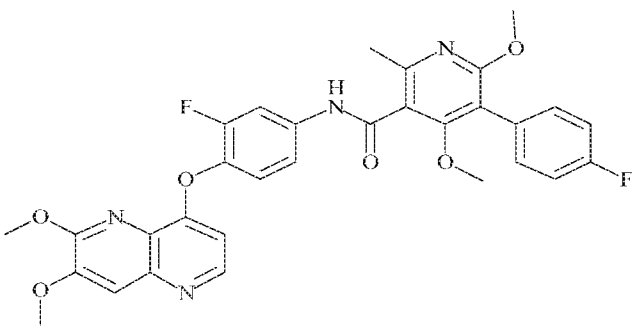
419		N-[4-[(7-ethyl-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
420		N-[4-[(7-ethyl-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
421		N-[4-[(7-ethyl-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
422		N-[4-[(7-ethenyl-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

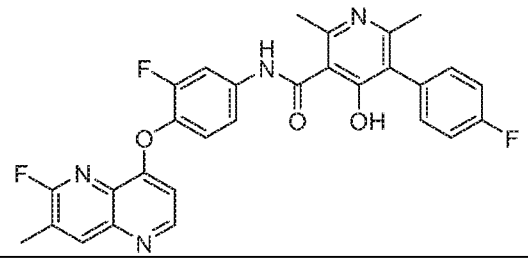
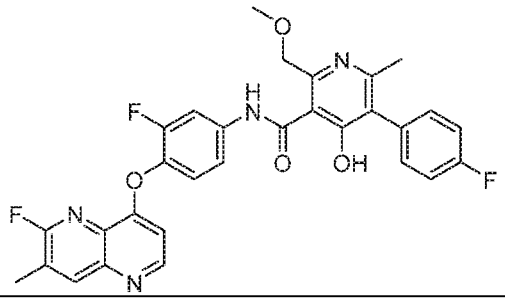
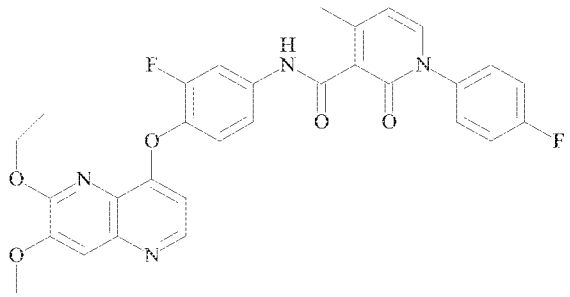
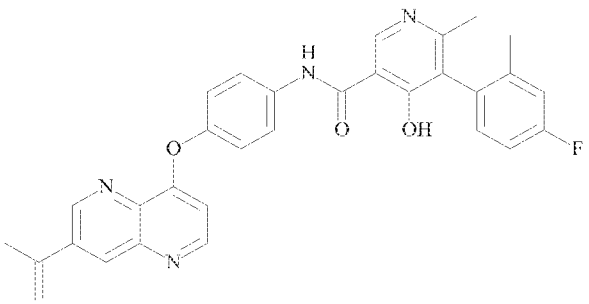
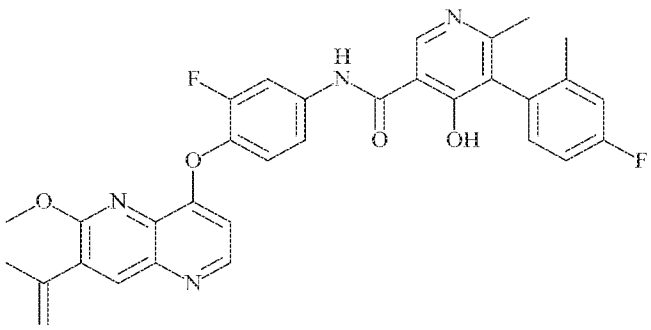
423		N-[4-[(7-ethenyl-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
424		N-[3-fluoro-4-[[7-methoxy-6-(3-morpholin-4-ylpropoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
425		N-[3-fluoro-4-[[7-methoxy-6-(3-morpholin-4-ylpropoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
426		N-[3-fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

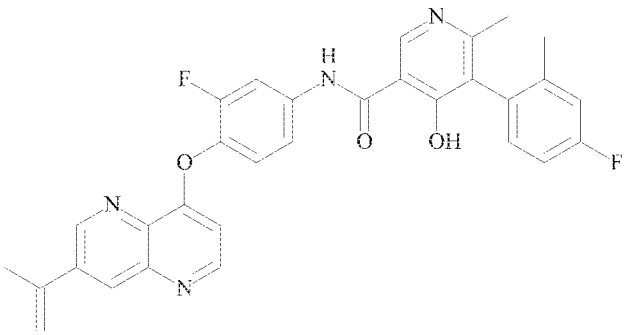
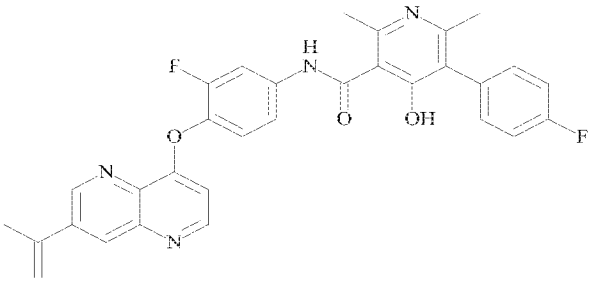
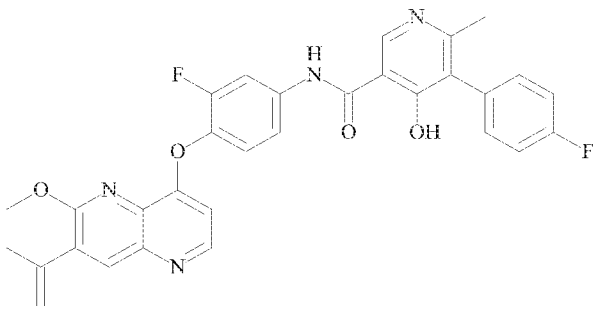
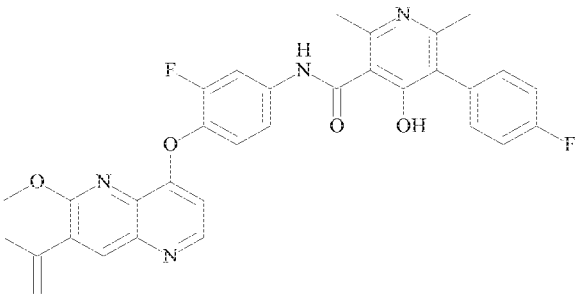
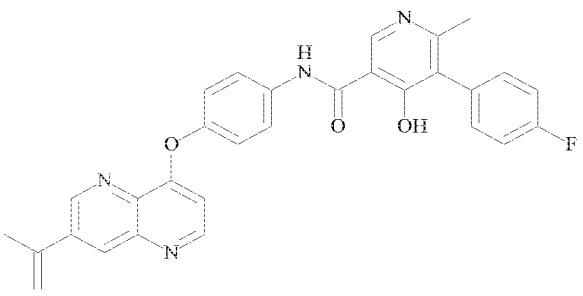
427		N-[3-fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
428		N-[3-fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
429		N-[3-fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
430		N-[3-fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridazine-3-carboxamide

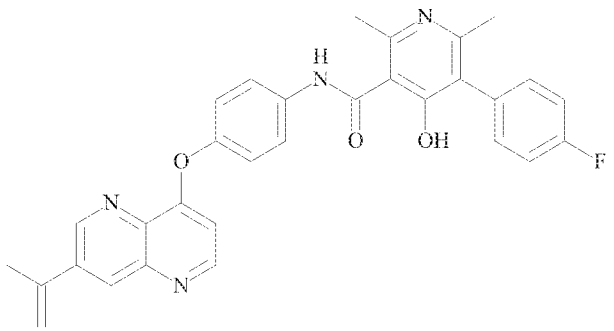
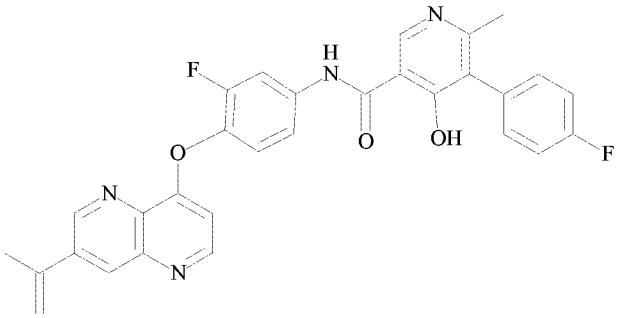
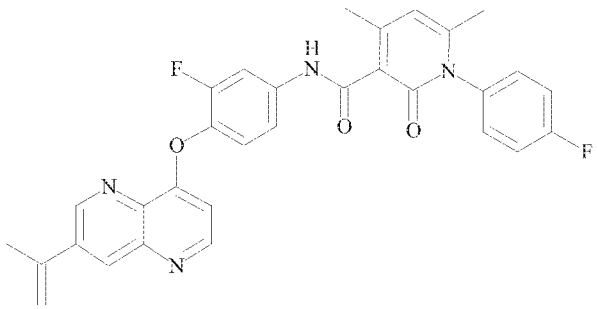
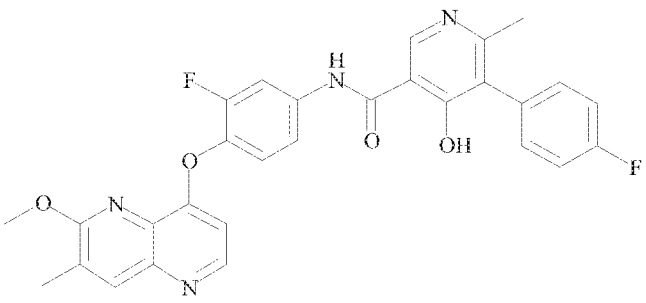
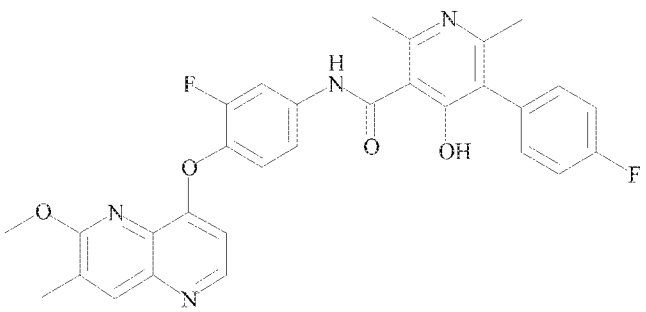
431		N-[3-fluoro-4-[(7-hydroxy-6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
432		N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
433		1-cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
434		1-cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
435		1-cyclopropyl-N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide

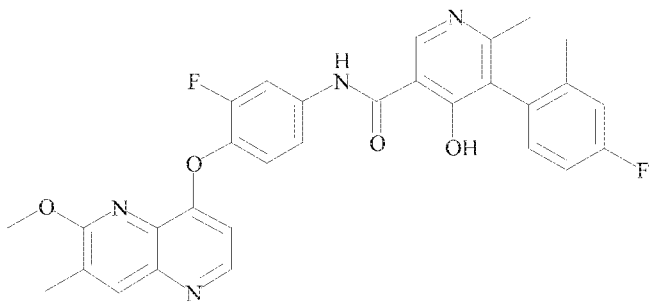
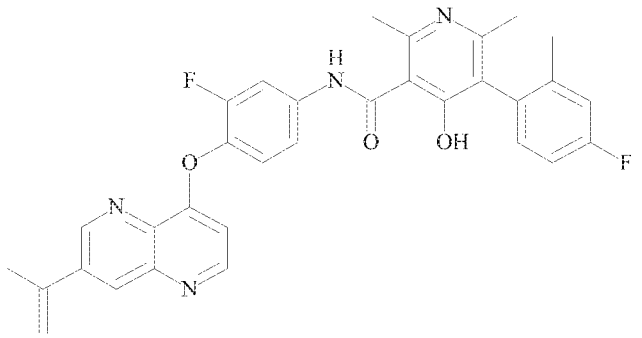
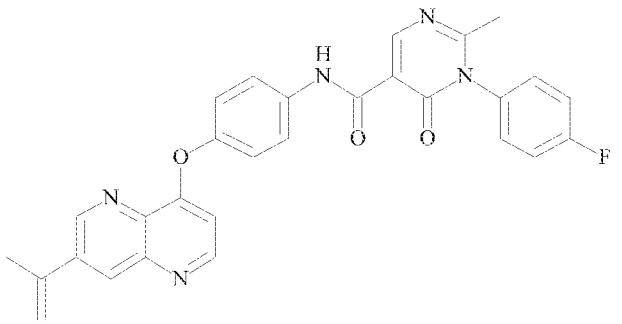
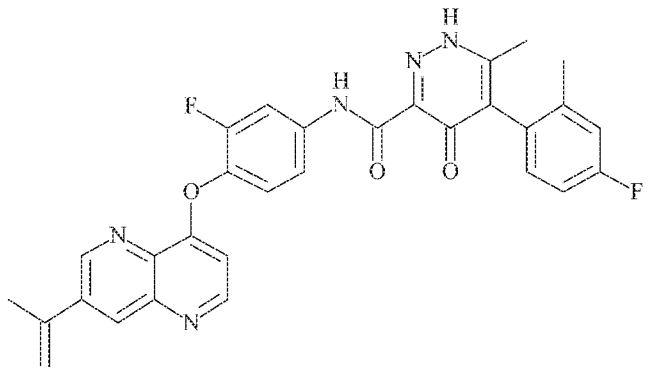
436		N-[3-fluoro-4-[[6-(2-methoxyethoxy)-7-methyl-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
437		5-(4-fluorophenyl)-4-hydroxy-N-[4-[[6-(2-methoxyethoxy)-7-methyl-1,5-naphthyridin-4-yl]oxy]phenyl]-6-methylpyridine-3-carboxamide
438		N-[3-fluoro-4-[[7-methyl-6-(3-morpholin-4-ylpropoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
439		1-cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide

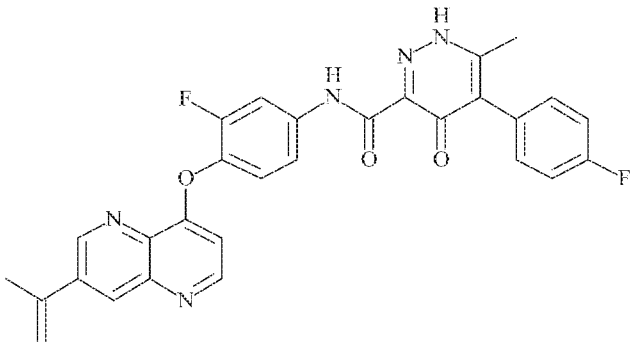
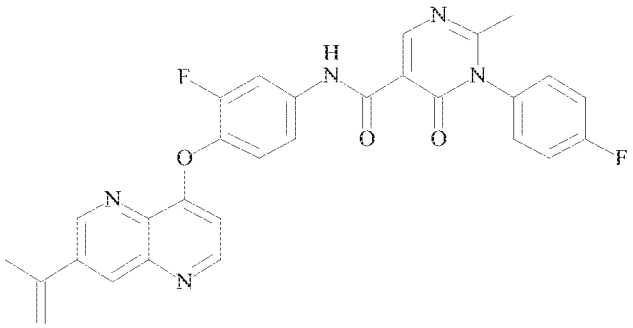
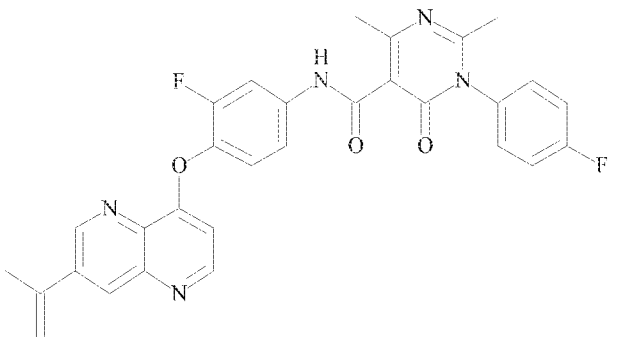
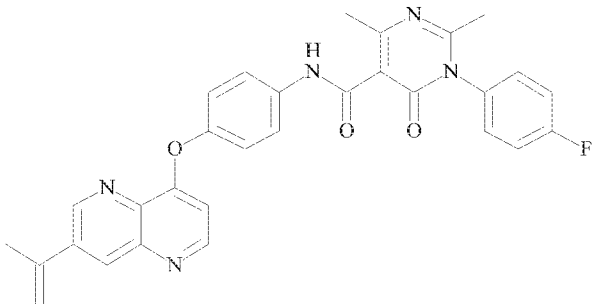
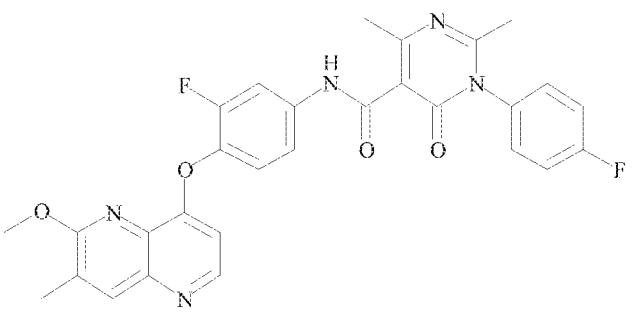
440		1-cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide
441		1-cyclopropyl-N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide
442		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methoxy-2-methylpyridine-3-carboxamide
443		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4,6-dihydroxy-2-methylpyridine-3-carboxamide
444		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4,6-dimethoxy-2-methylpyridine-3-carboxamide

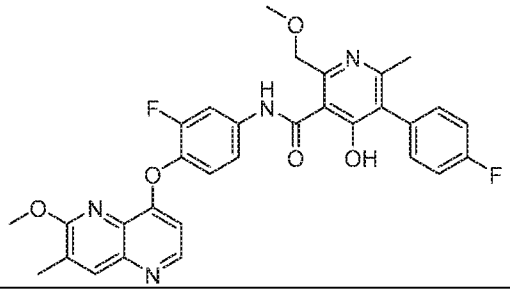
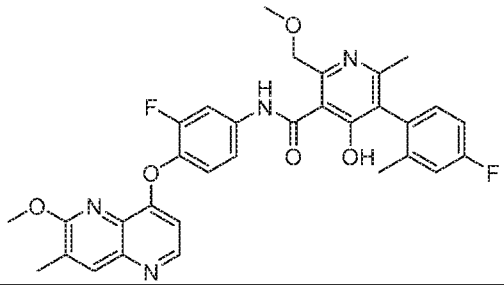
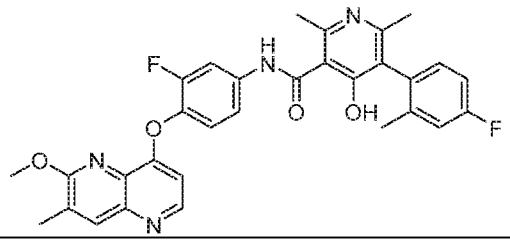
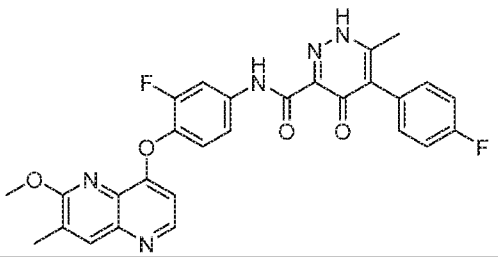
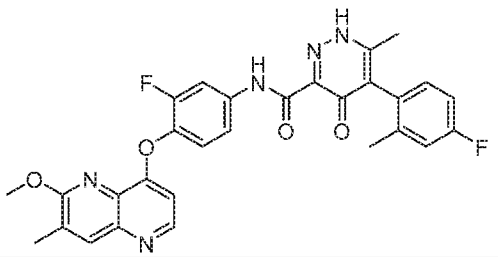
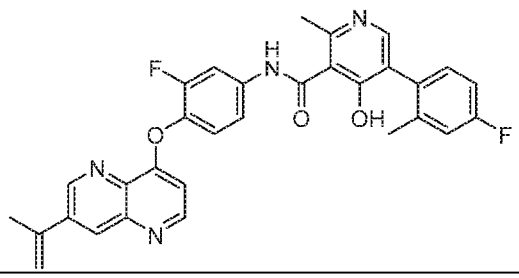
445		N-[3-fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
446		N-[3-fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
447		N-[4-[(6-ethoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide
448		5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methyl-N-[4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide
449		N-[3-fluoro-4-[(6-methoxy-7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

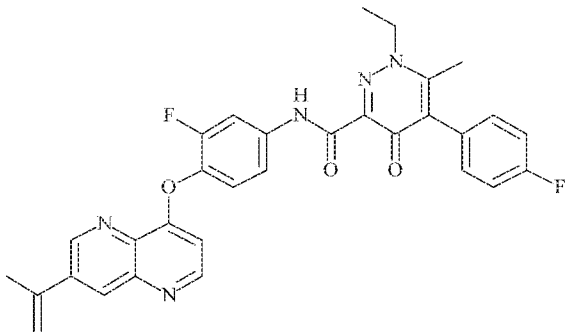
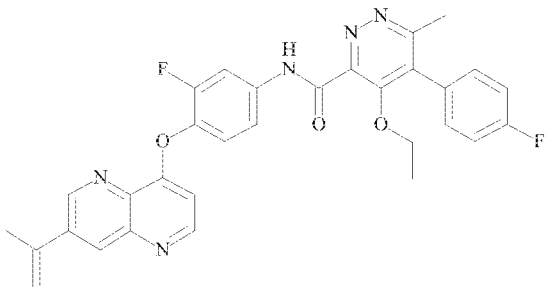
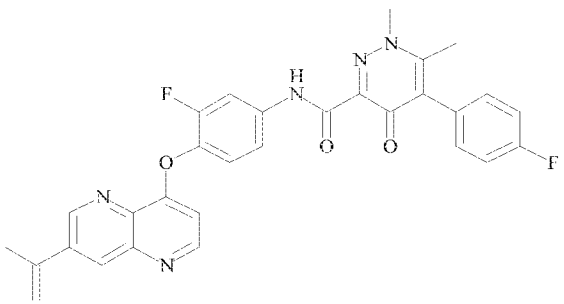
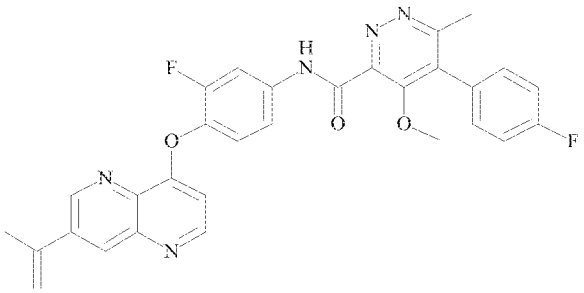
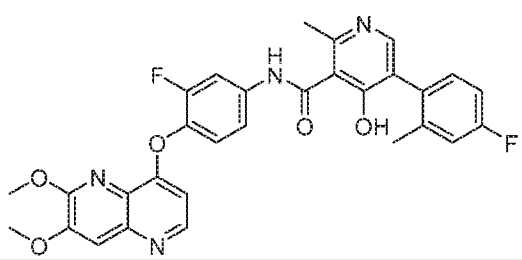
450		5-(4-fluoro-2-methylphenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide
451		5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
452		N-[3-fluoro-4-[(6-methoxy-7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
453		N-[3-fluoro-4-[(6-methoxy-7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
454		5-(4-fluorophenyl)-4-hydroxy-6-methyl-N-[4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide

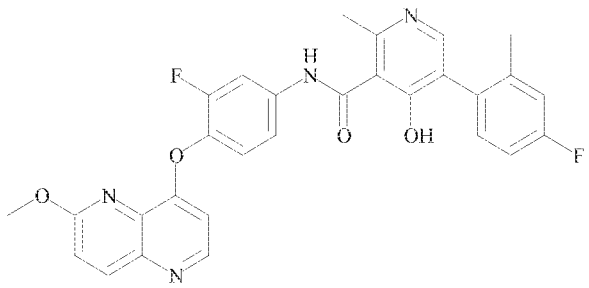
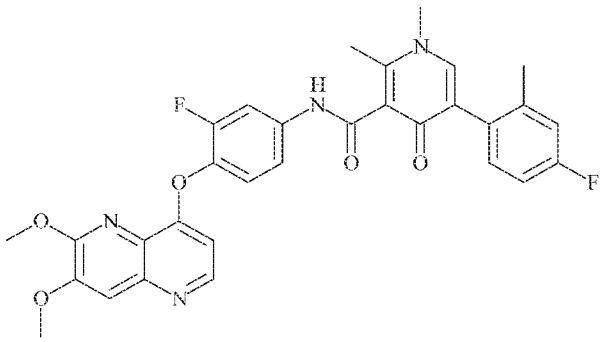
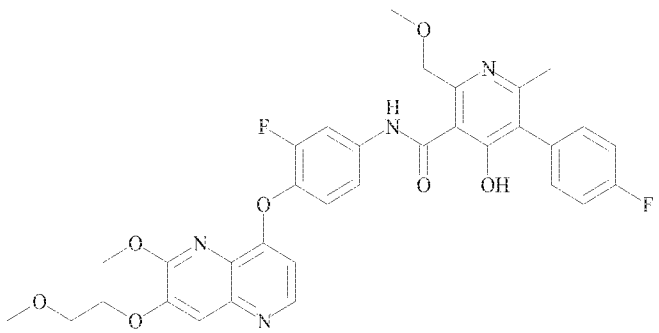
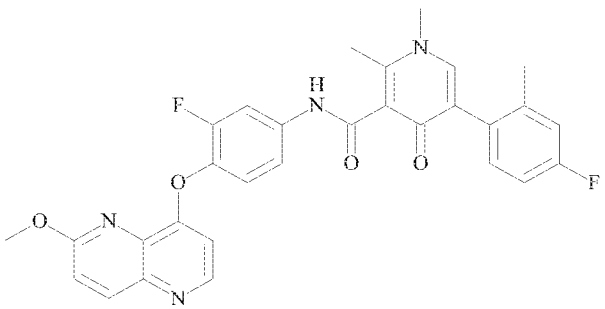
455		5-(4-fluorophenyl)-4-hydroxy-2,6-dimethyl-N-[4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide
456		5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide
457		1-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4,6-dimethyl-2-oxopyridine-3-carboxamide
458		N-[3-fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
459		N-[3-fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

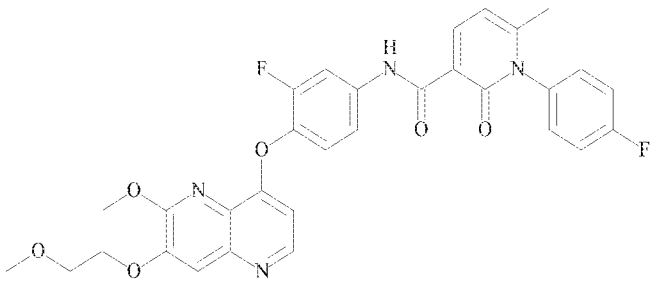
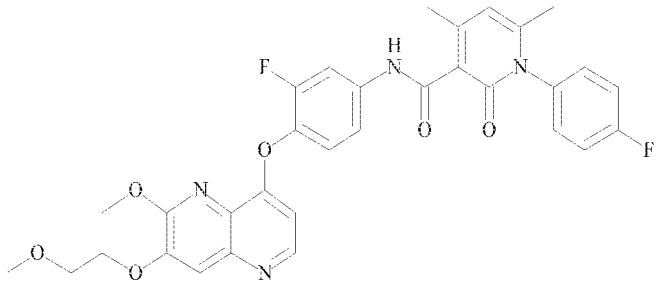
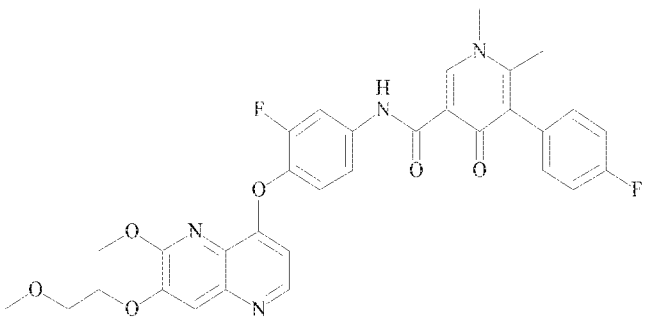
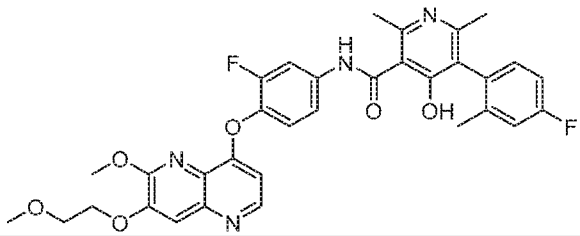
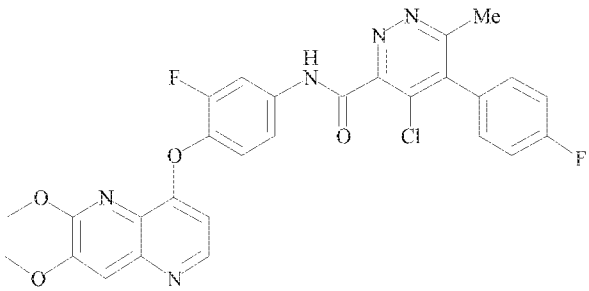
460		N-[3-fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
461		5-(4-fluoro-2-methylphenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
462		1-(4-fluorophenyl)-2-methyl-6-oxo-N-[4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyrimidine-5-carboxamide
463		5-(4-fluoro-2-methylphenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1H-pyridazine-3-carboxamide

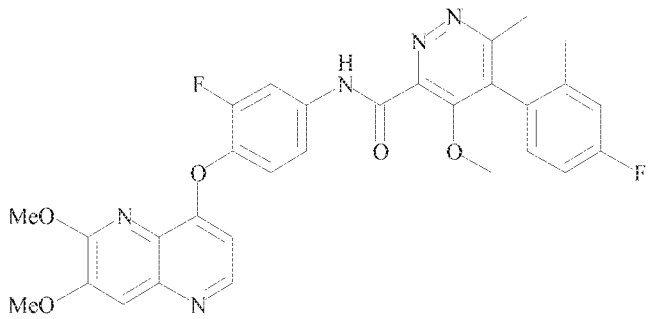
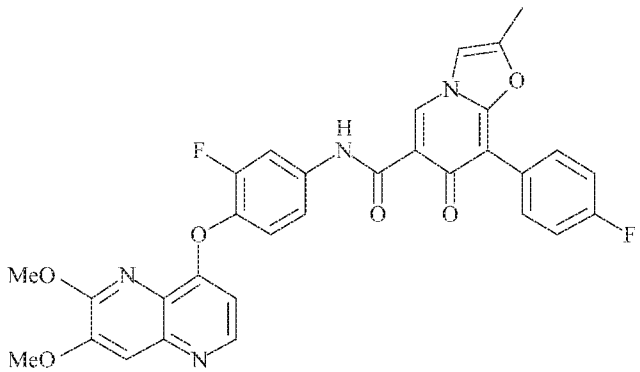
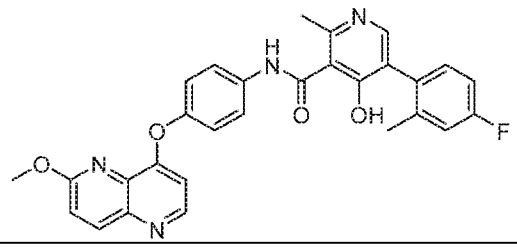
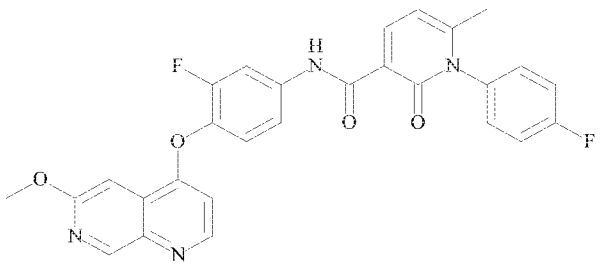
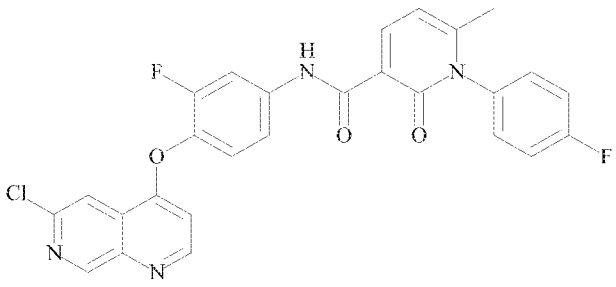
464		5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
465		1-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methyl-6-oxopyrimidine-5-carboxamide
466		1-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-2,4-dimethyl-6-oxopyrimidine-5-carboxamide
467		1-(4-fluorophenyl)-2,4-dimethyl-6-oxo-N-[4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyrimidine-5-carboxamide
468		N-[3-fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyrimidine-5-carboxamide

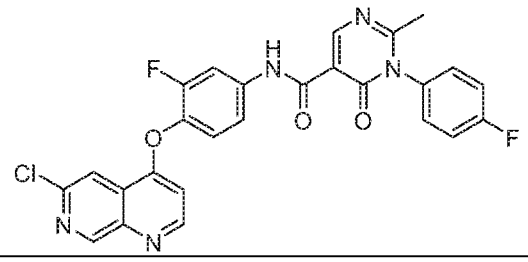
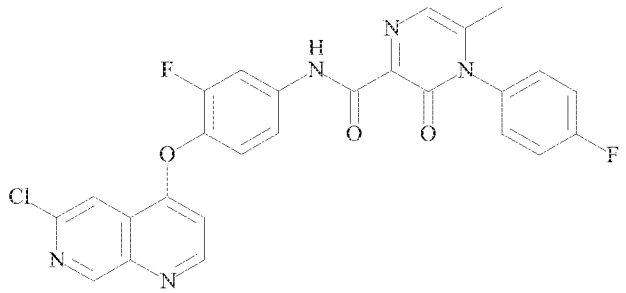
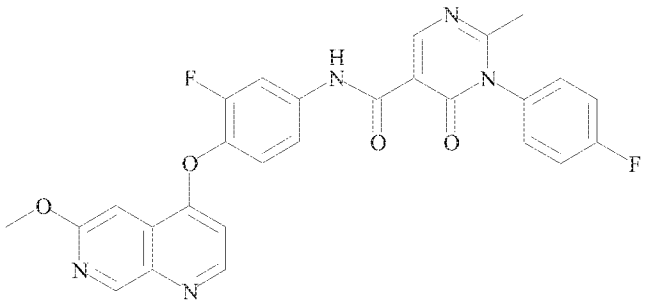
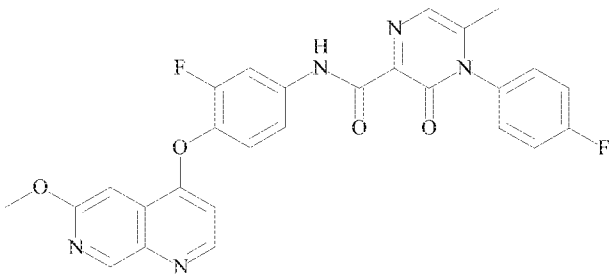
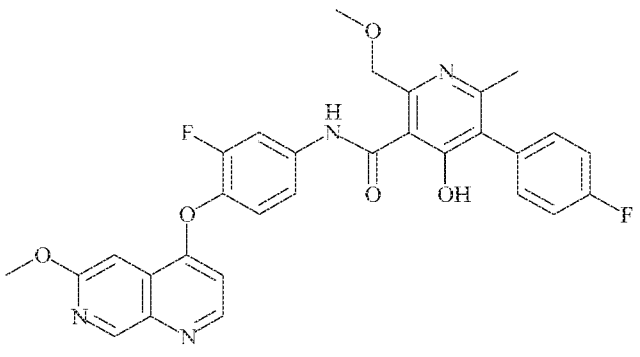
469		N-[3-fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
470		N-[3-fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
471		N-[3-fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
472		N-[3-fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
473		N-[3-fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide
474		5-(4-fluoro-2-methylphenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2-methylpyridine-3-carboxamide

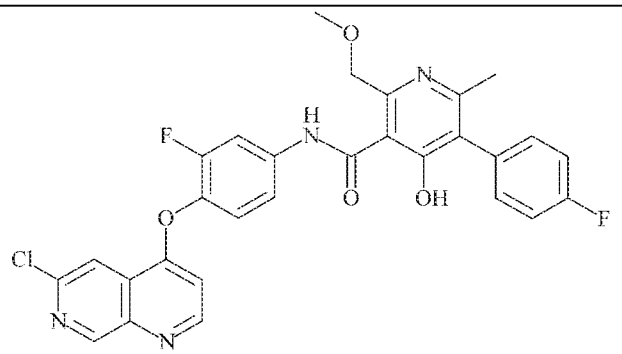
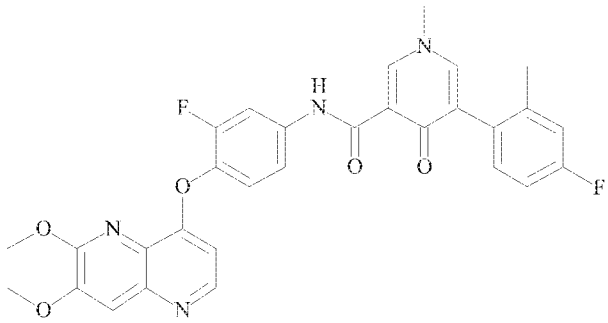
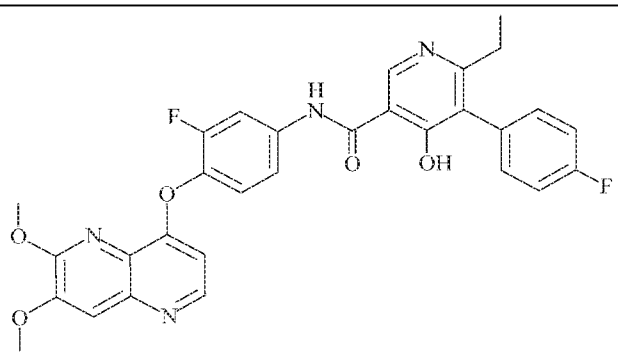
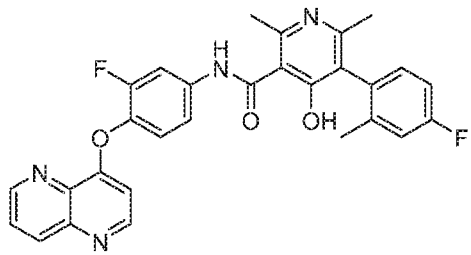
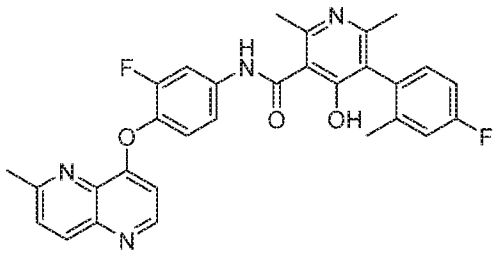
475		1-ethyl-5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridazine-3-carboxamide
476		4-ethoxy-5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridazine-3-carboxamide
477		5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridazine-3-carboxamide
478		5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-methoxy-6-methylpyridazine-3-carboxamide
479		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-methylpyridine-3-carboxamide

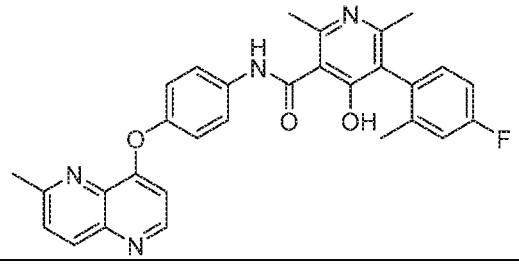
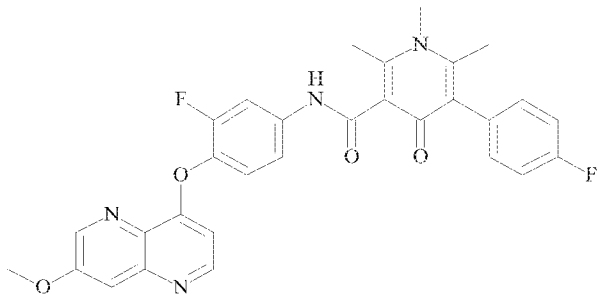
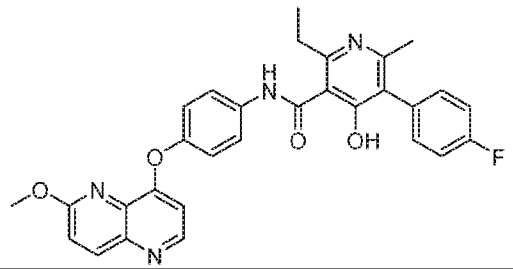
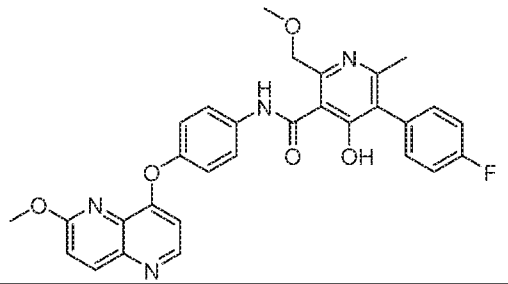
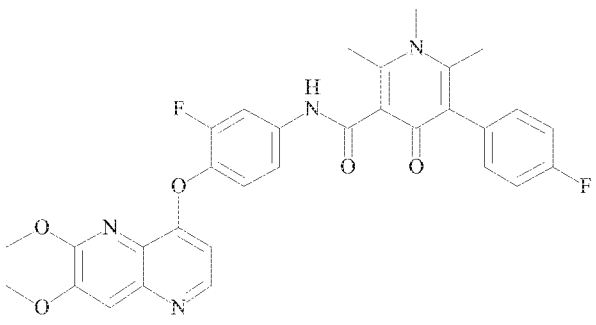
480		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-methylpyridine-3-carboxamide
481		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide
482		N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
483		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide

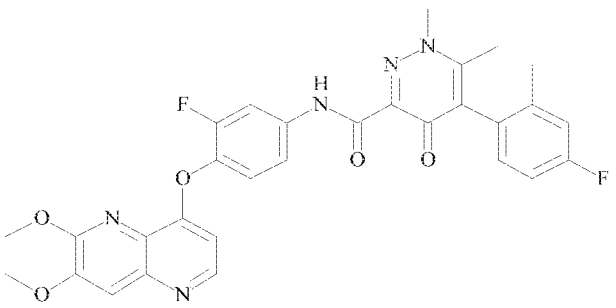
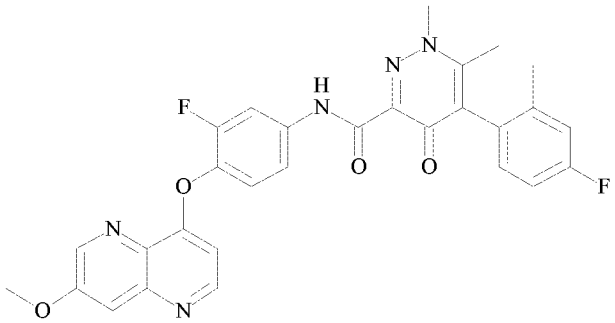
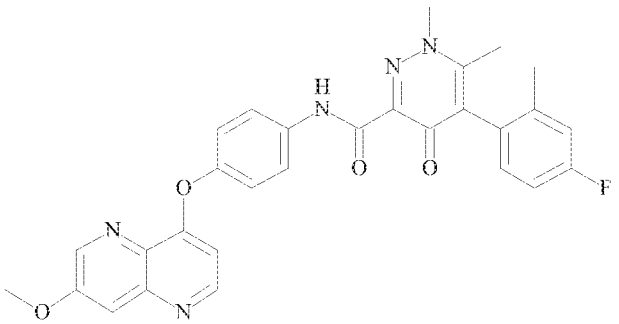
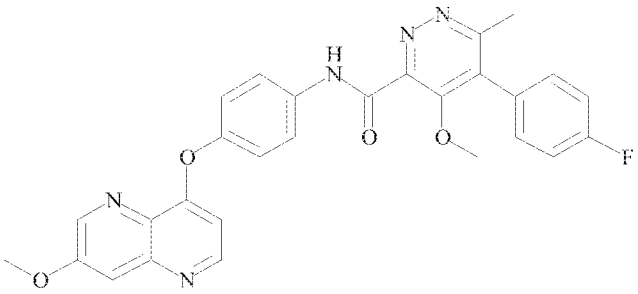
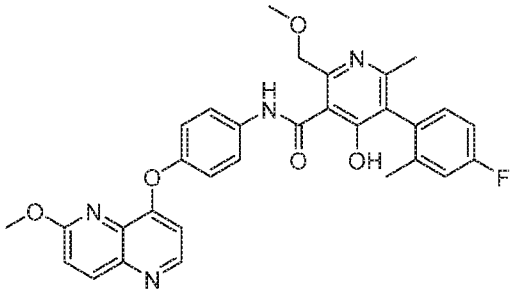
484		N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
485		N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
486		N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
487		N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
488		4-chloro-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxamide

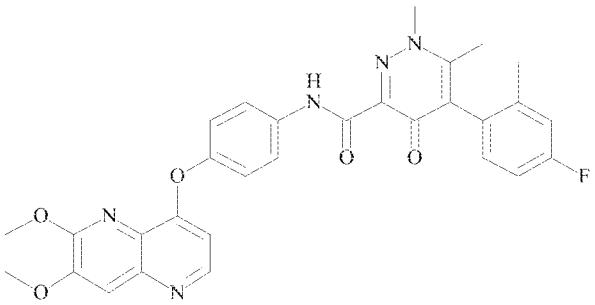
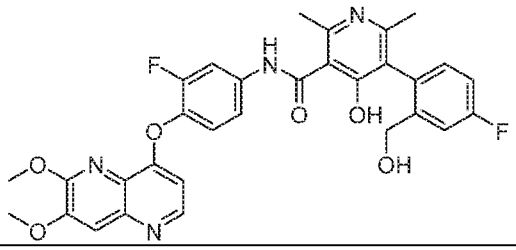
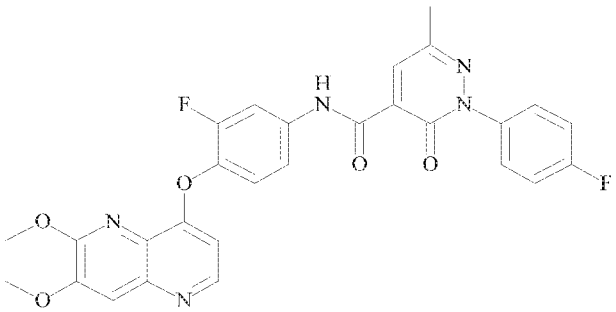
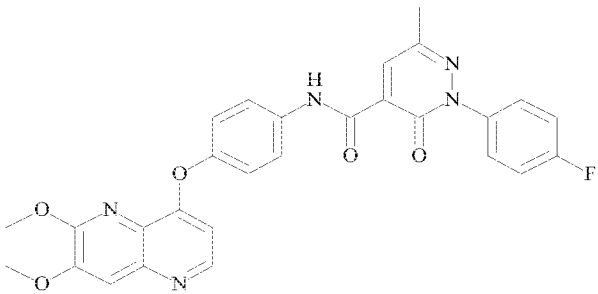
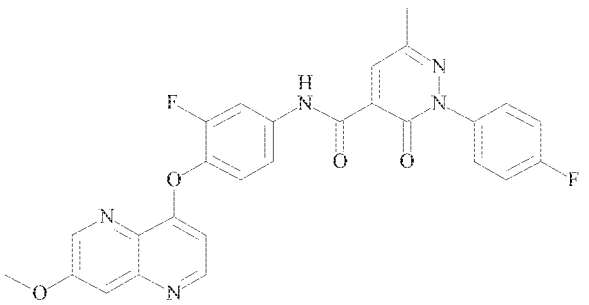
489		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-methoxy-6-methylpyridazine-3-carboxamide
491		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-8-(4-fluorophenyl)-2-methyl-7-oxo-[1,3]oxazolo[3,2-a]pyridine-6-carboxamide
493		5-(4-fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methylpyridine-3-carboxamide
494		N-[3-fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
496		N-[4-[(6-chloro-1,7-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide

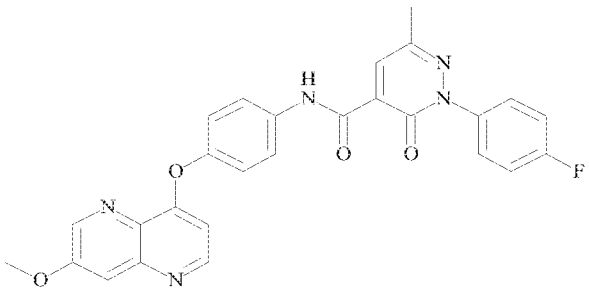
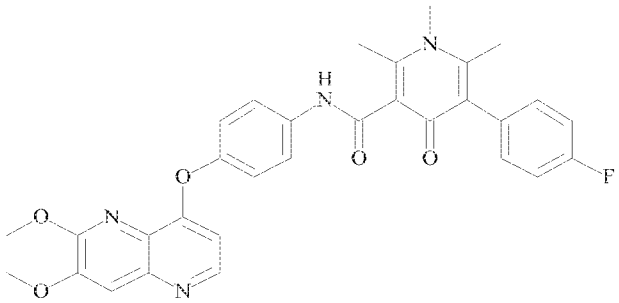
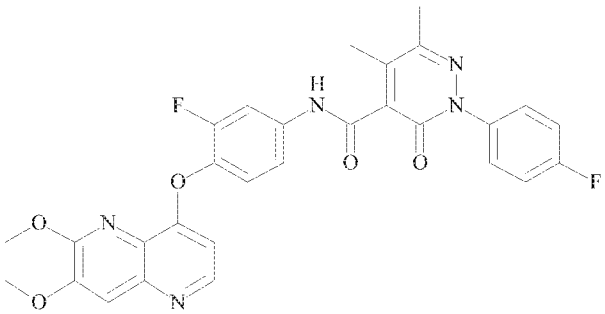
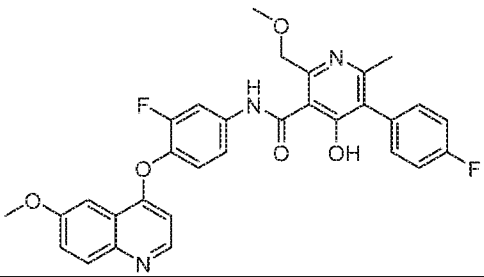
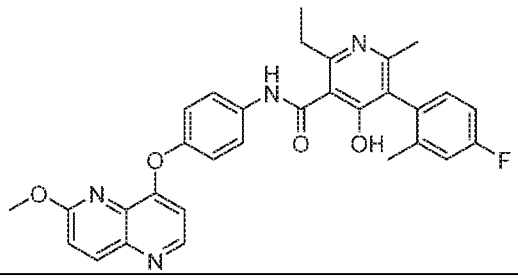
497		N-[4-[(6-chloro-1,7-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide
498		N-[4-[(6-chloro-1,7-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide
499		N-[3-fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide
500		N-[3-fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide
501		N-[3-fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide

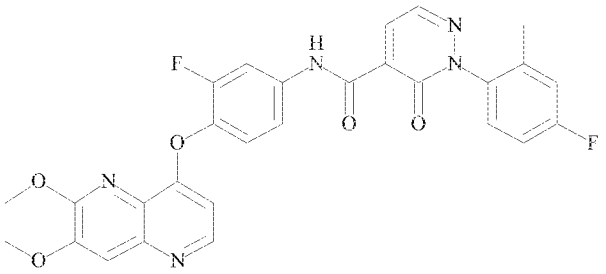
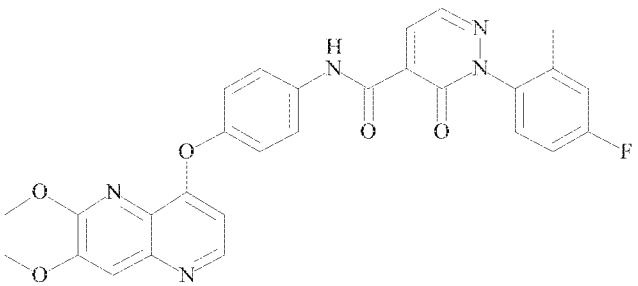
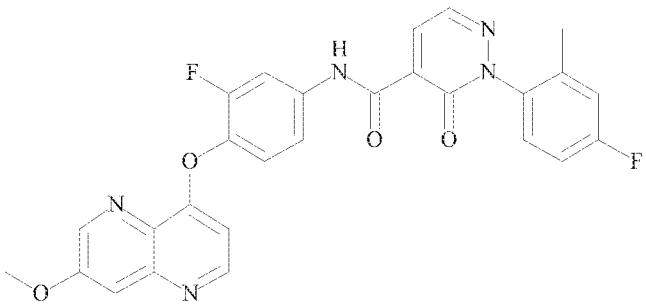
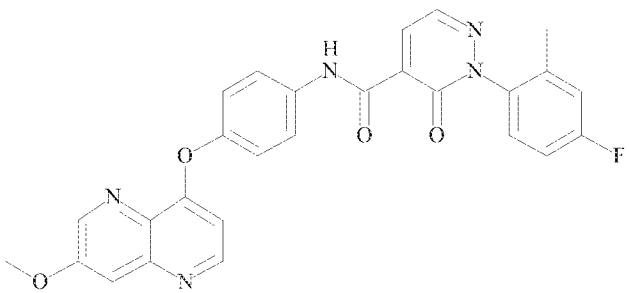
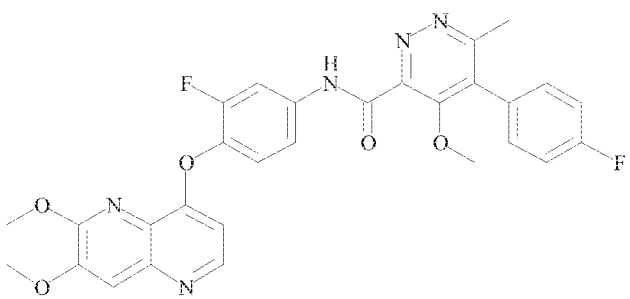
502		N-[4-[(6-chloro-1,7-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
503		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1-methyl-4-oxopyridine-3-carboxamide
504		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-ethyl-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide
505		5-(4-fluoro-2-methylphenyl)-N-[3-fluoro-4-(1,5-naphthyridin-4-yloxy)phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
506		N-[3-fluoro-4-[(6-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

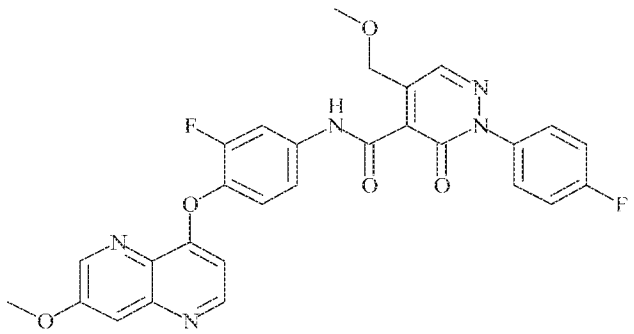
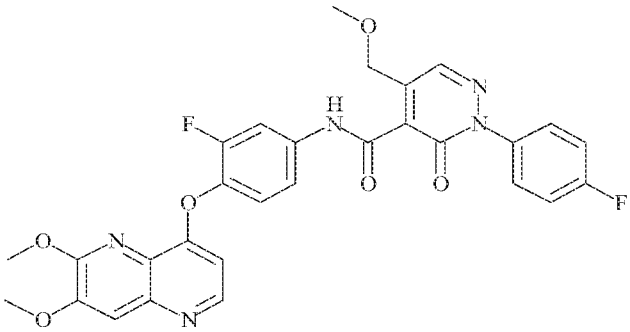
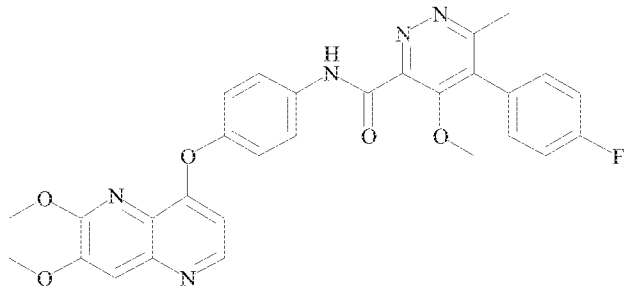
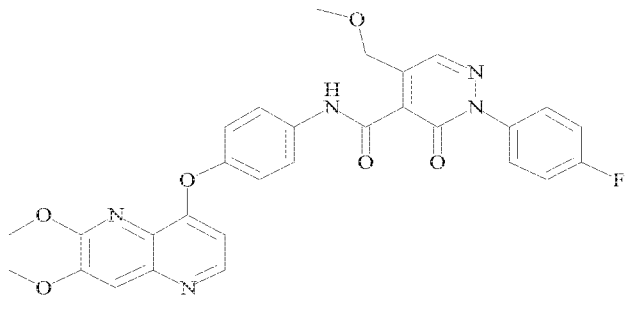
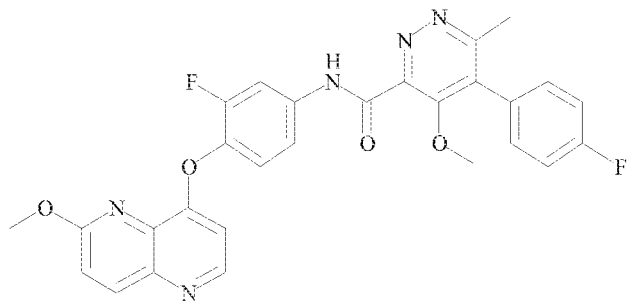
507		5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethyl-N-[4-[(6-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide
508		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide
509		2-ethyl-5-(4-fluorophenyl)-4-hydroxy-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
510		5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
511		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide

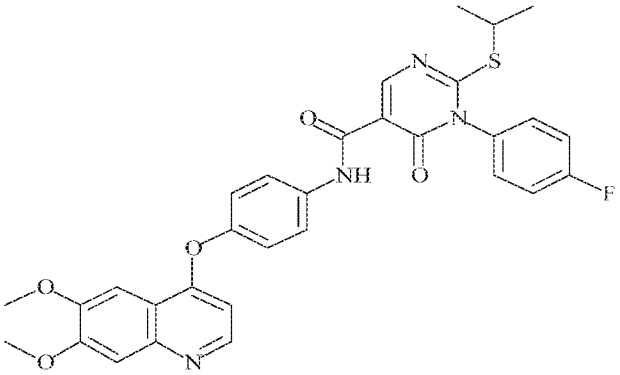
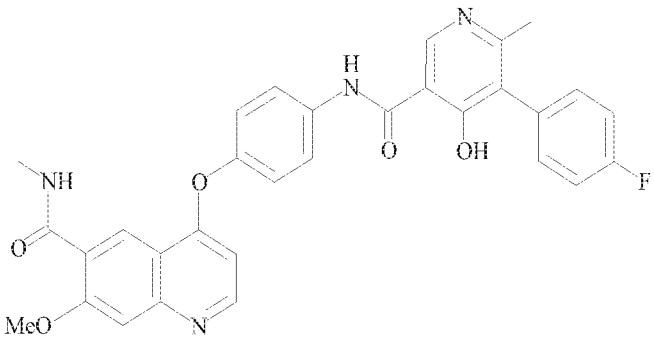
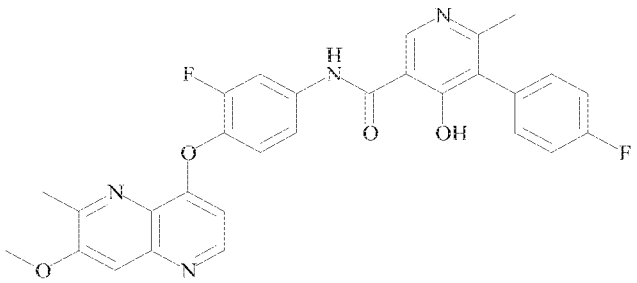
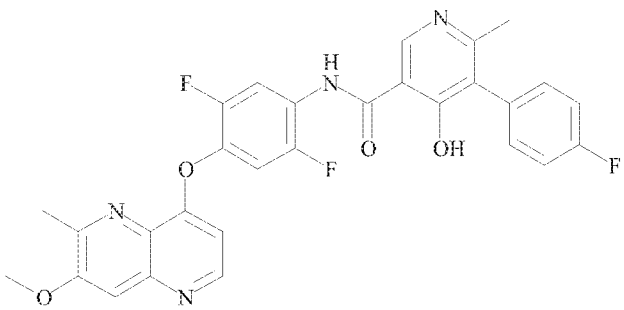
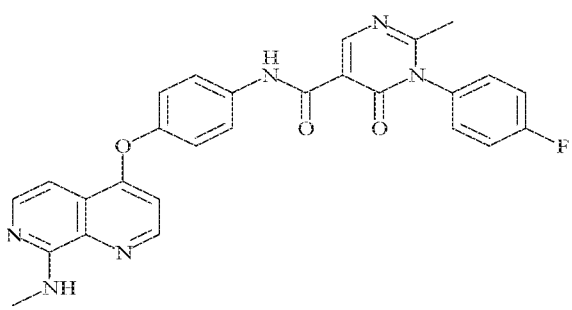
512		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide
513		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide
514		5-(4-fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridazine-3-carboxamide
515		5-(4-fluorophenyl)-4-methoxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridazine-3-carboxamide
516		5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide

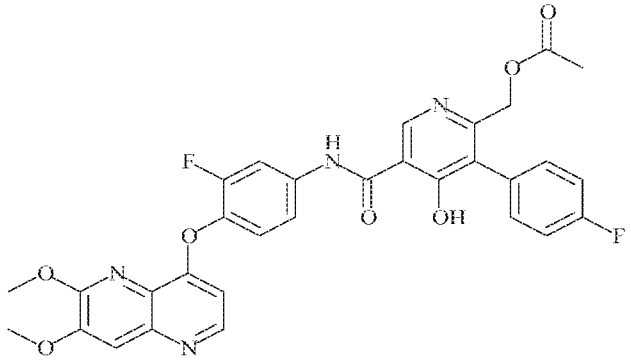
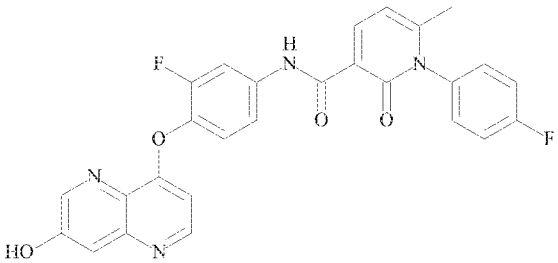
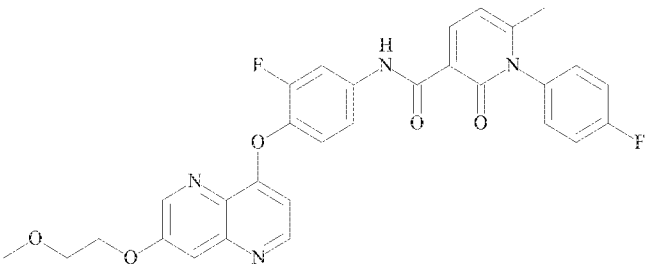
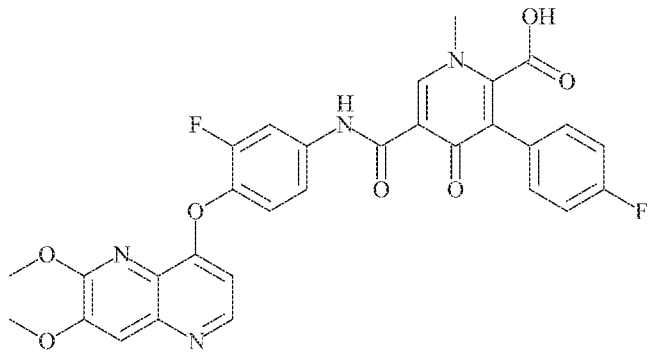
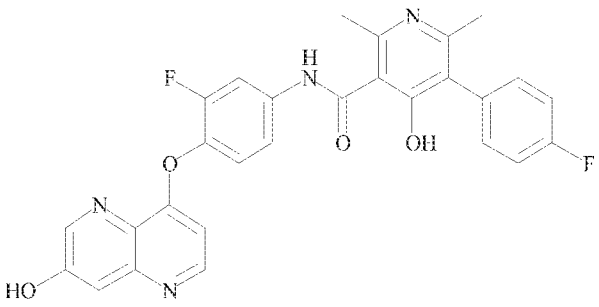
517		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide
518		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-[4-fluoro-2-(hydroxymethyl)phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
519		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(4-fluorophenyl)-6-methyl-3-oxopyridazine-4-carboxamide
520		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-6-methyl-3-oxopyridazine-4-carboxamide
521		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-6-methyl-3-oxopyridazine-4-carboxamide

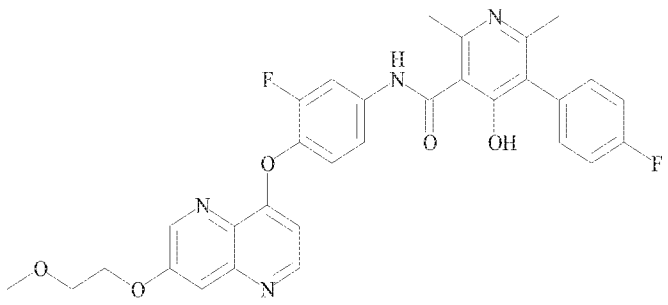
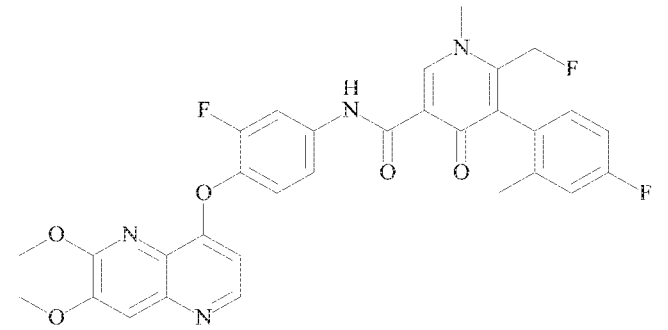
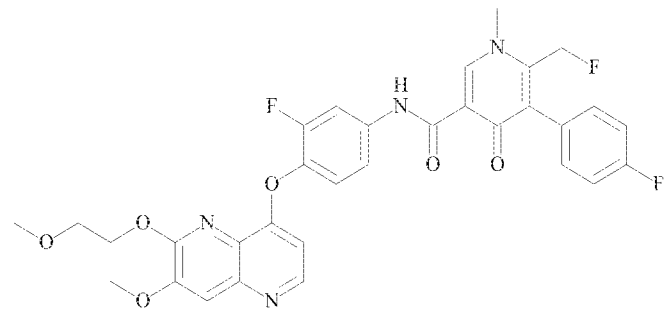
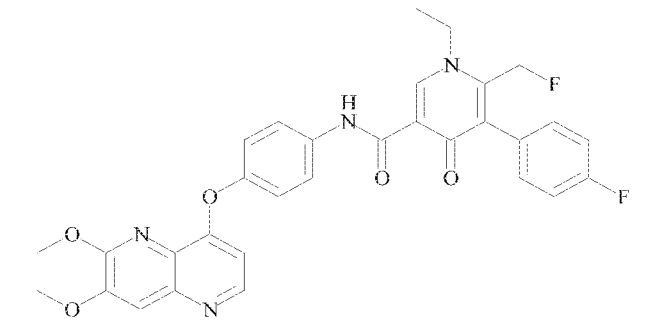
522		2-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-3-oxopyridazine-4-carboxamide
523		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide
524		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(4-fluorophenyl)-5,6-dimethyl-3-oxopyridazine-4-carboxamide
525		N-[3-fluoro-4-(6-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
526		2-ethyl-5-(4-fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide

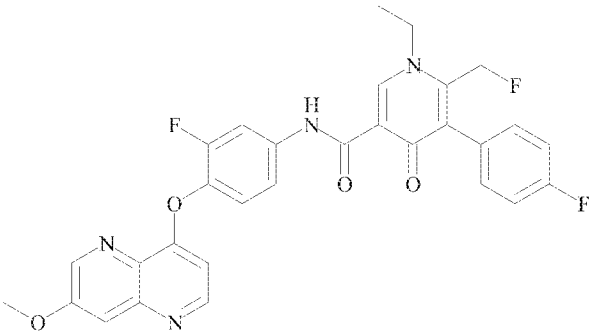
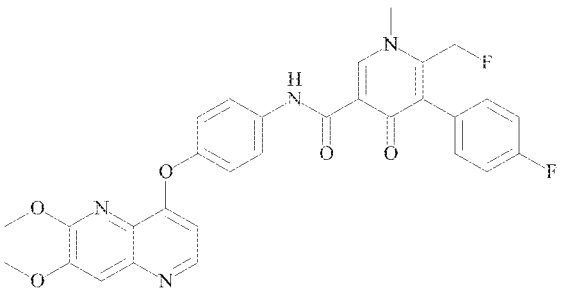
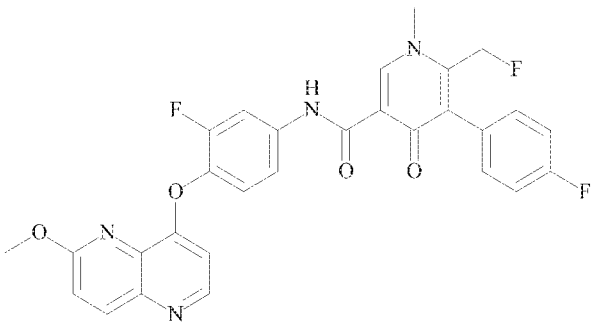
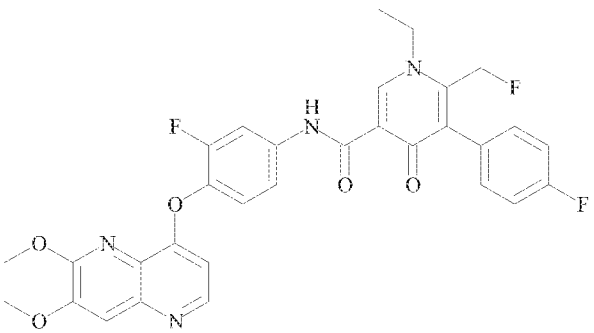
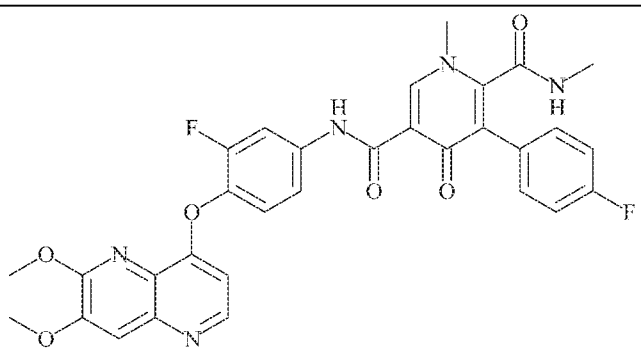
527		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(4-fluoro-2-methylphenyl)-3-oxopyridazine-4-carboxamide
528		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluoro-2-methylphenyl)-3-oxopyridazine-4-carboxamide
529		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluoro-2-methylphenyl)-3-oxopyridazine-4-carboxamide
530		2-(4-fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-3-oxopyridazine-4-carboxamide
531		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-methoxy-6-methylpyridazine-3-carboxamide

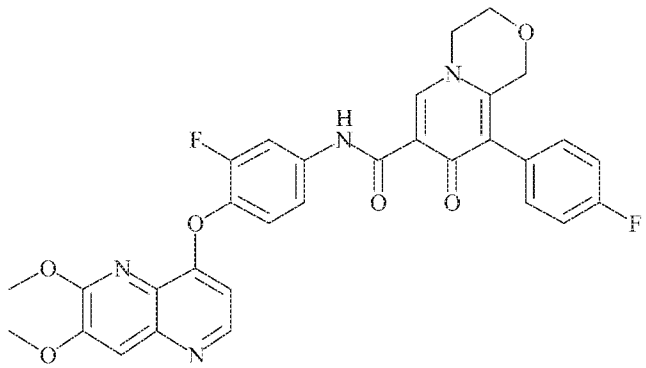
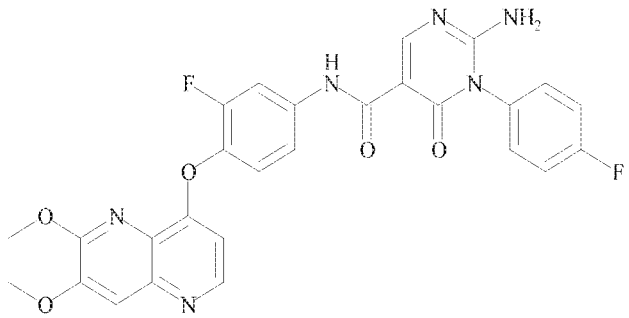
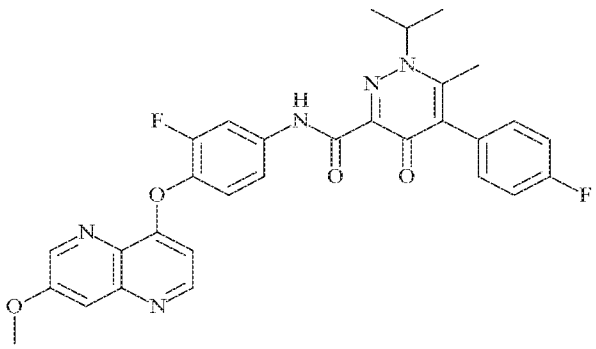
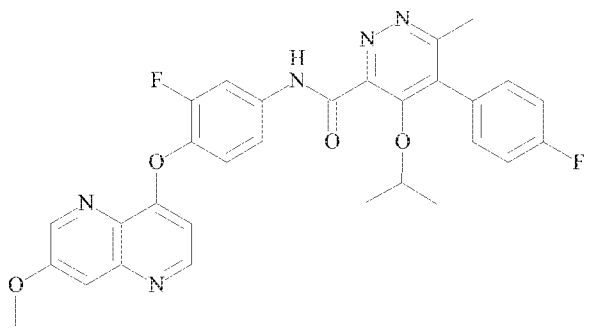
532		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-5-(methoxymethyl)-3-oxopyridazine-4-carboxamide
533		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(4-fluorophenyl)-5-(methoxymethyl)-3-oxopyridazine-4-carboxamide
534		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-methoxy-6-methylpyridazine-3-carboxamide
537		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-5-(methoxymethyl)-3-oxopyridazine-4-carboxamide
538		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-methoxy-6-methylpyridazine-3-carboxamide

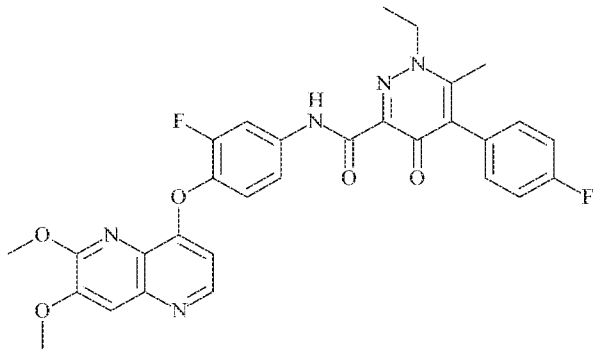
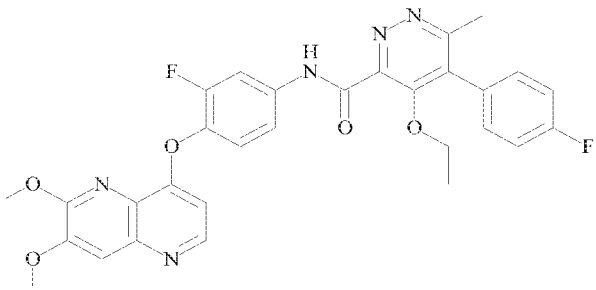
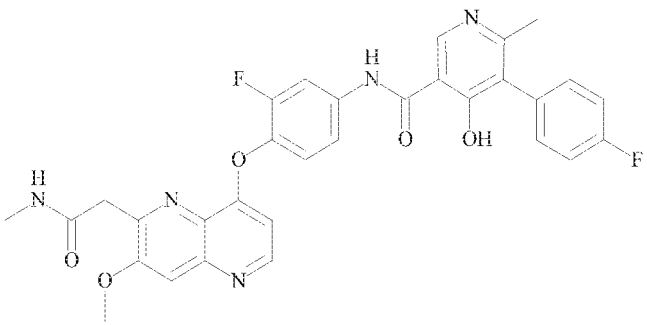
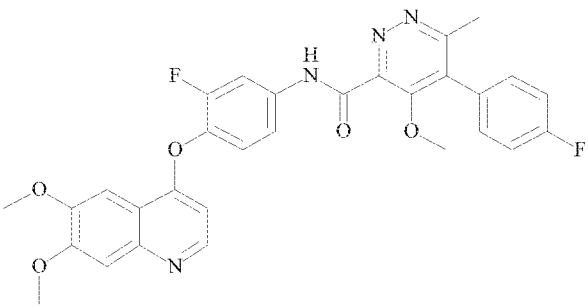
539		N-[4-(6,7-dimethoxyquinolin-4-yl)oxyphenyl]-1-(4-fluorophenyl)-6-oxo-2-propan-2-ylsulfanylpyrimidine-5-carboxamide
540		4-[4-[[5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carbonyl]amino]phenoxy]-7-methoxy-N-methylquinoline-6-carboxamide
541		N-[3-fluoro-4-[(7-methoxy-6-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
542		N-[2,5-difluoro-4-[(7-methoxy-6-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
543		1-(4-fluorophenyl)-2-methyl-N-[4-[[8-(methylamino)-1,7-naphthyridin-4-yl]oxy]phenyl]-6-oxopyrimidine-5-carboxamide

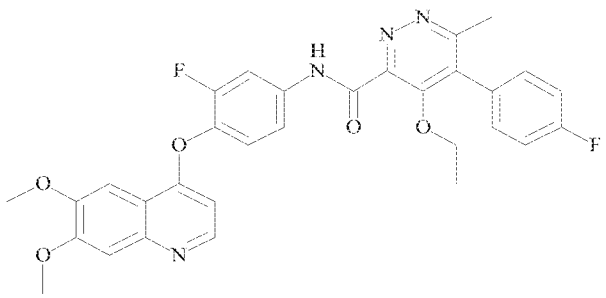
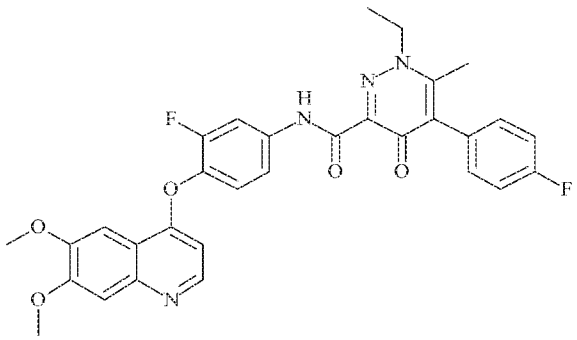
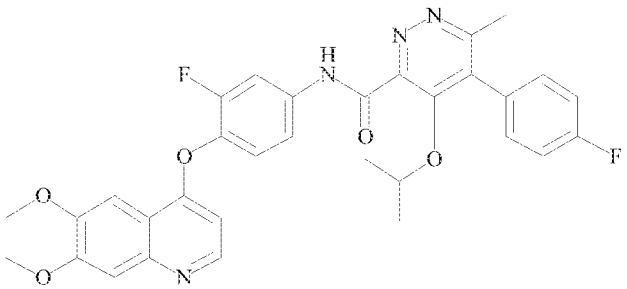
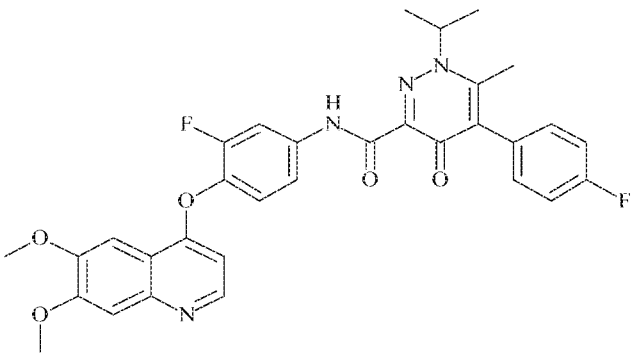
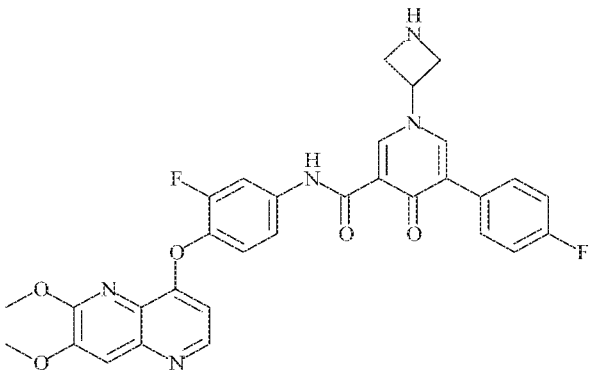
544		[5-[[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]carbamoyl]-3-(4-fluorophenyl)-4-hydroxypyridin-2-yl]methyl acetate
551		N-[3-fluoro-4-[(7-hydroxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
552		N-[3-fluoro-4-[[7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
553		5-[[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]carbamoyl]-3-(4-fluorophenyl)-1-methyl-4-oxopyridine-2-carboxylic acid
554		N-[3-fluoro-4-[(7-hydroxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

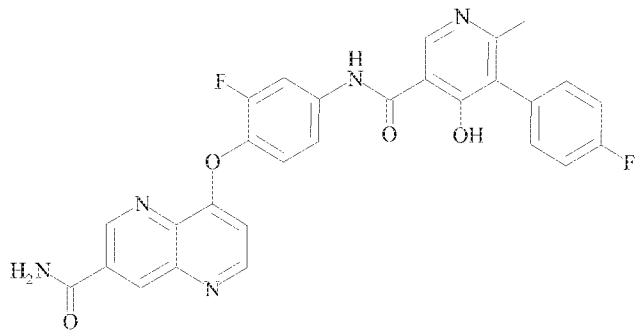
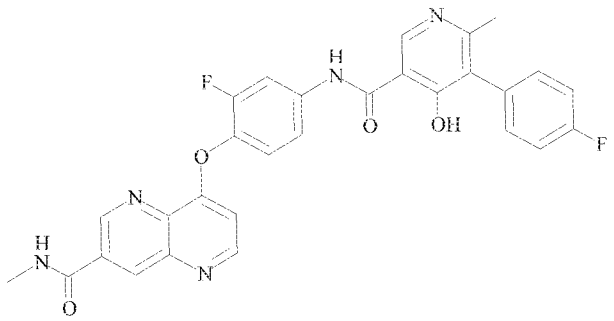
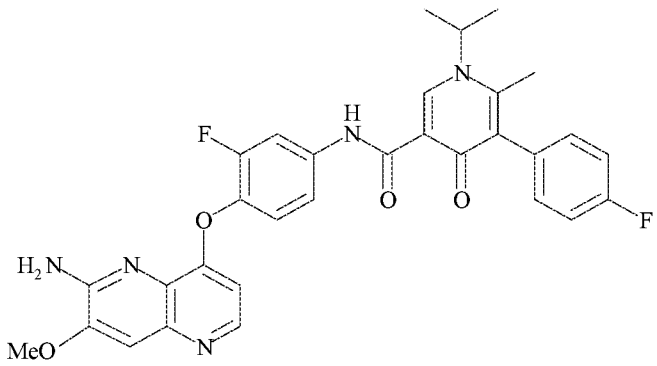
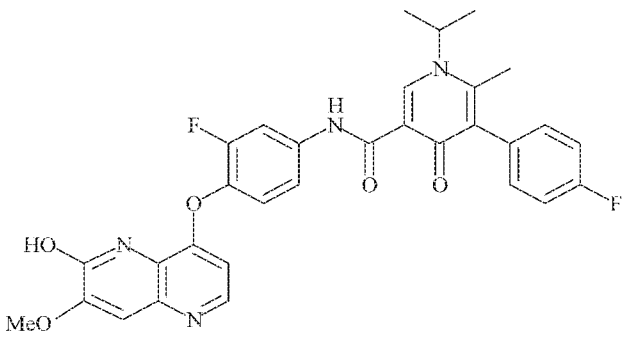
555		N-[3-fluoro-4-[[7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
556		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(fluoromethyl)-5-(4-fluoro-2-methylphenyl)-1-methyl-4-oxopyridine-3-carboxamide
557		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide
558		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-6-(fluoromethyl)-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide

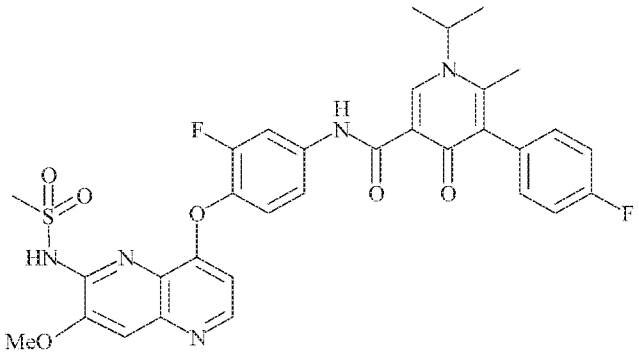
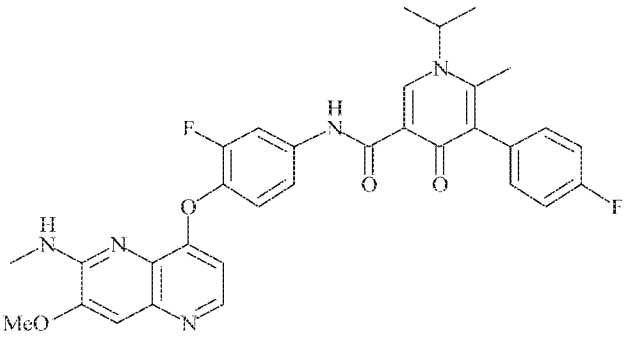
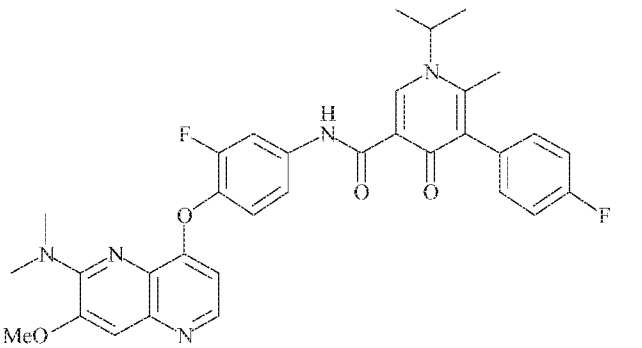
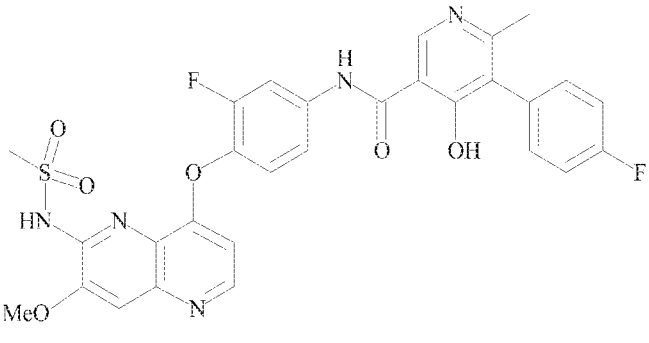
559		1-ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide
560		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide
561		N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide
562		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-6-(fluoromethyl)-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide
563		5-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-2-N,1-dimethyl-4-oxopyridine-2,5-dicarboxamide

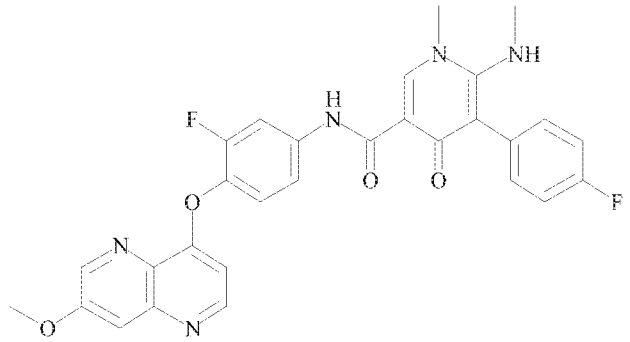
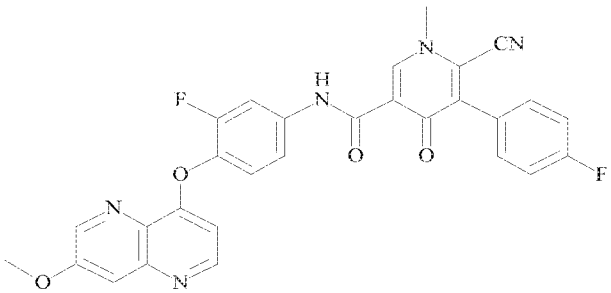
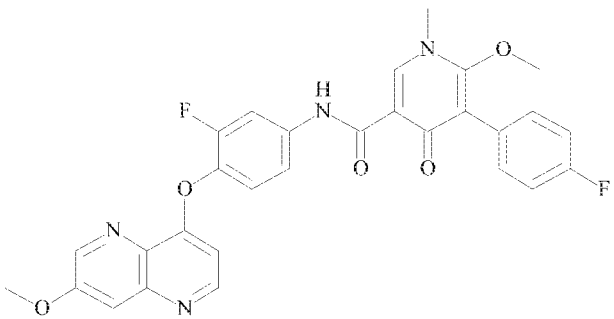
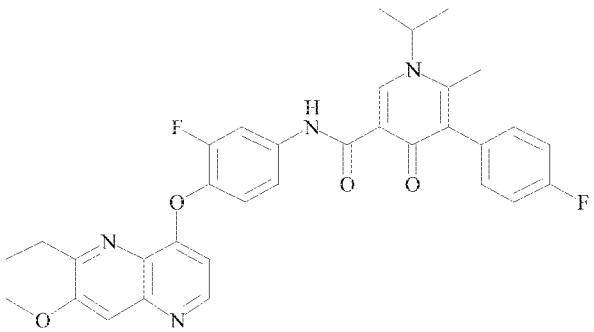
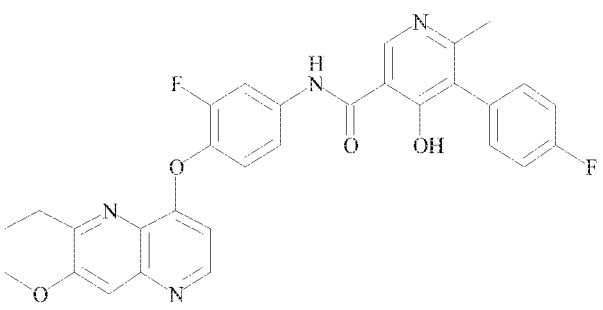
564		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-9-(4-fluorophenyl)-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-7-carboxamide
565		2-amino-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-oxopyrimidine-5-carboxamide
566		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridazine-3-carboxamide
567		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-propan-2-yloxypyridazine-3-carboxamide

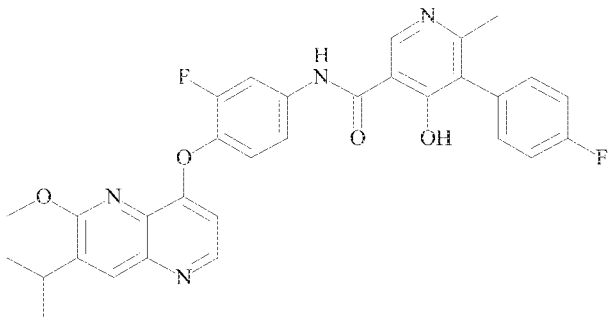
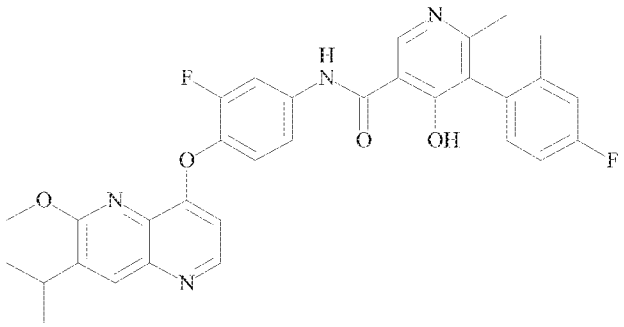
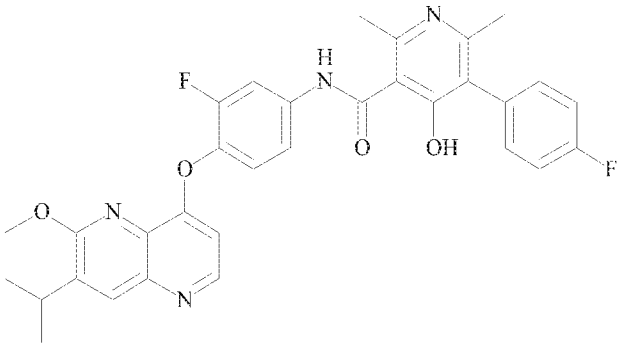
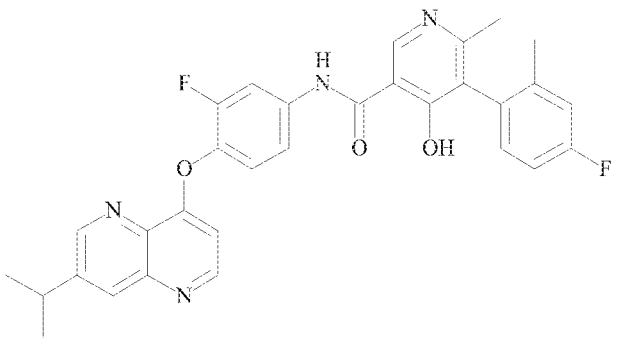
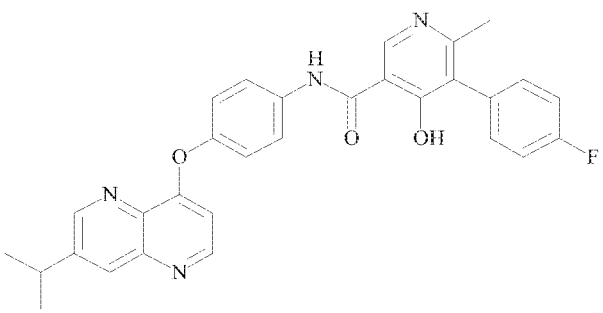
568		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-6-methyl-4-oxopyridazine-3-carboxamide
569		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-ethoxy-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxamide
570		N-[3-fluoro-4-[[7-methoxy-6-[2-(methylamino)-2-oxoethyl]-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
571		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-4-methoxy-6-methylpyridazine-3-carboxamide

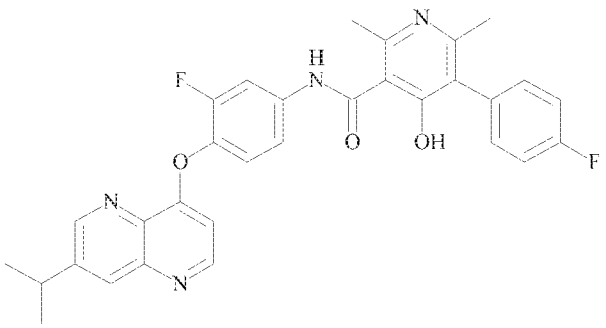
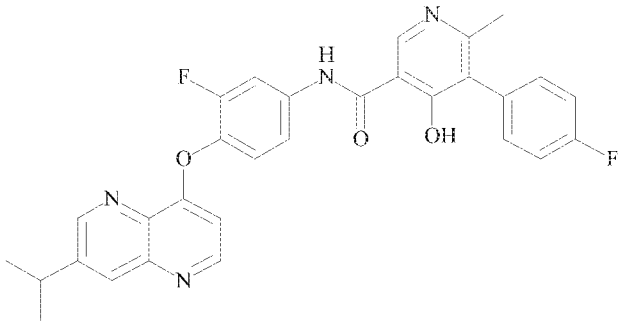
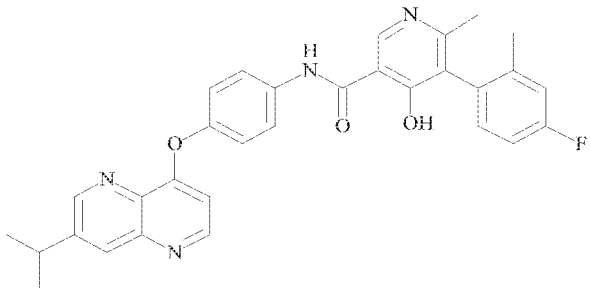
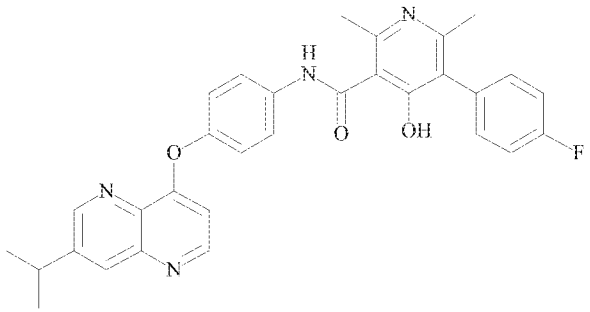
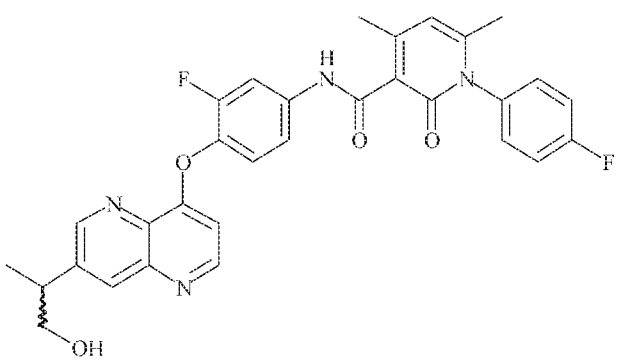
572		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-4-ethoxy-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxamide
573		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-6-methyl-4-oxopyridazine-3-carboxamide
574		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-propan-2-yloxypyridazine-3-carboxamide
575		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridazine-3-carboxamide
576		1-(azetidin-3-yl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide

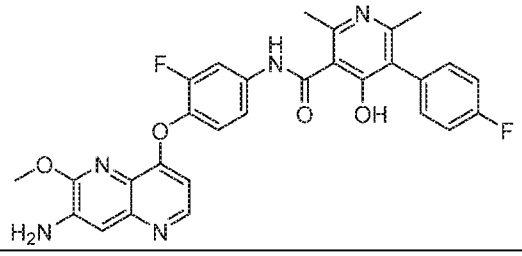
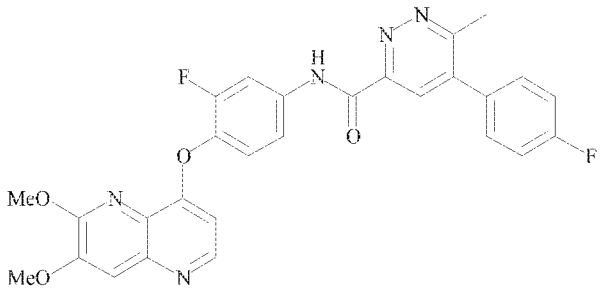
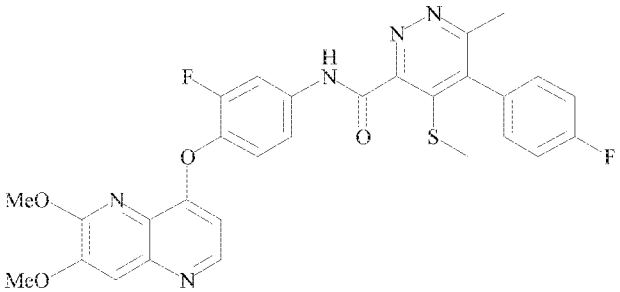
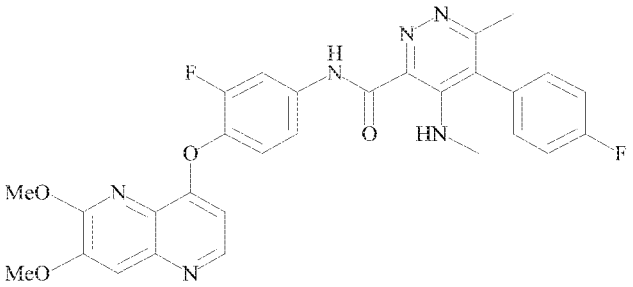
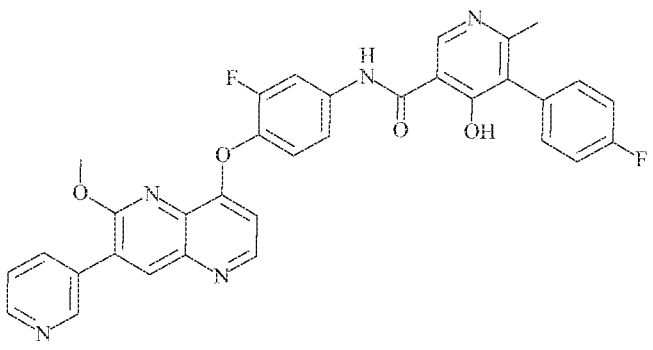
577		8-[2-fluoro-4-[[5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carbonyl]amino]phenoxy]-1,5-naphthyridine-3-carboxamide
578		8-[2-fluoro-4-[[5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carbonyl]amino]phenoxy]-N-methyl-1,5-naphthyridine-3-carboxamide
579		N-[4-[(6-amino-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
580		N-[3-fluoro-4-[(6-hydroxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide

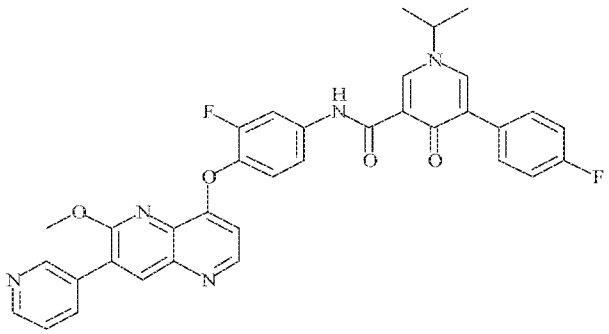
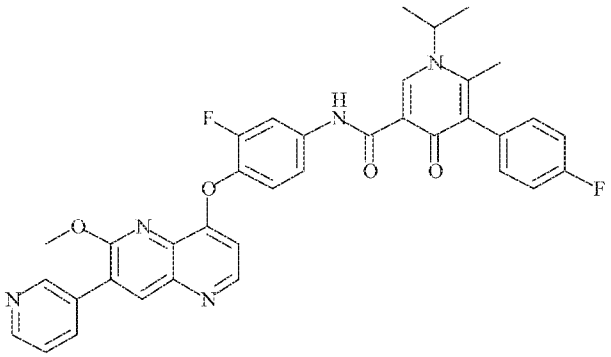
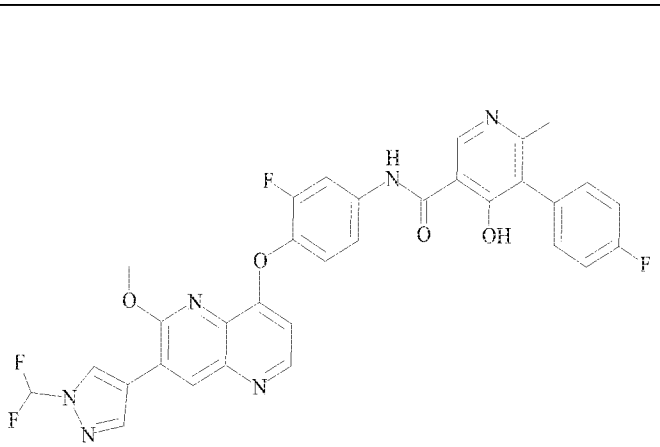
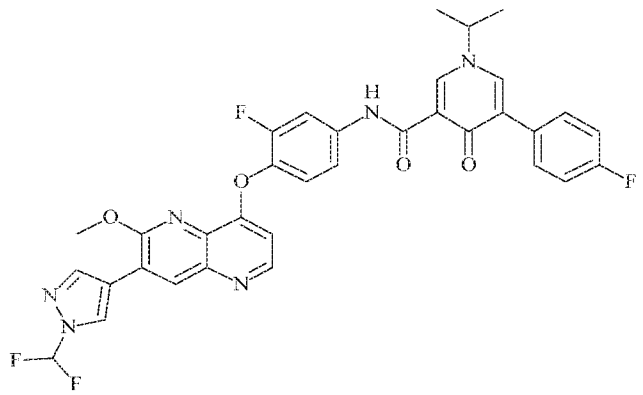
581		N-[3-fluoro-4-[[6-(methanesulfonamido)-7-methoxy-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
582		N-[3-fluoro-4-[[7-methoxy-6-(methylamino)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
583		N-[4-[[6-(dimethylamino)-7-methoxy-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
584		N-[3-fluoro-4-[[6-(methanesulfonamido)-7-methoxy-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

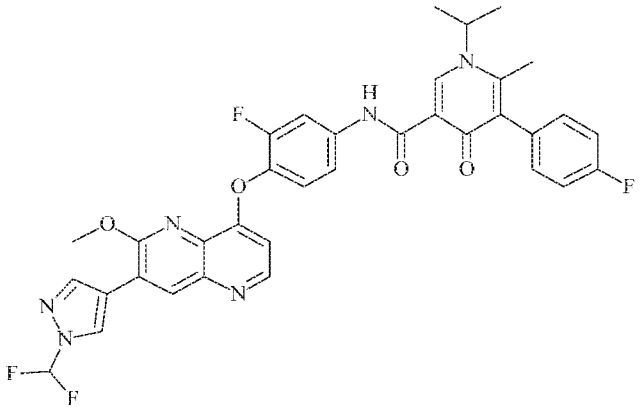
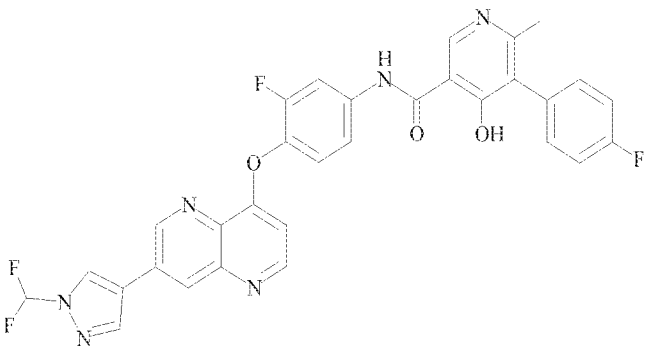
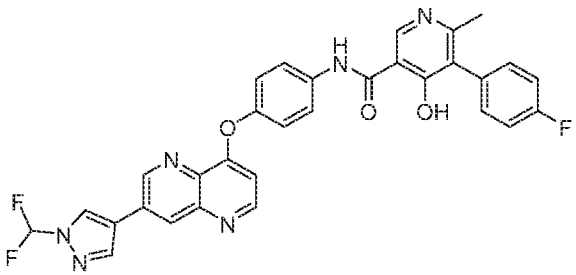
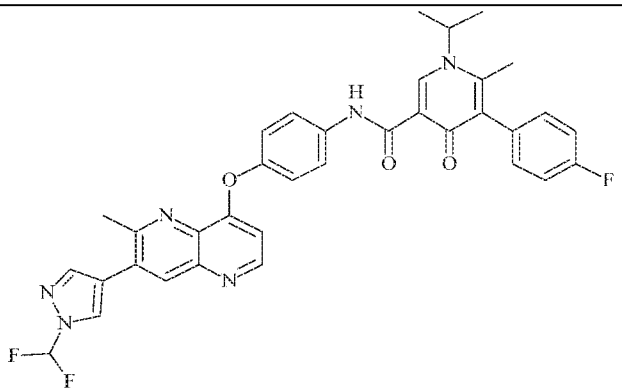
585		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methyl-6-(methylamino)-4-oxopyridine-3-carboxamide
586		6-cyano-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide
587		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methoxy-1-methyl-4-oxopyridine-3-carboxamide
588		N-[4-[(6-ethyl-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
589		N-[4-[(6-ethyl-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

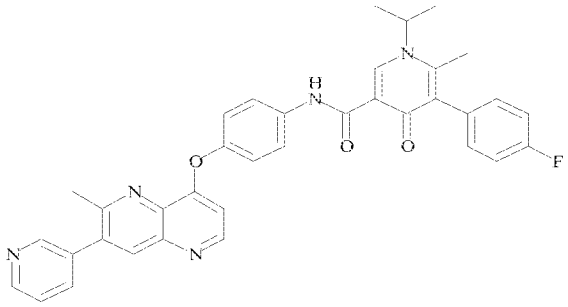
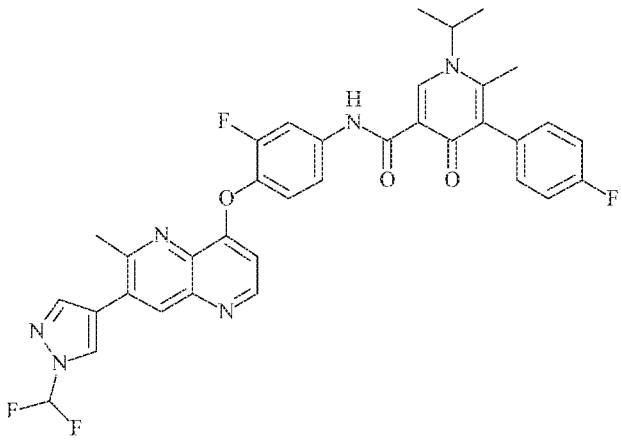
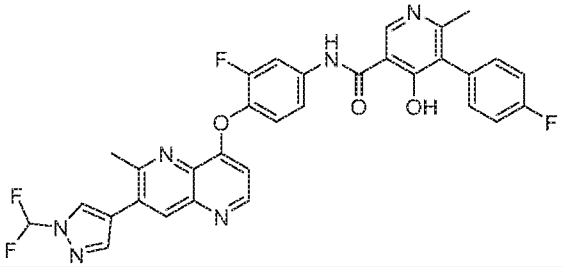
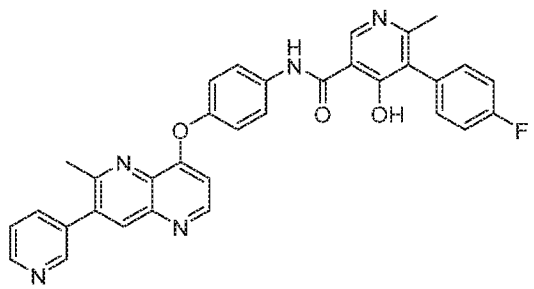
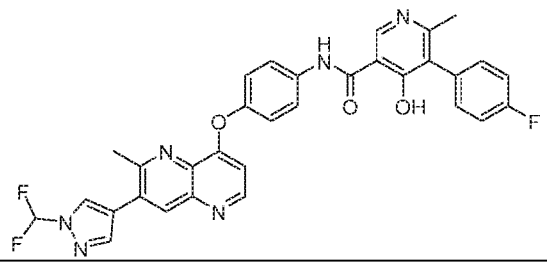
590		N-[3-fluoro-4-[(6-methoxy-7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
591		N-[3-fluoro-4-[(6-methoxy-7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
592		N-[3-fluoro-4-[(6-methoxy-7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
593		5-(4-fluoro-2-methylphenyl)-N-[3-fluoro-4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide
594		5-(4-fluorophenyl)-4-hydroxy-6-methyl-N-[4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide

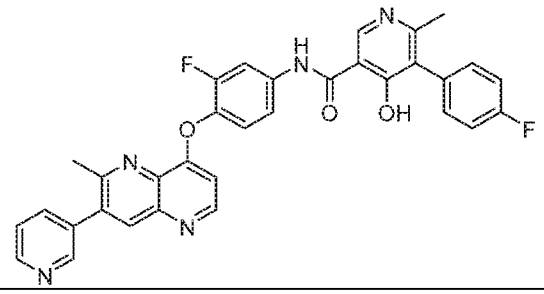
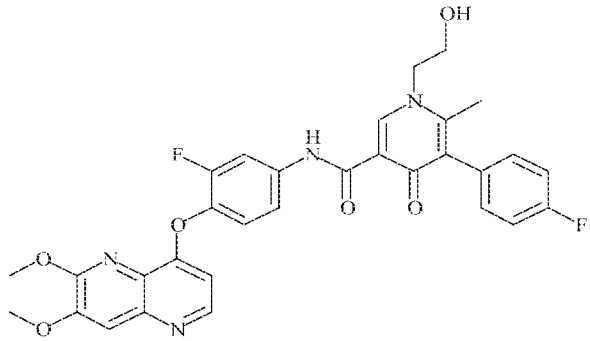
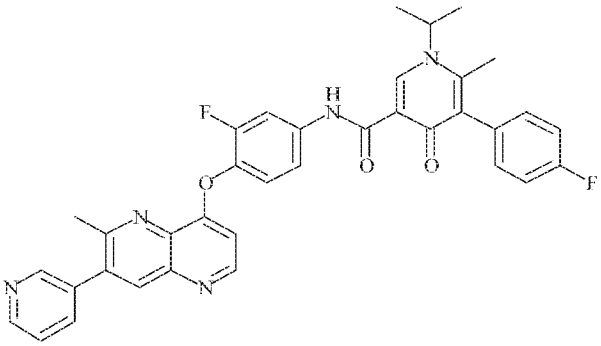
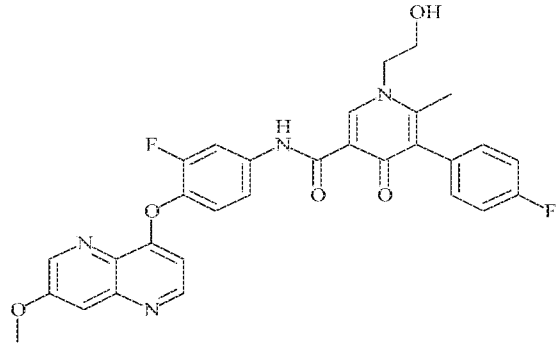
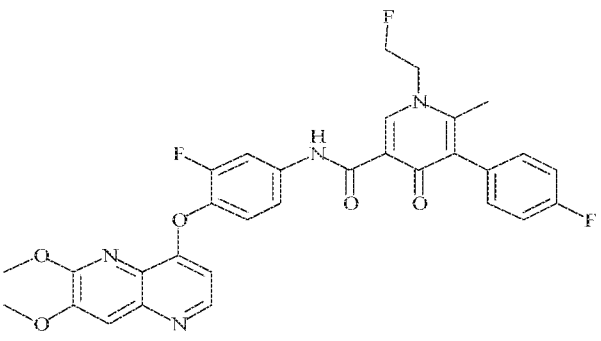
595		5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
596		5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide
597		5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methyl-N-[4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide
598		5-(4-fluorophenyl)-4-hydroxy-2,6-dimethyl-N-[4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide
599		N-[3-fluoro-4-[[7-(1-hydroxypropan-2-yl)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide

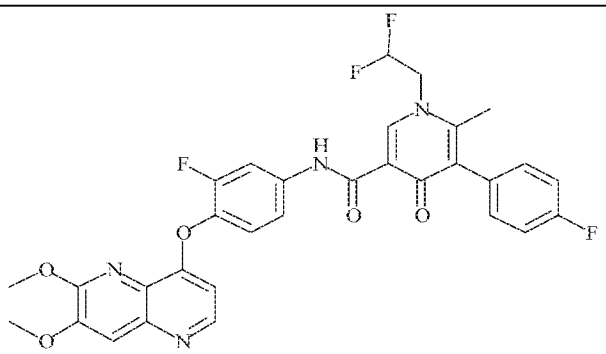
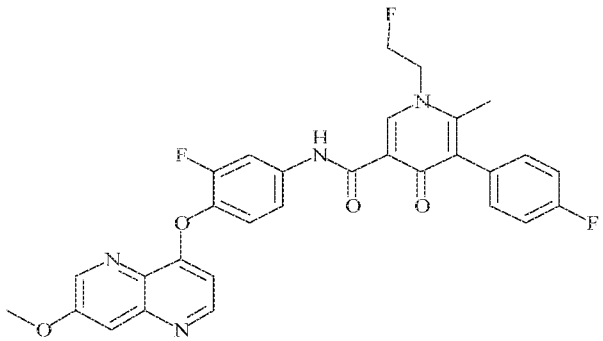
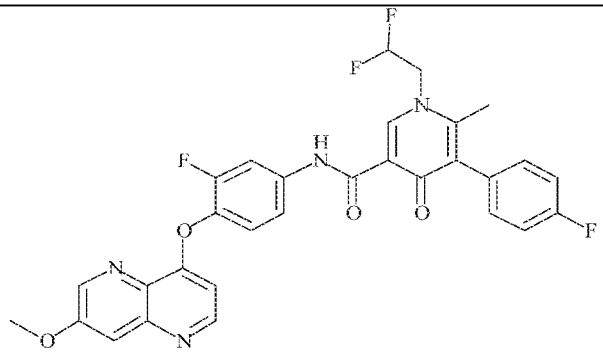
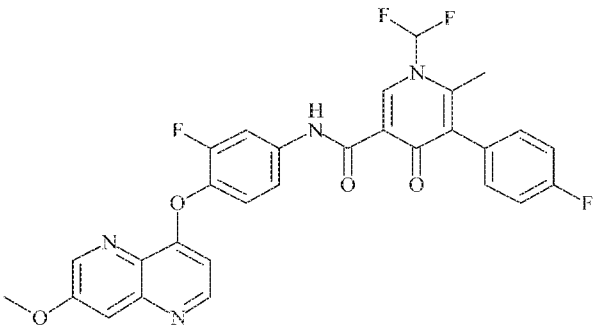
600		N-[4-[(7-amino-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
601		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxamide
602		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-methylsulfanylpyridazine-3-carboxamide
603		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-(methylamino)pyridazine-3-carboxamide
604		N-[3-fluoro-4-[(6-methoxy-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

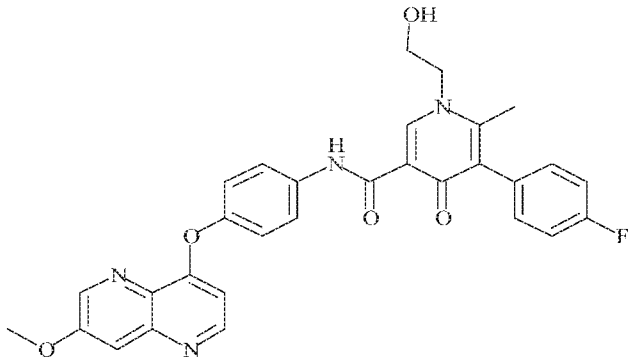
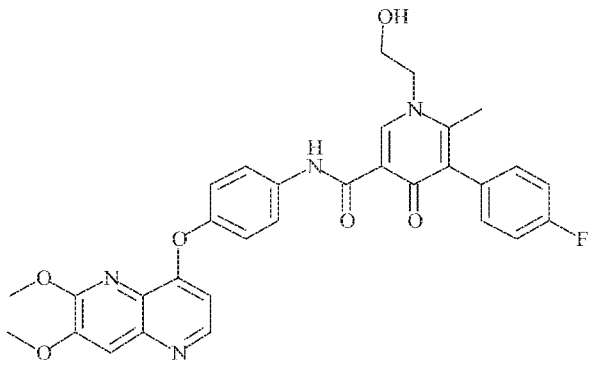
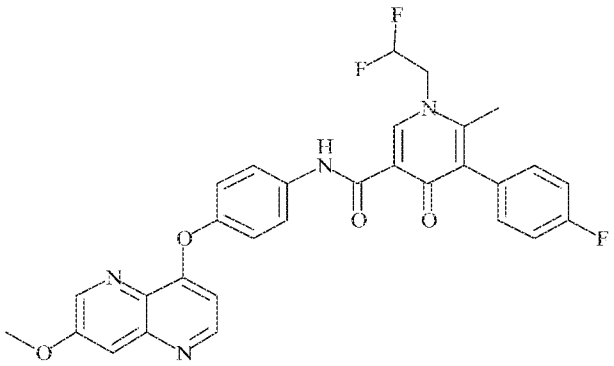
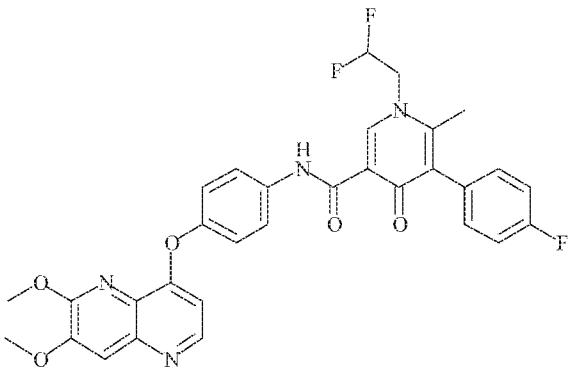
605		N-[3-fluoro-4-[(6-methoxy-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide
606		N-[3-fluoro-4-[(6-methoxy-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
607		N-[4-[[7-[1-(difluoromethyl)pyrazol-4-yl]-6-methoxy-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
608		N-[4-[[7-[1-(difluoromethyl)pyrazol-4-yl]-6-methoxy-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide

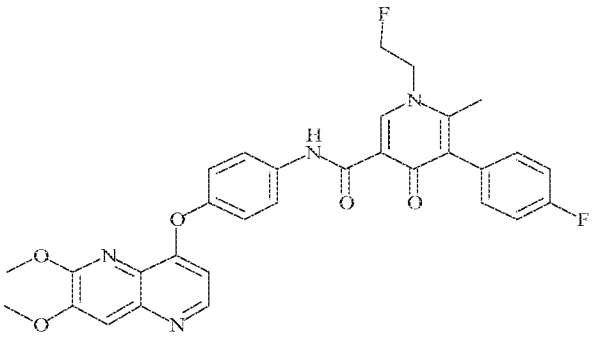
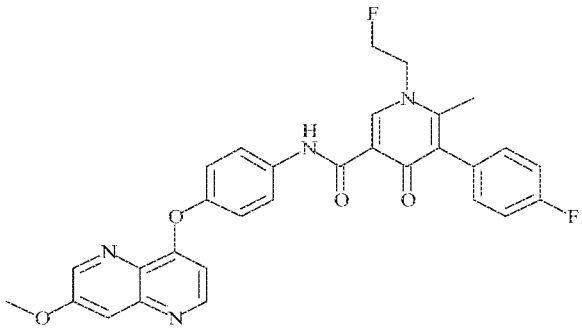
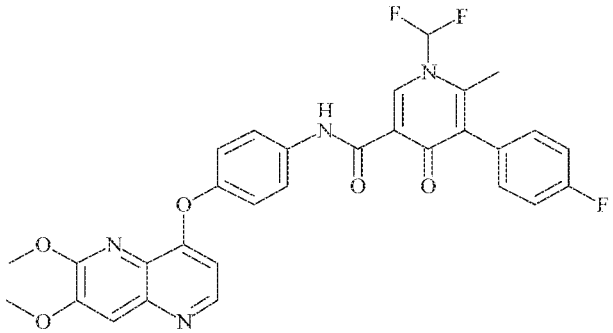
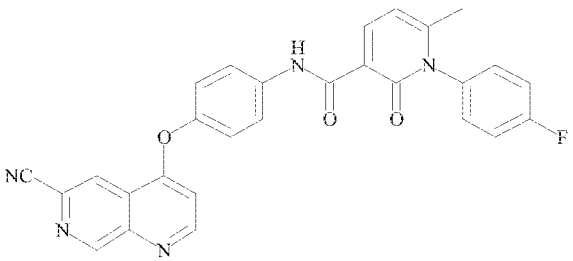
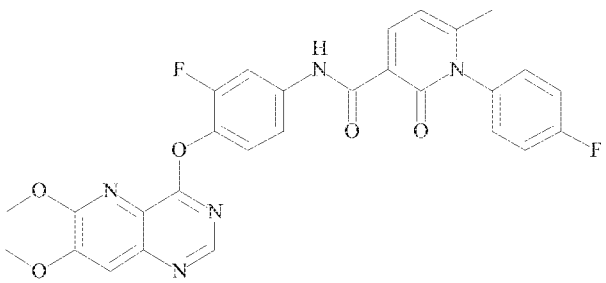
609		N-[4-[[7-[1-(difluoromethyl)pyrazol-4-yl]-6-methoxy-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
610		N-[4-[[7-[1-(difluoromethyl)pyrazol-4-yl]-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
611		N-[4-[[7-[1-(difluoromethyl)pyrazol-4-yl]-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
612		N-[4-[[7-[1-(difluoromethyl)pyrazol-4-yl]-6-methyl-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide

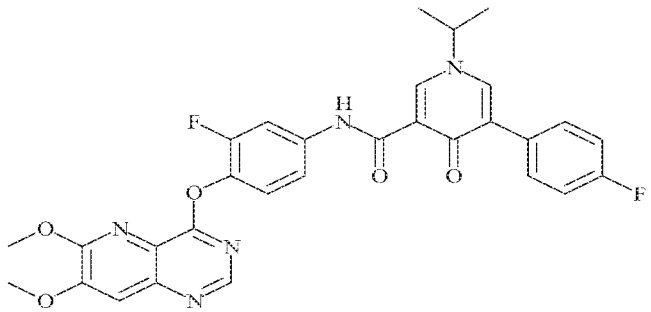
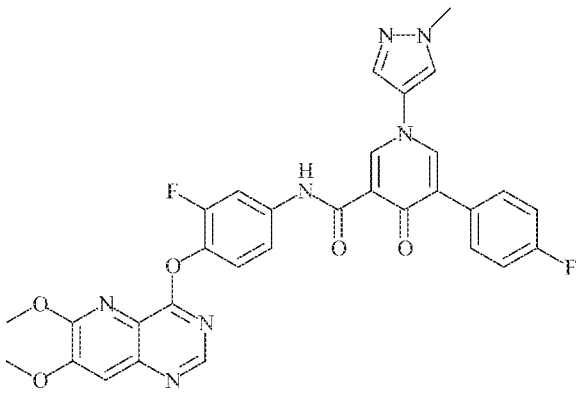
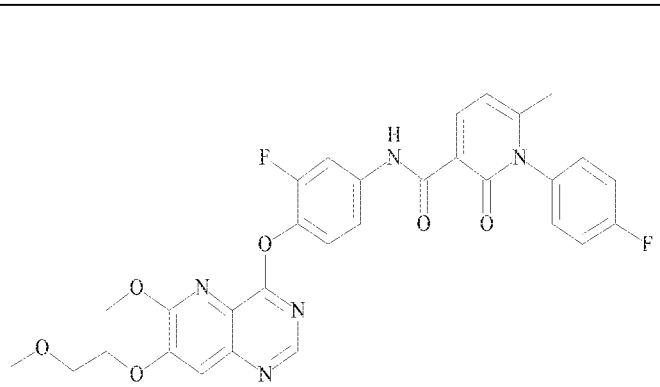
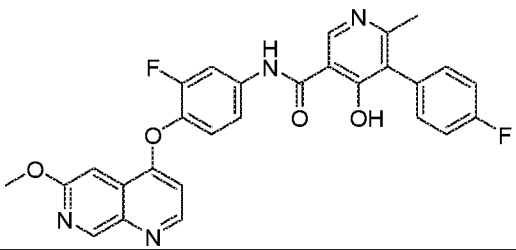
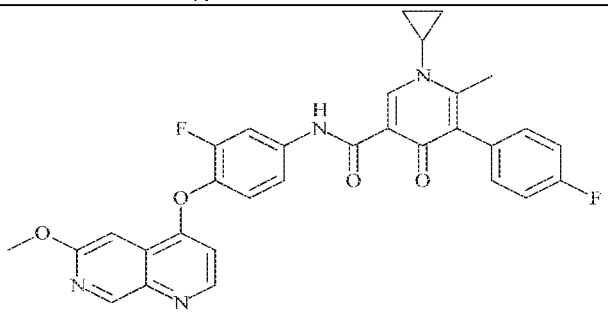
613		5-(4-fluorophenyl)-6-methyl-N-[4-[(6-methyl-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-oxo-1-propan-2-ylpyridine-3-carboxamide
614		N-[4-[[7-[1-(difluoromethyl)pyrazol-4-yl]-6-methyl-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
615		N-[4-[[7-[1-(difluoromethyl)pyrazol-4-yl]-6-methyl-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
616		5-(4-fluorophenyl)-4-hydroxy-6-methyl-N-[4-[(6-methyl-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide
617		N-[4-[[7-[1-(difluoromethyl)pyrazol-4-yl]-6-methyl-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

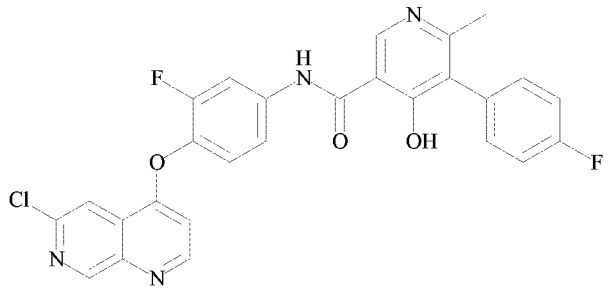
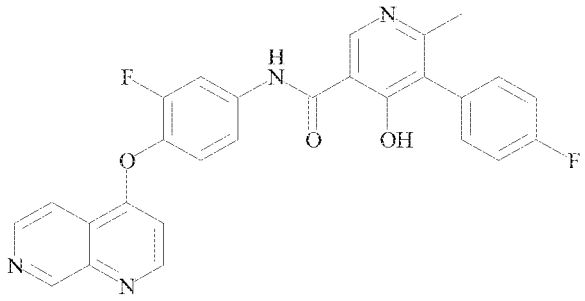
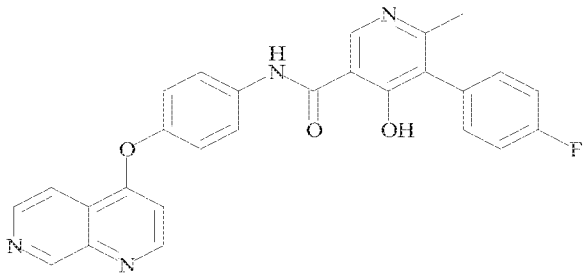
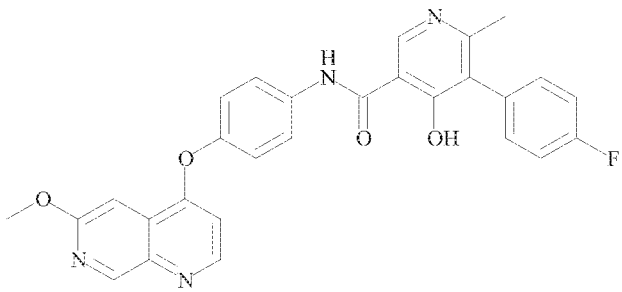
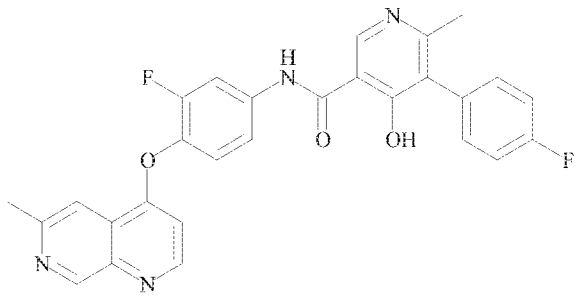
618		N-[3-fluoro-4-[(6-methyl-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
619		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(2-hydroxyethyl)-6-methyl-4-oxopyridine-3-carboxamide
620		N-[3-fluoro-4-[(6-methyl-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide
621		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-(2-hydroxyethyl)-6-methyl-4-oxopyridine-3-carboxamide
622		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide

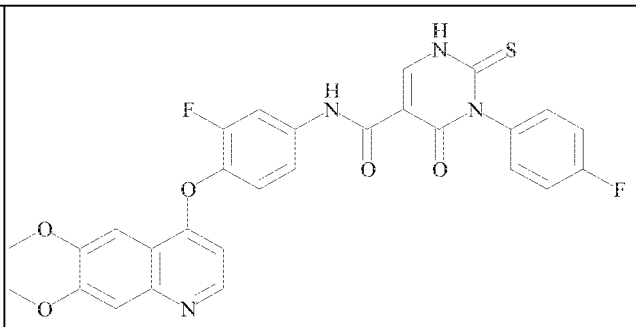
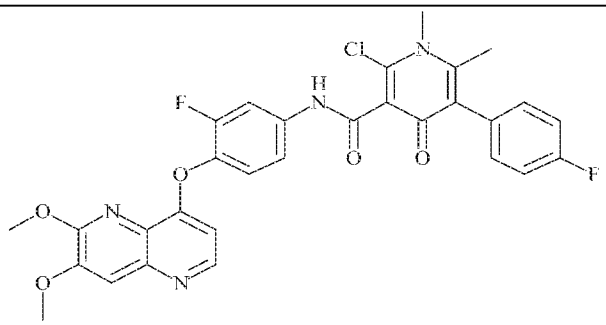
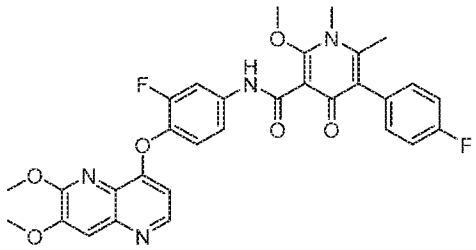
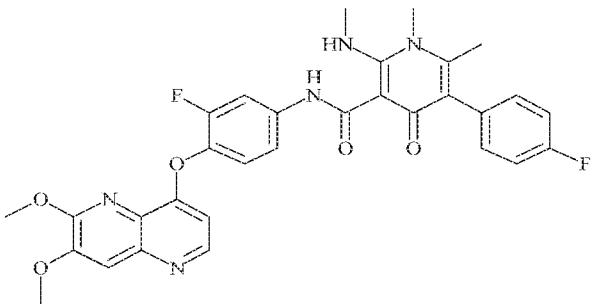
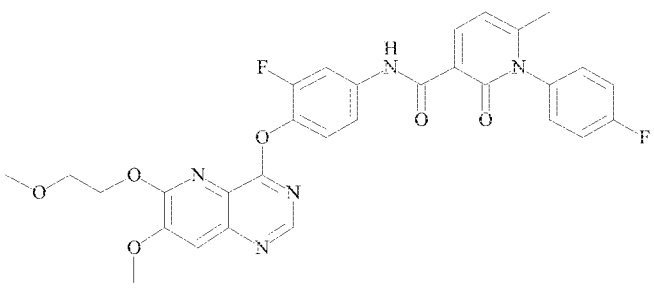
623		1-(2,2-difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
624		1-(2-fluoroethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
625		1-(2,2-difluoroethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
626		1-(difluoromethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide

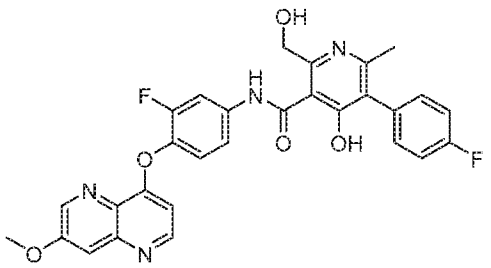
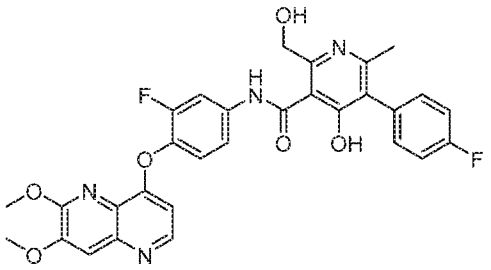
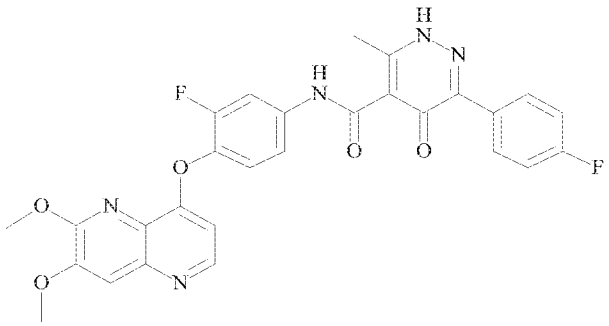
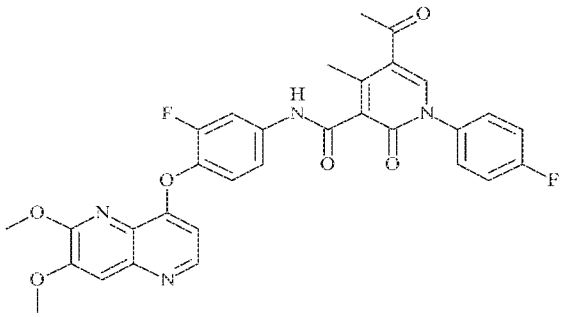
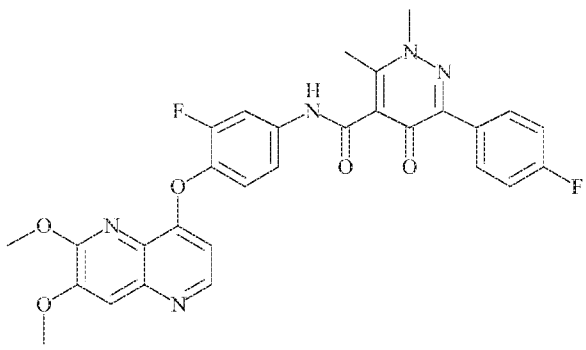
627		5-(4-fluorophenyl)-1-(2-hydroxyethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide
628		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-(2-hydroxyethyl)-6-methyl-4-oxopyridine-3-carboxamide
629		1-(2,2-difluoroethyl)-5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide
630		1-(2,2-difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide

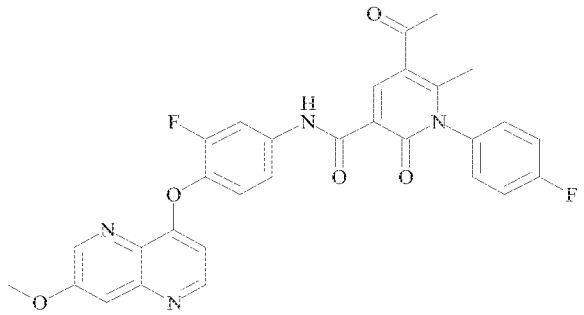
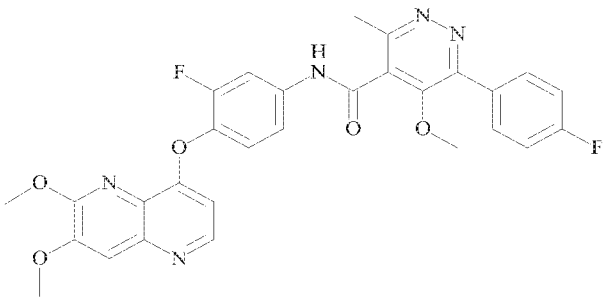
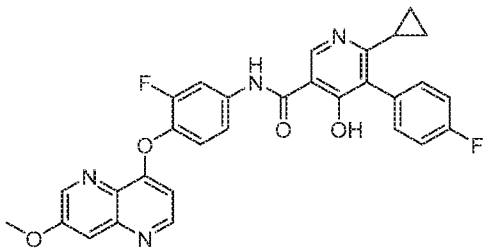
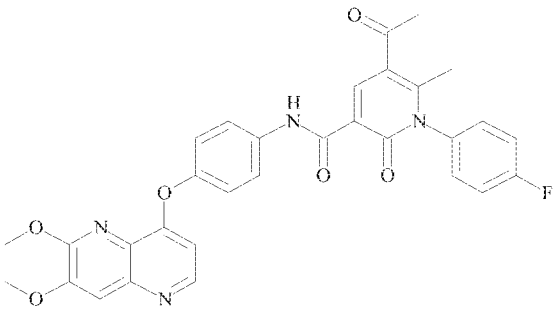
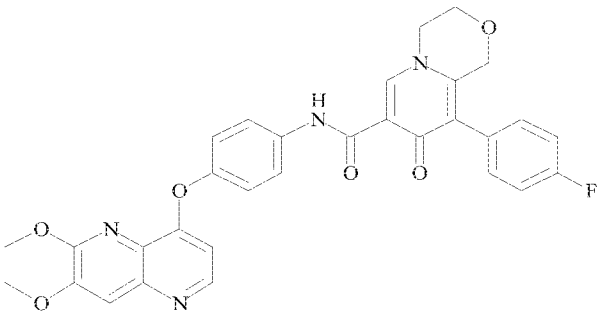
631		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
632		1-(2-fluoroethyl)-5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide
633		1-(difluoromethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
634		N-[4-[(6-cyano-1,7-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
635		N-[4-(6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide

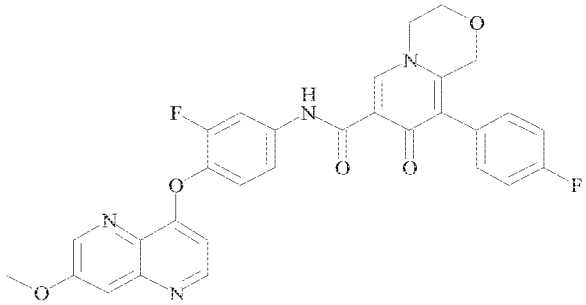
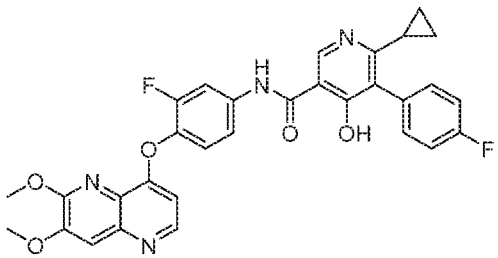
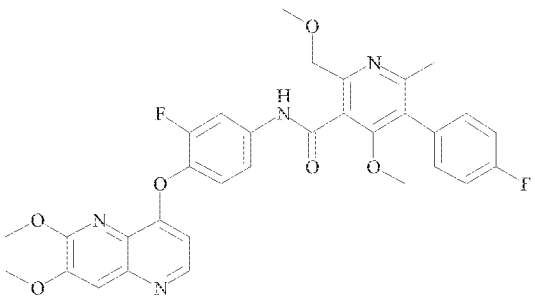
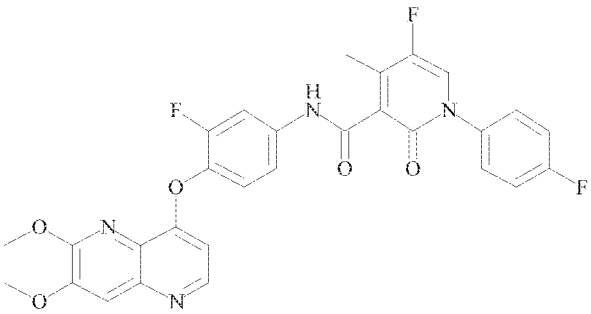
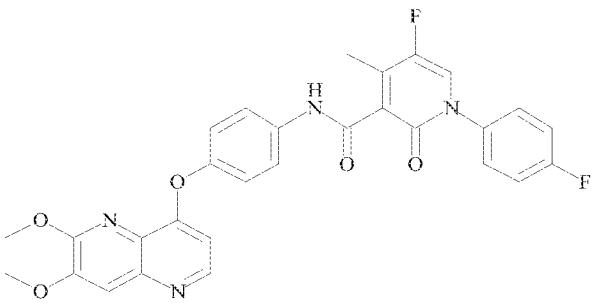
636		N-[4-(6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide
637		N-[4-(6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide
638		N-[3-fluoro-4-[6-methoxy-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
639		N-[3-fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
640		1-cyclopropyl-N-[3-fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide

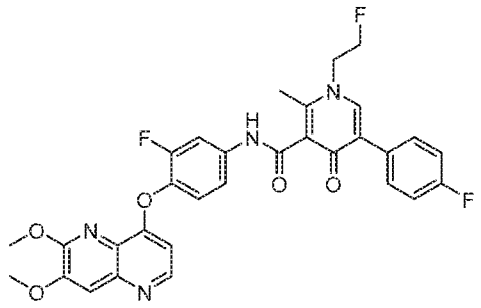
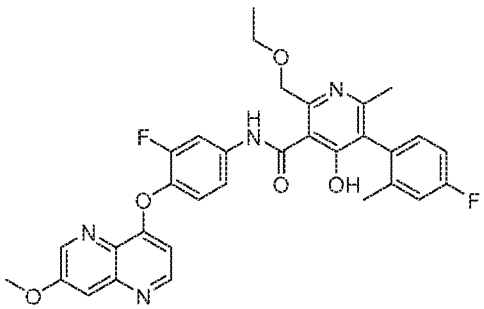
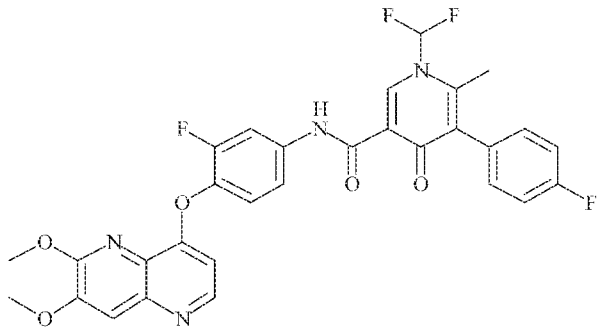
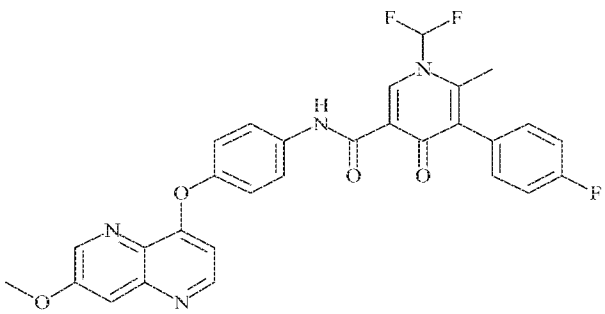
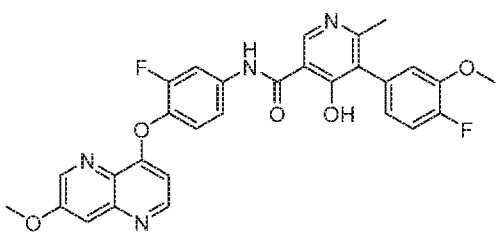
641		N-[4-[(6-chloro-1,7-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
642		N-[3-fluoro-4-(1,7-naphthyridin-4-yloxy)phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
643		5-(4-fluorophenyl)-4-hydroxy-6-methyl-N-[4-(1,7-naphthyridin-4-yloxy)phenyl]pyridine-3-carboxamide
644		5-(4-fluorophenyl)-4-hydroxy-N-[4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
645		N-[3-fluoro-4-[(6-methyl-1,7-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

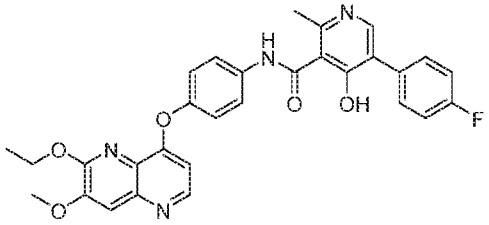
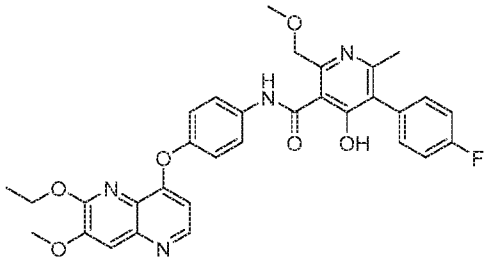
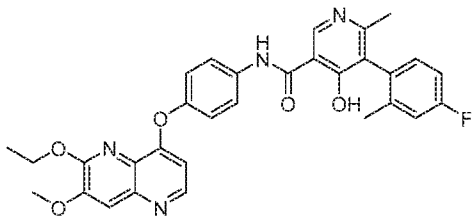
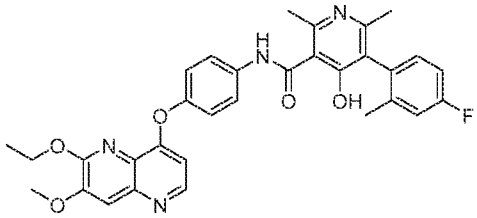
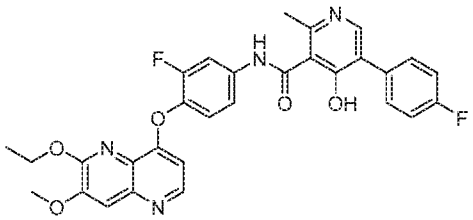
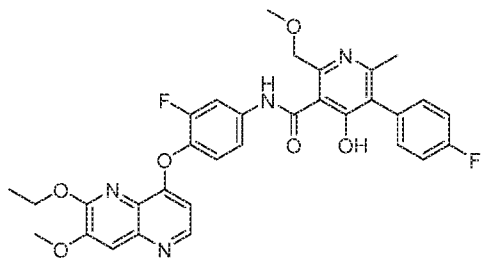
646		N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-3-(4-fluorophenyl)-4-oxo-2-sulfanylidene-1H-pyrimidine-5-carboxamide
647		2-chloro-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
648		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-2-methoxy-1,6-dimethyl-4-oxopyridine-3-carboxamide
649		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-2-(methylamino)-4-oxopyridine-3-carboxamide
650		N-[3-fluoro-4-[7-methoxy-6-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide

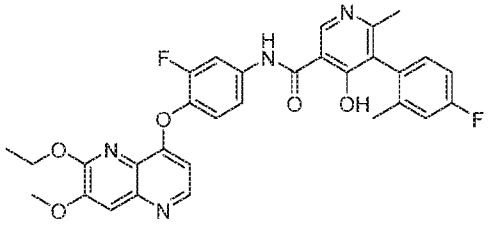
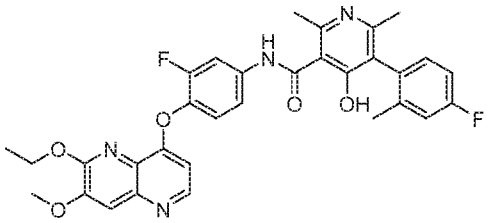
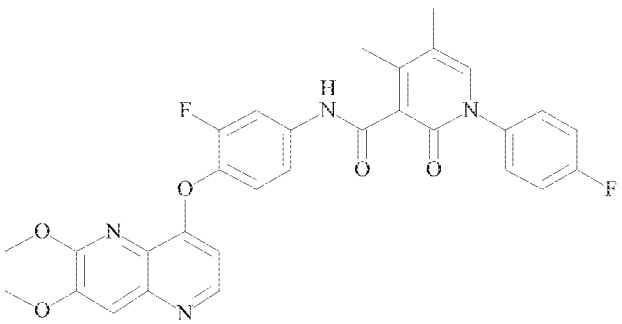
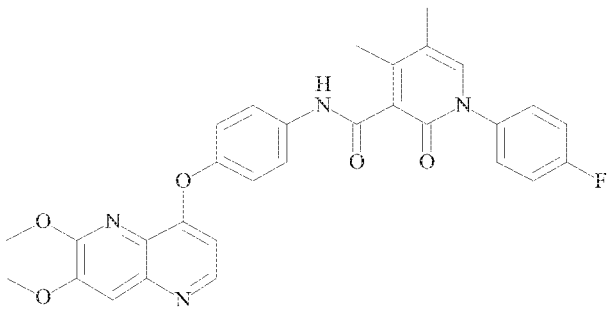
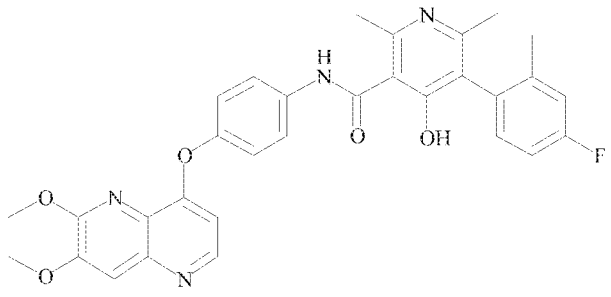
651		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(hydroxymethyl)-6-methylpyridine-3-carboxamide
652		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(hydroxymethyl)-6-methylpyridine-3-carboxamide
653		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-5-carboxamide
654		5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide
655		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-2,3-dimethyl-5-oxopyridazine-4-carboxamide

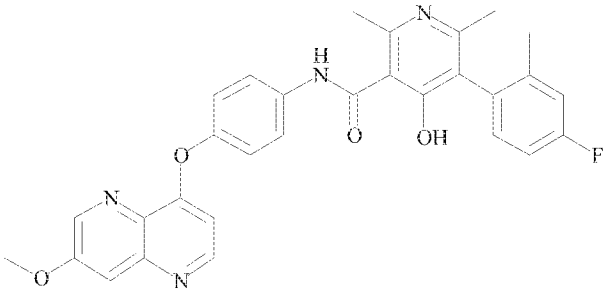
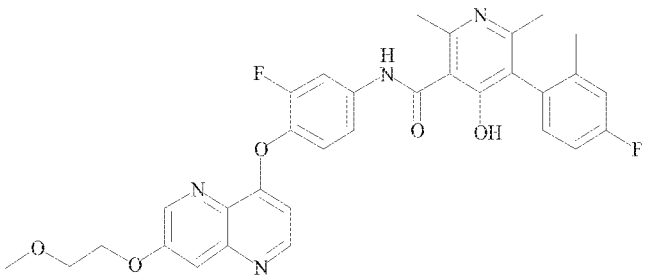
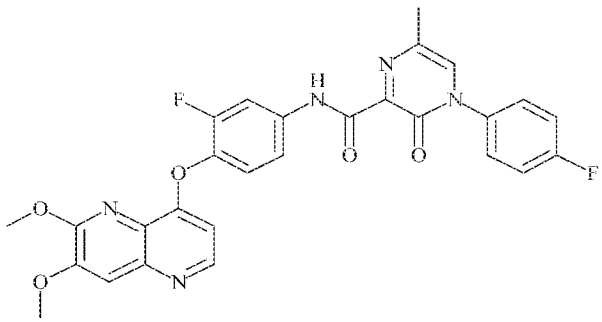
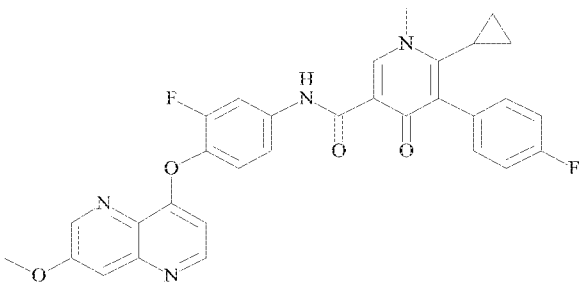
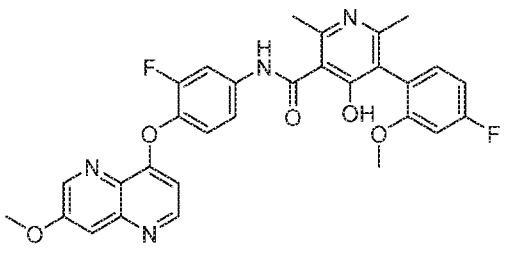
656		5-acetyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
657		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-5-methoxy-3-methylpyridazine-4-carboxamide
658		6-cyclopropyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide
659		5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
660		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-9-(4-fluorophenyl)-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-7-carboxamide

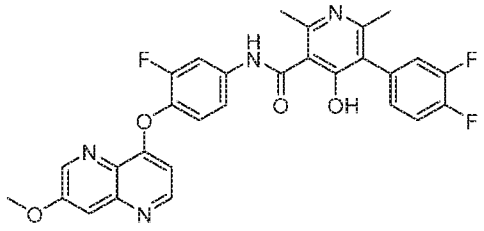
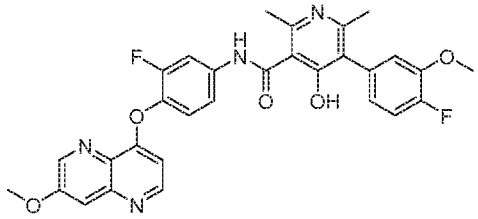
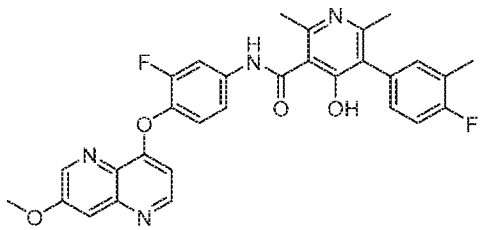
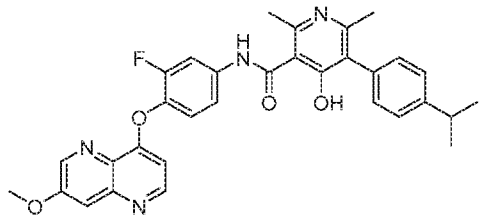
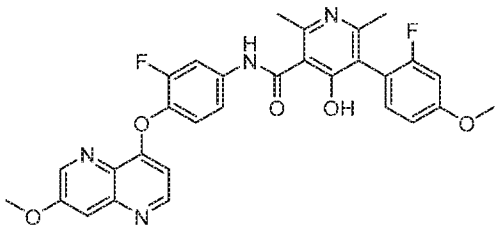
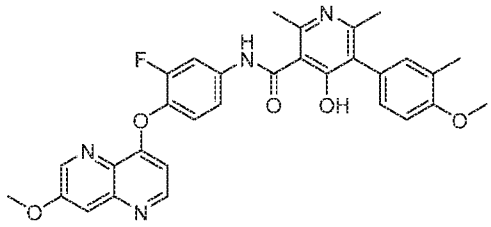
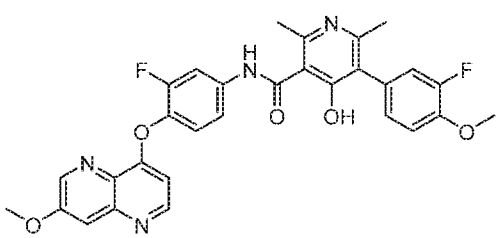
661		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-9-(4-fluorophenyl)-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-7-carboxamide
662		6-cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide
663		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-methoxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
664		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-fluoro-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide
665		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-fluoro-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide

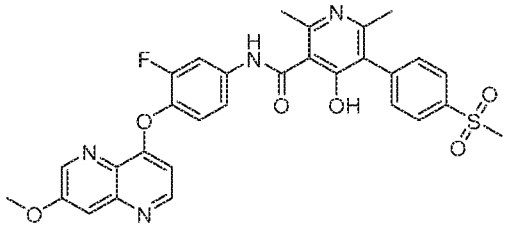
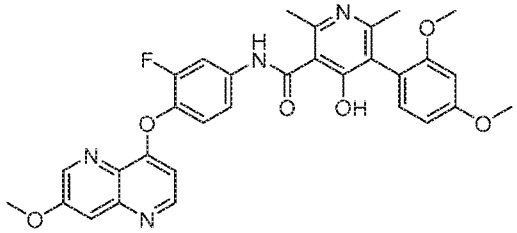
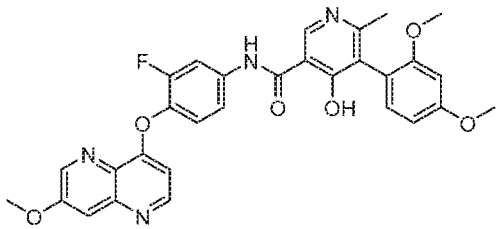
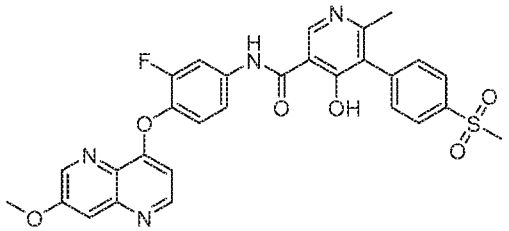
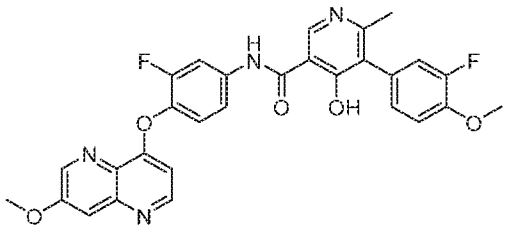
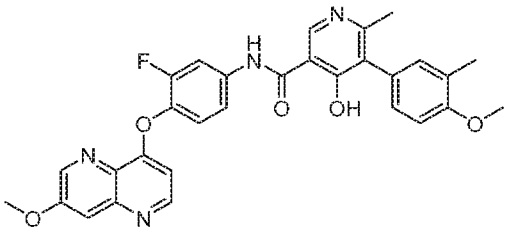
666		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide
667		2-(ethoxymethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
668		1-(difluoromethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide
669		1-(difluoromethyl)-5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide
670		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-3-methoxyphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide

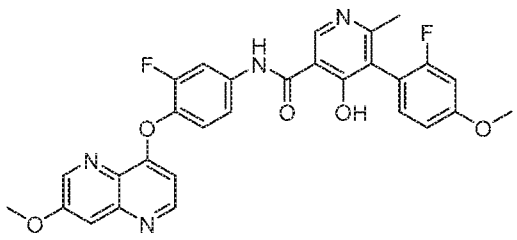
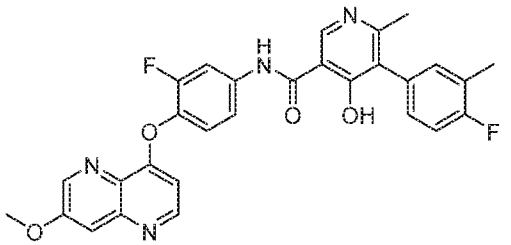
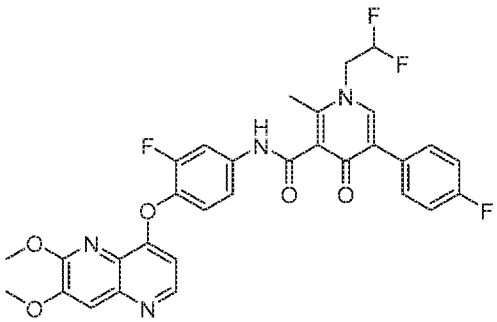
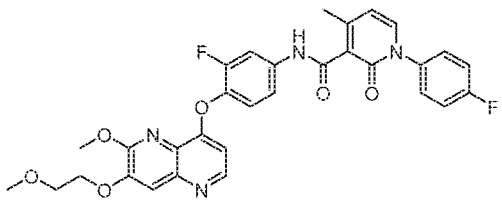
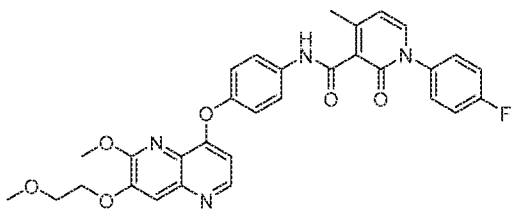
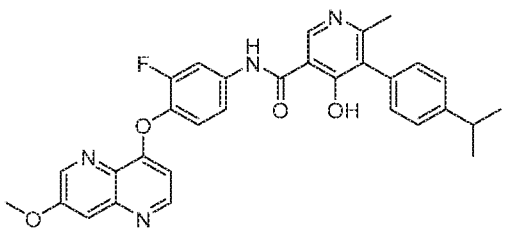
671		N-[4-[(6-ethoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide
672		N-[4-[(6-ethoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
673		N-[4-[(6-ethoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
674		N-[4-[(6-ethoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
675		N-[4-[(6-ethoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide
676		N-[4-[(6-ethoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide

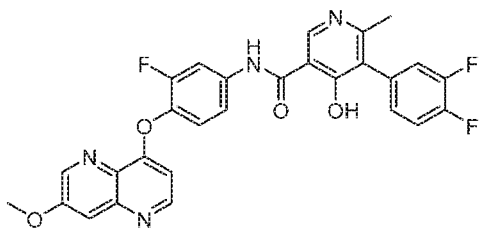
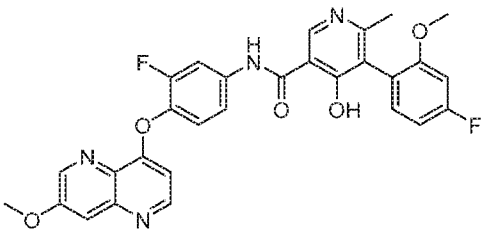
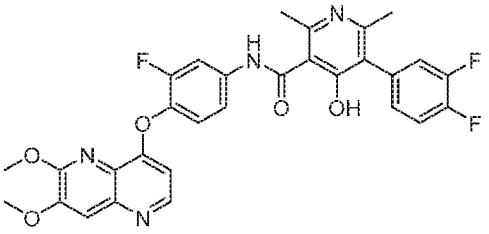
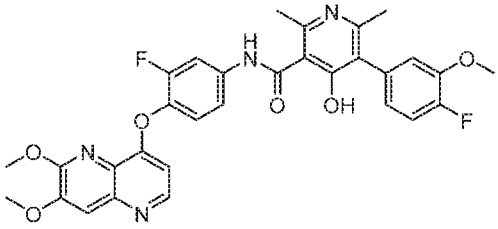
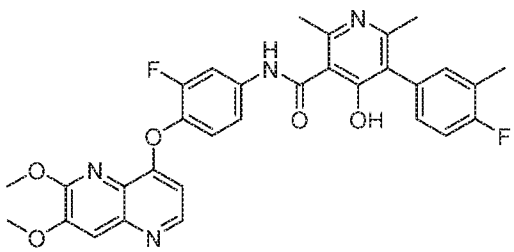
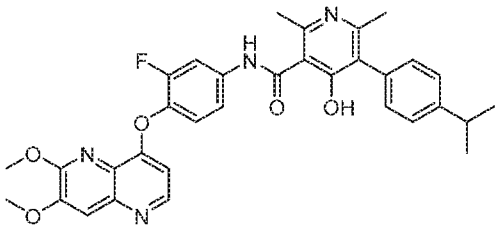
677		N-[4-[(6-ethoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
678		N-[4-[(6-ethoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
679		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4,5-dimethyl-2-oxopyridine-3-carboxamide
680		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,5-dimethyl-2-oxopyridine-3-carboxamide
681		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

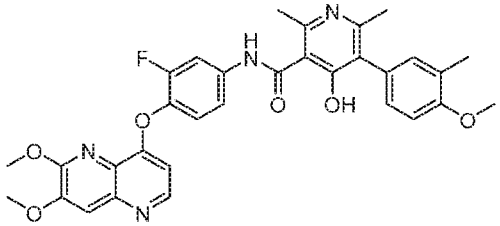
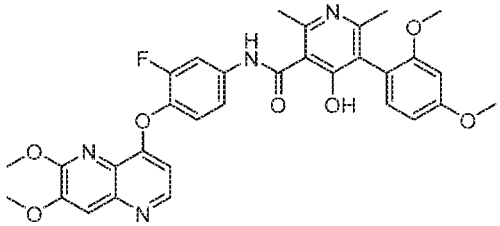
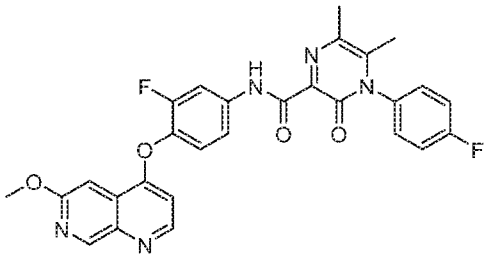
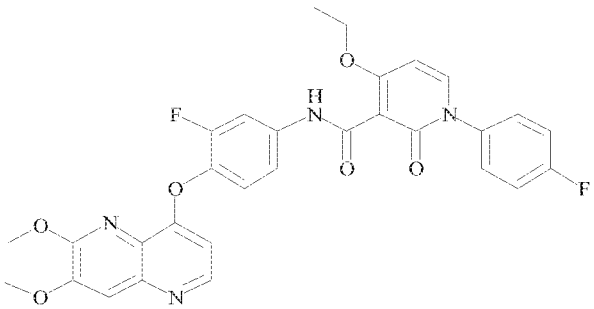
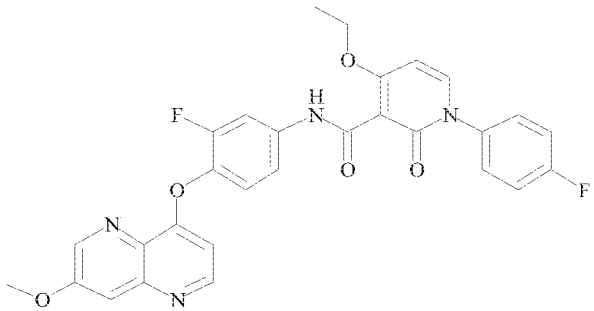
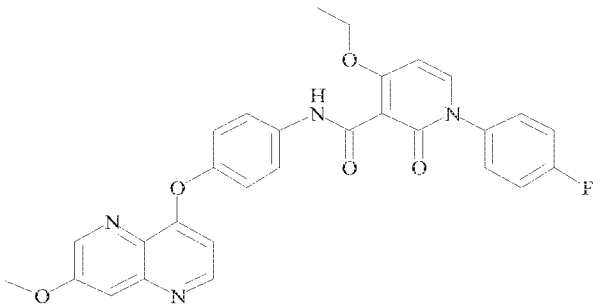
682		5-(4-fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2,6-dimethylpyridine-3-carboxamide
683		N-[3-fluoro-4-[[7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
684		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-6-methyl-3-oxopyrazine-2-carboxamide
685		6-cyclopropyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide
686		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methoxyphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

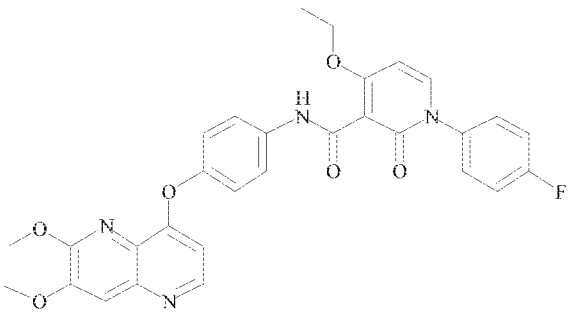
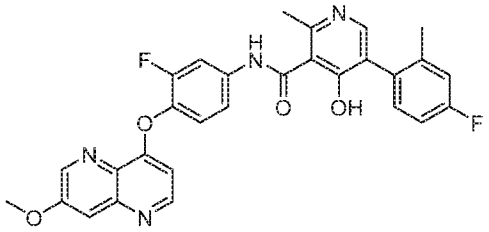
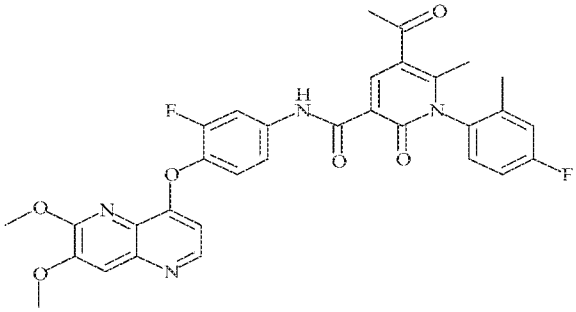
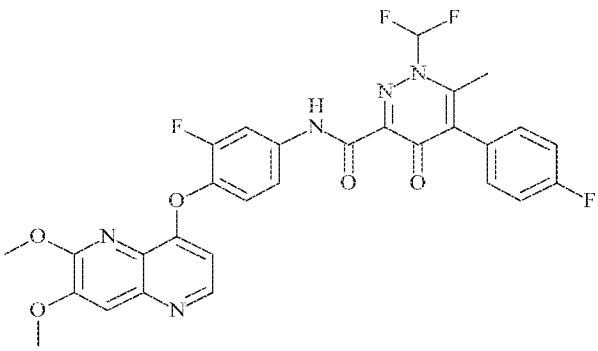
687		5-(3,4-difluorophenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
688		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-3-methoxyphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
689		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-3-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
690		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethyl-5-(4-propan-2-ylphenyl)pyridine-3-carboxamide
691		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(2-fluoro-4-methoxyphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
692		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-5-(4-methoxy-3-methylphenyl)-2,6-dimethylpyridine-3-carboxamide
693		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(3-fluoro-4-methoxyphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

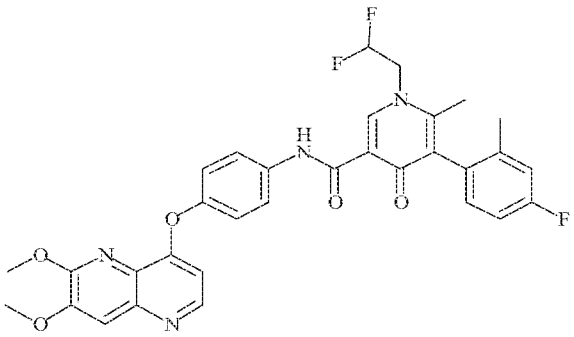
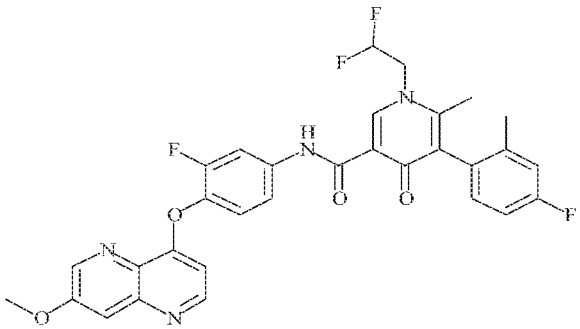
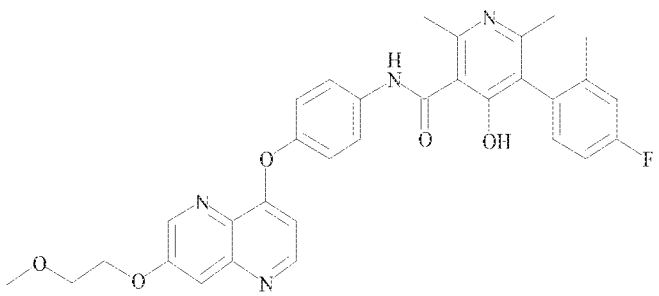
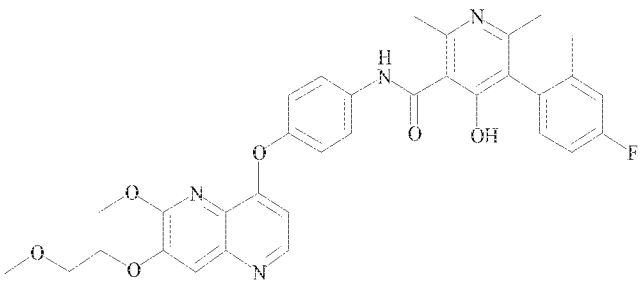
694		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethyl-5-(4-methylsulfonylphenyl)pyridine-3-carboxamide
695		5-(2,4-dimethoxyphenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
696		5-(2,4-dimethoxyphenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide
697		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methyl-5-(4-methylsulfonylphenyl)pyridine-3-carboxamide
698		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(3-fluoro-4-methoxyphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
699		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-5-(4-methoxy-3-methylphenyl)-6-methylpyridine-3-carboxamide

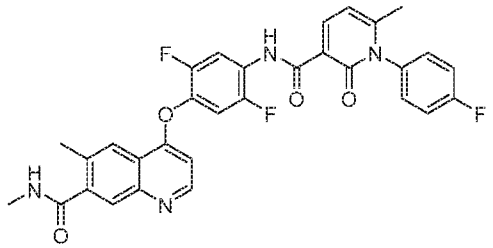
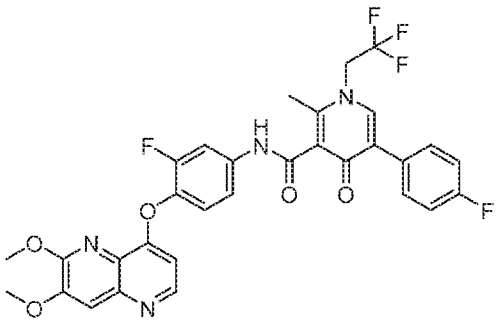
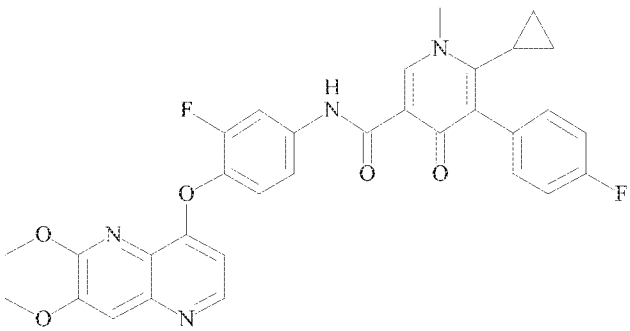
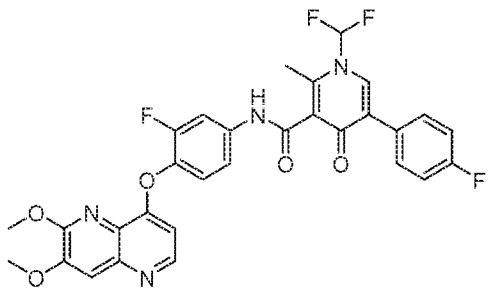
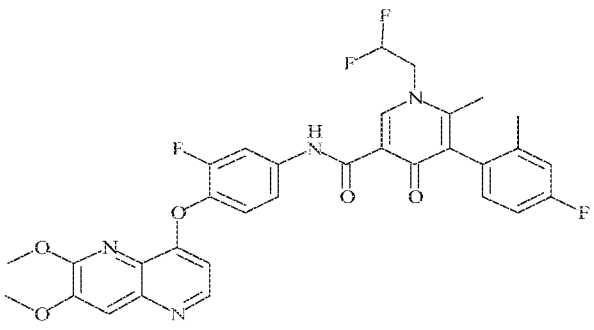
700		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(2-fluoro-4-methoxyphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
701		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-3-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
702		1-(2,2-difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide
703		N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide
704		1-(4-fluorophenyl)-N-[4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-4-methyl-2-oxopyridine-3-carboxamide
705		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methyl-5-(4-propan-2-ylphenyl)pyridine-3-carboxamide

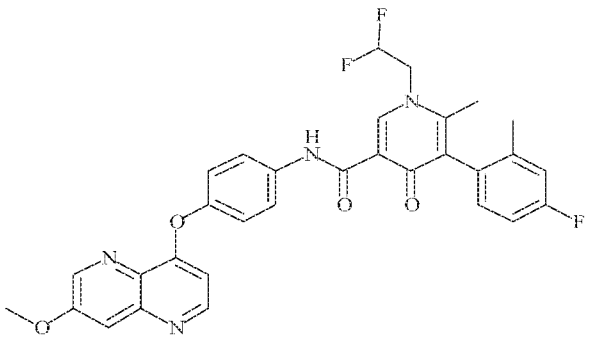
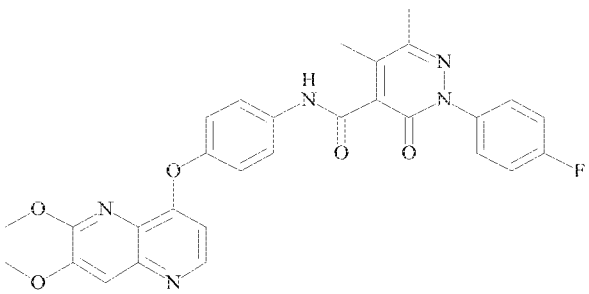
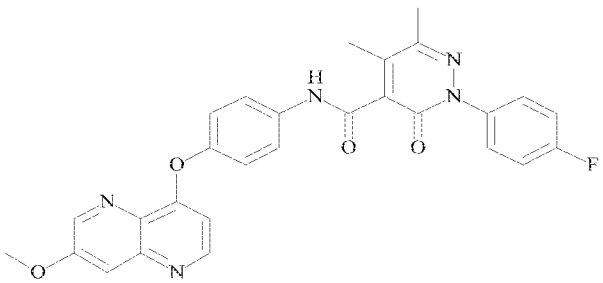
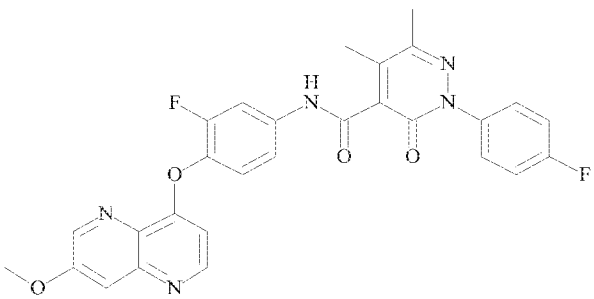
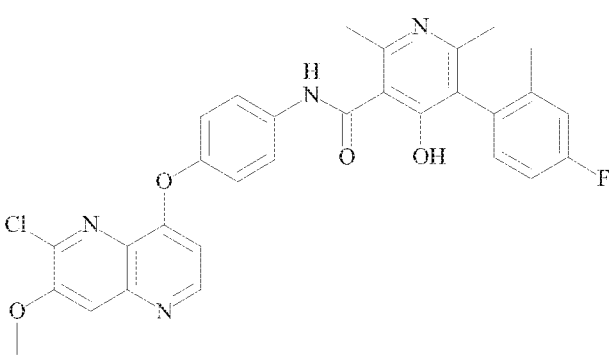
706		5-(3,4-difluorophenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide
707		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methoxyphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
708		5-(3,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
709		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-3-methoxyphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
710		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-3-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
711		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2,6-dimethyl-5-(4-propan-2-ylphenyl)pyridine-3-carboxamide

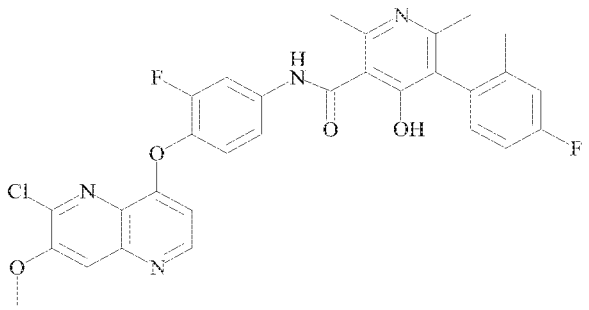
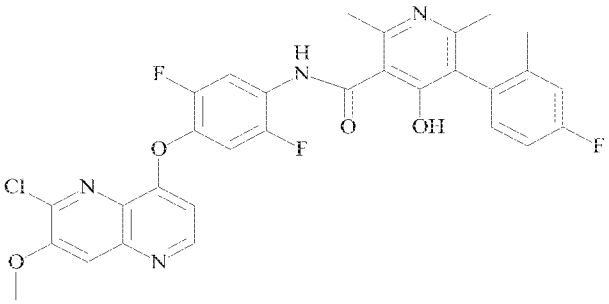
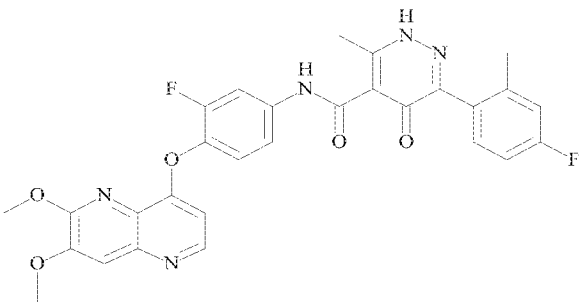
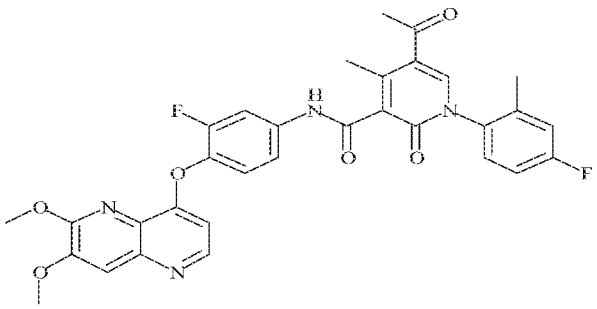
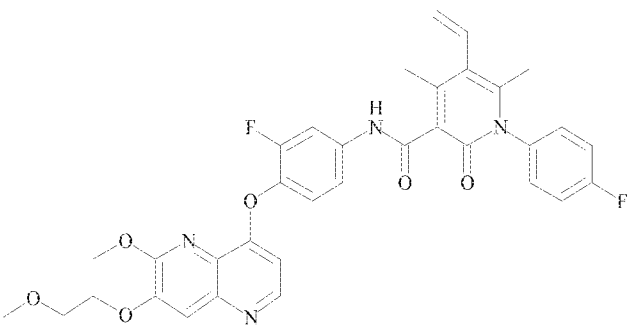
712		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-5-(4-methoxy-3-methylphenyl)-2,6-dimethylpyridine-3-carboxamide
713		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(2,4-dimethoxyphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
714		N-[3-fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-5,6-dimethyl-3-oxopyrazine-2-carboxamide
715		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-ethoxy-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide
716		4-ethoxy-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide
717		4-ethoxy-1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-oxopyridine-3-carboxamide

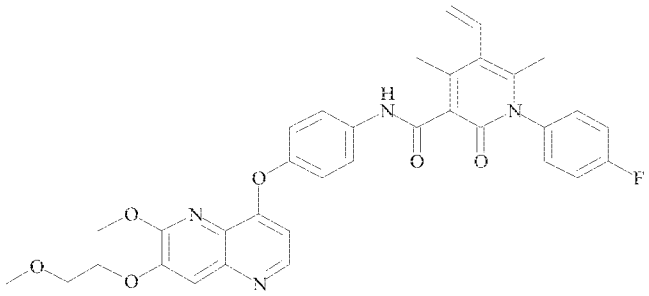
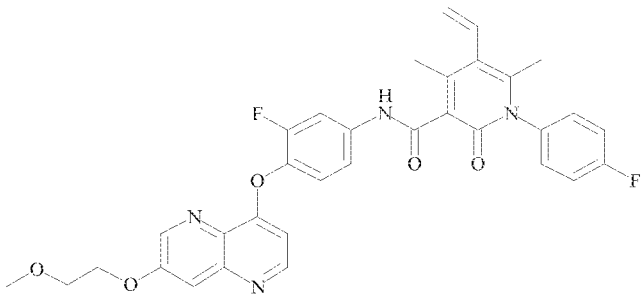
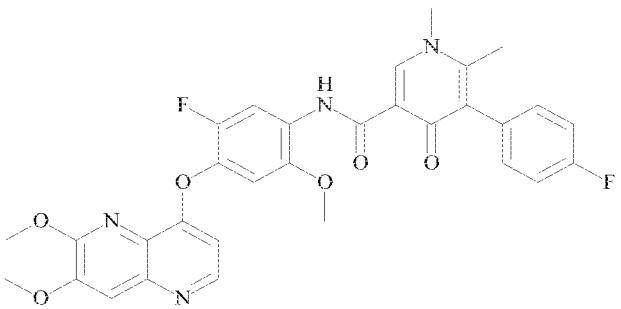
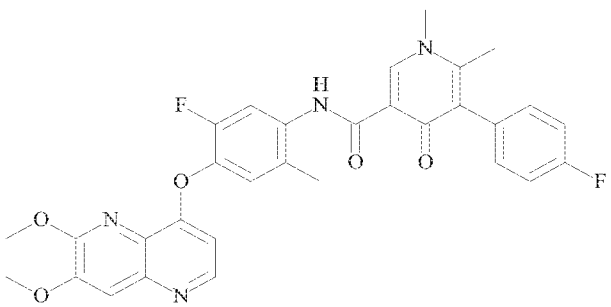
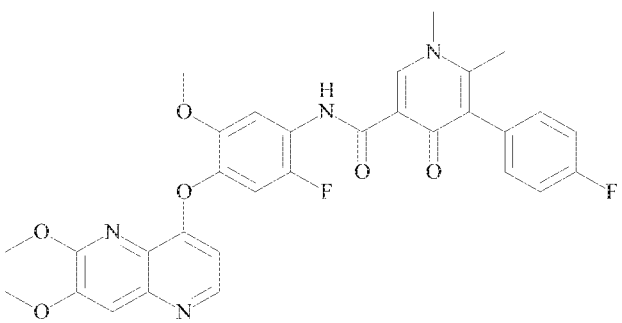
718		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-ethoxy-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide
719		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-methylpyridine-3-carboxamide
720		5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxopyridine-3-carboxamide
721		1-(difluoromethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridazine-3-carboxamide

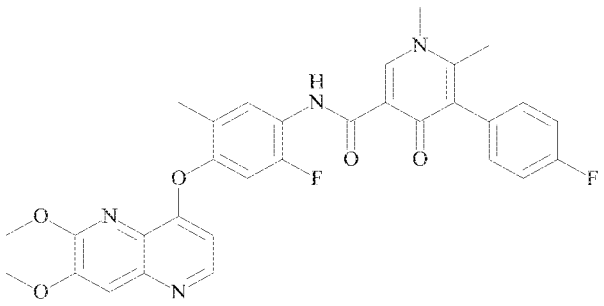
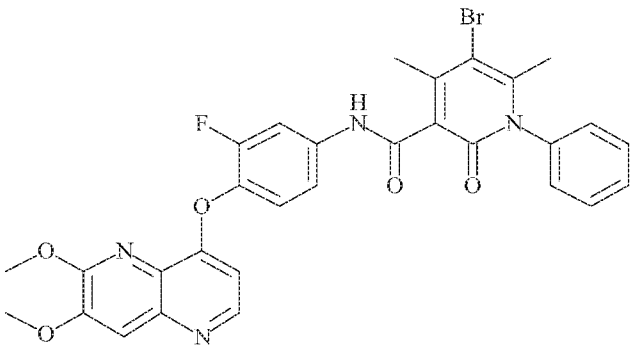
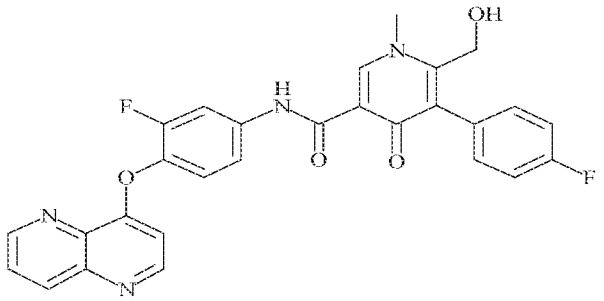
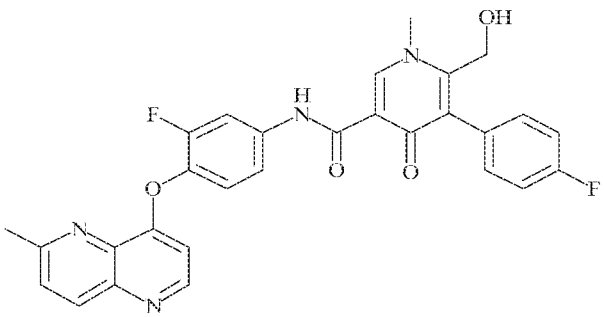
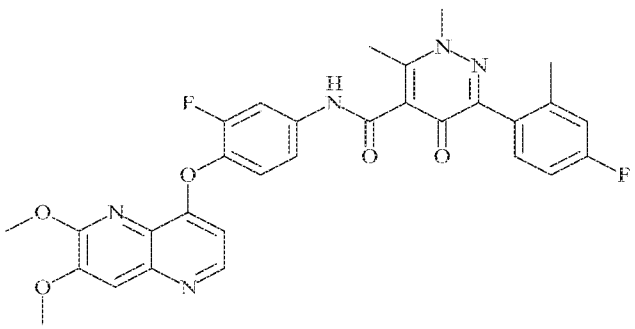
722		1-(2,2-difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide
723		1-(2,2-difluoroethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide
724		5-(4-fluoro-2-methylphenyl)-4-hydroxy-N-[4-[[7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-2,6-dimethylpyridine-3-carboxamide
725		5-(4-fluoro-2-methylphenyl)-4-hydroxy-N-[4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-2,6-dimethylpyridine-3-carboxamide

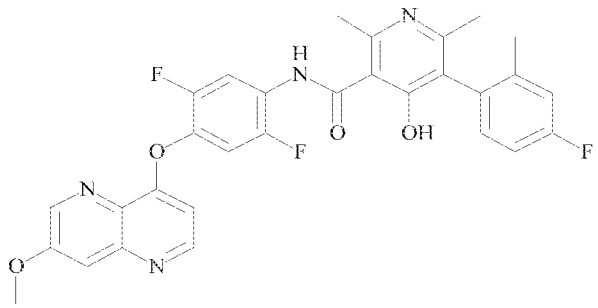
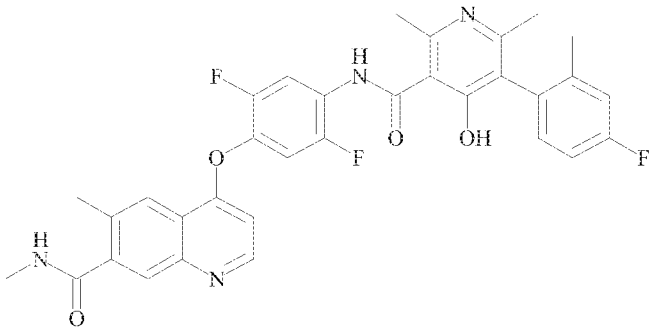
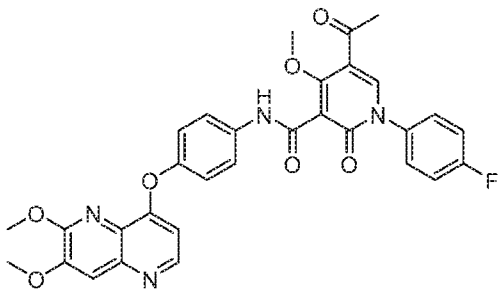
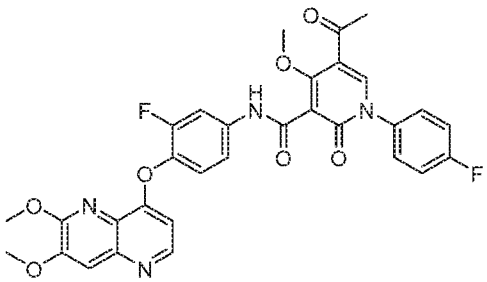
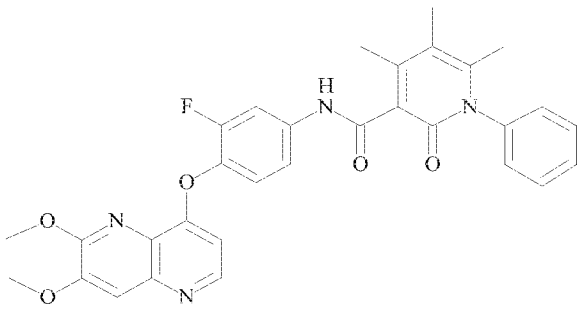
726		4-[2,5-difluoro-4-[[1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carbonyl]amino]phenoxy]-N,6-dimethylquinoline-7-carboxamide
727		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-2-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide
728		6-cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide
729		1-(difluoromethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide
730		1-(2,2-difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide

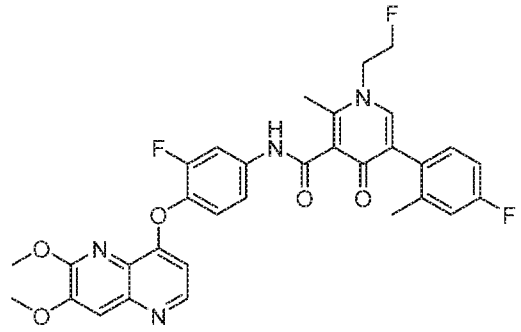
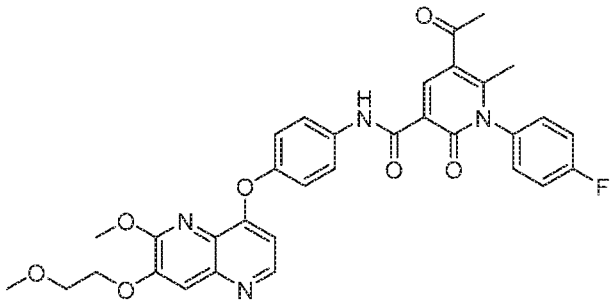
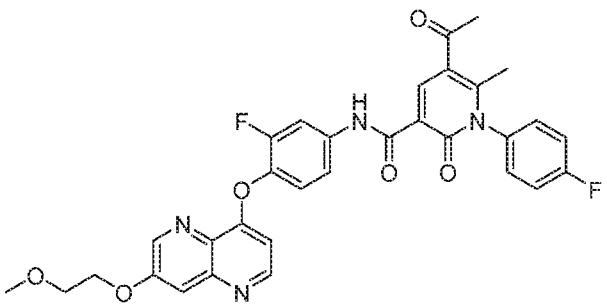
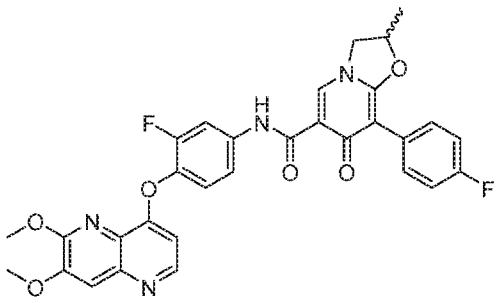
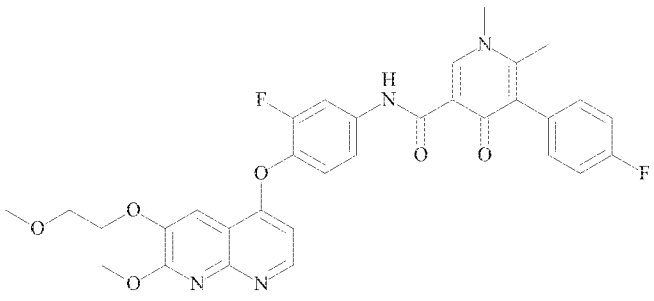
731		1-(2,2-difluoroethyl)-5-(4-fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide
732		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-5,6-dimethyl-3-oxopyridazine-4-carboxamide
733		2-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5,6-dimethyl-3-oxopyridazine-4-carboxamide
734		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-5,6-dimethyl-3-oxopyridazine-4-carboxamide
735		N-[4-[(6-chloro-7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide

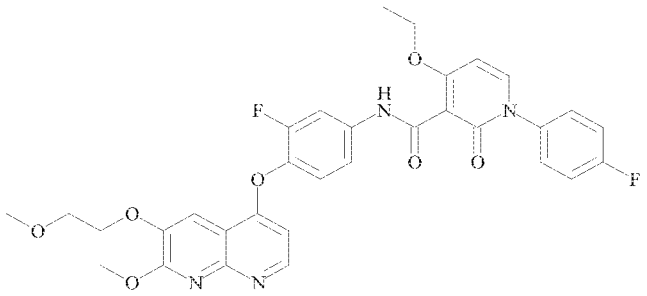
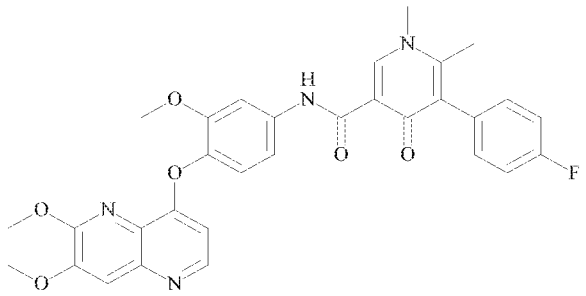
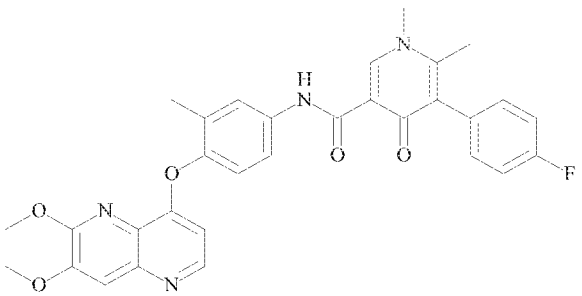
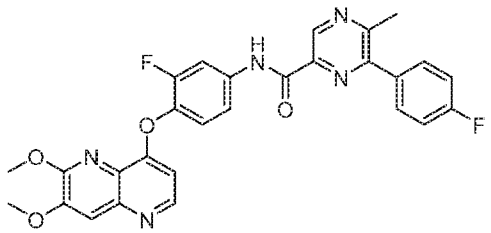
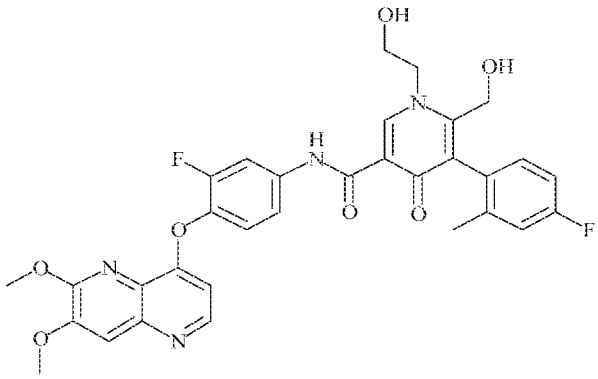
736		N-[4-[(6-chloro-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
737		N-[4-[(6-chloro-7-methoxy-1,5-naphthyridin-4-yl)oxy]-2,5-difluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
738		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-5-carboxamide
739		5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-4-methyl-2-oxopyridine-3-carboxamide
740		5-ethenyl-N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide

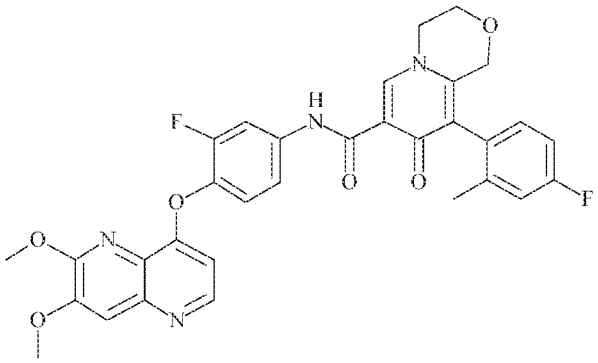
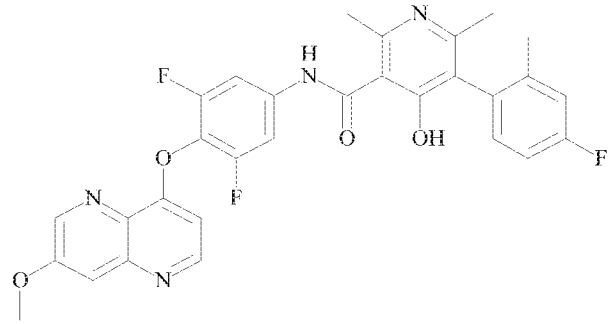
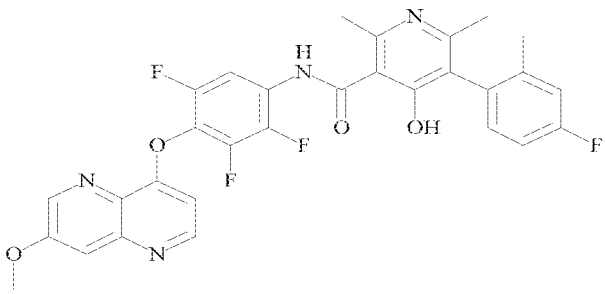
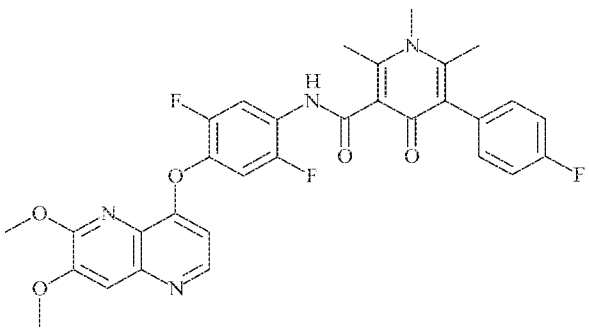
741		5-ethenyl-1-(4-fluorophenyl)-N-[4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-4,6-dimethyl-2-oxopyridine-3-carboxamide
742		5-ethenyl-N-[3-fluoro-4-[[7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide
743		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-5-fluoro-2-methoxyphenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
744		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-5-fluoro-2-methylphenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
745		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-2-fluoro-5-methoxyphenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide

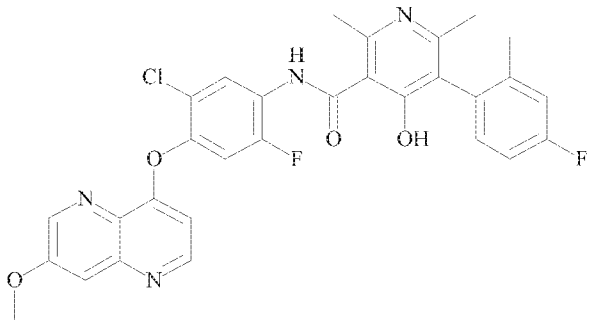
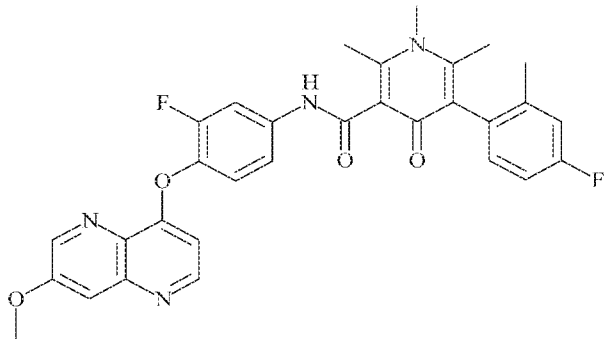
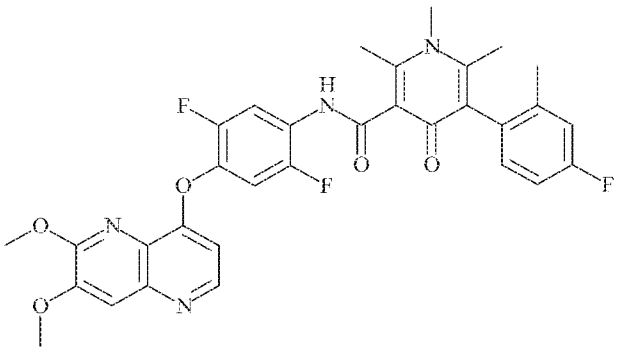
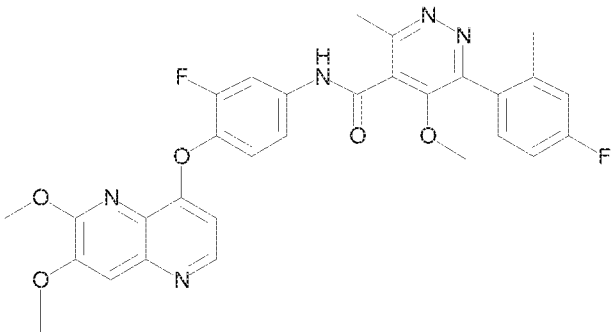
746		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-2-fluoro-5-methylphenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
747		5-bromo-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4,6-dimethyl-2-oxo-1-phenylpyridine-3-carboxamide
748		N-[3-fluoro-4-(1,5-naphthyridin-4-yloxy)phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide
749		N-[3-fluoro-4-[(6-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide
750		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluoro-2-methylphenyl)-2,3-dimethyl-5-oxopyridazine-4-carboxamide

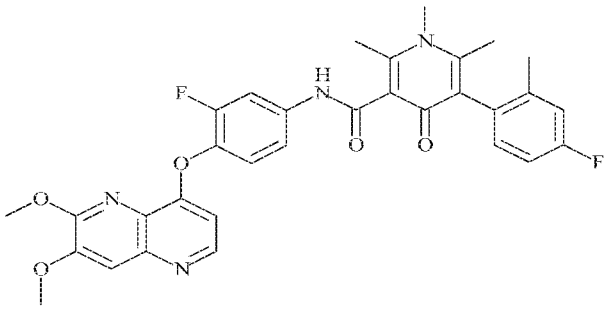
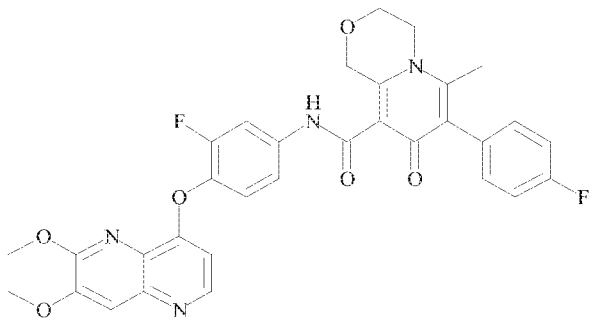
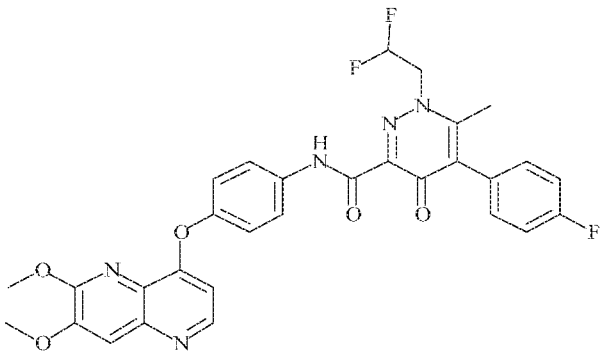
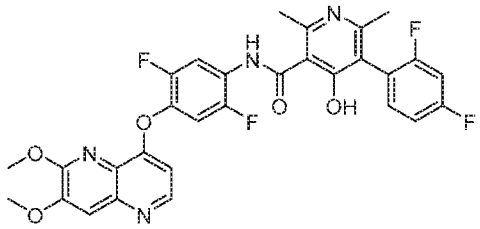
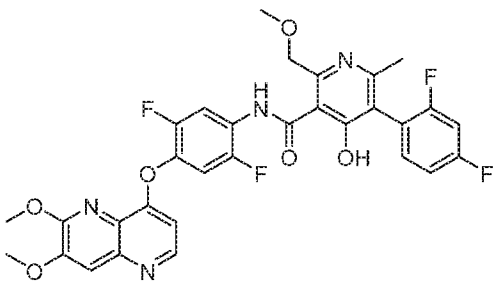
751		N-[2,5-difluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
752		4-[2,5-difluoro-4-[[5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carbonyl]amino]phenoxy]-N,6-dimethylquinoline-7-carboxamide
753		5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-2-oxopyridine-3-carboxamide
754		5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methoxy-2-oxopyridine-3-carboxamide
755		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4,5,6-trimethyl-2-oxo-1-phenylpyridine-3-carboxamide

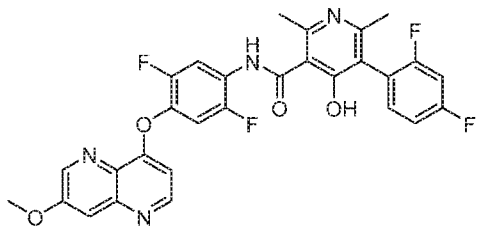
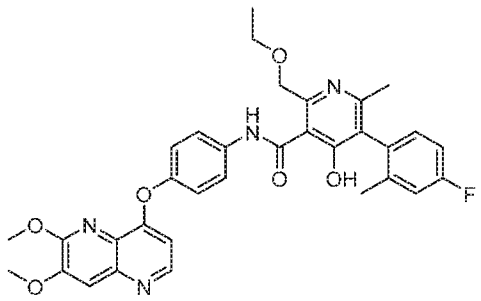
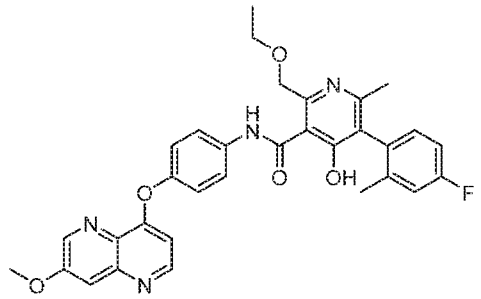
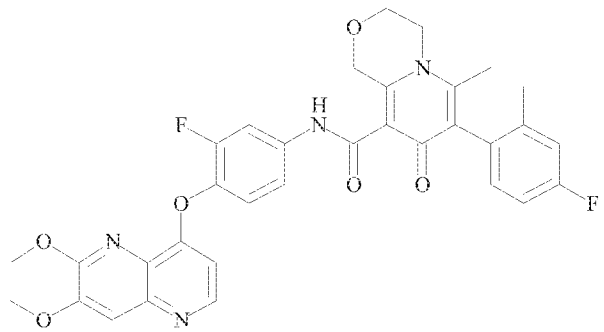
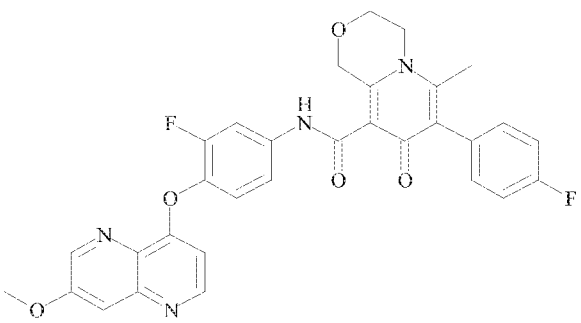
756		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(2-fluoroethyl)-5-(4-fluoro-2-methylphenyl)-2-methyl-4-oxopyridine-3-carboxamide
757		5-acetyl-1-(4-fluorophenyl)-N-[4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-6-methyl-2-oxopyridine-3-carboxamide
758		5-acetyl-N-[3-fluoro-4-[[7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide
759		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-8-(4-fluorophenyl)-2-methyl-7-oxo-2,3-dihydro-[1,3]oxazolo[3,2-a]pyridine-6-carboxamide
760		N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,8-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide

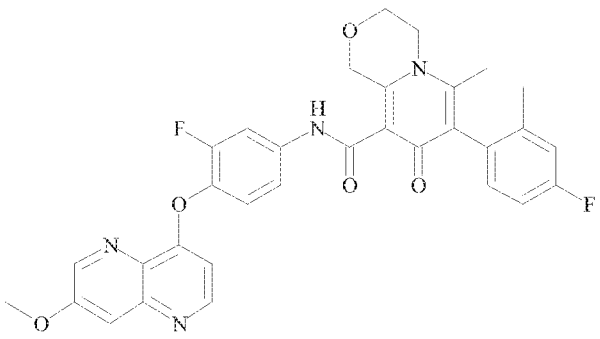
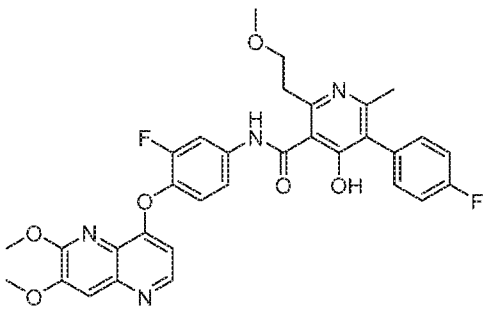
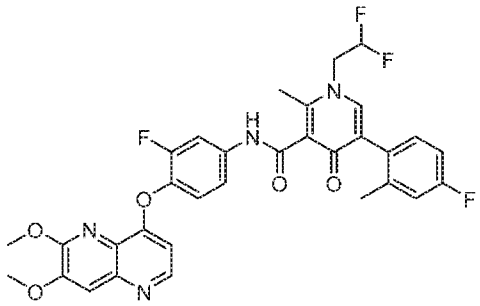
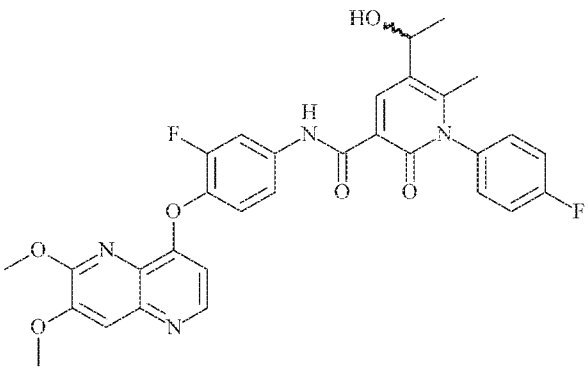
761		4-ethoxy-N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,8-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide
762		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-methoxyphenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
763		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-methylphenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
764		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-5-methylpyrazine-2-carboxamide
765		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1-(2-hydroxyethyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide

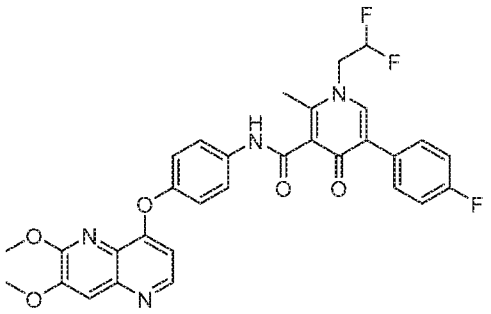
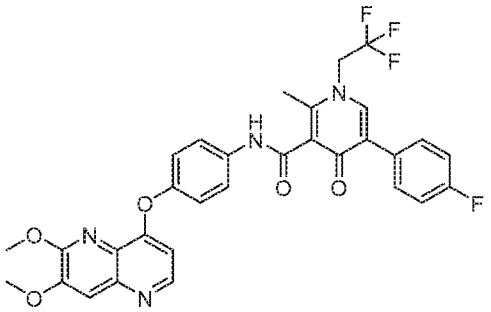
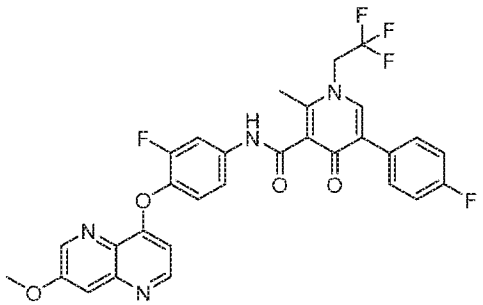
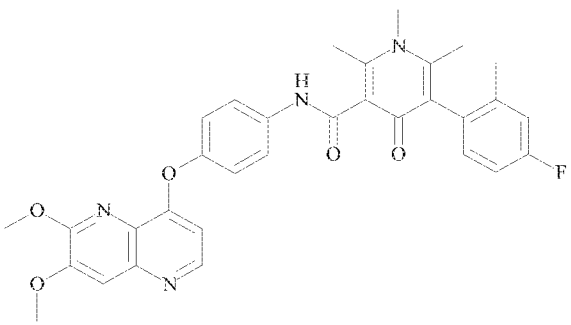
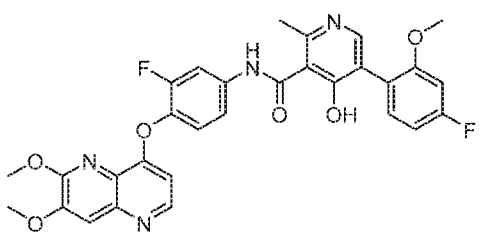
766		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-9-(4-fluoro-2-methylphenyl)-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-7-carboxamide
767		N-[3,5-difluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
768		5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethyl-N-[2,3,5-trifluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide
769		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-2,5-difluorophenyl]-5-(4-fluorophenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide

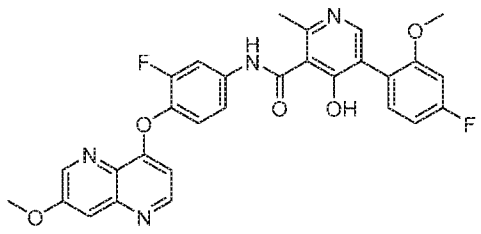
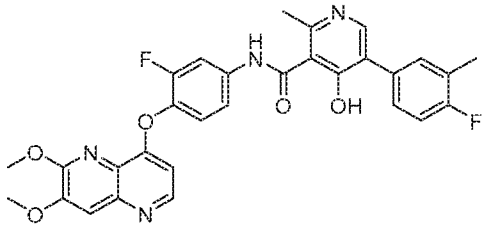
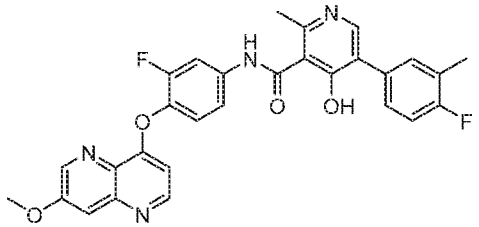
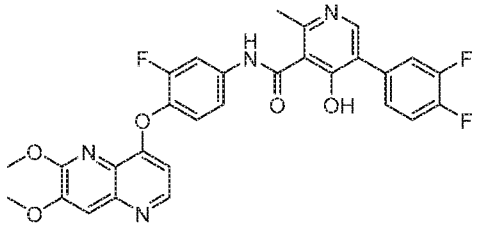
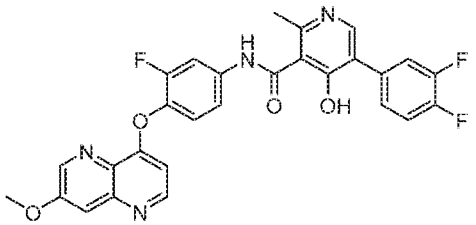
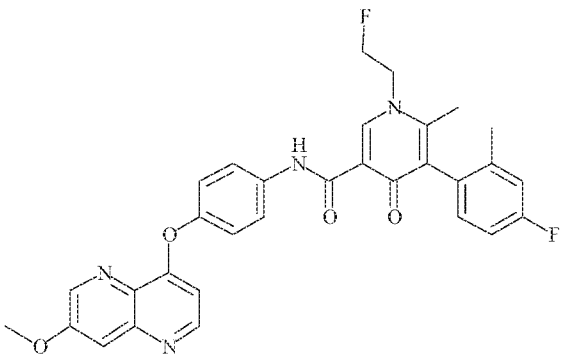
770		N-[5-chloro-2-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
771		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide
772		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-2,5-difluorophenyl]-5-(4-fluoro-2-methylphenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide
773		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluoro-2-methylphenyl)-5-methoxy-3-methylpyridazine-4-carboxamide

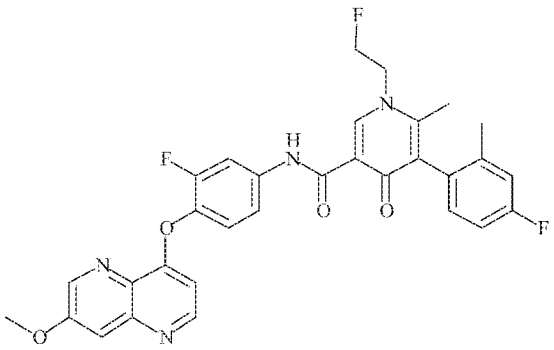
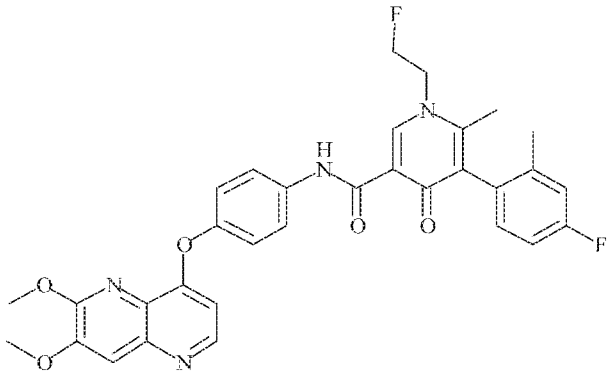
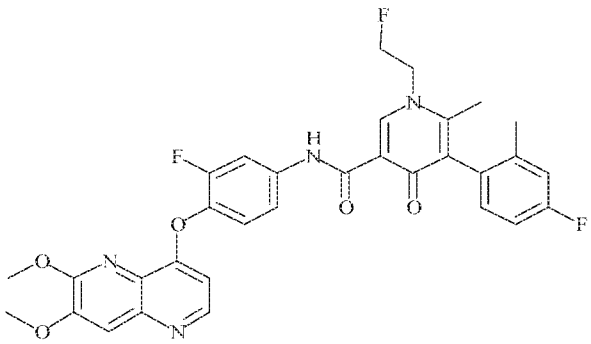
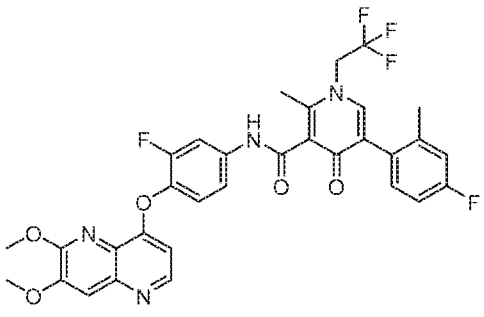
774		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide
775		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-7-(4-fluorophenyl)-6-methyl-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-9-carboxamide
776		1-(2,2-difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridazine-3-carboxamide
777		5-(2,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-2,5-difluorophenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
778		5-(2,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-2,5-difluorophenyl]-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide

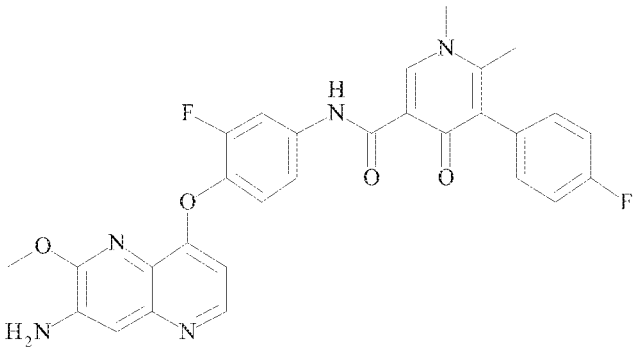
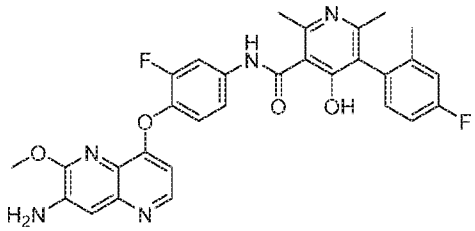
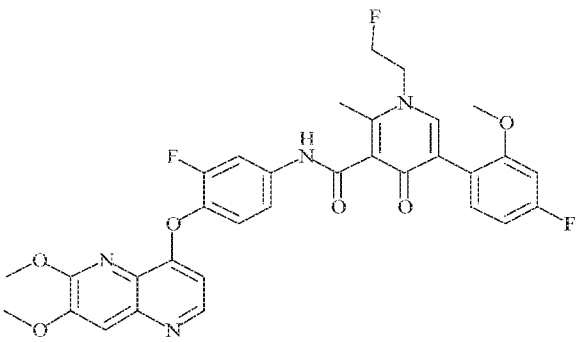
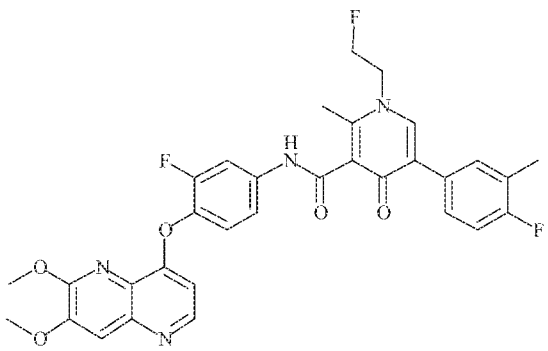
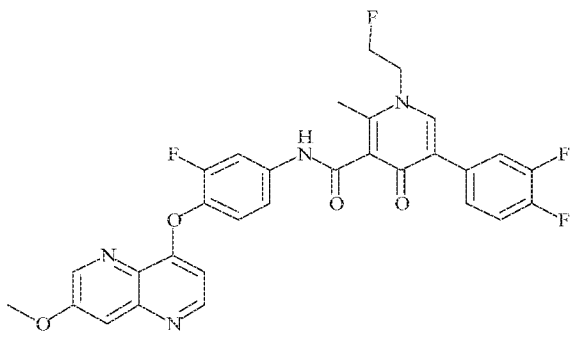
779		N-[2,5-difluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(2,4-difluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
780		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(ethoxymethyl)-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide
781		2-(ethoxymethyl)-5-(4-fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide
782		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-7-(4-fluoro-2-methylphenyl)-6-methyl-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-9-carboxamide
783		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-7-(4-fluorophenyl)-6-methyl-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-9-carboxamide

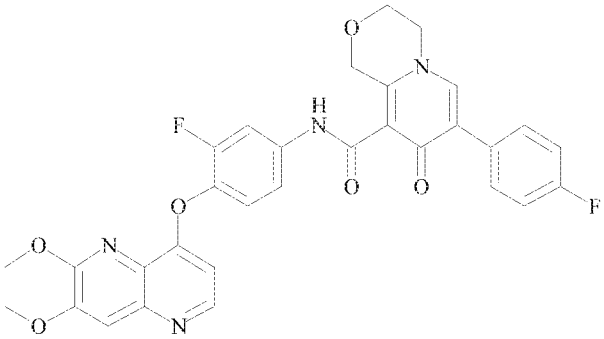
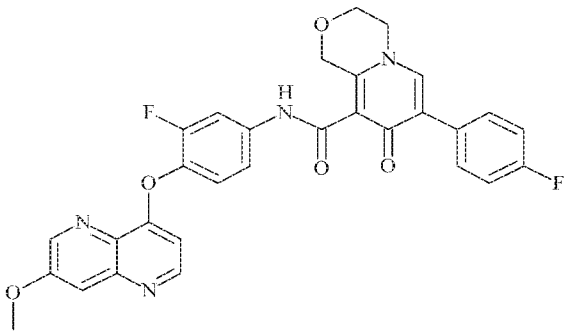
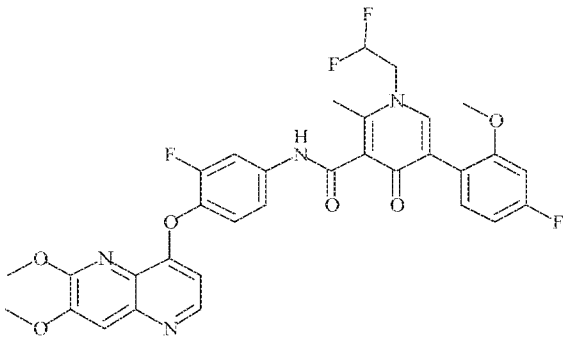
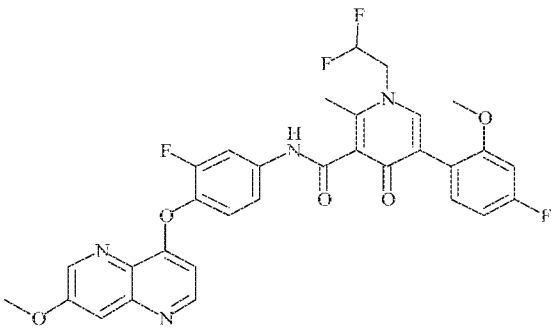
784		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-7-(4-fluoro-2-methylphenyl)-6-methyl-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-9-carboxamide
785		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(2-methoxyethyl)-6-methylpyridine-3-carboxamide
786		1-(2,2-difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-2-methyl-4-oxopyridine-3-carboxamide
787		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-5-(1-hydroxyethyl)-6-methyl-2-oxopyridine-3-carboxamide

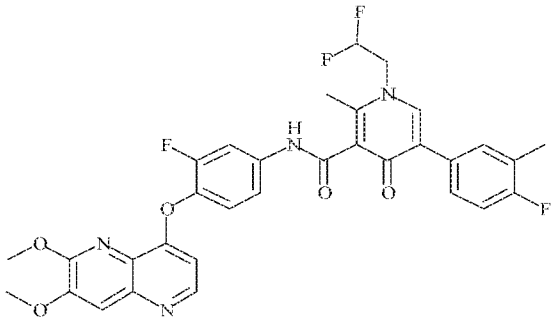
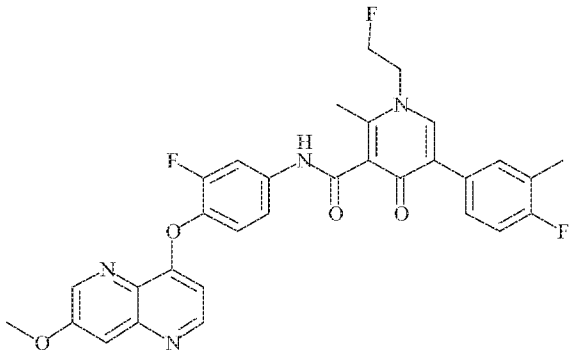
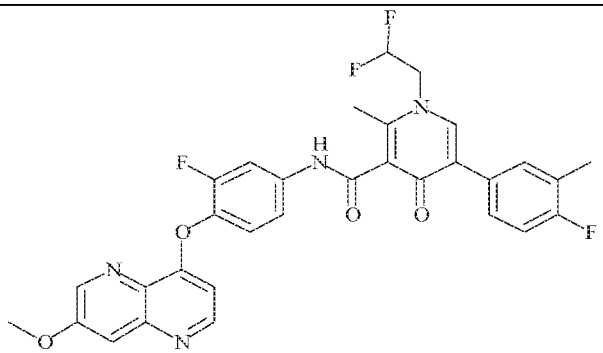
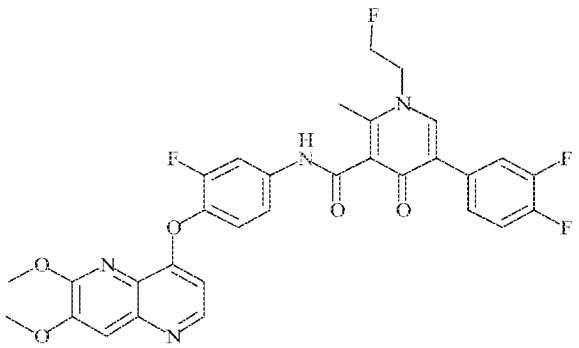
788		1-(2,2-difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide
789		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-2-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide
790		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-2-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide
791		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide
792		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methoxyphenyl)-4-hydroxy-2-methylpyridine-3-carboxamide

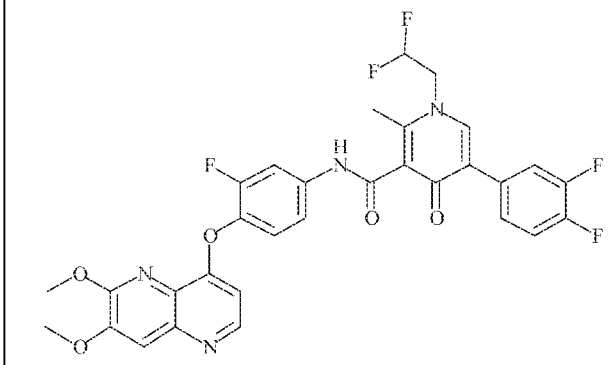
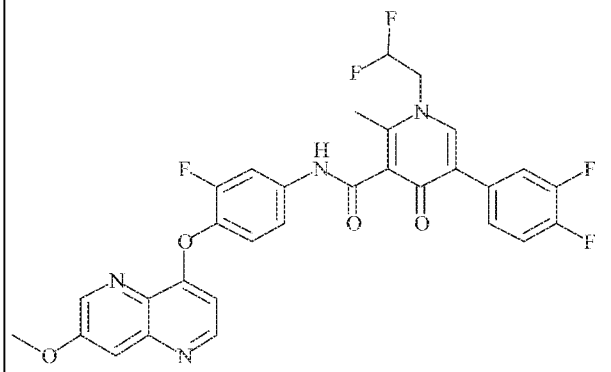
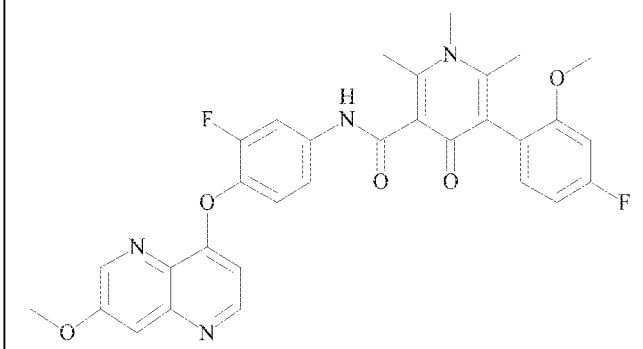
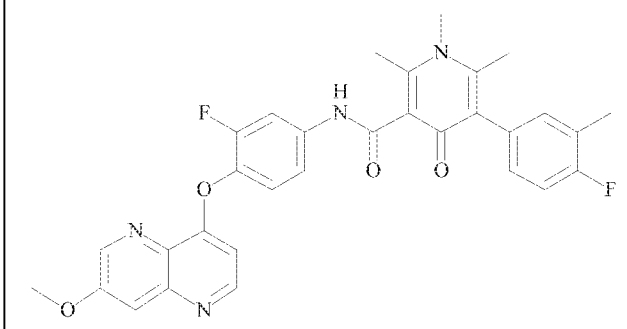
793		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methoxyphenyl)-4-hydroxy-2-methylpyridine-3-carboxamide
794		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-3-methylphenyl)-4-hydroxy-2-methylpyridine-3-carboxamide
795		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-3-methylphenyl)-4-hydroxy-2-methylpyridine-3-carboxamide
796		5-(3,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2-methylpyridine-3-carboxamide
797		5-(3,4-difluorophenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2-methylpyridine-3-carboxamide
798		1-(2-fluoroethyl)-5-(4-fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide

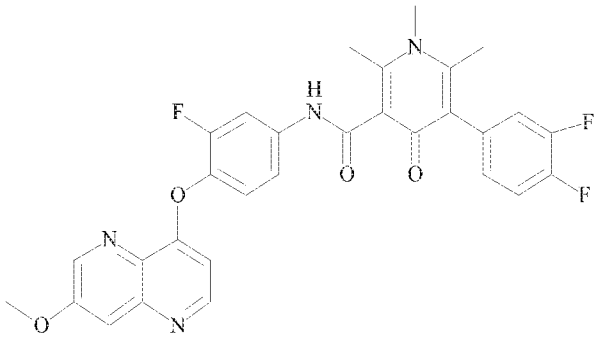
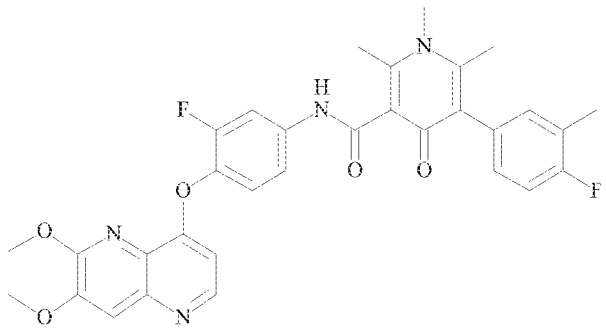
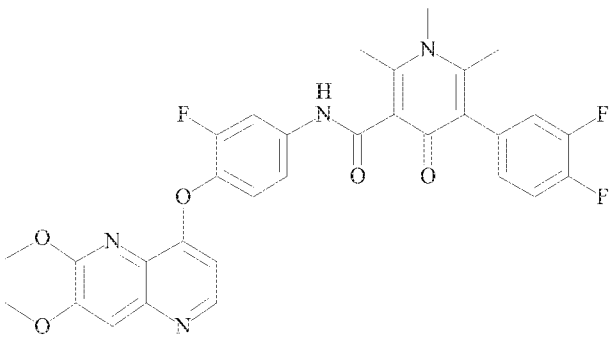
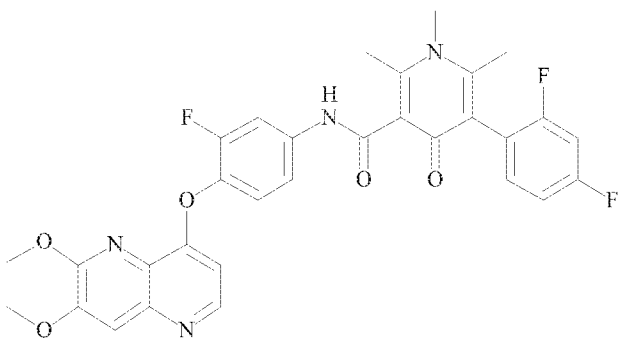
799		1-(2-fluoroethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide
800		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(2-fluoroethyl)-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide
801		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(2-fluoroethyl)-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide
802		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-2-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide

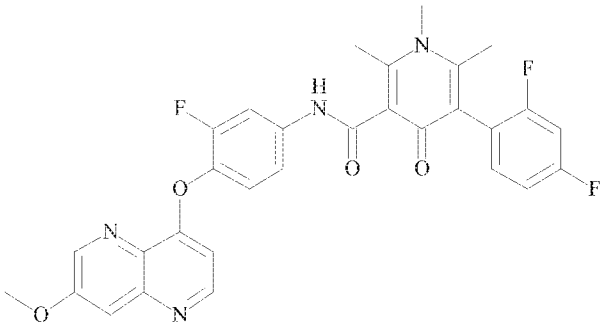
803		N-[4-[(7-amino-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide
804		N-[4-[(7-amino-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide
805		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(2-fluoroethyl)-5-(4-fluoro-2-methoxyphenyl)-2-methyl-4-oxopyridine-3-carboxamide
806		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(2-fluoroethyl)-5-(4-fluoro-3-methylphenyl)-2-methyl-4-oxopyridine-3-carboxamide
807		5-(3,4-difluorophenyl)-1-(2-fluoroethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methyl-4-oxopyridine-3-carboxamide

808		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-7-(4-fluorophenyl)-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-9-carboxamide
809		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-7-(4-fluorophenyl)-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-9-carboxamide
810		1-(2,2-difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methoxyphenyl)-2-methyl-4-oxopyridine-3-carboxamide
811		1-(2,2-difluoroethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methoxyphenyl)-2-methyl-4-oxopyridine-3-carboxamide

812		1-(2,2-difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-3-methylphenyl)-2-methyl-4-oxopyridine-3-carboxamide
813		1-(2-fluoroethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-3-methylphenyl)-2-methyl-4-oxopyridine-3-carboxamide
814		1-(2,2-difluoroethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-3-methylphenyl)-2-methyl-4-oxopyridine-3-carboxamide
815		5-(3,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(2-fluoroethyl)-2-methyl-4-oxopyridine-3-carboxamide

816		1-(2,2-difluoroethyl)-5-(3,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-methyl-4-oxopyridine-3-carboxamide
817		1-(2,2-difluoroethyl)-5-(3,4-difluorophenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methyl-4-oxopyridine-3-carboxamide
818		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methoxyphenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide
819		N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-3-methylphenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide

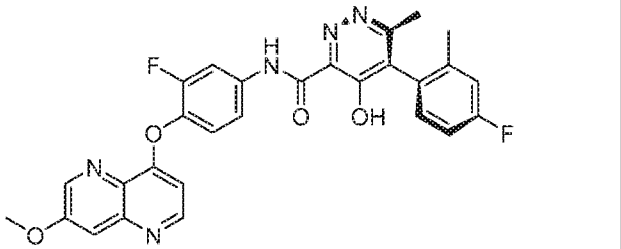
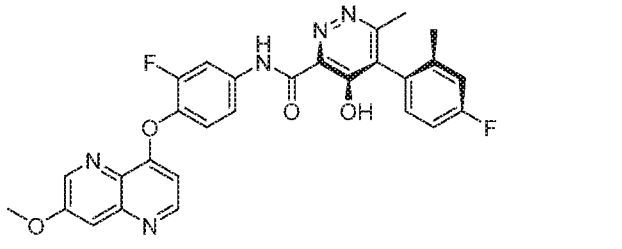
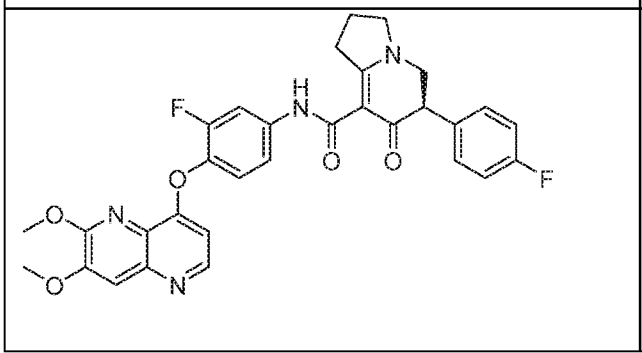
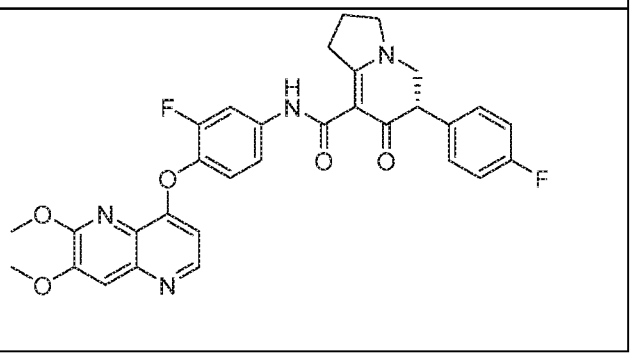
820		5-(3,4-difluorophenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,2,6-trimethyl-4-oxopyridine-3-carboxamide
821		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-3-methylphenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide
822		5-(3,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1,2,6-trimethyl-4-oxopyridine-3-carboxamide
823		5-(2,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1,2,6-trimethyl-4-oxopyridine-3-carboxamide

824		5-(2,4-difluorophenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,2,6-trimethyl-4-oxopyridine-3-carboxamide

[0148] Some embodiments provide for a compound of Table 1 or a pharmaceutically acceptable salt, a stereoisomer, or a mixture of stereoisomers thereof.

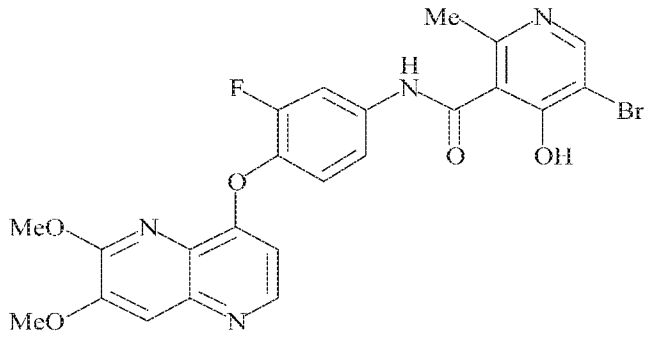
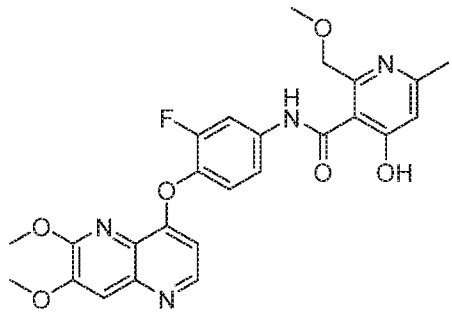
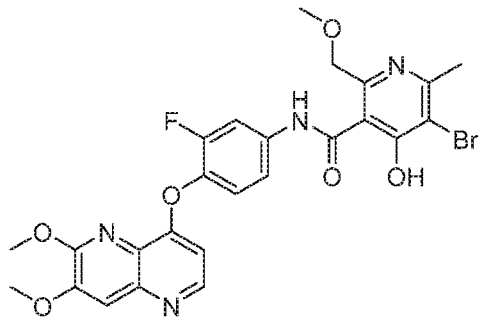
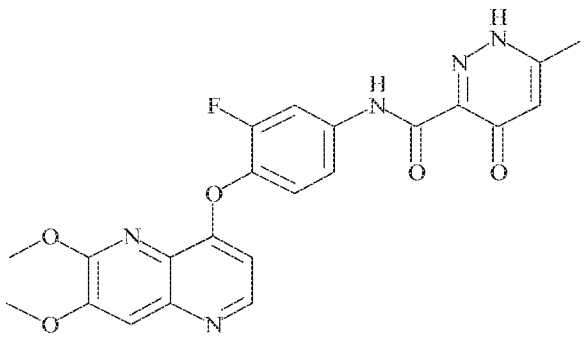
[0149] In some embodiments, provided is a compound, or a pharmaceutically acceptable salt or a stereoisomer thereof, of Table 2:

Table 2

[0150] In some embodiments, provided is a compound, or a pharmaceutically acceptable salt thereof, of Table 3:

Table 3

Cpd #	Structure	IUPAC Name
490		5-bromo-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2-methylpyridine-3-carboxamide
492		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
535		5-bromo-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide
536		N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-1H-pyridazine-3-carboxamide

Treatment Methods and Uses

[0151] "Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: a)

inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more clinical symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (e.g., metastasis) of the disease or condition); and/or c) relieving the disease, that is, causing the regression of clinical symptoms (e.g., ameliorating the disease state, providing partial or total remission of the disease or condition, enhancing effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival.

[0152] "Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0153] "Subject" refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal. In one embodiment, the subject is a human.

[0154] The term "therapeutically effective amount" or "effective amount" of a compound described herein or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, prodrug, or deuterated analog thereof means an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration of symptoms or slowing of disease progression. For example, a therapeutically effective amount may be an amount sufficient to decrease a symptom of a sickle cell disease. The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one or ordinary skill in the art.

[0155] The methods described herein may be applied to cell populations in vivo or ex vivo. "In vivo" means within a living individual, as within an animal or human. In this context, the methods described herein may be used therapeutically in an individual. "Ex vivo" means outside of a living individual. Examples of ex vivo cell populations include in vitro cell cultures and biological samples including fluid or tissue samples obtained from individuals. Such samples may be obtained by methods well known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine, and saliva. In this context, the compounds and compositions described herein may be used for a variety of purposes, including therapeutic and experimental purposes. For example, the compounds and compositions described herein may be used *ex vivo* to determine the optimal schedule and/or dosing of administration of a compound of the present disclosure for a given indication, cell type, individual, and other parameters. Information gleaned from such use may be used for experimental purposes or in the clinic to set protocols for *in vivo* treatment. Other *ex vivo* uses for which the compounds and compositions

described herein may be suited are described below or will become apparent to those skilled in the art. The selected compounds may be further characterized to examine the safety or tolerance dosage in human or non-human subjects. Such properties may be examined using commonly known methods to those skilled in the art.

[0156] Some embodiments provide for a method of modulating in vivo activity of a protein kinase in a subject, the method comprising: administering to the subject a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition as described herein.

[0157] Some embodiments provide for methods of modulating in vivo activity of a protein kinase in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, or a pharmaceutical composition as described herein.

[0158] Some embodiments provide for a method of treating a disease, disorder, or syndrome in a subject, the method comprising: administering to the subject in need thereof a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition as described herein, wherein the disease, disorder, or syndrome is mediated at least in part by modulating in vivo activity of a protein kinase.

[0159] Some embodiments provide for methods of treating a disease, disorder, or syndrome in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, or a pharmaceutical composition as described herein, wherein the disease, disorder, or syndrome is mediated at least in part by modulating in vivo activity of a protein kinase.

[0160] In some embodiments, the protein kinase is AXL, KDR, Mer, or Met. In some embodiments, the disease is cancer.

[0161] Some embodiments provide for methods of treating a disease, disorder, or syndrome in a subject, the method comprising: administering to the subject in need thereof a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition as described herein, in combination with a therapeutic agent or therapy.

[0162] Some embodiments provide for methods of treating a disease, disorder, or syndrome in a subject, the method comprising: administering to the subject in need thereof a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, or a pharmaceutical composition as described herein, in combination with a therapeutic agent or therapy.

[0163] In some embodiments, the therapeutic agent is an immunotherapeutic agent or a cancer vaccine. In some embodiments, the immunotherapeutic agent is an anti-PD-1 antibody or anti-PD-L1 antibody.

[0164] Provided herein are methods for treating cancer.

[0165] "Cancer" includes tumor types such as tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas as well as other cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinorna, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia, renal cell carcinoma), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma, small cell carcinoma of the prostate), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis defornians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma; as well as cancers of the thyroid including medullary thyroid cancer.

Thus, the term "cancerous cell," as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0166] In one embodiment, the cancer is selected from ovarian cancer, prostate cancer, lung cancer, medullary thyroid cancer, liver cancer, gastrointestinal cancer, pancreatic cancer, bone cancer, hematologic cancer, skin cancer, kidney cancer, breast cancer, colon cancer, and fallopian tube cancer.

[0167] In some embodiments, the cancer is clear cell carcinoma, clear cell renal cell carcinoma, non-clear cell carcinoma, non-clear cell renal cell carcinoma, urothelial carcinoma, salivary gland cancer, penile squamous cell carcinoma, neuroendocrine tumors, adrenocortical carcinoma, or merkel cell carcinoma.

[0168] In another embodiment, the disease or disorder is ovarian cancer.

[0169] In another embodiment, the disease or disorder is prostate cancer.

[0170] In another embodiment, the disease or disorder is lung cancer.

[0171] In another embodiment, the disease or disorder is medullary thyroid cancer.

[0172] In another embodiment, the disease or disorder is liver cancer.

[0173] In another embodiment, the disease or disorder is gastrointestinal cancer.

[0174] In another embodiment, the disease or disorder is pancreatic cancer.

[0175] In another embodiment, the disease or disorder is bone cancer.

[0176] In another embodiment, the disease or disorder is hematologic cancer.

[0177] In another embodiment, the disease or disorder is skin cancer.

[0178] In another embodiment, the disease or disorder is kidney cancer.

[0179] In another embodiment, the disease or disorder is breast cancer.

[0180] In another embodiment, the disease or disorder is colon cancer. In another embodiment, the disease or disorder is fallopian cancer. In another embodiment, the disease or disorder is liver cancer, wherein the liver cancer is hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, or hemagioma.

[0181] In another embodiment, the disease or disorder is gastrointestinal cancer, wherein the gastrointestinal cancer is cancer of the esophagus which is squamous cell carcinoma, adenocarcinoma, or leiomyosarcoma; cancer of the stomach which is carcinoma, or lymphoma; cancer of the pancreas, which is ductal adenocarcinoma, insulinoma, gucagonoma, gastrinoma, carcinoid tumors, or vipoma; cancer of the small bowel, which is adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemagioma, lipoma, or cancer of the large bowel, which is adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, or leiomyoma.

[0182] In another embodiment, the disease or disorder is cancer of the pancreas, wherein the cancer of the pancreas is ductal adenocarcinoma, insulinoma, gucagonoma, gastrinoma, carcinoid tumors, or vipoma.

[0183] In another embodiment, the disease or disorder is bone cancer, wherein the bone cancer is osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma,

malignant reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteocartiliginous exostoses, chondroblastoma, chondromyxofibroma, or osteoid osteoma.

[0184] In another embodiment, the disease or disorder is hematologic cancer, wherein the hematologic cancer is myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, or myelodysplastic syndrome.

[0185] In another embodiment, the disease or disorder is skin cancer, wherein the skin cancer is malignant melanoma, basal cell carcinoma, squamous cell carcinoma, or Karposi's sarcoma.

[0186] In another embodiment, the disease or disorder is a renal tumor or renal cell carcinoma.

[0187] In another embodiment, the disease or disorder is breast cancer.

[0188] In another embodiment, the disease or disorder is a colon cancer tumor.

[0189] In another embodiment, the disease or disorder is fallopian tube carcinoma.

Combination Therapies

[0190] A compound as disclosed herein can be administered as a single therapy or in combination ("co-administered") with one or more additional therapies for the treatment of a disease or disorder, for instance a disease or disorder associated with hyper-proliferation such as cancer. Therapies that may be used in combination with a compound disclosed herein include: (i) surgery; (ii) radiotherapy (for example, gamma radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes); (iii) endocrine therapy; (iv) adjuvant therapy, immunotherapy, CAR T- cell therapy; and (v) other chemotherapeutic agents.

[0191] The term "co-administered" ("co-administering") refers to either simultaneous administration, or any manner of separate sequential administration, of a compound as described herein, and a further active pharmaceutical ingredient or ingredients, including cytotoxic agents and radiation treatment. If the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

[0192] Typically, any agent that has activity against a disease or condition being treated may be co-administered. Examples of such agents for cancer treatment can be found, for instance, at https://www.cancer.gov/about-cancer/treatment/drugs and in publicly available sources such as Cancer Principles and Practice of Oncology by V. T. Devita and S. Hellman (editors), 1 Ith edition (2018), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the disease involved.

[0193] In one embodiment, the treatment method includes the co-administration of a compound as disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, and at least one immunotherapy. Immunotherapy (also called biological response modifier therapy, biologic therapy, biotherapy, immune therapy, or biological therapy) is treatment that uses parts of the immune system to fight disease. Immunotherapy can help the immune system recognize cancer cells, or

enhance a response against cancer cells. Immunotherapies include active and passive immunotherapies. Active immunotherapies stimulate the body's own immune system while passive immunotherapies generally use immune system components created outside of the body.

[0194] Examples of active immunotherapies include, but are not limited to vaccines including cancer vaccines, tumor cell vaccines (autologous or allogeneic), dendritic cell vaccines, antigen vaccines, anti-idiotype vaccines, DNA vaccines, viral vaccines, or Tumor- Infiltrating Lymphocyte (TIL) Vaccine with Interleukin-2 (IL-2) or Lymphokine- Activated Killer (LAK) Cell Therapy.

[0195] Examples of passive immunotherapies include but are not limited to monoclonal antibodies and targeted therapies containing toxins. Monoclonal antibodies include naked antibodies and conjugated monoclonal antibodies (also called tagged, labeled, or loaded antibodies). Naked monoclonal antibodies do not have a drug or radioactive material attached whereas conjugated monoclonal antibodies are joined to, for example, a chemotherapy drug (chemolabeled), a radioactive particle (radiolabeled), or a toxin (immunotoxin). Examples of these naked monoclonal antibody drugs include, but are not limited to rituximab (Rituxan), an antibody against the CD20 antigen used to treat, for example, B cell non-Hodgkin lymphoma; trastuzumab (Herceptin), an antibody against the HER2 protein used to treat, for example, advanced breast cancer; alemtuzumab (Campath), an antibody against the CD52 antigen used to treat, for example, B cell chronic lymphocytic leukemia (B-CLL); cetuximab (Erbitux), an antibody against the EGFR protein used, for example, in combination with irinotecan to treat, for example, advanced colorectal cancer and head and neck cancers; and bevacizumab (Avastin) which is an antiangiogenesis therapy that works against the VEGF protein and is used, for example, in combination with chemotherapy to treat, for example, metastatic colorectal cancer. Examples of the conjugated monoclonal antibodies include, but are not limited to Radiolabeled antibody ibritumomab tiuxetan (Zevalin) which delivers radioactivity directly to cancerous B lymphocytes and is used to treat, for example, B cell non-Hodgkin lymphoma; radiolabeled antibody tositumomab (Bexxar) which is used to treat, for example, certain types of non-Hodgkin lymphoma; and immunotoxin gemtuzumab ozogamicin (Mylotarg) which contains calicheamicin and is used to treat, for example, acute myelogenous leukemia (AML). BL22 is a conjugated monoclonal antibody for treating, for example, hairy cell leukemia, immunotoxins for treating, for example, leukemias, lymphomas, and brain tumors, and radiolabeled antibodies such as OncoScint for example, for colorectal and ovarian cancers and ProstaScint for example, for prostate cancers.

[0196] Further examples of therapeutic antibodies that can be used include, but are not limited to, HERCEPTIN® (trastuzumab) (Genentech, Calif.) which is a humanized anti- HER2 monoclonal antibody for the treatment of patients with metastatic breast cancer; REOPRO® (abciximab) (Centocor) which is an anti-glycoprotein Ilb/IIIa receptor on the platelets for the prevention of clot formation; ZENAPAX™ (daclizumab) (Roche Pharmaceuticals, Switzerland) which is an immunosuppressive, humanized anti-CD25 monoclonal antibody for the prevention of acute renal allograft rejection; PANOREX™ which is a murine anti-l7-IA cell surface antigen IgG2a antibody (Glaxo

Wellcome/Centocor); BEC2 which is a murine anti-idiotype (GD3epitope) IgG antibody (ImClone System); IMC-C225 which is a chimeric anti-EGFR IgG antibody (ImClone System); VITAXIN™ which is a humanized anti-alpha V beta 3 integrin antibody (Applied Molecular Evolution/Medlmmune); Campath 1H/LDP-03 which is a humanized anti CD52 IgGl antibody (Leukosite); Smart M195 which is a humanized anti-CD33 IgG antibody (Protein Design Lab/Kanebo); RITETXAN™ which is a chimeric anti-CD20 IgGl antibody (IDEC Pharm/Genentech, Roche/Zettyaku); LYMPHOCIDE™ which is a humanized anti- CD22 IgG antibody (Immunomedics); LYMPHOCIDE™ Y-90 (Immunomedics); Lymphoscan (Tc-99m-labeled; radioimaging; Immunomedics); Nuvion (against CD3; Protein Design Labs); CM3 is a humanized anti-ICAM3 antibody (ICOS Pharm); IDEC-l 14 is a primatized anti-CD80 antibody (IDEC Pharm/Mitsubishi); ZEVALIN™ is a radiolabeled murine anti-CD20 antibody (IDEC/Schering AG); IDEC-131 is a humanized anti-CD40L antibody (IDEC/Eisai); IDEC-151 is a primatized anti-CD4 antibody (IDEC); IDEC-152 is a primatized anti-CD23 antibody (IDEC/Seikagaku); SMART anti-CD3 is a humanized anti- CD3 IgG (Protein Design Lab); 5G1.1 is a humanized anti-complement factor 5 (C5) antibody (Alexion Pharm); D2E7 is a humanized anti-TNF-alpha antibody (CAT/BASF); CDP870 is a humanized anti-TNF-alpha. Fab fragment (Celltech); IDEC-l 51 is a primatized anti-CD4 IgGl antibody (IDEC Pharm/SmithKline Beecham); MDX-CD4 is a human anti-CD4 IgG antibody (Medarex/Eisai/Genmab); CD20-sreptdavidin (+biotin-yttrium 90; NeoRx); CDP571 is a humanized anti-TNF-alpha. IgG4 antibody (Celltech); LDP-02 is a humanized anti-alpha4 beta7 antibody (LeukoSite/Genentech); OrthoClone OKT4A is a humanized anti-CD4 IgG antibody (Ortho Biotech); ANTOVA (ruplizumab) is a humanized anti-CD40L IgG antibody (Biogen); ANTEGREN™ is a humanized anti-VLA-4 IgG antibody (Elan); and CAT-152 is a human anti-TGF-beta$_2$ antibody (Cambridge Ab Tech).

[0197] Immunotherapies that can be used in combination with a compound as disclosed herein include adjuvant immunotherapies. Examples include cytokines, such as granulocyte- macrophage colony-stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF), macrophage inflammatory protein (MIP)-l -alpha, interleukins (including IL-l, IL-2, IL-4, IL-6, IL-7, IL-12, IL-15, IL-18, IL-21, and IL-27), tumor necrosis factors (including TNF-alpha), and interferons (including IFN-alpha, IFN-beta, and IFN-gamma); aluminum hydroxide (alum); Bacille Calmette-Guerin (BCG); Keyhole limpet hemocyanin (KLH); Incomplete Freund's adjuvant (IF A); QS-21; DETOX; Levamisole; and Dinitrophenyl (DNP), and combinations thereof, such as, for example, combinations of, interleukins, for example, IL-2 with other cytokines, such as IFN-alpha.

[0198] In various embodiments, an immunological therapy or an immunological therapeutic agent can include, one or more of the following: an adoptive cell transfer, an angiogenesis inhibitor, Bacillus Calmette-Guerin therapy, biochemotherapy, a cancer vaccine, a chimeric antigen receptor (CAR) T-cell therapy, a cytokine therapy, gene therapy, an immune checkpoint modulator, an immunoconjugate, a radioconjugate, an oncolytic virus therapy, or a targeted drug therapy. The function or at least one of the

functions of the immunological therapy or immunological therapeutic agent, collectively referred to herein as an "immunotherapeutic agent."

[0199] In various embodiments described herein, an exemplary immunotherapeutic agent is an immune cell (e.g. T-cell, dendritic cell, a natural killer cell and the like) modulator chosen from an agonist or an activator of a costimulatory molecule, wherein the modulator is a monoclonal antibody, a bispecific antibody comprising one or more immune checkpoint antigen binding moieties, a trispecific antibody, or an immune cell-engaging multivalent antibody/fusion protein/construct known in the art). In some embodiments, the immunotherapeutic agent can be an antibody that modulates a costimulatory molecule, bind to an antigen on the surface of an immune cell, or a cancer cell. In each of these different embodiments, the antibody modulator can be a monoclonal antibody, a polyclonal antibody, a bispecific antibody, a trispecific or multispecific format antibody, a fusion protein, or a fragment thereof, for example, a Diabody, a Single-chain (sc)- diabody (scFv)2, a Miniantibody, a Minibody, a Bamase-barstar, a scFv-Fc, a sc(Fab)2, a Trimeric antibody construct, a Triabody antibody construct, a Trimerbody antibody construct, a Tribody antibody construct, a Collabody antibody construct, a (scFv-TNFa)3, or a F(ab)3/DNL antibody construct.

[0200] In certain embodiments of each of the aforementioned aspects, as well as other aspects and embodiments described elsewhere herein, the immunotherapeutic agent is an agent that modulates immune responses, for example, a checkpoint inhibitor or a checkpoint agonist. In some embodiments, the immunotherapeutic agent is an agent that enhances anti-tumor immune responses. In some embodiments, the immunotherapeutic agent is an agent that increases cell-mediated immunity. In some embodiments, the immunotherapeutic agent is an agent that increases T-cell activity. In some embodiments, the immunotherapeutic agent is an agent that increases cytolytic T-cell (CTL) activity. In some embodiments, the immunotherapeutic agent is an antibody modulator that targets PD-1, PD-L1, PD-L2, CEACAM (e g., CEACAM-l, -3 and/or -5), CTLA-4, TIM-3, LAG-3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, TGF beta, 0X40, 41BB, LIGHT, CD40, GITR, TGF-beta, TIM-3, SIRP-alpha, VSIG8, BTLA, SIGLEC7, SIGLEC9, ICOS, B7H3, B7H4, FAS, and/or BTNL2 among others known in the art. In some embodiments, the immunotherapeutic agent is an agent that increases natural killer (NK) cell activity. In some embodiments, the immunotherapeutic agent is an agent that inhibits suppression of an immune response. In some embodiments, the immunotherapeutic agent is an agent that inhibits suppressor cells or suppressor cell activity. In some embodiments, the immunotherapeutic agent is an agent or therapy that inhibits Treg activity. In some embodiments, the immunotherapeutic agent is an agent that inhibits the activity of inhibitory immune checkpoint receptors.

[0201] In some embodiments, the immunotherapeutic agent includes a T cell modulator chosen from an agonist or an activator of a costimulatory molecule. In one embodiment, the agonist of the costimulatory molecule is chosen from an agonist (e.g., an agonistic antibody or antigen-binding fragment thereof, or a soluble fusion) of GITR, 0X40, ICOS, SLAM (e.g., SLAMF7), HVEM, LIGHT, CD2, CD27, CD28, CDS, ICAM-l, LFA-l (CD1 la/CDl8), ICOS (CD278), 4-1BB (CD137), CD30,

CD40, BAFFR, CD7, NKG2C, NKp80, CD160, B7-H3, or CD83 ligand. In other embodiments, the effector cell combination includes a bispecific T cell engager (e.g., a bispecific antibody molecule that binds to CD3 and a tumor antigen (e.g., EGFR, PSCA, PSMA, EpCAM, HER2 among others).

[0202] In some embodiments, the immunotherapeutic agent is a modulator of PD-1 activity, a modulator of PD-L 1 activity, a modulator of PD-L2 activity, a modulator of CTLA-4 activity, a modulator of CD28 activity, a modulator of CD80 activity, a modulator of CD86 activity, a modulator of 4-1BB activity, an modulator of 0X40 activity, a modulator of KIR activity, a modulator of Tim-3 activity, a modulator of LAG3 activity, a modulator of CD27 activity, a modulator of CD40 activity, a modulator of GITR activity, a modulator of TIGIT activity, a modulator of CD20 activity, a modulator of CD96 activity, a modulator of IDOl activity, a modulator of SIRP-alpha activity, a modulator of TIGIT activity, a modulator of VSIG8 activity, a modulator of BTLA activity, a modulator of SIGLEC7 activity, a modulator of SIGLEC9 activity, a modulator of ICOS activity, a modulator of B7H3 activity, a modulator of B7H4 activity, a modulator of FAS activity, a modulator of BTNL2 activity, a cytokine, a chemokine, an interferon, an interleukin, a lymphokine, a member of the tumor necrosis factor (TNF) family, or an immunostimulatory oligonucleotide. In some embodiments, the immunotherapeutic agent is an immune checkpoint modulator (e.g., an immune checkpoint inhibitor e.g. an inhibitor of PD-1 activity, a modulator of PD-L 1 activity, a modulator of PD-L2 activity, a modulator of CTLA-4, or a CD40 agonist (e.g., an anti-CD40 antibody molecule), (xi) an 0X40 agonist (e.g., an anti- 0X40 antibody molecule), or (xii) a CD27 agonist (e.g., an anti-CD27 antibody molecule). In one embodiment, the immunomodulator is an inhibitor of PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, LAG-3, CEACAM (e.g., CEACAM-l, -3 and/or -5), VISTA, BTLA, TIGIT, LAIR1, CD 160, 2B4 and/or TGF beta. In one embodiment, the inhibitor of an immune checkpoint molecule inhibits PD-1, PD-L1, LAG-3, TIM-3, CEACAM (e.g., CEACAM-l, -3 and/or -5), CTLA-4, or any combination thereof.

[0203] Inhibition of an inhibitory molecule can be performed at the DNA, RNA or protein level. In embodiments, an inhibitory nucleic acid (e.g., a dsRNA, siRNA or shRNA), can be used to inhibit expression of an inhibitory molecule. In other embodiments, the inhibitor of an inhibitory signal is, a polypeptide e.g., a soluble ligand (e.g., PD-l-Ig or CTLA-4 Ig), or an antibody or antigen-binding fragment thereof,, for example, a monoclonal antibody, a bispecific antibody comprising one or more immune checkpoint antigen binding moieties, a trispecific antibody, or an immune cell-engaging multivalent antibody/fusion protein/construct known in the art that binds to the inhibitory molecule; e.g., an antibody or fragment thereof (also referred to herein as "an antibody molecule") that binds to PD-1, PD-Ll, PD-L2, CEACAM (e.g., CEACAM-l, -3 and/or -5), CTLA-4, TIM-3, LAG-3, VISTA, BTLA, TIGIT, LAIR1, CD 160, 2B4, TGF beta, or a combination thereof.

[0204] In one embodiment, the treatment method includes the co-administration of a compound as disclosed herein or a pharmaceutically acceptable salt thereof and at least one cytotoxic agent. The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes

(e.g., At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu); chemotherapeutic agents; growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof.

[0205] Exemplary cytotoxic agents can be selected from anti -microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, inhibitors of LDH-A; inhibitors of fatty acid biosynthesis; cell cycle signaling inhibitors; HDAC inhibitors, proteasome inhibitors; and inhibitors of cancer metabolism.

[0206] "Chemotherapeutic agents" include chemical compounds useful in the treatment of cancer. Examples of chemotherapeutic agents include erlotinib (TARCEVA®, Genentech/OSI Pharm.), bortezomib (VELCADE®, Millennium Pharm.), disulfiram, epigallocatechin gallate, salinosporamide A, carfilzomib, 17-AAG(geldanamycin), radicicol, lactate dehydrogenase A (LDH-A), fulvestrant (FASLODEX®, AstraZeneca), sunitib (SETTENT®, Pfizer/Sugen), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®, Novartis), fmasunate (VATALANIB®, Novartis), oxaliplatin (ELOXATIN®, Sanofi), 5-FET (5-fluorouracil), leucovorin, rapamycin (Sirolimus, RAPAMUNE®, Wyeth), lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), lonafamib (SCH 66336), sorafenib (NEXAVAR®, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), AG1478; alkylating agents such as thiotepa and CYTOXAN®; cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including topotecan and irinotecan); bryostatin; cally statin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); adrenocorticosteroids (including prednisone and prednisolone); cyproterone acetate; 5 alpha-reductases including finasteride and dutasteride); vorinostat, romidepsin, panobinostat, valproic acid, mocetinostat dolastatin; aldesleukin, talc duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancrati statin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlomaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gamma II and calicheamicin omega I (Angew Chem. Inti. Ed. Engl. 1994 33: 183-186); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin,

caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin), morpholino-doxorubicin, cyanomorpholino- doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 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; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamnol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Ore.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside "Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE® (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Ill.), and TAXOTERE® (docetaxel, doxetaxel; Sanofi-Aventis); chloranmbucil; GEMZAR® (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®); ibandronate; CPT-l l; topoisomerase inhibitor RFS 2000; difluorom ethyl ornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0207] Chemotherapeutic agent also includes (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, iodoxyfene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifme citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide and goserelin; buserelin, tripterelin,

medroxyprogesterone acetate, diethylstilbestrol, premarin, fluoxymesterone, all transretionic acid, fenretinide, as well as troxacitabine (a l,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors; (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Ralf and H-Ras; (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN®, rIL-2; a topoisomerase 1 inhibitor such as LEIRTOTECAN®; ABARELIX®; and (ix) pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0208] Chemotherapeutic agents also include antibodies, as described above, including alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITETX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITETXAN®, Genentech/Biogen Idee), pertuzumab (OMNITARG®, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixia), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG®, Wyeth). Additional humanized monoclonal antibodies with therapeutic potential as agents in combination with the compounds of the invention include: apolizumab, aselizumab, atlizumab, bapineuzumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nivolumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, ustekinumab, visilizumab, and the anti-interleukin-l2 (ABT-8744695, Wyeth Research and Abbott Laboratories) which is a recombinant exclusively human-sequence, full-length $IgG_1\lambda$ antibody genetically modified to recognize interleukin- 12 p40 protein.

[0209] Chemotherapeutic agents also include "tyrosine kinase inhibitors" including the EGFR inhibitors; small molecule HER2 tyrosine kinase inhibitor such as mubritonib (TAK165, Takeda); CP-724.714, (Axon Medchem BV, an oral selective inhibitor of the ErbB2 receptor tyrosine kinase); dual-HER inhibitors such as EKB-569 (available from Wyeth) which preferentially binds EGFR but inhibits both HER2 and EGFR-overexpressing cells; lapatinib (GSK572016; available from Glaxo- SmithKline), an oral HER2 and EGFR tyrosine kinase inhibitor; PKI-166 (available from Novartis); pan-HER inhibitors such as canertinib (CI-1033; Pharmacia); Raf-l inhibitors such as antisense agent ISIS-5132 available from ISIS Pharmaceuticals which inhibit Raf-l signaling; non-HER targeted TK inhibitors such as imatinib mesylate (GLEEVEC®, available from Glaxo SmithKline); multi -targeted tyrosine kinase inhibitors such as sunitinib (SLTTENT®, available from Pfizer); VEGF receptor tyrosine kinase

inhibitors such as vatalanib (PTK787/ZK222584, available from Novartis/Schering AG); MAPK extracellular regulated kinase 1 inhibitor Cl- 1040 (available from Pharmacia); quinazolines, such as PD 153035, 4-(3-chloroanilino) quinazoline; pyridopyrimidines; pyrimidopyrimidines; pyrrolopyrimidines, such as CGP 59326, CGP 60261 and CGP 62706; pyrazolopyrimidines, 4-(phenylamino)-7H-pyrrolo[2,3-d] pyrimidines; curcumin (diferuloyl methane, 4,5-bis (4-fluoroanilino)phthalimide); tyrphostines containing nitrothiophene moieties; antisense molecules (e.g. those that bind to HER-encoding nucleic acid); quinoxalines (U.S. Pat. No. 5,804,396); tryphostins (U.S. Pat. No. 5,804,396); affmitac (ISIS 3521; Isis/Lilly); PKI166 (Novartis); Semaxinib (Pfizer); INC-1C11 (Imclone), rapamycin (sirolimus, RAPAMUNE®); or as described in any of the following patent publications: ET.S. Pat. No. 5,804,396; WO 1999/09016 (American Cyanamid); WO 1998/43960 (American Cyanamid); WO 1997/38983 (Warner Lambert); WO 1999/06378 (Warner Lambert); WO 1999/06396 (Warner Lambert); WO 1996/30347 (Pfizer, Inc); WO 1996/33978 (Zeneca); WO 1996/3397 (Zeneca) and WO 1996/33980 (Zeneca). Tyrosine kinase inhibitors also include erlotinib (Tarceva®), gefitinib (Iressa®), dasatinib (Sprycel®), nilotinib (Tasigna®), crizotinib (Xalkori®), ruxolitinib (Jakafi®), vemurafenib (Zelboraf®), Vandetanib (Caprelsa®), pazopanib (Votrient®), afatinib, alisertib, amuvatinib, axitinib, bosutinib, brivanib, canertinib, cabozantinib, cediranib, crenolanib, dabrafenib, dacomitinib, danusertib, dovitinib, foretinib, ganetespib, ibrutinib, iniparib, lenvatinib, linifanib, linsitinib, masitinib, momelotinib, motesanib, neratinib, niraparib, oprozomib, olaparib, pictilisib, ponatinib, quizartinib, regorafenib, rigosertib, rucaparib, saracatinib, saridegib, tandutinib, tasocitinib, telatinib, tivantinib, tivozanib, tofacitinib, trametinib, veliparib, vismodegib, volasertib, cobimetinib (Cotellic®), and others.

[0210] Chemotherapeutic agents also include dexamethasone, interferons, colchicine, metoprine, cyclosporine, amphotericin, metronidazole, alemtuzumab, alitretinoin, allopurinol, amifostine, arsenic trioxide, asparaginase, BCG live, bevacuzimab, bexarotene, cladribine, clofarabine, darbepoetin alfa, denileukin, dexrazoxane, epoetin alfa, elotinib, filgrastim, histrelin acetate, ibritumomab, interferon alfa-2a, interferon alfa-2b, lenalidomide, levamisole, mesna, methoxsalen, nandrolone, nelarabine, nofetumomab, oprelvekin, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, plicamycin, porfimer sodium, quinacrine, rasburicase, sargramostim, temozolomide, VM-26, 6-TG, toremifene, tretinoin, ATRA, valrubicin, zoledronate, and zoledronic acid, and pharmaceutically acceptable salts thereof.

[0211] Chemotherapeutic agents also include hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone, hydrocortisone-l7-butyrate, hydrocortisone- 17-valerate, aclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-l 7-butyrate, clobetasol-l 7-propionate, fluocortolone caproate, fluocortolone pivalate and fluprednidene acetate; immune selective anti-inflammatory peptides (ImSAIDs) such as phenylalanine-glutamine-glycine (FEG) and its D-isomeric form (feG) (IMULAN

BioTherapeutics, LLC); anti-rheumatic drugs such as azathioprine, ciclosporin (cyclosporine A), D-penicillamine, gold salts, hydroxychloroquine, leflunomideminocycline, sulfasalazine, tumor necrosis factor alpha (TNF alpha) blockers such as etanercept (Enbrel), infliximab (Remicade), adalimumab (l-Iumira), certolizumab pegol (Cimzia), golimumab (Simponi), Interleukin 1 (IL-l) blockers such as anakinra (Kineret), T cell costimulation blockers such as abatacept (Orencia), Interleukin 6 (IL-6) blockers such as tocilizumab (ACTEMERA®); Interleukin 13 (IL-l 3) blockers such as lebrikizumab; Interferon alpha (IFN) blockers such as Rontalizumab; Beta 7 integrin blockers such as rhuMAb Beta7; IgE pathway blockers such as Anti-Ml prime; Secreted homotrimeric LTa3 and membrane bound heterotrimer LTal/l32 blockers such as Anti-lymphotoxin alpha (LTa); miscellaneous investigational agents such as thioplatin, PS-341, phenylbutyrate, ET- I8-OCH3, or famesyl transferase inhibitors (L-739749, L-744832); polyphenols such as quercetin, resveratrol, piceatannol, epigallocatechine gallate, theaflavins, flavanols, procyanidins, betulinic acid and derivatives thereof; autophagy inhibitors such as chloroquine; delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; acetylcamptothecin, scopolectin, and 9- aminocamptothecin); podophyllotoxin; tegafur (UFTORAL®); bexarotene (TARGRETIN®); bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine; perifosine, COX-2 inhibitor (e.g. celecoxib or etoricoxib), proteosome inhibitor (e.g. PS341); CCI-779; tipifamib (R11577); orafenib, ABT510; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE) pixantrone; farnesyltransferase inhibitors such as lonafamib (SCH 6636, SARASAR™); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone; and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATIN™) combined with 5-FU and leucovorin. [000354] Chemotherapeutic agents also include Poly ADP ribose polymerase (PARP) inhibitors: olaparib (Lynparza®), rucaprib (Rubraca®) niraparib (Zejula®), talzoparib (Talzenna®).

[0212] In some embodiments, compounds as disclosed herein may be used in combination therapy with any of the kinase inhibitors disclosed herein for the treatment of diseases such as cancer. Exemplary kinase inhibitors include imatinib, baricitinib gefitinib, erlotinib, sorafenib, dasatinib, sunitinib, lapatinib, nilotinib, pirfenidone, pazopanib, crizotinib, vemurafenib, vandetanib, ruxolitinib, axitinib, bosutinib, regorafenib, tofacitinib, cabozantinib, ponatinib, trametinib, dabrafenib, afatinib, ibrutinib, ceritinib, idelalisib, nintedanib, palbociclib, lenvatinib, cobimetinib, abemaciclib, acalabrutinib, alectinib, binimetinib, brigatinib, encorafenib, erdafitinib, everolimus, fostamatinib, gilter, larotrectinib, lorlatinib, netarsudil, osimertinib, pexidartinib, ribociclib, temsirolimus, XL-092, XL-147, XL-765, XL-499, and XL-880. In some embodiments, a compound as described herein can be used in combination with a HSP90 inhibitor (e.g., XL888), liver X receptor (LXR) modulators, retinoid-related orphan receptor

gamma (RORγ) modulators, a CK1 inhibitor, a CKl-a inhibitor, a Wnt pathway inhibitor (e.g., SST-215), or a mineralocorticoid receptor inhibitor, (e.g., esaxerenone or XL- 550) for the treatment of a disease disclosed herein such as cancer.

[0213] In some embodiments, for treatment of cancer, compounds as disclosed herein may be used in combination with inhibitors of PD-1 or inhibitors of PD-L1, e.g., an anti-PD-1 monoclonal antibody, an anti-PD-1 bispecific antibody or an anti-PD-L 1 monoclonal antibody, an anti-PD-L1 bispecific antibody, for example, nivolumab (Opdivo), pembrolizumab (Keytruda, MK-3475), atezolizumab, avelumab, AB122, AMP-224, AMP- 514, PDR001, durvalumab, pidilizumab (Imfinzi®, CT-011), CK-301, BMS 936559, and MPDL3280A; CTLA-4 inhibitors, e.g., an anti-CTLA-4 antibody, for example, ipilimumab (Yervoy) and tremelimumab; and phosphatidylserine inhibitors, for example, bavituximab (PGN401); antibodies to cytokines (IL-10, TGF-b, and the like.); other anti-cancer agents such as cemiplimab. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab or pembrolizumab.

[0214] In some embodiments, a compound as described herein can be used in combination with a vaccination protocol for the treatment of cancer. In some embodiments, a compound as described herein can be used in combination with vaccines, to stimulate the immune response to pathogens, toxins, and self-antigens. Examples of pathogens for which this therapeutic approach may be particularly useful, include pathogens for which there is currently no effective vaccine, or pathogens for which conventional vaccines are less than completely effective. These include, but are not limited to, HIV, Hepatitis (A, B, & C), Influenza, Herpes, Giardia, Malaria, Leishmania, Staphylococcus aureus, Pseudomonas Aeruginosa.

[0215] In some embodiments, compounds as disclosed herein may be used in combination with inhibitors of PARP, for example, olaparib (Lynparza®), rucaprib (Rubraca®), niraparib (Zejula®), talzoparib (Talzenna®) for the treatment of cancer.

[0216] In some embodiments, compounds as disclosed herein may be used in combination with esaxerenone (XL-550) or XL-888 for the treatment of cancer.

[0217] In some embodiments, the compounds as disclosed herein can be combined with one or more inhibitors of the following kinases for the treatment of cancer: Akt1, Akt2, Akt3, TGF-βR, PKA, PKG, PKC, CaM-kinase, phosphorylase kinase, MEKK, ERK, MAPK, mTOR, EGFR, HER2, HER3, HER4, 1NS-R, IGF-1R, IR-R, PDGFαR, PDGFβ/R, CSFIR, KIT, FLK-II, KDR/FLK-1, FLK-4, flt-1, FGFR1, FGFR2, FGFR3, FGFR4, Ron, Sea, TRKA, TRKB, TRKC, FLT3, VEGFR/Flt2, Flt4, EphAl, EphA2, EphA3, EphB2, EphB4, Tie2, Src, Fyn, Lck, Fgr, Btk, Fak, SYR, FRK, JAK, ABL, ALK, CDK7, CDK12, KRAS, and B-Raf.

Pharmaceutical Compositions and Modes of Administration

[0218] Compounds provided herein are usually administered in the form of pharmaceutical compositions. Thus, provided herein are also pharmaceutical compositions that comprise one or more of the compounds described herein or a pharmaceutically acceptable salt, a stereoisomer, or a mixture of stereoisomers thereof and one or more pharmaceutically acceptable vehicles selected from carriers, adjuvants and excipients. Suitable pharmaceutically acceptable vehicles may include, for example, inert

solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. See, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0219] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical composition may be administered by various methods including, for example, rectal, buccal, intranasal and transdermal routes. In certain embodiments, the pharmaceutical composition may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[0220] One mode for administration is parenteral, for example, by injection. The forms in which the pharmaceutical compositions described herein may be incorporated for administration by injection include, for example, aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[0221] Oral administration may be another route for administration of the compounds described herein. Administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound described herein or a pharmaceutically acceptable salt, a stereoisomer, or a mixture of stereoisomers thereof, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0222] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0223] The compositions that include at least one compound described herein or a pharmaceutically acceptable salt, a stereoisomer, or a mixture of stereoisomers thereof can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-

polymer matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345. Another formulation for use in the methods disclosed herein employ transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds described herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0224] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein or a pharmaceutically acceptable salt, a stereoisomer, or a mixture of stereoisomers thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0225] The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0226] Compositions for inhalation or insufflation may include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described herein. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. In other embodiments, compositions in pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

Dosing

[0227] The specific dose level of a compound of the present application for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the subject undergoing therapy. For example, a dosage may be expressed as a number of milligrams of a compound described herein per kilogram of the subject's body weight (mg/kg). Dosages of between about 0.1 and 150 mg/kg may be

appropriate. In some embodiments, about 0.1 and 100 mg/kg may be appropriate. In other embodiments a dosage of between 0.5 and 60 mg/kg may be appropriate. Normalizing according to the subject's body weight is particularly useful when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject.

Synthesis of the Compounds

[0228] The compounds may be prepared using the methods disclosed herein and routine modifications thereof, which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of typical compounds described herein may be accomplished as described in the following examples. If available, reagents may be purchased commercially, *e.g.*, from Sigma Aldrich or other chemical suppliers.

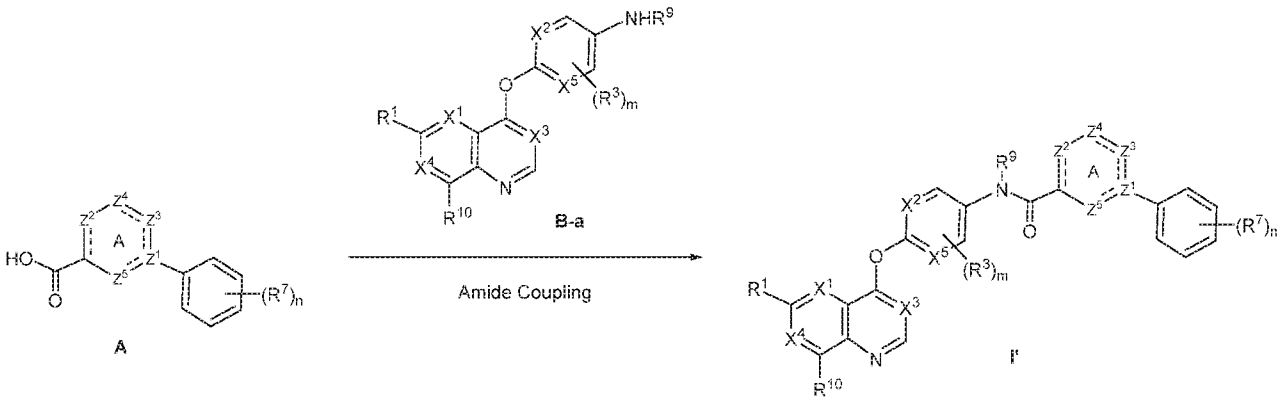
[0229] Typical embodiments of compounds described herein may be synthesized using the general reaction schemes described below. It will be apparent given the description herein that the general schemes may be altered by substitution of the starting materials with other materials having similar structures to result in products that are correspondingly different. Descriptions of syntheses follow to provide numerous examples of how the starting materials may vary to provide corresponding products. Given a desired product for which the substituent groups are defined, the necessary starting materials generally may be determined by inspection. Starting materials are typically obtained from commercial sources or synthesized using published methods. For synthesizing compounds which are embodiments described in the present disclosure, inspection of the structure of the compound to be synthesized will provide the identity of each substituent group. The identity of the final product will generally render apparent the identity of the necessary starting materials by a simple process of inspection, given the examples herein. In general, compounds described herein are typically stable and isolatable at room temperature and pressure.

[0230] Preparation of compounds as disclosed herein can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups is described, *e.g.*, in Kocienski, *Protecting Groups*, (Thieme, 2007); Robertson, *Protecting Group Chemistry*, (Oxford University Press, 2000); Smith *et al.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th Ed. (Wiley, 2007); Peturssion *et al.*, "Protecting Groups in Carbohydrate Chemistry," *J. Chem. Educ.*, 1997, *74*(11), 1297; and Wuts *et al.*, *Protective Groups in Organic Synthesis*, 4th Ed., (Wiley, 2006).

[0231] The Schemes below provide general guidance in connection with preparing the compounds of the invention. One skilled in the art would understand that the preparations shown in the Schemes can be modified or optimized using general knowledge of organic chemistry to prepare various compounds of the invention.

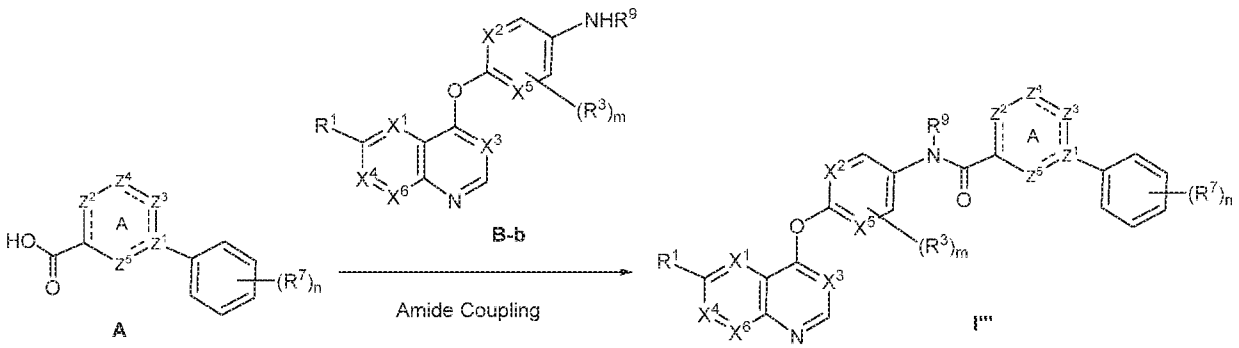
[0232] Compounds of formula (I), formula (I'), formula (I'''), or any subformulas as disclosed herein and certain intermediates can be prepared, for example, using a process as illustrated in Schemes 1A-5C. The variables employed in the Schemes below are as defined throughout the specification.

Scheme 1A.



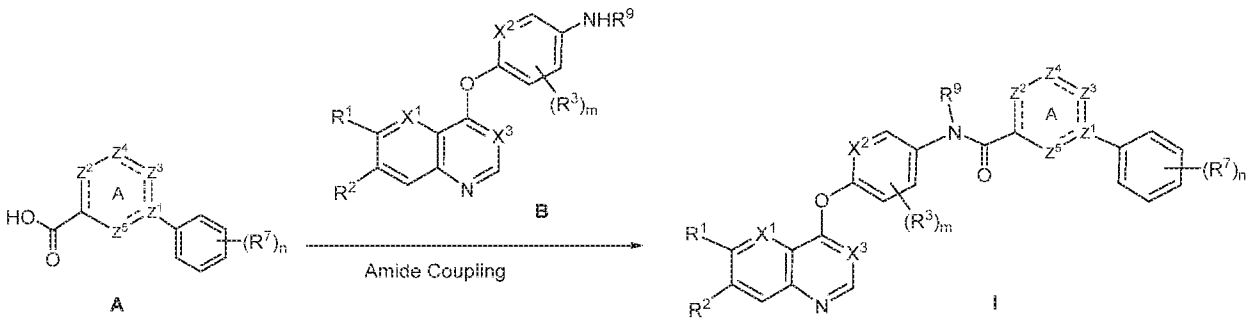
[0233] As shown in Scheme 1A, a compound of formula (**I'**) can be synthesized from carboxylic acid **A** and aniline **B-a** by standard methods to form amide bonds using coupling agents appropriate for this transformation that are well known in the art such as HATU in the presence of a base such as DIEA in organic solvents such as DMF at room or elevated temperatures.

Scheme 1B.



[0234] As shown in Scheme 1B, a compound of formula (**I'''**) can be synthesized from carboxylic acid **A** and aniline **B-b** by standard methods to form amide bonds using coupling agents appropriate for this transformation that are well known in the art such as HATU in the presence of a base such as DIEA in organic solvents such as DMF at room or elevated temperatures.

Scheme 1C.



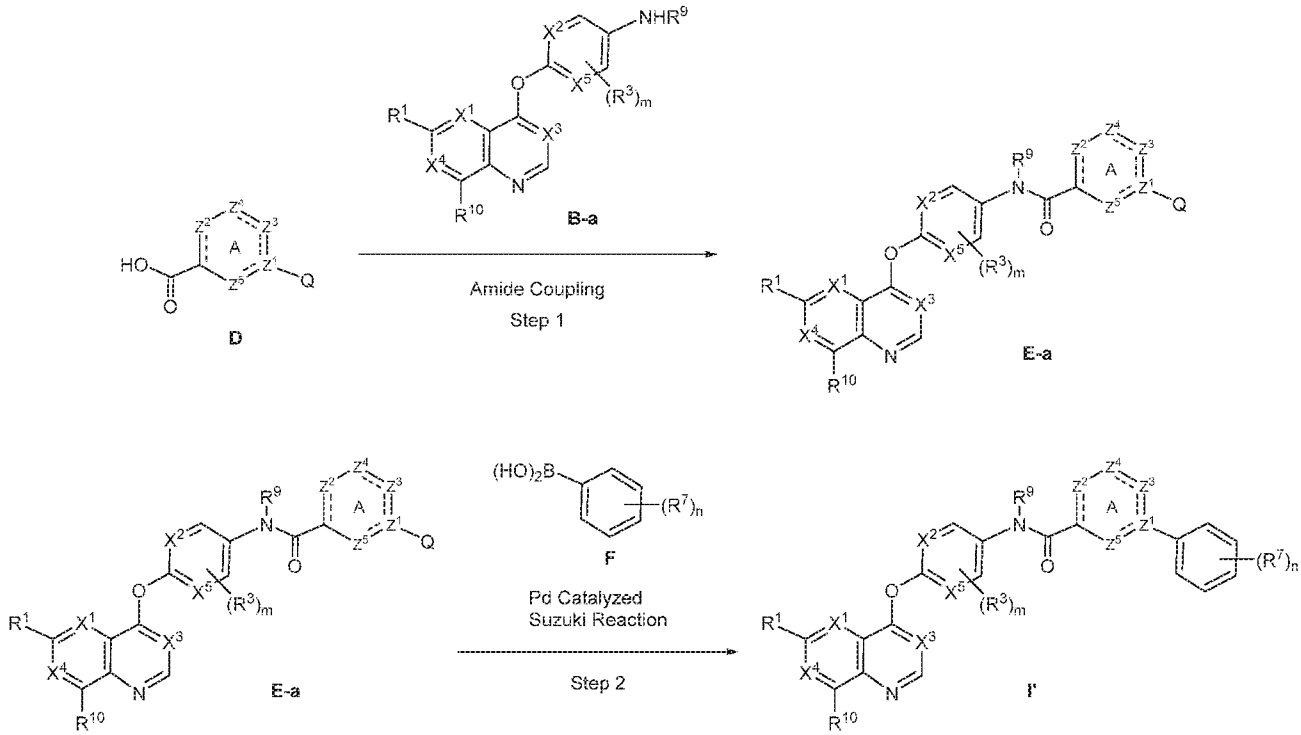
[0235] As shown in Scheme 1C, a compound of formula (**I**) can be synthesized from carboxylic acid **A** and aniline **B** by standard methods to form amide bonds using coupling agents appropriate for this transformation that are well known in the art such as HATU in the presence of a base such as DIEA in organic solvents such as DMF at room or elevated temperatures.

[0236] In some embodiments, provided is a process for preparing a compound of formula (I'), comprising contacting a compound of formula A with a compound of formula B-a, under conditions suitable to provide a compound of formula (I').

[0237] In some embodiments, provided is a process for preparing a compound of formula (I'"), comprising contacting a compound of formula A with a compound of formula B-b, under conditions suitable to provide a compound of formula (I'").

[0238] In some embodiments, provided is a process for preparing a compound of formula (I), comprising contacting a compound of formula A with a compound of formula B, under conditions suitable to provide a compound of formula (I).

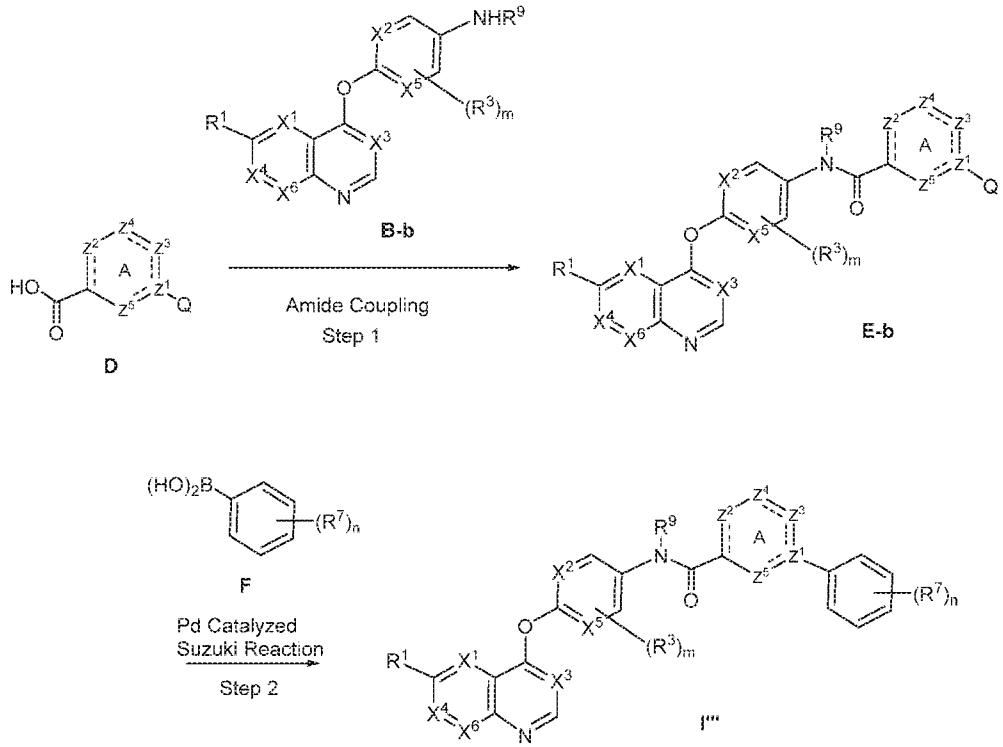
Scheme 2A.



[0239] As shown in Scheme 2A, a compound of formula (**I'**) can be made from a two-step process starting from bromocarboxylic acid **D**, where Q is a leaving group (including Cl, Br, I, triflate and the like), and aniline **B-a** which are coupled together by standard methods to form amide bonds using coupling agents appropriate for this transformation that are well known in the art such as HATU in the presence of a base such as DIEA in organic solvents such as DMF at room or elevated temperatures to form a compound of formula **E-a**. In a second step, compounds of formula **E-a** can be converted to compounds of formula (**I'**) by coupling with boron compounds of the formula **F** using coupling chemistry known to those skilled in the art. Typical procedures to accomplish this type of coupling

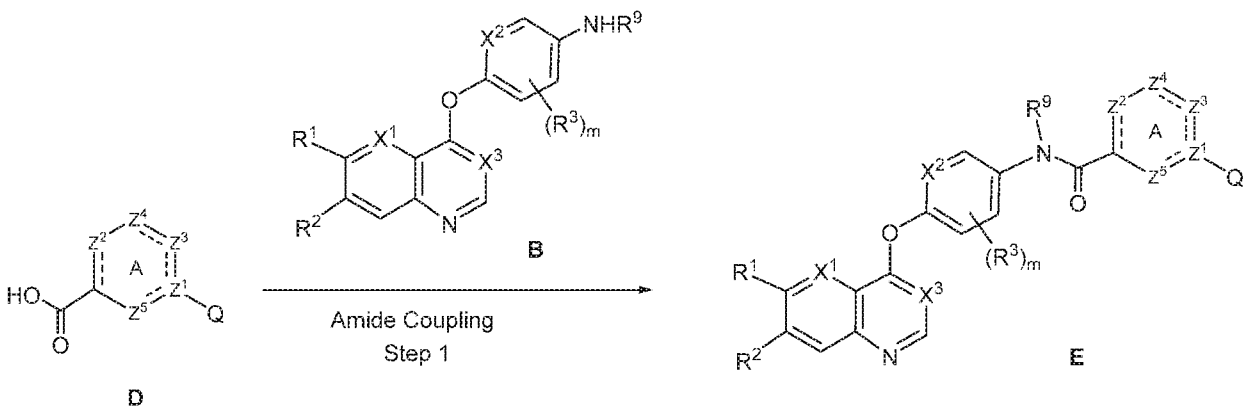
involve the use palladium-containing complexes as a catalyst in the presence of an inorganic base such as tripotassium phosphate in a mixture of water and a water-miscible solvent such as dioxane.

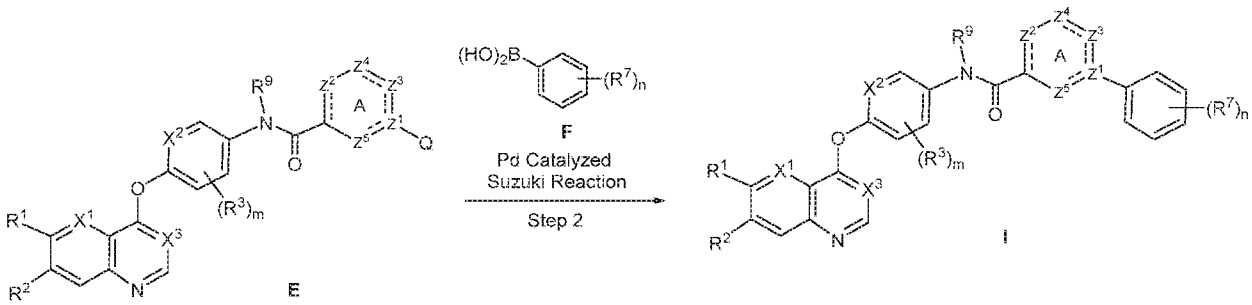
Scheme 2B.



[0240] As shown in Scheme 2B, a compound of formula (**I'''**) can be made from a two-step process starting from bromocarboxylic acid **D**, where Q is a leaving group (including Cl, Br, I, triflate and the like), and aniline **B-b** which are coupled together by standard methods to form amide bonds using coupling agents appropriate for this transformation that are well known in the art such as HATU in the presence of a base such as DIEA in organic solvents such as DMF at room or elevated temperatures to form a compound of formula **E-b**. In a second step, compounds of formula **E-b** can be converted to compounds of formula (**I'''**) by coupling with boron compounds of the formula **F** using coupling chemistry known to those skilled in the art. Typical procedures to accomplish this type of coupling involve the use palladium-containing complexes as a catalyst in the presence of an inorganic base such as tripotassium phosphate in a mixture of water and a water-miscible solvent such as dioxane.

Scheme 2C.





[0241] As shown in Scheme 2C, a compound of formula **(I)** can be made from a two-step process starting from bromocarboxylic acid **D**, where Q is a leaving group, including Cl, Br, I or triflate, and aniline **B** which are coupled together by standard methods to form amide bonds using coupling agents appropriate for this transformation that are well known in the art such as HATU in the presence of a base such as DIEA in organic solvents such as DMF at room or elevated temperatures to form a compound of formula **E**. In a second step, compounds of formula **E** can be converted to compounds of formula **(I)** by coupling with boron compounds of the formula **F** using coupling chemistry known to those skilled in the art. Typical procedures to accomplish this type of coupling involve the use palladium-containing complexes as a catalyst in the presence of an inorganic base such as tripotassium phosphate in a mixture of water and a water-miscible solvent such as dioxane.

[0242] In some embodiments, provided is a process for preparing a compound of formula (I'), comprising:

contacting a compound of formula D with a compound of formula B-a, under conditions suitable to provide a compound of formula E-a; and

contacting a compound of formula E-a with a compound of formula F, under conditions suitable to provide a compound of Formula (I').

[0243] In some embodiments, provided is a process for preparing a compound of formula (I'''), comprising:

contacting a compound of formula D with a compound of formula B-b, under conditions suitable to provide a compound of formula E-b; and

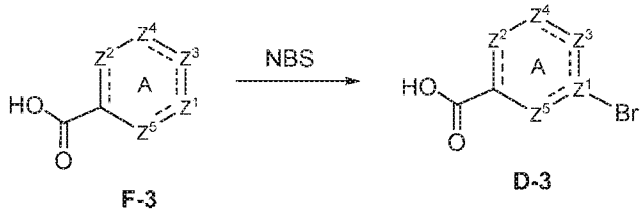
contacting a compound of formula E-b with a compound of formula F, under conditions suitable to provide a compound of Formula (I''').

[0244] In some embodiments, provided is a process for preparing a compound of formula (I), comprising:

contacting a compound of formula D with a compound of formula B, under conditions suitable to provide a compound of formula E; and

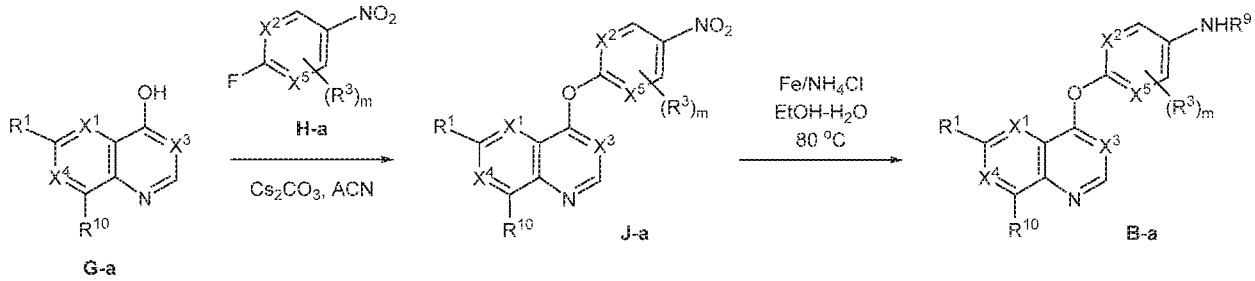
contacting a compound of formula E with a compound of formula F, under conditions suitable to provide a compound of Formula (I).

Scheme 3.



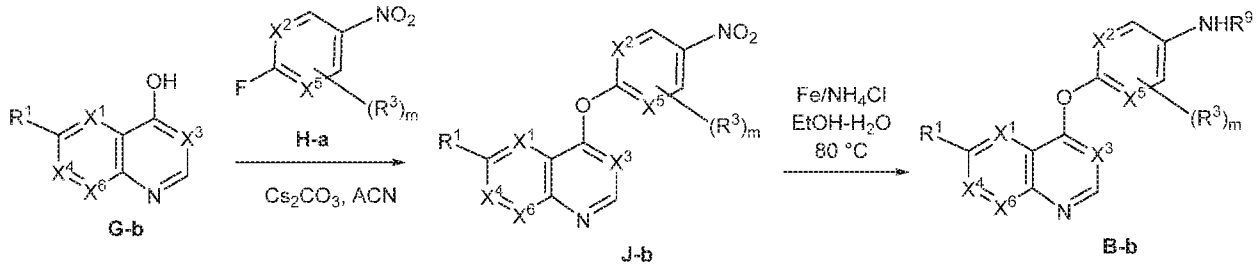
[0245] As shown in Scheme 3, a compound of formula **D-3** (Q = Br) can be prepared from carboxylic acid **F-3** through treatment with NBS in an appropriate solvent typically at room temperature.

Scheme 4A.



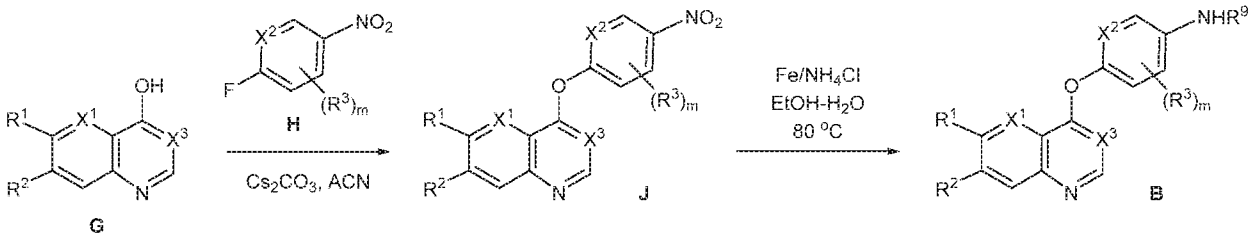
[0246] As shown in Scheme 4A, a compound of formula **J-a** can be prepared by reacting a compound of formula **G-a** with a compound of formula **H-a** in the presence of a base such as cesium carbonate in an appropriate organic solvent, typically at room temperature. A compound of formula **B-a** can be made from a compound of formula **J-a** by reducing the nitro group with a mixture of ammonium chloride and iron typically in a solvent mixture of water and an alcohol such as methanol or ethanol at elevated temperatures.

Scheme 4B.



[0247] As shown in Scheme 4B, a compound of formula **J-b** can be prepared by reacting a compound of formula **G-b** with a compound of formula **H-a** in the presence of a base such as cesium carbonate in an appropriate organic solvent, typically at room temperature. A compound of formula **B-b** can be made from a compound of formula **J-b** by reducing the nitro group with a mixture of ammonium chloride and iron typically in a solvent mixture of water and an alcohol such as methanol or ethanol at elevated temperatures.

Scheme 4C.



[0248] As shown in Scheme 4C, a compound of formula **J** can be prepared by reacting a compound of formula **G** with a compound of formula **H** in the presence of a base such as cesium carbonate in an appropriate organic solvent, typically at room temperature. A compound of formula **B** can be made from a compound of formula **J** by reducing the nitro group with a mixture of ammonium chloride and iron typically in a solvent mixture of water and an alcohol such as methanol or ethanol at elevated temperatures.

[0249] In some embodiments, provided is a process for preparing a compound of formula B-a, comprising:

contacting a compound of formula G-a with a compound of formula H-a, under conditions suitable to provide a compound of formula J-a; and

reducing a compound of formula J-a under conditions suitable to provide a compound of formula B-a.

[0250] In some embodiments, provided is a process for preparing a compound of formula B-b, comprising:

contacting a compound of formula G-b with a compound of formula H-a, under conditions suitable to provide a compound of formula J-b; and

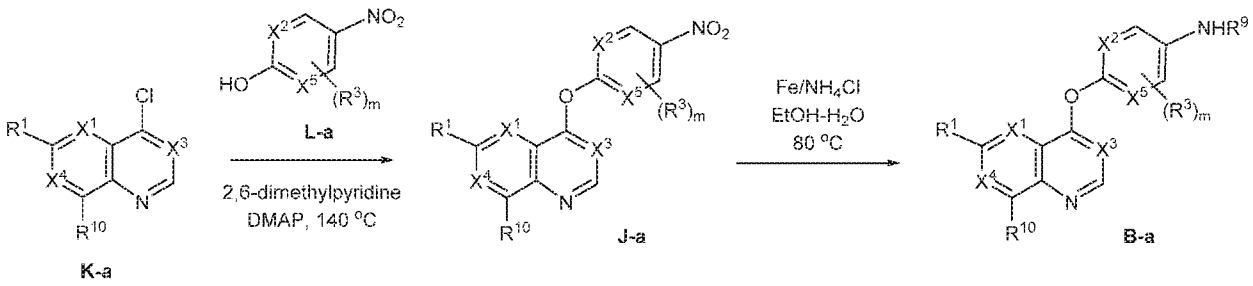
reducing a compound of formula J-b under conditions suitable to provide a compound of formula B-b.

[0251] In some embodiments, provided is a process for preparing a compound of formula B, comprising:

contacting a compound of formula G with a compound of formula H, under conditions suitable to provide a compound of formula J; and

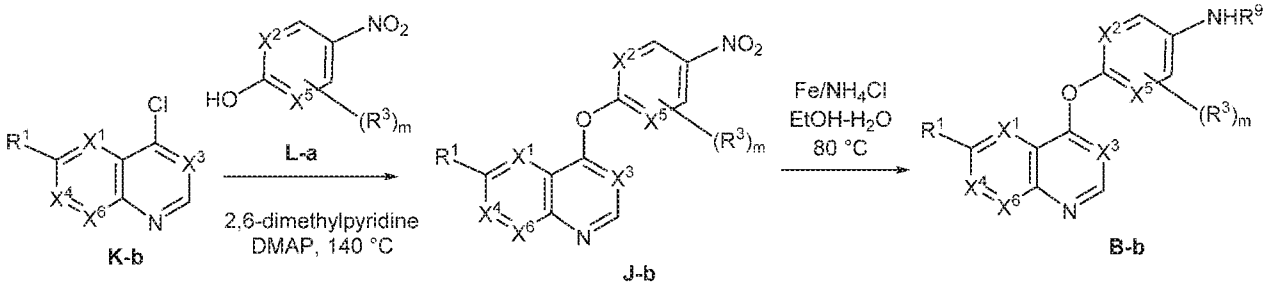
reducing a compound of formula J under conditions suitable to provide a compound of formula B.

Scheme 5A.



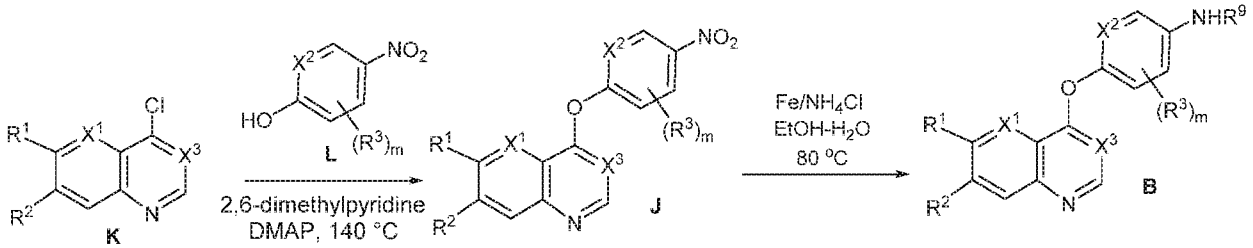
[0252] As shown in Scheme 5A, a compound of formula **J-a** can also be synthesized by reacting a compound of formula **K-a** with a compound of formula **L-a** in an appropriate solvent such as 2,6-dimethylpyridine in the presence of a catalytic amount of dimethylaminopyridine at elevated temperatures. A compound of formula **B-a** can be prepared from a compound of formula **J-a** by reducing the nitro group with a mixture of ammonium chloride and iron typically in a solvent mixture of water and an alcohol such as methanol or ethanol at elevated temperatures.

Scheme 5B.



[0253] As shown in Scheme 5B, a compound of formula **J-b** can also be synthesized by reacting a compound of formula **K-b** with a compound of formula **L-a** in an appropriate solvent such as 2,6-dimethylpyridine in the presence of a catalytic amount of dimethylaminopyridine at elevated temperatures. A compound of formula **B-b** can be prepared from a compound of formula **J-b** by reducing the nitro group with a mixture of ammonium chloride and iron typically in a solvent mixture of water and an alcohol such as methanol or ethanol at elevated temperatures.

Scheme 5C.



[0254] As shown in Scheme 5C, a compound of formula **J** can also be synthesized by reacting a compound of formula **K** with a compound of formula **L** in an appropriate solvent such as 2,6-dimethylpyridine in the presence of a catalytic amount of dimethylaminopyridine at elevated temperatures. A compound of formula **B** can be prepared from a compound of formula **J** by reducing the

nitro group with a mixture of ammonium chloride and iron typically in a solvent mixture of water and an alcohol such as methanol or ethanol at elevated temperatures.

[0255] In some embodiments, provided is a process for preparing a compound of formula B-a, comprising:

contacting a compound of formula K-a with a compound of formula L-a, under conditions suitable to provide a compound of formula J-a; and

reducing a compound of formula J-a under conditions suitable to provide a compound of formula B-a.

[0256] In some embodiments, provided is a process for preparing a compound of formula B-b, comprising:

contacting a compound of formula K-b with a compound of formula L-a, under conditions suitable to provide a compound of formula J-b; and

reducing a compound of formula J-b under conditions suitable to provide a compound of formula B-b.

[0257] In some embodiments, provided is a process for preparing a compound of formula B, comprising:

contacting a compound of formula K with a compound of formula L, under conditions suitable to provide a compound of formula J; and

reducing a compound of formula J under conditions suitable to provide a compound of formula B.

EXAMPLES

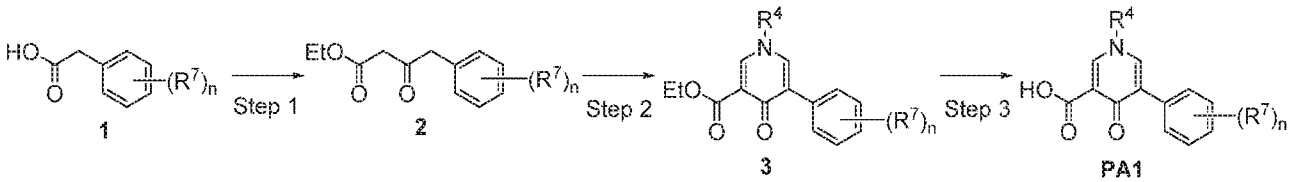
[0258] The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques to function well in the practice of the disclosure, and thus can be considered to constitute specific modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

Synthetic Examples

[0259] The following examples are provided for the purpose of further illustration and are not intended to limit the scope of the claimed invention.

Intermediate Synthesis – General Procedures

General Procedure A: 4-Pyridone carboxylic acids (PA1)

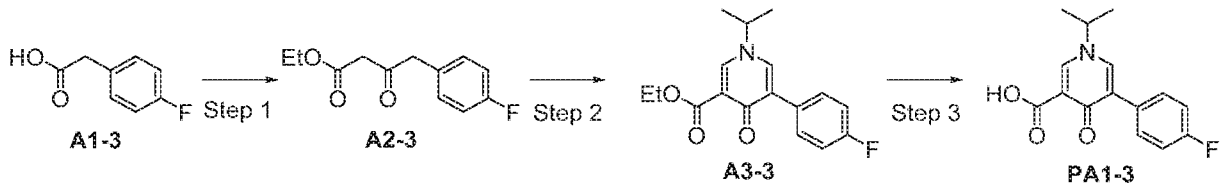


[0260] **Step 1:** To a stirred solution of Compound **1** (65 mmol, 1 eq), Meldrum's acid (9.4 g, 65 mmol, 1 eq) and DMAP (15.8 g, 130 mmol, 2 eq) in DCM (200 mL, 3 mL/mmol of **1**) was added DCC (13.4 g, 65 mmol, 1 eq) in portions. After stirring at room temperature overnight, the reaction mixture was filtered through Celite. The filtrate was washed with aq. 1N HCl (2x), water and aq. saturated NaCl. The resulting organic solution was dried over anhyd Na_2SO_4 and concentrated under vacuum to provide the acyl Meldrum's acid derivative. This material was then dissolved in absolute EtOH (250 mL, 3.8 mL/mmol of **1**) and the resulting solution refluxed overnight. The mixture was concentrated under vacuum and the resulting residue purified by silica gel column chromatography, eluted with 0-15% EtOAc in hexanes, to give Compound **2**.

[0261] **Step 2:** N,N-Dimethylformamide dimethylacetal (DMF-DMA) (2 – 10 eq) was added to a solution of Compound **2** (1 eq) in toluene (2 – 3 mL/mmol of substrate (**2**)) at room temperature. The mixture was stirred at 90 – 100 °C overnight. The volatiles were removed under reduced pressure and EtOH (2 – 4 mL/mmol of **2** used) was added, followed by addition of amine, R^4-NH_2 (1 – 3 eq). The mixture was stirred at 60 °C until the rearrangement was complete as monitored by LC-MS and/or TLC (several hours). The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography, eluted with 0-100% EtOAc in hexanes to give Compound **3**.

[0262] **Step 3:** Compound **3** (1 eq) was mixed with NaOH (2M, 1 – 20 eq) in THF or MeOH (5 – 20 mL/mmol of **3**) and stirred at room temperature until hydrolysis was complete as monitored by LC-MS and/or TLC. The mixture was diluted with water (5 – 20 mL/mmol of **3**) and washed with an organic solvent such as EtOAc or DCM (2x). The aqueous phase was acidified to pH 2 with aq. 6M HCl. If acidification gave a precipitate, the resulting suspension was filtered, and the material was washed with water and dried to give Compound **PA1**. If acidification did not give a filterable precipitate, the aqueous solution was extracted with an organic solvent such as EtOAc or DCM (3x). The combined extracts were dried over anhyd. Na_2SO_4 and concentrated under vacuum to give crude Compound **PA1** which was generally used in subsequent reactions without further purification.

Example of General Procedure A: 5-(4-Fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-3)



A1-3 A2-3 A3-3 PA1-3

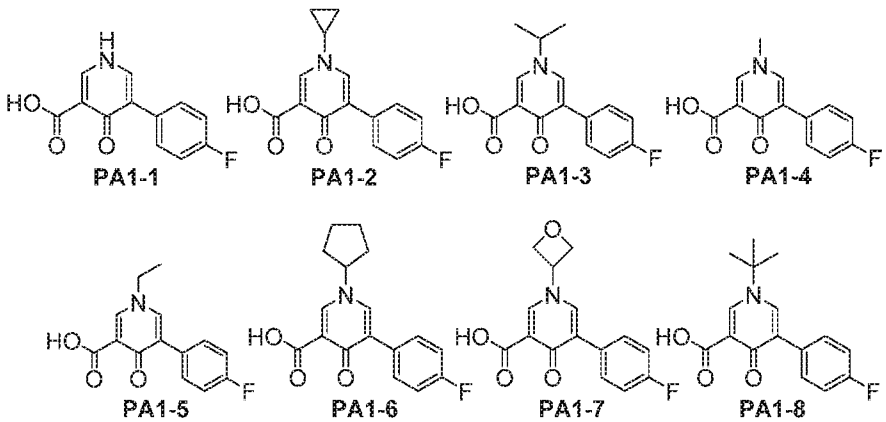
[0263] **Step 1: Ethyl 4-(4-fluorophenyl)-3-oxobutanoate (A2-3):** To a stirred solution of Compound **A1-3** (10 g, 65 mmol, 1 eq), Meldrum's acid (9.4 g, 65 mmol, 1 eq) and DMAP (15.8 g, 130 mmol, 2 eq) in DCM (200 mL), was added DCC (13.4 g, 65 mmol, 1 eq) in portions. After stirring at room temperature overnight, the reaction mixture was filtered through Celite and the filtrate was washed with aq. 1 N HCl (2x), washed with water, washed with aq. saturated NaCl, dried over anhyd. Na_2SO_4 and concentrated to provide the acyl Meldrum's acid derivative. This solid was dissolved in absolute EtOH

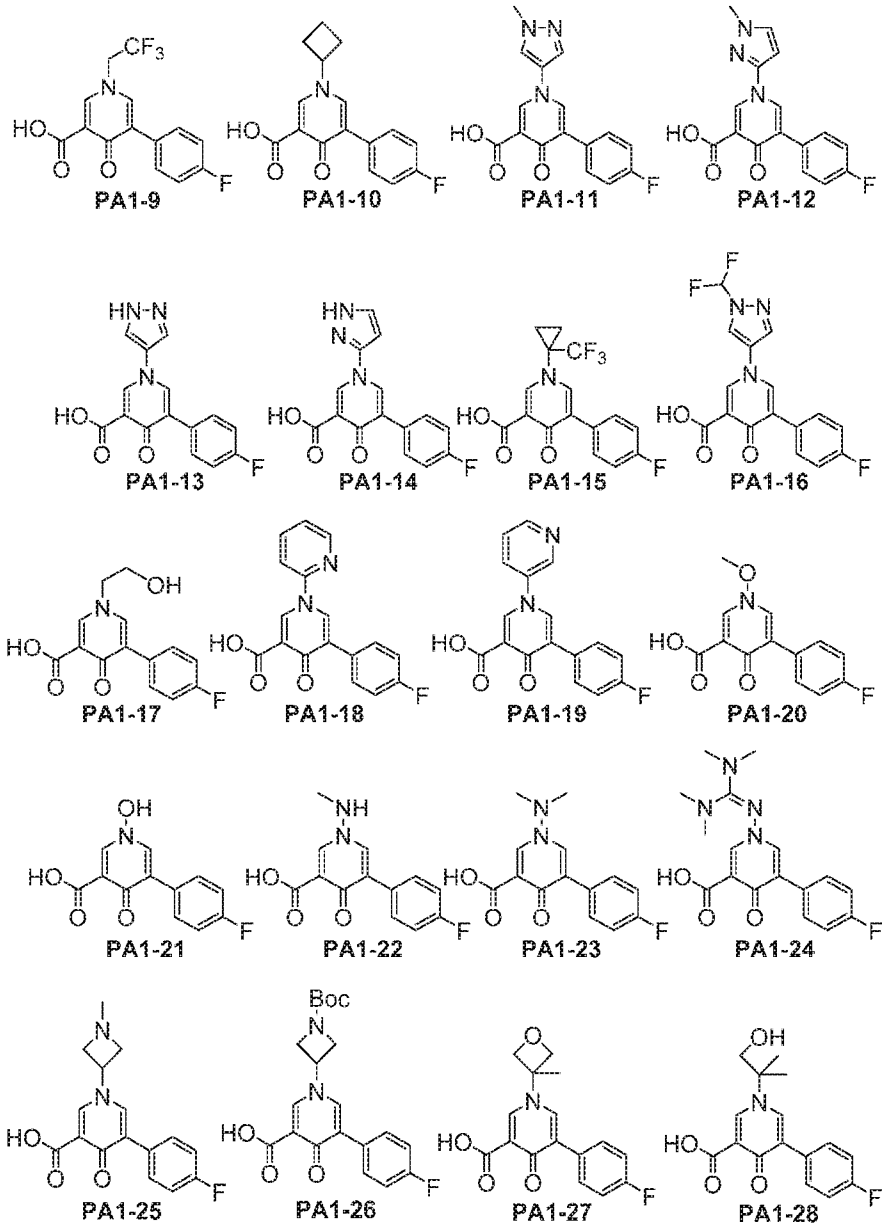
(250 mL) and the resulting solution refluxed overnight. The reaction mixture was concentrated, and the resulting residue was purified by silica gel column chromatography (0-15% EtOAc in hexanes) to give Compound **A2-3**. MS for $C_{12}H_{13}FO_3$: *m/z* 225 (MH+).

[0264] Step 2: Ethyl 5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxylate (A3-3): DMF-DMA (1.0 mL, 13 mmol, 5.8 eq) was added to a solution of Compound **A2-3** (500 mg, 2.23 mmol, 1 eq) in toluene (5 mL) at room temperature, and the mixture was stirred at 100 °C overnight. The reaction mixture was concentrated under reduced pressure to dryness and EtOH (8 mL) was added, followed by the addition of isopropylamine (0.5 mL, 6.1 mmol, 2.7 eq). The mixture was stirred at 60 °C for 8 h, concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (0-100% EtOAc in hexanes) to give Compound **A3-3**. MS for $C_{17}H_{18}FNO_3$: *m/z* 304 (MH+).

[0265] Step 3: 5-(4-Fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-3): A mixture of Compound **A3-3** (480 mg, 1.58 mmol, 1 eq) and aq 2 N NaOH (5 mL) in MeOH (15 mL) was stirred at room temperature for 1 h and then concentrated to remove most of the MeOH. The resulting residue was diluted with water (15 mL) and washed with EtOAc. The aqueous phase was acidified to pH 2 with aq. 6 N HCl and extracted with EtOAc (3x). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated to give Compound **PA1-3**, which was used in subsequent reactions without further purification. MS for $C_{15}H_{14}FNO_3$: *m/z* 276 (MH+).

[0266] The following intermediates were made following **General Procedure A** for the synthesis of 4-pyridone carboxylic acids, **PA1**:





[0267] **5-(4-Fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-1):** MS for $C_{12}H_8FNO_3$: *m/z* 234 (MH+).

[0268] **1-Cyclopropyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-2):** MS for $C_{15}H_{12}FNO_3$: *m/z* 274 (MH+).

[0269] **5-(4-Fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-3):** MS for $C_{15}H_{14}FNO_3$: *m/z* 276 (MH+).

[0270] **5-(4-Fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-4):** MS for $C_{13}H_{10}FNO_3$: *m/z* 248 (MH+).

[0271] **1-Ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-5):** MS for $C_{14}H_{12}FNO_3$: *m/z* 262 (MH+).

[0272] **1-Cyclopentyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-6):** MS for $C_{17}H_{16}FNO_3$: *m/z* 302 (MH+).

[0273] 5-(4-Fluorophenyl)-1-(oxetan-3-yl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-7): MS for $C_{15}H_{12}FNO_4$: *m/z* 290 (MH+).

[0274] 1-(tert-Butyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-8): MS for $C_{16}H_{16}FNO_3$: *m/z* 290 (MH+).

[0275] 5-(4-Fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylic acid (PA1-9): MS for $C_{14}H_9F_4NO_3$: *m/z* 316 (MH+).

[0276] 1-Cyclobutyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-10): MS for $C_{16}H_{14}FNO_3$: *m/z* 288 (MH+).

[0277] 5-(4-Fluorophenyl)-1-(1-methyl-1H-pyrazol-4-yl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-11): MS for $C_{16}H_{12}FN_3O_3$: *m/z* 314 (MH+).

[0278] 5-(4-Fluorophenyl)-1-(1-methyl-1H-pyrazol-3-yl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-12): MS for $C_{16}H_{12}FN_3O_3$: *m/z* 314 (MH+).

[0279] 5-(4-Fluorophenyl)-4-oxo-1-(1H-pyrazol-4-yl)-1,4-dihydropyridine-3-carboxylic acid (PA1-13): MS for $C_{15}H_{10}FN_3O_3$: *m/z* 300 (MH+).

[0280] 5-(4-Fluorophenyl)-4-oxo-1-(1H-pyrazol-3-yl)-1,4-dihydropyridine-3-carboxylic acid (PA1-14): MS for $C_{15}H_{10}FN_3O_3$: *m/z* 300 (MH+).

[0281] 5-(4-Fluorophenyl)-4-oxo-1-(1-(trifluoromethyl)cyclopropyl)-1,4-dihydropyridine-3-carboxylic acid (PA1-15): MS for $C_{16}H_{11}F_4NO_3$: *m/z* 342 (MH+).

[0282] 1-(1-(Difluoromethyl)-1H-pyrazol-4-yl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-16): MS for $C_{16}H_{10}F_3N_3O_3$: *m/z* 350 (MH+).

[0283] 5-(4-Fluorophenyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-17): MS for $C_{14}H_{12}FNO_4$: *m/z* 278 (MH+).

[0284] 5-(4-Fluorophenyl)-4-oxo-4H-[1,2'-bipyridine]-3-carboxylic acid (PA1-18): MS for $C_{17}H_{11}FN_2O_3$: *m/z* 311 (MH+).

[0285] 5-(4-Fluorophenyl)-4-oxo-4H-[1,3'-bipyridine]-3-carboxylic acid (PA1-19): MS for $C_{17}H_{11}FN_2O_3$: *m/z* 311 (MH+).

[0286] 5-(4-Fluorophenyl)-1-methoxy-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-20): MS for $C_{13}H_{10}FNO_4$: *m/z* 264 (MH+).

[0287] 5-(4-Fluorophenyl)-1-hydroxy-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-21): MS for $C_{12}H_8FNO_4$: *m/z* 250 (MH+).

[0288] 5-(4-Fluorophenyl)-1-(methylamino)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-22): MS for $C_{13}H_{11}FN_2O_3$: *m/z* 263 (MH+).

[0289] 1-(Dimethylamino)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-23): MS for $C_{14}H_{13}FN_2O_3$: *m/z* 277 (MH+).

[0290] 1-((bis(Dimethylamino)methylene)amino)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-24): MS for $C_{17}H_{19}FN_4O_3$: *m/z* 347(MH+).

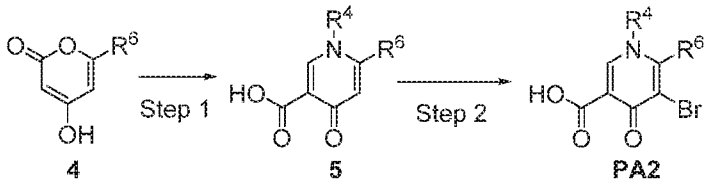
[0291] 5-(4-Fluorophenyl)-1-(1-methylazetidin-3-yl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-25): MS for $C_{16}H_{15}FN_2O_3$: *m/z* 303 (MH+).

[0292] 1-(1-(tert-Butoxycarbonyl)azetidin-3-yl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-26): MS for $C_{20}H_{21}FN_2O_5$: *m/z* 389 (MH+).

[0293] 5-(4-Fluorophenyl)-1-(3-methyloxetan-3-yl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-27): MS for $C_{16}H_{14}FNO_4$: *m/z* 304 (MH+).

[0294] 5-(4-Fluorophenyl)-1-(1-hydroxy-2-methylpropan-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA1-28): MS for $C_{16}H_{16}FNO_4$: *m/z* 306(MH+).

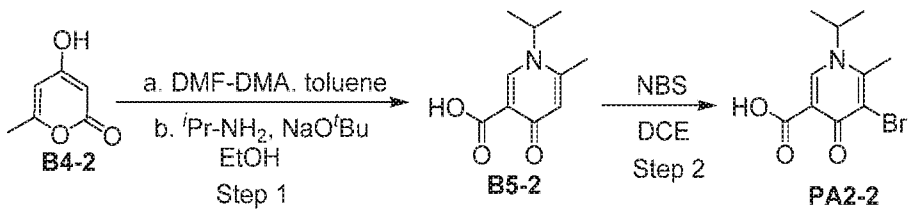
General Procedure B: 5-Bromo-4-Pyridone carboxylic acids (PA2)



[0295] Step 1: To a solution of Compound **4** (100 mmol) in toluene (35 mL) was added DMF-DMA (14 ml, 105 mmol). The resulting solution was stirred at room temperature for 3 h and then concentrated. A mixture of this material (50 mmol), amine R^4-NH_2 (61 mmol) and sodium tert-butoxide (5.6 g, 58 mmol) in EtOH (30 mL) was stirred at 90 °C for 24 h, cooled to room temperature, concentrated and treated with water and DCM. The phases were separated, and the aqueous layer was acidified to pH 2 with aq. 6 N HCl and extracted with DCM. The combined DCM extracts were washed with water, aq. saturated NaCl, dried over anhyd. Na_2SO_4 and concentrated to give the crude Compound **5**.

[0296] Step 2: To a solution of crude Compound **5** (31.3 mmol) in DCE (100 mL) was added solid NBS (9.0 g, 50.6 mmol) in portions. The mixture was stirred at room temperature overnight, diluted with DCM, washed with water, aq. saturated NaCl, dried over anhyd. Na_2SO_4 and concentrated to give the crude Compound **PA2** which was generally used in subsequent reactions without further purification.

Example of General Procedure B: 5-Bromo-1-isopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA2-2)

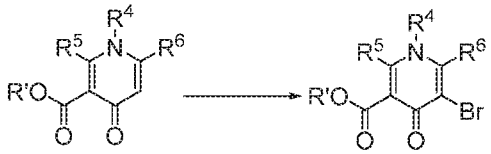


[0297] Step 1: 1-Isopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (B5-2): To a suspension of Compound **B4-2** (15 g, 119 mmol, 1 eq) in toluene (40 mL) was added DMF-DMA (15.2 g, 127 mmol, 1.1 eq). The resulting mixture was stirred at 15 °C for 2 h. The reaction mixture was concentrated under reduced pressure and co-evaporated with toluene (50 mL) 3 times and DCM (50 mL) 2 times to give the enamine intermediate, (E)-3-((dimethylamino)methylene)-6-methyl-2H-pyran-2,4(3H)-dione. This enamine intermediate (11 g, 60.7 mmol, 1 eq) was suspended in EtOH (50 mL), and i-PrNH_2 (7.9 mL, 92 mmol, 1.5 eq) was added, followed by the addition of t-BuONa (8.6 g, 90 mmol, 1.5

eq). The resulting suspension was stirred at 90 °C for 15 h. The reaction mixture was concentrated under reduced pressure. To the resulting residue was diluted with water (150 mL) and acidified with aq. 4 N HCl to pH 2-3 and extracted with DCM (2 x 50 mL). The combined organic extracts were concentrated under reduced pressure to give Compound **B5-2,** which was used in subsequent reactions without further purification.

[0298] Step 2: 5-Bromo-1-isopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA2-2). Compound **PA2-2** was synthesized from Compound **B5-2** using a closely related version of **General Procedure B** as outlined in **General Procedure B1** below. ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.31 (br s, 1H), 8.59 (s, 1H), 4.80-4.70 (m, 1H), 2.80 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H); MS for $C_{10}H_{12}BrNO_3$: *m/z* 275.8 (MH+).

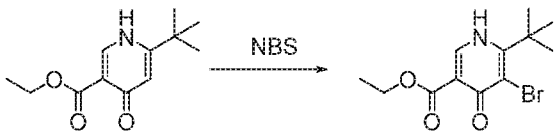
General Procedure B1: Bromination of 4-Pyridone carboxylic acids or esters (PA2a)



5B **PA2a**

[0299] Step 1: Commercially available pyridone carboxylic acids or esters or any pyridone carboxylic acids or esters **(5B)** generated by the methods described within were brominated using NBS in appropriate organic solvents such as, but not limited to, DCE, NMP or ACN. To a solution of crude **5B** (1 eq) in solvent (1.1-3.2 mL/mmol of **5B**) was added solid NBS (1-1.6 eq) in portions. The resulting mixture was stirred at room temperature (30 min to overnight). Upon completion of the reaction as monitored by LC-MS and/or TLC, the reaction mixture was typically worked up by one of the following methods or a very similar variation. Method 1: The reaction mixture was diluted with DCM, washed with water, washed with aq saturated NaCl, dried over anhyd. Na_2SO_4 and concentrated to give crude brominated product **PA2a.** Method 2: To the reaction mixture was added water and the resulting mixture was stirred at room temperature for 15 min. The resulting precipitate was filtered, washed with water and allowed to air-dry to give crude brominated product **PA2a.** Regardless of the method of work up, the crude **PA2a** was generally used in subsequent reactions without further purification.

Example of General Procedure B1: Ethyl 5-bromo-6-(tert-butyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (PA2a-3)

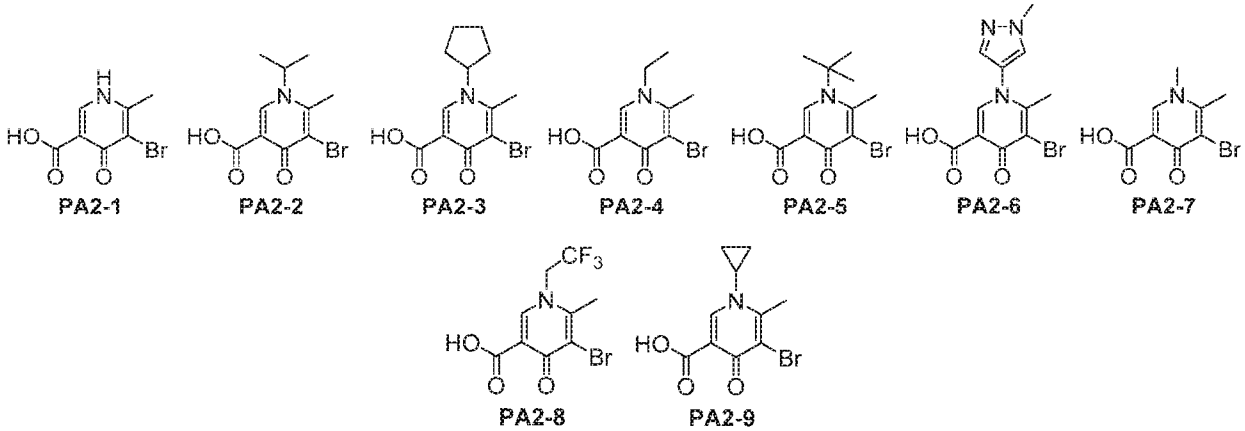


PA2a-3

[0300] Ethyl 5-bromo-6-(tert-butyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (PA2a-3): To a solution of commercially available ethyl 6-(tert-butyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (1 g, 4.48 mmol, 1 eq) in NMP (5 mL) was added NBS (797 mg, 4.48 mmol, 1 eq) in one portion. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with water and

continued stirring for another 15 min. The resulting solid was filtered, washed with water and allowed to dry in the open air to give Compound **PA2a-3.** MS for $C_{12}H_{16}BrNO_3$: *m/z*: 302 (MH+).

[0301] The following intermediates were made following **General Procedure B** or **General Procedure B1** for the synthesis of 5-bromo 4-pyridone carboxylic acids, **PA2** or **PA2a**:



[0302] **5-Bromo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA2-1):** MS for $C_7H_6BrNO_3$: *m/z* 232/234 (MH+).

[0303] **5-Bromo-1-isopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA2-2):** MS $C_{10}H_{12}BrNO_3$: *m/z* 274/276 (MH+).

[0304] **5-Bromo-1-cyclopentyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA2-3):** MS for $C_{12}H_{14}BrNO_3$: *m/z* 300/302 (MH+).

[0305] **5-Bromo-1-ethyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA2-4):** MS for $C_9H_{10}BrNO_3$: *m/z* 260/262 (MH+).

[0306] **5-Bromo-1-(tert-butyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA2-5):** MS for $C_{12}H_{16}BrNO_3$: *m/z* 302 (MH+).

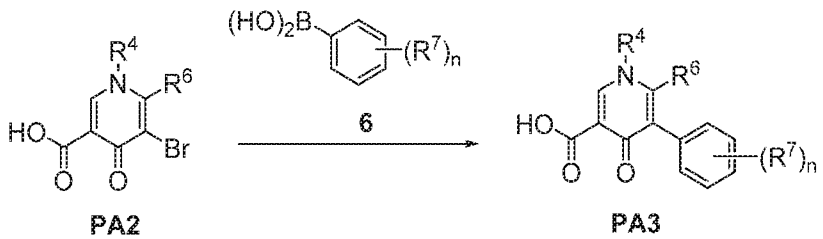
[0307] **5-Bromo-6-methyl-1-(1-methyl-1H-pyrazol-4-yl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA2-6):** MS for $C_{11}H_{10}BrN_3O_3$: *m/z* 312/314 (MH+).

[0308] **5-Bromo-1,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA2-7):** MS for C_8H_8BrNO: *m/z* 246/248 (MH+).

[0309] **5-Bromo-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylic acid (PA2-8):** MS for $C_9H_7BrF_3NO_3$: *m/z* 314.1/316.1 (MH+).

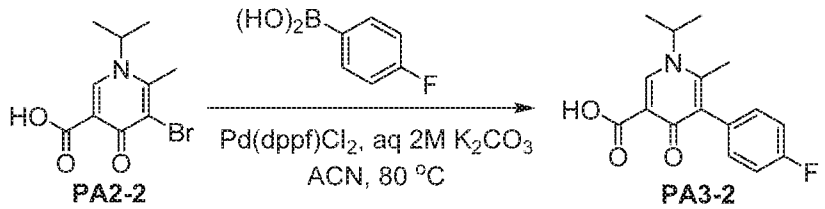
[0310] **5-Bromo-1-cyclopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA2-9):** MS for $C_{10}H_{10}BrNO_3$: *m/z* 272.2/274.2 (MH+).

General Procedure C: 4-Pyridone carboxylic acids (PA3)



[0311] A mixture of compound **PA2** (12.8 mmol), boronic acid **6** (14.3 mmol), K_2CO_3, (4.0 g, 29.0 mmol), $Pd(PPh_3)_4$ (1.2 g, 1.0 mmol) in water (20 mL) and dioxane (40 mL) was degassed with nitrogen for 5 min and then stirred at 90 °C until the reaction was complete as monitored by LC-MS and/or TLC. The reaction mixture was filtered through Celite and the filtrate was concentrated under vacuum to remove dioxane. The resulting residue was diluted with aq. NaOH (20 mL, 2.0 M) and washed with EtOAc (2x). The aqueous phase was then acidified to pH 2-3 with aq. 6 M HCl. The resulting precipitate was filtered, washed with water and dried to give Compound **PA3** which was typically used in subsequent reactions without further purification.

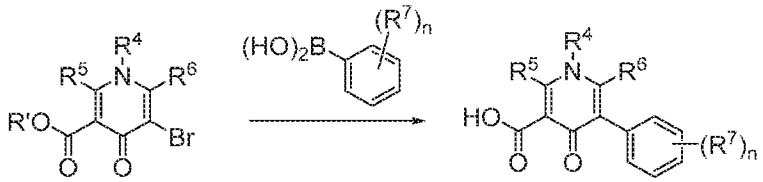
Example of General Procedure C: 5-(4-Fluorophenyl)-1-isopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-2)



PA2-2 PA3-2

[0312] **5-(4-Fluorophenyl)-1-isopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-2):** Compound **PA3-2** was synthesized using a closely related version of **General Procedure C** as outlined in **General Procedure C1** below. MS for $C_{16}H_{16}FNO_3$: *m/z* 289.9 (MH+).

General Procedure C1: Suzuki reactions with 5-bromo-4-pyridone carboxylic acids or esters

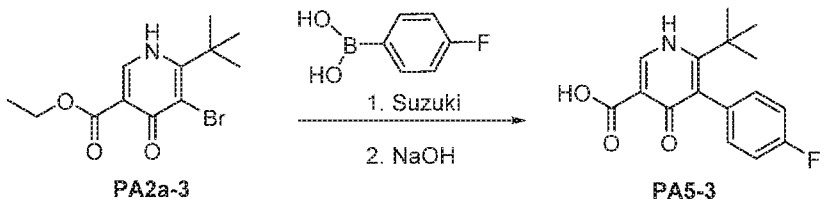


PA-Br PA-Ph

[0313] To a solution of compound **PA-Br**, which can include compounds of type **PA2** or **PA2**, (1 eq) and an appropriately substituted phenyl boronic acid or ester (1.1-2.5 eq) in an appropriate solvent mixture such as, but not limited to, 2:1 dioxane:water or 4:1 ACN:water (1.8-4.7 mL/mmol of **PA-Br**) was added an appropriate base (2-3 eq) and palladium catalyst (0.03-0.08 eq). Appropriate bases include, but are not limited to, K_2CO_3, K_3PO_4 or KH_2PO_4. Appropriate palladium sources include, but are not limited to, $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, $Pd_2(dba)_3$ or $Amphos_2PdCl_2$. The resulting mixture was degassed with nitrogen and then stirred at 80-100 °C until the reaction was complete as monitored by LC-MS and/or TLC. The resulting reaction mixture was worked up by one of the following methods or a very similar variation. Method 1: The reaction mixture was filtered through Celite and the filtrate was concentrated under vacuum to remove dioxane. The resulting residue was diluted with aq. 2 N NaOH (1.6 mL/mmol of **PA-Br** used) and washed with EtOAc (2x). The aqueous phase was then acidified to pH 2-3 with aq. 6 N HCl. The resulting precipitate was filtered, washed with water and dried to give crude **PA-Ph**. Method 2: The reaction mixture was diluted with water (1.8 mL/mmol of **PA-Br** used), the resulting mixture was washed with EtOAc and the layers were separated. The organic layer

was extracted with aq. 1 N NaOH (2x). The combined aqueous phases were washed with EtOAc (3x). The resulting aqueous phase was then acidified with aq. 6 N HCl to pH 2-3. The resulting precipitate was filtered and allowed to air-dry to give crude **PA-Ph**. Method 3: Where **PA-Br** is a carboxylic ester (R' is Me or Et) that was partially hydrolyzed to the carboxylic acid during the reaction, to push the hydrolysis to completion, 1 N NaOH (3.0 mL/mmol of **PA-Br** used) was added to the reaction mixture and heating continued at 60 °C for another 30 min or until the hydrolysis was complete as monitored by LC-MS and/or TLC. The reaction mixture was cooled to room temperature, diluted with water (3.0 mL/mmol of **PA-Br** used) and washed with EtOAc (3x). The aqueous phase was acidified using aq. 6 N HCl to pH 2. The resulting solid was filtered and dried to give **PA-Ph**. Regardless of the method of work up, the crude **PA-Ph** was generally used in subsequent reactions without further purification.

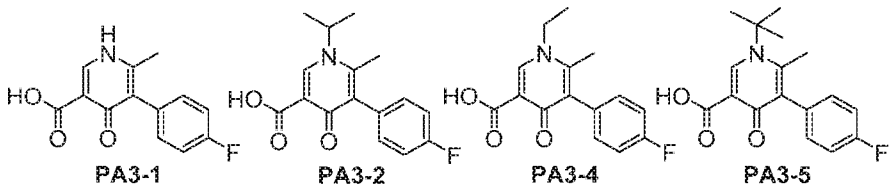
Example of General Procedure C1: 6-(tert-Butyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-3)



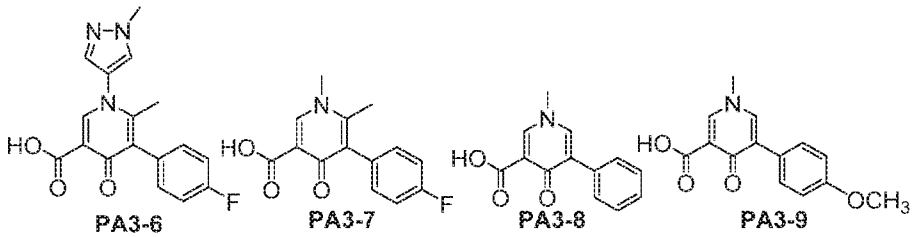
PA2a-3 PA5-3

[0314] **6-(tert-Butyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-3)**: To a solution of Compound **PA2a-3** (200 mg, 0.66 mmol, 1 eq) in 2:1 dioxane:water (3.0 mL) was added (4-fluorophenyl)boronic acid (184 mg, 1.32 mmol, 2 eq), K_2CO_3 (274 mg, 1.98 mmol, 3 eq) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 0.03 eq). The resulting mixture was purged with nitrogen three times and heated to 90 °C overnight. The ester was partially hydrolyzed. To the reaction mixture was added aq. 1 N NaOH (2 mL) and the heating was continued at 60 °C for another 30 min to push the hydrolysis of the ester to completion. The reaction mixture was cooled to room temperature, diluted with water (2 mL) and washed with EtOAc (3x). The aqueous phase was acidified with aq. 6 N HCl to pH 2. The solid that formed was filtered and allowed to dry in the open air to give **PA5-3**. MS for $C_{16}H_{16}FNO_3$: *m/z*: 290 (MH+).

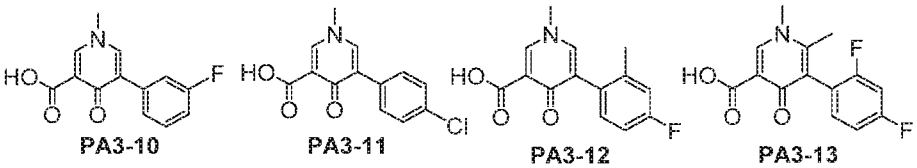
[0315] The following intermediates were made following **General Procedure C** or **General Procedure C1**:

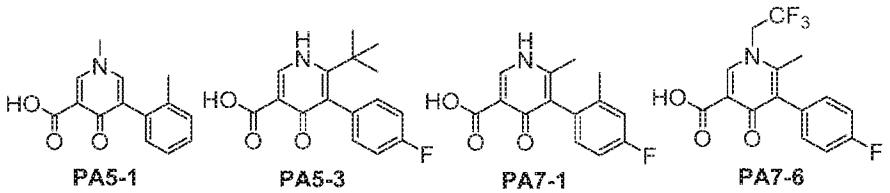


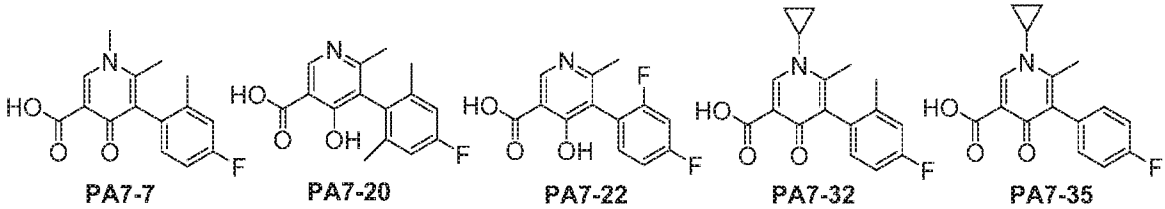
PA3-1 PA3-2 PA3-4 PA3-5



PA3-6 PA3-7 PA3-8 PA3-9







[0316] 5-(4-Fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-1): MS for $C_{13}H_{10}FNO_3$: *m/z* 247.9 (MH+).

[0317] 5-(4-Fluorophenyl)-1-isopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-2): MS for $C_{16}H_{16}FNO_3$: *m/z* 290 (MH+).

[0318] 1-Ethyl-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-4): MS for $C_{15}H_{14}FNO_3$: *m/z* 276 (MH+).

[0319] 1-(tert-Butyl)-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-5): MS for $C_{17}H_{18}FNO_3$: *m/z* 304 (MH+).

[0320] 5-(4-Fluorophenyl)-6-methyl-1-(1-methyl-1H-pyrazol-4-yl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-6): MS for $C_{17}H_{14}FN_3O_3$: *m/z* 328 (MH+).

[0321] 5-(4-fluorophenyl)-1,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-7): MS for $C_{14}H_{12}FNO_3$: *m/z* 262 (MH+).

[0322] 1-Methyl-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxylic acid (PA3-8): MS for $C_{13}H_{11}NO_3$: *m/z* 230 (MH+).

[0323] 5-(4-Methoxyphenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-9): MS for $C_{14}H_{13}NO_4$: *m/z* 260 (MH+).

[0324] 5-(3-Fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-10): MS for $C_{13}H_{10}FNO_3$: *m/z* 248 (MH+).

[0325] 5-(4-Chlorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-11): MS for $C_{13}H_{10}ClNO_3$: *m/z* 264 (MH+).

[0326] 5-(4-Fluoro-2-methylphenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-12): MS for $C_{14}H_{12}FNO_3$: *m/z* 262 (MH+).

[0327] 5-(2,4-Difluorophenyl)-1,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA3-13).

[0328] 1-Methyl-4-oxo-5-(o-tolyl)-1,4-dihydropyridine-3-carboxylic acid (PA5-1): calculated MS for $C_{14}H_{13}NO_3$: *m/z* 244 (MH+)

[0329] 6-(tert-Butyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-3): MS for $C_{16}H_{16}FNO_3$: *m/z* 290 (MH+).

[0330] 5-(4-Fluoro-2-methylphenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-1): MS for $C_{14}H_{12}FNO_3$: *m/z* 262 (MH+).

[0331] 5-(4-Fluorophenyl)-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylic acid (PA7-6): MS for $C_{15}H_{11}F_4NO_3$: *m/z* 330.3 (MH+).

[0332] 5-(4-Fluoro-2-methylphenyl)-1,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-7): MS for $C_{15}H_{14}FNO_3$: *m/z* 276 (MH+).

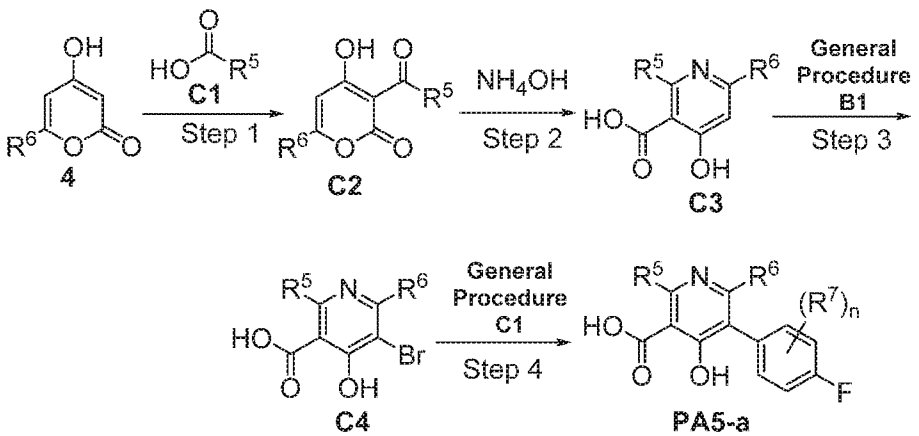
[0333] 5-(4-Fluoro-2,6-dimethylphenyl)-4-hydroxy-6-methylnicotinic acid (PA7-20): In this particular case, the amount of catalyst used ($Pd_2(dba)_3$) was increased to 0.46 eq and the reaction was heated at 100 °C overnight. After work-up the crude product was purified by prep HPLC. MS for $C_{15}H_{14}FNO_3$: *m/z* 276.3 (MH+).

[0334] 5-(2,4-Difluorophenyl)-4-hydroxy-6-methylnicotinic acid (PA7-22): MS for $C_{13}H_9F_2NO_3$: *m/z* 266.2 (MH+).

[0335] 1-Cyclopropyl-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-32): MS for $C_{17}H_{16}FNO_3$: *m/z* 302.3 (MH+).

[0336] 1-Cyclopropyl-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-35): MS for $C_{16}H_{14}FNO_3$: *m/z* 288.3 (MH+).

General Procedure C2: 4-Hydroxy-2H-pyran-2-one method to form 2,6-disubstituted 4-hydroxypyridines (PA5-a)



[0337] Step 1: To a solution of Compound **4** (1 eq) in toluene (1.2 mL/mmol of 4) was added acid **C1** (1 eq), DCC (1 eq) and DMAP (1 eq). The resulting mixture was heated to 50 °C. The resulting solid crude product was filtered and then purified by flash silica gel column chromatography to give Compound **C2**.

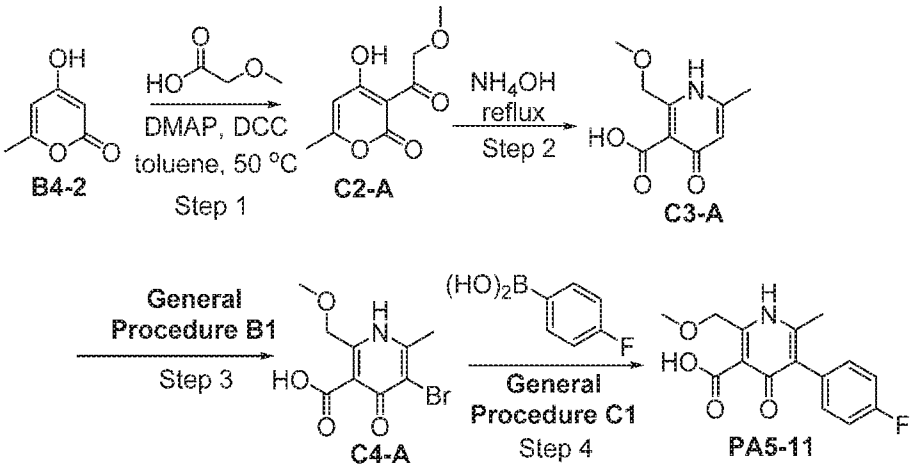
[0338] Step 2: To a solution of Compound **C2** (1 eq) in water (1.0-3.2 mL/mmol of **C2**) was added 30-40% ammonium hydroxide in water (0.9-1.0 mL/mmol of **C2**). The resulting mixture was heated to

reflux overnight. The reaction mixture was cooled to room temperature and solvent was partially removed in vacuo. The resulting reaction mixture was cooled to 0 °C and acidified using aq. 6 N HCl to pH 2. The resulting solid was filtered and dried in the open air to give Compound **C3**.

[0339] **Step 3:** See **General Procedure B1** above for the bromination of 4-pyridone carboxylic acids or esters.

[0340] **Step 4:** See **General Procedure C1** above for Suzuki reactions with 5-bromo-4-pyridone carboxylic acids or esters.

Example A of General Procedure C2: 5-(4-Fluorophenyl)-2-(methoxymethyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-11)



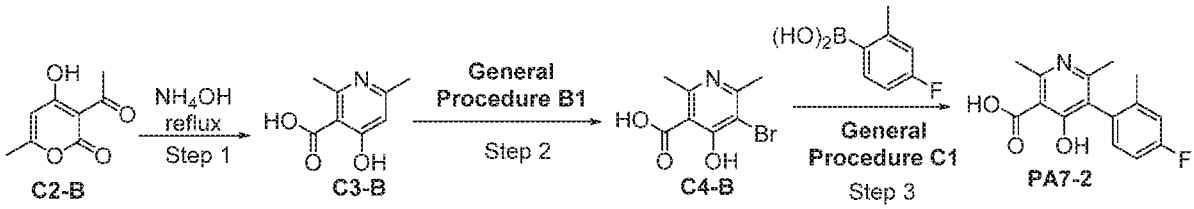
[0341] **Step 1: 4-Hydroxy-3-(2-methoxyacetyl)-6-methyl-2H-pyran-2-one (C2-A)**: To a solution of Compound **B4-2** (10 g, 79 mmol, 1 eq) in toluene (100 mL) was added 2-methoxyacetic acid (7.1 g, 79 mmol, 1 eq), DCC (16.3 g, 79 mmol, 1 eq) and DMAP (9.6 g, 79 mmol, 1 eq). The resulting mixture was heated to 50 °C. The resulting solid was filtered and then purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to give Compound **C2-A**. MS for $C_9H_{10}O_5$: *m/z* 199 (MH+).

[0342] **Step 2: 2-(Methoxymethyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (C3-A):** To a solution of Compound **C2-A** (12.5 g, 63 mmol, 1eq) in water (200 mL) was added ammonium hydroxide (40% in water, 60 mL). The resulting mixture was heated to reflux overnight. After allowing the reaction mixture to cool to room temperature, the solvent was partially removed under vacuum. The resulting mixture was cooled to 0 °C and acidified to pH 2 using aq. 6 N HCl. The resulting solid was filtered and allowed to dry in the open air to give Compound **C3-A**. MS for $C_9H_{11}NO_4$: *m/z* 198 (MH+).

[0343] **Step 3: 5-Bromo-2-(methoxymethyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (C4-A):** Compound **C4-A** was synthesized from Compound **C3-A** using **General Procedure B1**. MS for $C_9H_{10}BrNO_4$: *m/z* 276 (MH+).

[0344] **Step 4: 5-(4-Fluorophenyl)-2-(methoxymethyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-11):** Compound **PA5-11** was synthesized from Compound **C4-A** using **General Procedure C1**. MS for $C_{15}H_{14}FNO_4$: *m/z* 292 (MH+).

Example B of General Procedure C2: 5-(4-Fluoro-2-methylphenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-2)

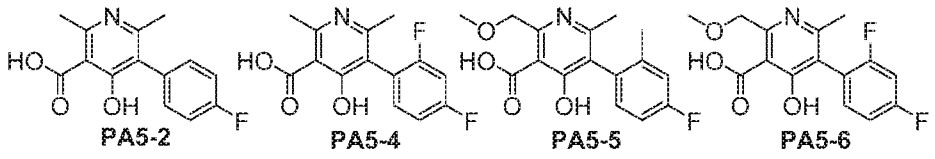


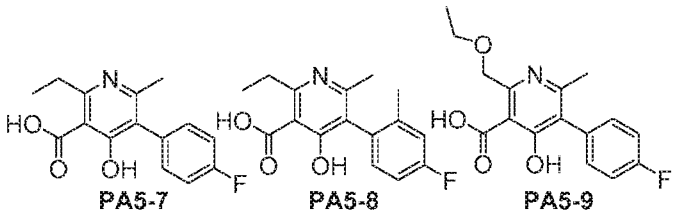
[0345] **Step 1: 2,6-Dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (C3-B):** To a solution of commercially available Compound **C2-B** (10 g, 59.88 mmol) in water (60 mL) was added ammonium hydroxide (60 mL, 30% in water). The resulting mixture was heated to reflux overnight. The mixture was partially concentrated and then acidified to pH 2 with aq. 6 M HCl. The resulting precipitate was filtered and allowed to dry in the open air to afford Compound **C3-B** as a white solid (2.5 g, 25% yield). MS for $C_8H_9NO_3$: *m/z* 168 (MH+).

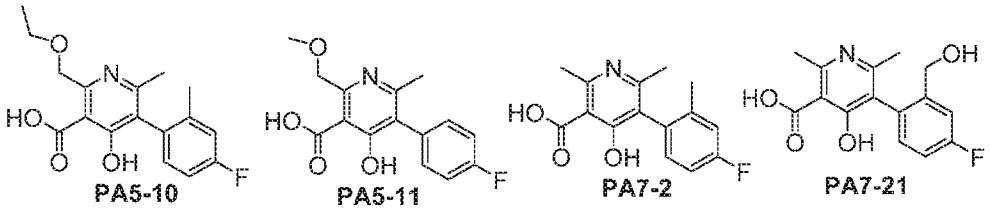
[0346] **Step 2: 5-Bromo-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (C4-B):** Compound **C4-B** was synthesized from Compound **C3-B** using **General Procedure B1**. MS for $C_8H_8BrNO_3$: *m/z* 246 (MH+).

[0347] **Step 3: 5-(4-Fluoro-2-methylphenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-2):** Compound **PA7-2** was synthesized from Compound **C4-B** using a procedure similar to **General Procedure C1**. Specifically, to a solution of Compound **C4-B** (1 g, 4.1 mmol) in dioxane/water (10 mL/ 5 mL) was added (4-fluoro-2-methylphenyl)boronic acid (10.2 mmol, 2.5 eq) , $Pd(Amphos)Cl_2$ (0.24 mmol, 0.06 eq) and K_3PO_4 (12.2 mmol, 3 eq). The resulting mixture was heated to 90 °C overnight. The resulting phases were separated. The organic phase was diluted with EtOAc and extracted with aq. 1 N NaOH (2x). The combined aqueous layers (original aqueous phase from the crude reaction mixture and the aqueous extracts) were combined and washed with EtOAc (3x) and then acidified to pH 2 using aq. 6 M HCl. The resulting precipitate was filtered and allowed to dry in the open air to give Compound **PA7-2** as a white solid (642 mg. 57% yield). MS for $C_{15}H_{14}FNO_3$: *m/z* 276 (MH+).

[0348] The following intermediates were made following **General Procedure C2** for the 4-hydroxy-2H-pyran-2-one method to form 2,6-disubstituted 4-hydroxypyridines: **PA5-a,**







[0349] **5-(4-Fluorophenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-2):** MS for $C_{14}H_{12}FNO_3$: *m/z* 262 (MH+).

[0350] **5-(2,4-Difluorophenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-4):** MS for $C_{14}H_{11}F_2NO_3$: *m/z* 280 (MH+).

[0351] **5-(4-Fluoro-2-methylphenyl)-2-(methoxymethyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-5):** MS for $C_{16}H_{16}FNO_4$: *m/z* 306 (MH+).

[0352] **5-(2,4-Difluorophenyl)-2-(methoxymethyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-6):** MS for $C_{15}H_{13}F_2NO_4$: *m/z* 310 (MH+).

[0353] **2-Ethyl-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-7):** MS for $C_{15}H_{14}FNO_3$: *m/z* 276 (MH+).

[0354] **2-Ethyl-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-8):** MS for $C_{16}H_{16}FNO_3$: *m/z* 290 (MH+).

[0355] **2-(Ethoxymethyl)-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-9):** MS for $C_{16}H_{16}FNO_4$: *m/z* 306 (MH+).

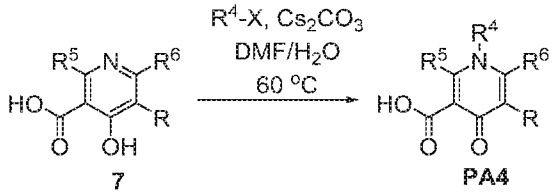
[0356] 2-**(Ethoxymethyl)-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-10):** MS for $C_{17}H_{18}FNO_4$: *m/z* 320 (MH+).

[0357] **5-(4-Fluorophenyl)-2-(methoxymethyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA5-11):** MS for $C_{15}H_{14}FNO_4$: *m/z* 292 (MH+).

[0358] **5-(4-Fluoro-2-methylphenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-2):** MS for $C_{15}H_{14}FNO_3$: *m/z* 276 (MH+).

[0359] **5-(4-Fluoro-2-(hydroxymethyl)phenyl)-4-hydroxy-2,6-dimethylnicotinic acid (PA7-21)**: MS for $C_{15}H_{14}FNO_4$: *m/z* 292 (MH+).

General Procedure D: 4-Pyridone carboxylic acids (PA4)

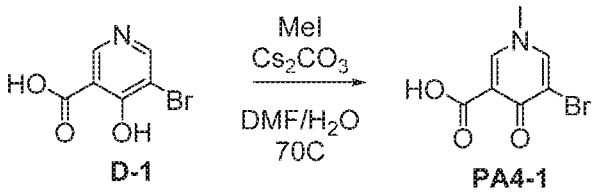


R = Cl, Br, I or Triflate

[0360] To a solution of pyridine acid **7** in (8.1 mmol) in DMF (10 mL)/water (10 mL) was added alkyl halide (R^4-X) (2 eq) and cesium carbonate (3 eq). The resulting mixture was heated to 60 °C overnight. The reaction mixture was allowed to cool to room temperature and filtered through Celite. The filtrate was concentrated under vacuum. The crude residue was brought up in MeOH (5 mL) and 1 N NaOH (5 mL) was added. The resulting mixture was stirred at room temperature for 1 h. MeOH was removed in

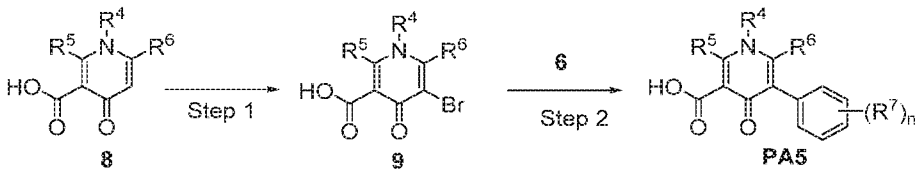
vacuo and the resulting aqueous mixture was washed with EtOAc (3x). The aqueous phase was acidified with aq. 6 N HCl to pH 2-3. The resulting material was filtered and allowed to air-dry to give Compound **PA4** which was generally used in subsequent reactions without further purification.

Example of General Procedure D: 5-Bromo-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA4-1)



[0361] 5-Bromo-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA4-1): To a solution of Compound **D-1** (4.8 g, 22 mmol, 1 eq) in 2:1 DMF:water (30 mL) was added Cs_2CO_3 (21.4 g, 65.6 mmol, 3 eq) and MeI (9.3 g, 65.6 mmol, 3 eq). The resulting mixture was heated to 70 °C for 10 min. The reaction mixture was allowed to cool to room temperature, diluted with water (10 ml) and washed with EtOAc (3x). The aqueous phase was acidified to pH 3-4 using aq. 6 N HCl. The resulting solid was filtered and allowed to dry in the open air to give Compound **PA4-1** as a light-yellow solid (4.1 g, 82% yield). MS for $C_7H_6BrNO_3$: *m/z* 232/234 (MH+).

General Procedure E: 4-Pyridone carboxylic acids (PA5)

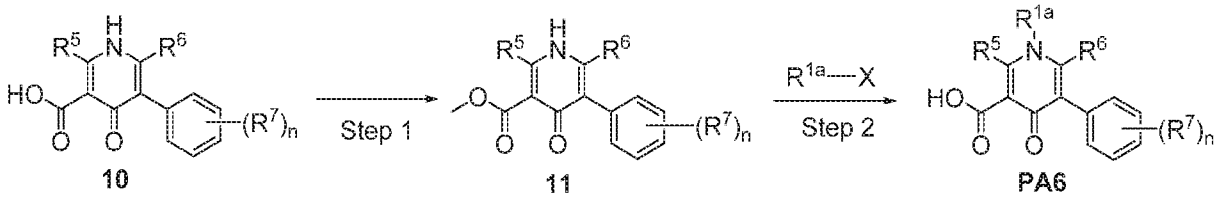


[0362] Step 1: Following procedures similar to Step 2 of **General Procedure B** or **General Procedure B1,** pyridone carboxylic acids **8** (32.7 mmol) were brominated using NBS (1 eq) in an organic solvent such as NMP or ACN (0.5M) for 30 min. Upon completion of the reaction as determined by monitoring with LC-MS, water was added to the reaction mixture and the resulting mixture was stirred at room temperature for 15 min. The resulting precipitate was filtered, washed with water and allowed to air-dry to afford Compound **9** which was generally used in subsequent reactions without further purification. The same procedure can also be carried out on esters of Compound **8**.

[0363] Step 2: Following procedures similar to **General Procedure C** or **General Procedure C1,** Compound **9** recovered from **Step 1** was dissolved in a mixture of dioxane and water (40/20 mL, 1:1 vv). Boronic acid **6** (1.5-2.5 eq) was added to the resulting solution of Compound **9** followed by the addition of K_2CO_3 or KH_3PO_4 (3 eq) and a palladium source such as tetrakis or $Amphos_2PdCl_2$ (0.06 eq). The reaction mixture was purged with nitrogen 3 times and then heated to 90 °C for 1 h. Upon completion of the reaction as monitored by LC-MS, the reaction mixture was allowed to cool to room temperature followed by dilution with water (60 mL). The resulting mixture was washed with EtOAc and layers were separated. The organic layer was extracted with 1 N NaOH (2x). The combined aqueous phases were washed with EtOAc (3x). The resulting aqueous phase was then acidified with aq. 6 N HCl to pH 2-3.

The resulting precipitate was filtered and allowed to air-dry to give Compound **PA5** which was generally used in subsequent reactions without further purification.

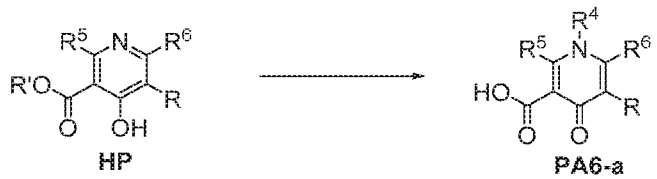
General Procedure F: 4-Pyridone carboxylic acids (PA6)



[0364] **Step 1:** Note: Compound **10** in this procedure can be any **PA1**, **PA2**, or **PA5** synthesized according to the previous general procedures where R^4 is hydrogen. To a solution of Compound **10** (2.18 mmol) in anhyd. MeOH (5 mL) was added HCl (2 mL, 4 M in dioxane). The resulting mixture was stirred at room temperature overnight. Solvents were removed under reduced pressure and the resulting crude Compound **11** was used for the next step without further purification.

[0365] **Step 2**: To Compound **11** (0.38 mmol) in DMF (2 mL) was added alkyl halide R^{1a}-X (1.2 eq) and Cs_2CO_3 (3 eq). The resulting mixture was heated to 60 °C overnight. The reaction mixture was allowed to cool to room temperature and filtered through Celite. The filtrate was concentrated under reduced pressure. The resulting crude residue was brought up in MeOH (1 mL) and aq. 1 N NaOH (1 mL) was added. The resulting mixture was stirred at room temperature for 1 h. MeOH was removed under vacuum and remaining aqueous mixture was washed with EtOAc (3x). The resulting aqueous phase was acidified with aq. 6 N HCl to pH 2-3. The resulting precipitate was filtered and air-dried to give crude Compound **PA6** which was generally used in subsequent reactions without further purification.

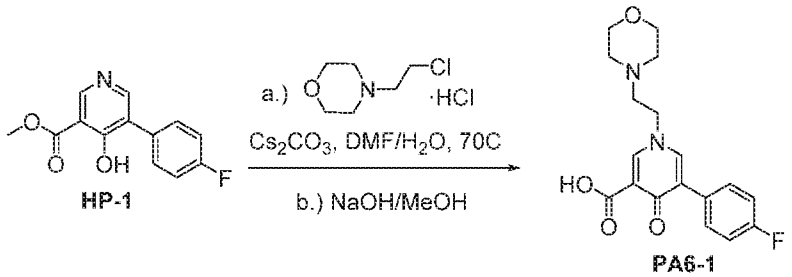
General Procedure F1: N-Alkylation 4-hydroxypyridines (PA6-a)



[0366] To a solution of a hydroxypyridine (**HP**) carboxylic acid (R' = H) or ester (R' typically = Me or Et) (1 eq) in an appropriate solvent (1.4-5.3 mL/mmol of **HP**) such as, but not limited to, DMF, a 2:1 mixture of DMF and water, or ACN was added alkyl halide (R^4-X) (1.2-3 eq) and an appropriate base such as, but not limited to, Cs_2CO_3 or K_2CO_3 (3 eq). The resulting mixture was heated to 60-70 °C until reaction was complete as monitored by LC-MS and/or TLC. After cooling to room temperature, the reaction mixture was worked up using one of the following methods depending on whether **HP** was a carboxylic acid, an ester, or whether the ester formed from the carboxylic acid as a side product during the alkylation reaction. Method 1 (**HP** = carboxylic acid): The cooled reaction mixture was diluted with water and washed with EtOAc (3x). The aqueous phase was acidified to pH 3-4 with aq. 6 N HCl. The resulting solid was filtered and dried to give Compound **PA6-a**. Method 2 (**HP** = Me or Et ester or side product ester formed during the alkylation reaction): The cooled reaction mixture was diluted with water

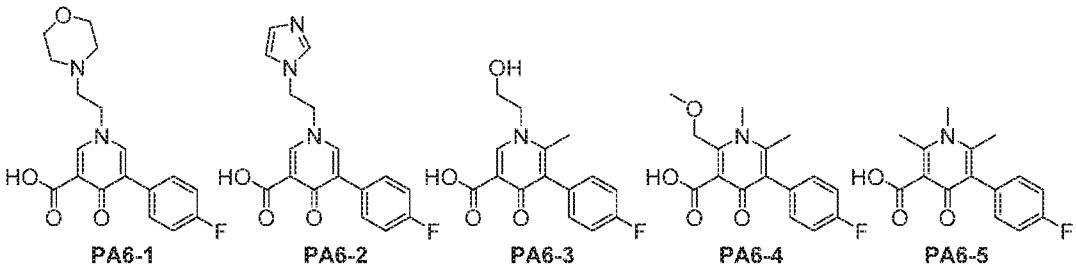
and extracted with EtOAc (3x). The combined organic extracts were washed with water, washed with aq. saturated NaCl, dried over anhyd. Na_2SO_4 and concentrated in vacuo. The crude residue was dissolved in MeOH (0.6-5.2 mL/mmol of **HP** used) to which was added aq. 1 N NaOH (0.6-5.2 mL/mmol of **HP** used) The resulting mixture was stirred at room temperature long enough to ensure complete hydrolysis of the ester to the corresponding carboxylic acid as monitored by LC-MS and/or TLC. MeOH was removed in vacuo and the resulting aqueous mixture was washed with EtOAc (3x). The aqueous phase was acidified with aq. 6 N HCl to pH 2-7. The resulting material was filtered, and the resulting solid allowed to air-dry to give crude Compound **PA6-a**. Regardless of the method, crude **PA6-a** was generally used in subsequent reactions without further purification. The carboxylic acids of **HP** can be generated by any of the methods described within. The esters of **HP** can be generated en route to the carboxylic acids previously described such as intermediate **C3** in **General Procedure C** or can be generated from the acids by standard esterification techniques. For example, to form the methyl ester of the carboxylic acid of **HP**, the acid can be dissolved in anhyd. MeOH to which is added 4 M HCl in dioxane. After stirring the resulting mixture at room temperature overnight, the corresponding crude methyl ester is recovered by concentration of the reaction mixture under vacuum.

Example of General Procedure F1: 5-(4-Fluorophenyl)-1-(2-morpholinoethyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA6-1)



[0367] 5-(4-Fluorophenyl)-1-(2-morpholinoethyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA6-1): To a solution of Compound **HP-1** (100 mg, 0.38 mmol, 1eq) in DMF (2 mL) was added Cs_2CO_3 (375 mg, 1.15 mmol, 3 eq) and 4-(2-chloroethyl)morpholine hydrochloride (86 mg, 0.46 mmol, 1.2 eq). The resulting mixture was heated to 60 °C for 15 min. The reaction mixture was allowed to cool to room temperature, diluted with water (3 ml) and extracted with EtOAc (3x). The combined organic extracts were washed with water, washed with aq. saturated NaCl, dried over anhyd. Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (2 mL) and 1 N NaOH (2 mL) was added. The resulting solution was stirred at room temperature for 2 h. The solvent was partially removed, and the resulting aqueous mixture was washed with EtOAc (3x). The aqueous layer was acidified with aq. 6 N HCl to pH neutral. The resulting precipitate was filtered and allowed to dry in the open air to give Compound **PA6-1** (66 mg, 50% yield) which was used in subsequent steps without further purification. MS of $C_{18}H_{19}FN_2O_4$: *m/z*: 347 (MH+).

[0368] The following intermediates were made following **General Procedure F** or **General Procedure F1** for the synthesis of 4-pyridone carboxylic acids **PA6** or **PA6-a**:



[0369] 5-(4-Fluorophenyl)-1-(2-morpholinoethyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA6-1): MS of $C_{18}H_{19}FN_2O_4$: *m/z*: 347 (MH+).

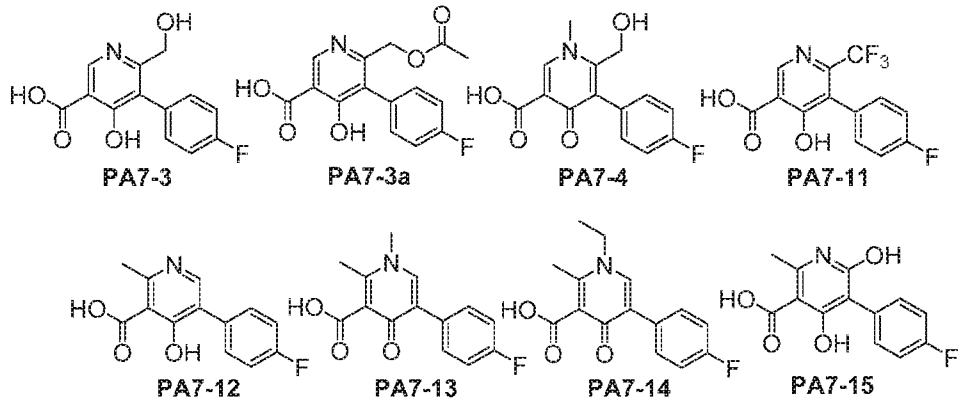
[0370] 1-(2-(1H-Imidazol-1-yl)ethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA6-2): MS for $C_{17}H_{14}FN_3O_3$: *m/z* 328 (MH+).

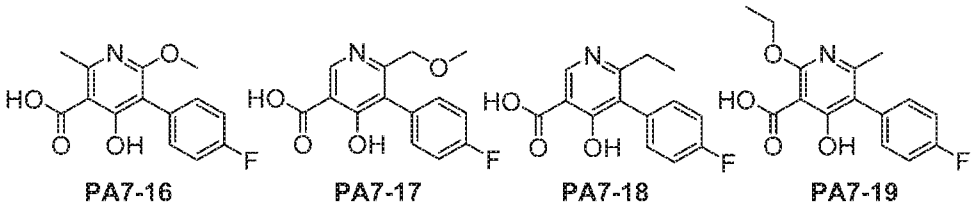
[0371] 5-(4-Fluorophenyl)-1-(2-hydroxyethyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA6-3): MS for $C_{15}H_{14}FNO_4$: *m/z* 292 (MH+).

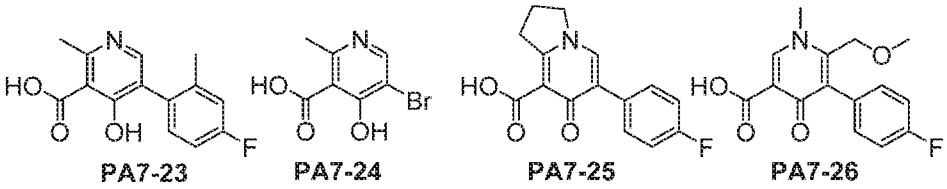
[0372] 5-(4-Fluorophenyl)-2-(methoxymethyl)-1,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA6-4): MS for $C_{16}H_{16}FNO_4$: *m/z* 306.1 (MH+).

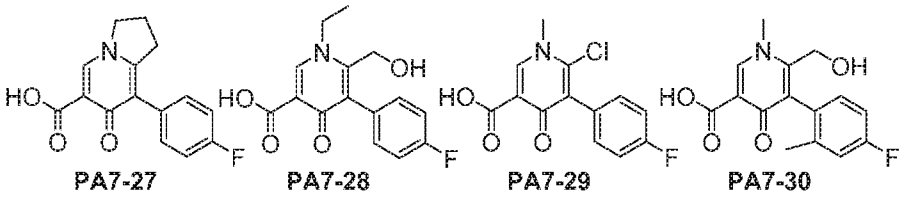
[0373] 5-(4-Fluorophenyl)-1,2,6-trimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA6-5): MS for $C_{15}H_{14}FNO_3$: *m/z* 276 (MH+).

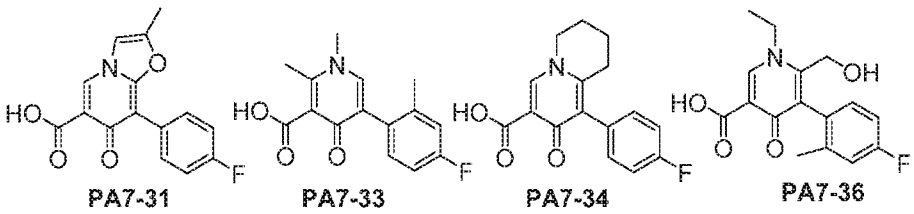
[0374] The following additional intermediates have been made using the synthetic methods detailed in **Examples 5 -61**:

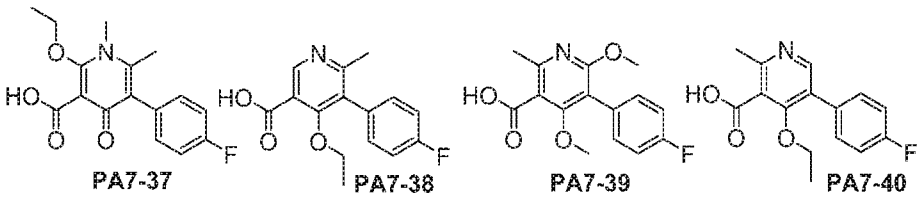


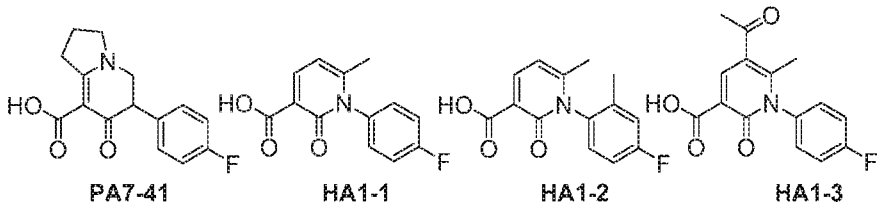

PA7-16 PA7-17 PA7-18 PA7-19

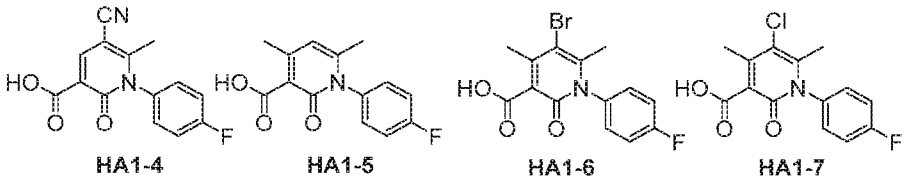

PA7-23 PA7-24 PA7-25 PA7-26

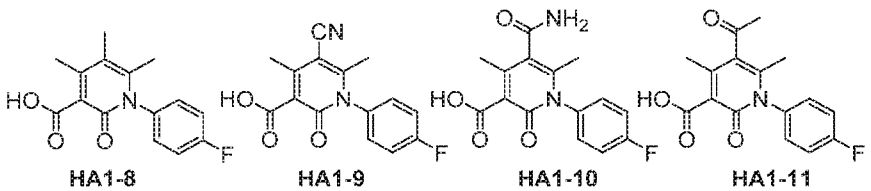

PA7-27 PA7-28 PA7-29 PA7-30

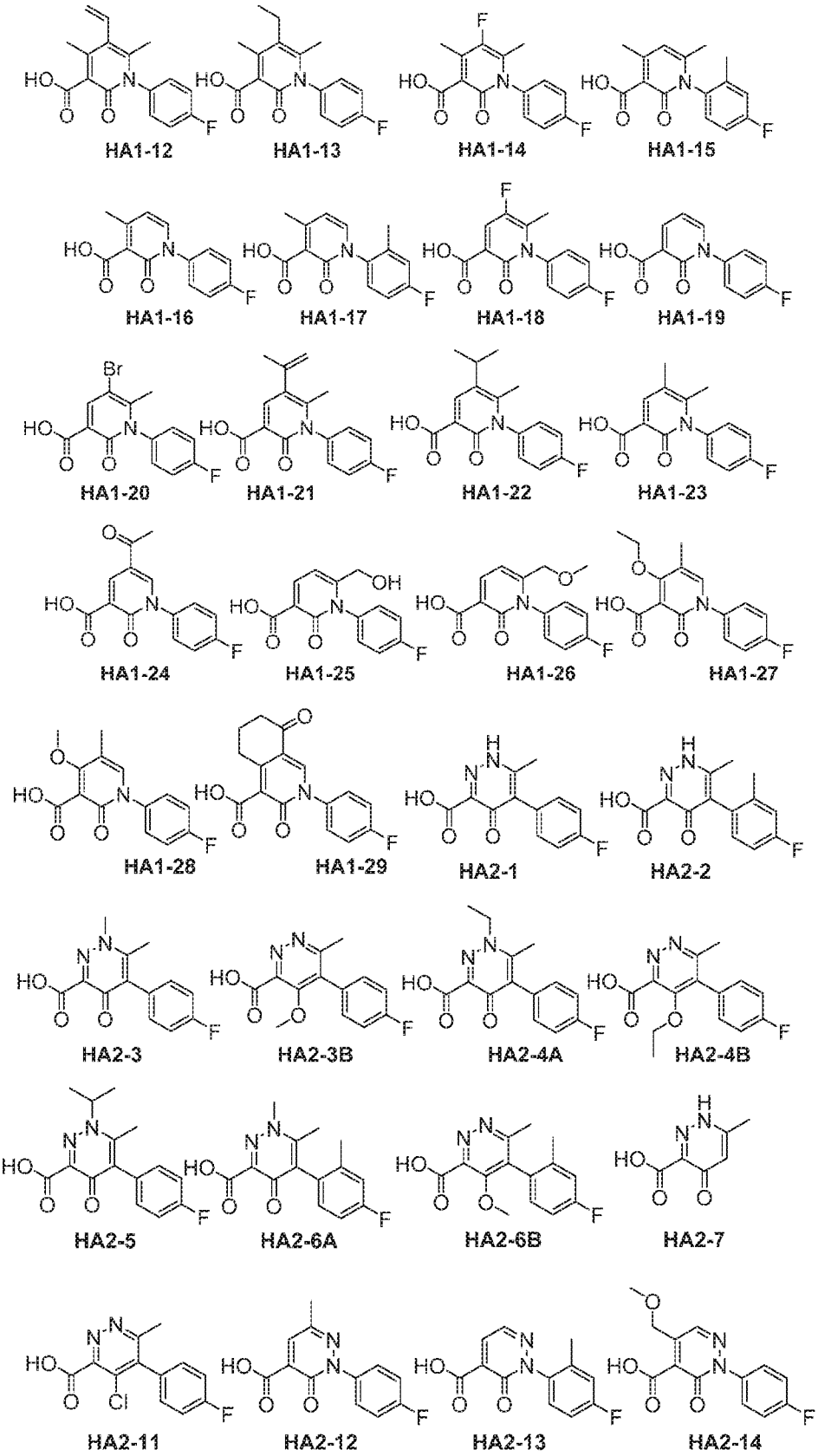

PA7-31 PA7-33 PA7-34 PA7-36

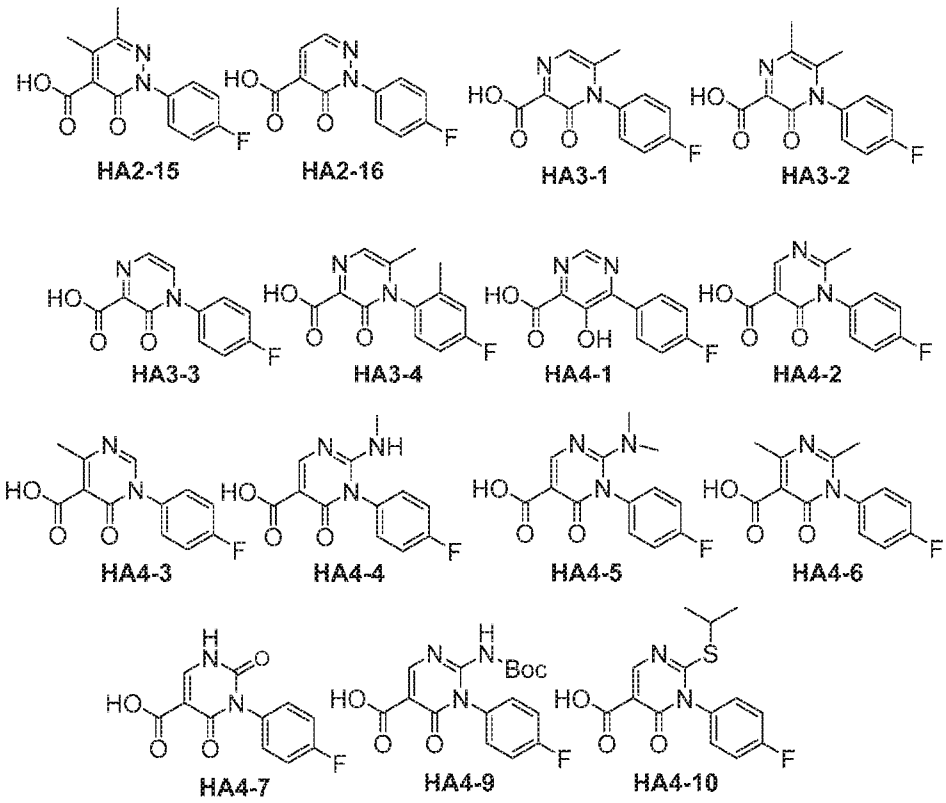

PA7-37 PA7-38 PA7-39 PA7-40


PA7-41 HA1-1 HA1-2 HA1-3

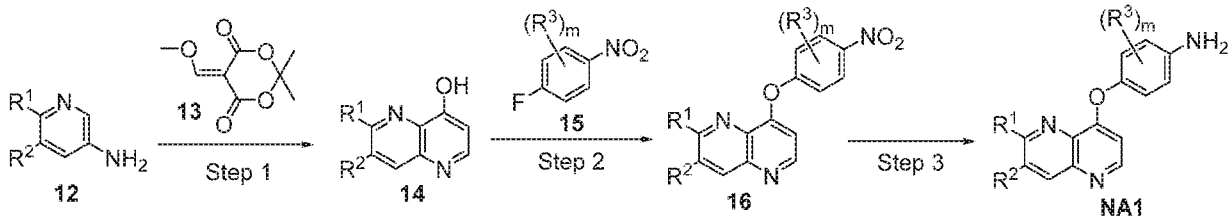

HA1-4 HA1-5 HA1-6 HA1-7


HA1-8 HA1-9 HA1-10 HA1-11


HA1-12
HA1-13
HA1-14
HA1-15
HA1-16
HA1-17
HA1-18
HA1-19
HA1-20
HA1-21
HA1-22
HA1-23
HA1-24
HA1-25
HA1-26
HA1-27
HA1-28
HA1-29
HA2-1
HA2-2
HA2-3
HA2-3B
HA2-4A
HA2-4B
HA2-5
HA2-6A
HA2-6B
HA2-7
HA2-11
HA2-12
HA2-13
HA2-14



General Procedure G: 4-((1,5-Naphthyridin-4-yl)oxy)anilines (NA1)



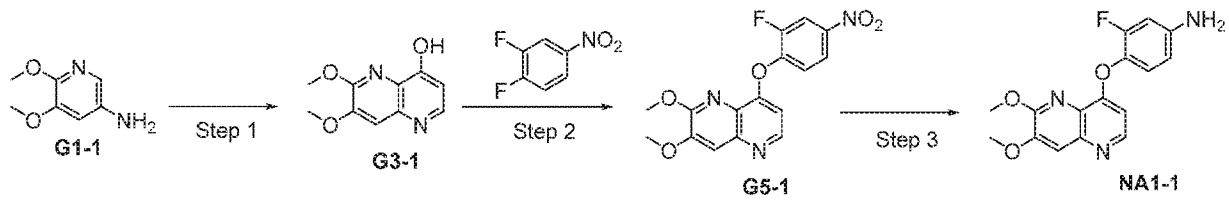
[0375] **Step 1:** A mixture of Compound **12** (32 mmol, 1 eq) and Compound **13** (5.92 g, 32 mmol, 1 eq) in toluene (50 mL, 1.5-1.6 mL/mmol of **12**) was stirred at 105 °C for 1.5 h and cooled to room temperature. Hexane (50 mL, 1.5-1.6 mL/mmol of **12** used) was added and the suspension filtered. This material was mixed with Ph_2O (50 mL, 1.5-1.6 mL/mmol of **12** used) and the resulting mixture was stirred at 220-230 °C for 1 h, cooled to room temperature and poured into Et_2O (100 mL, 3.0-3.2 mL/mmol of **12** used). The resulting suspension was filtered, washed with Et_2O and dried to give Compound **14**. Compound **13** can easily be generated from heating Meldrum's acid (1 eq) in trimethyl orthoformate (10 eq) at 110 °C for 1-2 h.

[0376] **Step 2:** A mixture of Compound **14** (4.8 mmol, 1 eq), Compound **15** (6.8 mmol, 1.4 eq), and Cs_2CO_3 (6.6 g, 20 mmol, 4.2 eq) in acetonitrile (20 mL, 4.2 mL/mmol of **14**) was stirred at room temperature overnight. EtOAc (80 mL, 16-17 mL/mmol of **14** was used) was added and the resulting mixture filtered. The filtrate was evaporated, and residue purified by silica gel column chromatography to give Compound **16**.

[0377] **Step 3:** A mixture of Compound **16** (1.8 mmol, 1 eq), NH_4Cl (500 mg, 9.3 mmol, 5.2 eq), and Fe (260 mg, 4.6 mmol, 2.6 eq) in MeOH / water (20 / 5 mL) (11 mL MeOH/mmol of **16** and 2.8 mL

water/mmol of **16**) was refluxed for 1 h and then cooled to room temperature. The resulting mixture was filtered through Celite and the filtrate concentrated to remove MeOH. To the residue was added aq. saturated $NaHCO_3$ (6 mL, 3.3 mL/mmol of **16** used) and the resulting aqueous mixture was extracted with EtOAc. The organic extract was dried over anhyd. Na_2SO_4 and evaporated give Compound **NA1**.

Example of General Procedure G: 4-((6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-1)

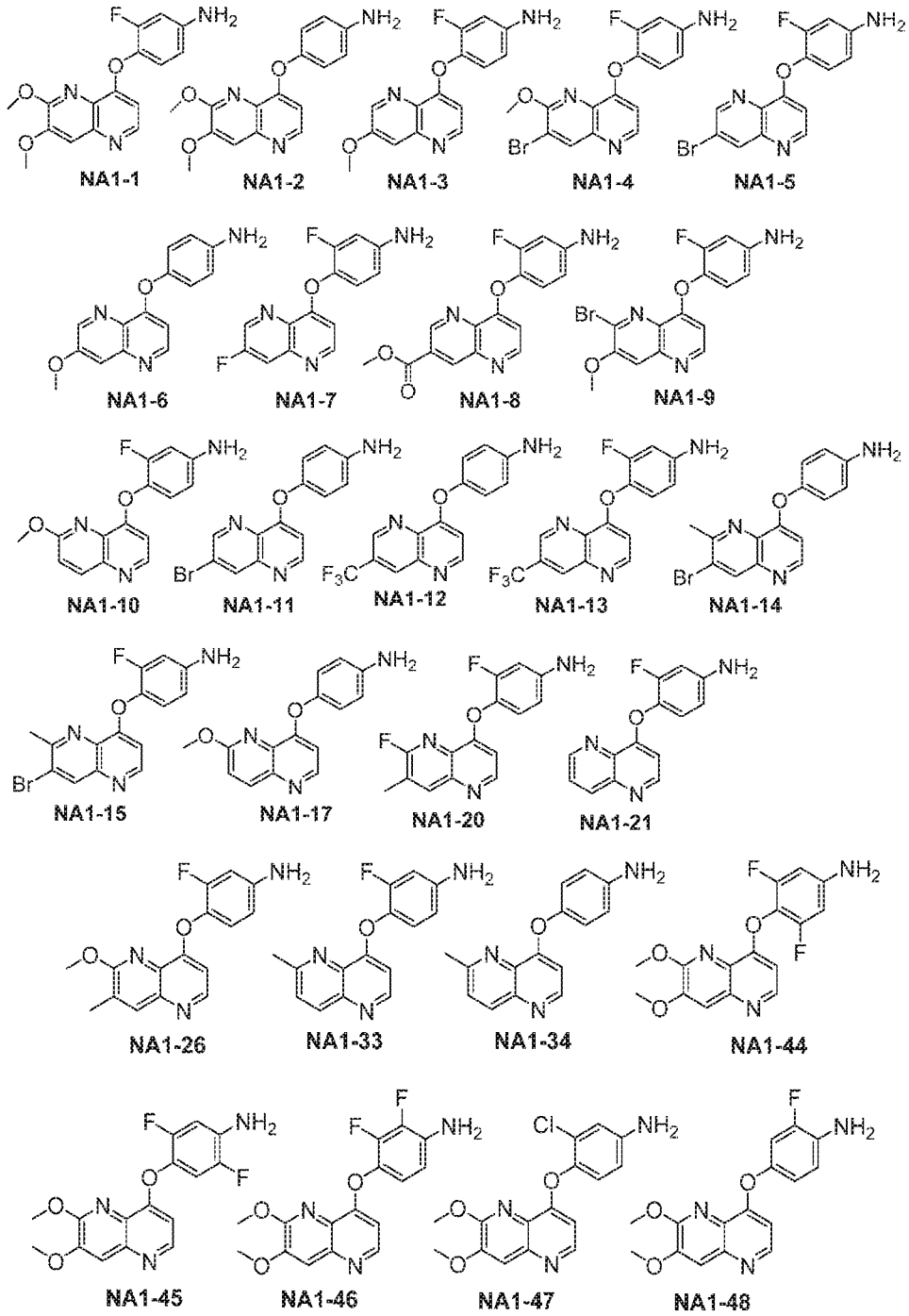


[0378] Step 1: 6,7-Dimethoxy-1,5-naphthyridin-4-ol (G3-1): A mixture of 2,2-dimethyl-1,3-dioxane-4,6-dione (2.7 g, 18.7 mmol, 1 eq) in trimethoxymethane (19.6 g, 185 mmol, 20.3 mL, 10 eq) was stirred at 110 °C for 1.5 h to form a yellow solution of Compound **13**. Compound **G1-1** (2.8 g, 18.5 mmol, 1 eq) was added to the above solution and the mixture was stirred at 110 °C for 0.5 h. The resulting brown suspension was filtered and the solid washed with petroleum ether (2 x 30 mL) and dried under vacuum to give the intermediate 5-[(E)-(5,6-dimethoxy-3-pyridyl)iminomethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione. A portion of this compound (2.2 g, 7.1 mmol) in Ph_2O (25 mL) was stirred at 230 °C for 0.5 h. To the reaction mixture was added methyl tert-butyl ether (MTBE) (100 mL) and the mixture stirred for 5 min and then filtered. The resulting solid was washed with MTBE (2 x 30 mL) and dried under vacuum to give Compound **G3-1** from the intermediate 5-[(E)-(5,6-dimethoxy-3-pyridyl)iminomethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (br s, 1H), 7.93-7.79 (m, 1H), 7.27 (s, 1H), 6.28-6.08 (m, 1H), 3.94 (s, 3H), 3.88 (s, 3H).

[0379] Step 2: 8-(2-Fluoro-4-nitrophenoxy)-2,3-dimethoxy-1,5-naphthyridine (G5-1): To mixture of Compound **G3-1** (2.1 g, 10.2 mmol, 1 eq) and 1,2-difluoro-4-nitro-benzene (1.6 g, 10.2 mmol, 1.13 mL, 1 eq) in ACN (50 mL) was added Cs_2CO_3 (6.6 g, 20.4 mmol, 2 eq) and the resulting mixture was stirred at room temperature for 15 h. The reaction mixture was filtered, and any solids washed with ACN (2 x 30 mL) and the resulting filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc) to give Compound G5-1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, 1H), 8.12 (dd, 1H), 8.01-7.96 (m, 1H), 7.53 (s, 1H), 7.17 (d, 1H), 7.03 (dd, 1H), 4.02 (s, 3H), 3.75 (s, 3H).

[0380] Step 3: 4-((6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-1): To a mixture of Compound **G5-1** (1.4 g, 3.9 mmol, 1 eq) in EtOH (20 mL) and water (5 mL) was added Fe (1.1 g, 19 mmol, 5 eq) and NH_4Cl (2.1 g, 39 mmol, 10 eq) and the resulting mixture was stirred at 80 °C for 15 h. The reaction mixture was filtered, and the filter cake was washed with MeOH (2 x 30 mL) and the filtrate concentrated under reduced pressure. The resulting solid was washed with water (2 x 50 mL) and dried under vacuum to give Compound **NA1-1**, which was used in subsequent reactions without further purification. MS of $C_{16}H_{14}FN_3O_3$: *m/z*: 315.9 (MH+).

[0381] The following intermediates were made following **General Procedure G** for the synthesis of 4-((1,5-Naphthyridin-4-yl)oxy)anilines **NA1**:



[0382] **4-((6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-1):** MS for $C_{16}H_{14}FN_3O_3$: *m/z* 316 (MH+).

[0383] **4-((6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy)aniline (NA1-2):** MS for $C_{16}H_{15}N_3O_3$: *m/z* 298 (MH+).

[0384] **3-Fluoro-4-((7-methoxy-1,5-naphthyridin-4-yl)oxy)aniline (NA1-3):** MS for $C_{15}H_{12}FN_3O_2$: *m/z* 286 (MH+).

[0385] **4-((7-Bromo-6-methoxy-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-4):** MS for $C_{15}H_{11}BrFN_3O_2$: *m/z* 364/366 (MH+).

[0386] **4-((7-Bromo-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-5):** MS for $C_{14}H_9BrFN_3O$: *m/z* 334/336 (MH+).

[0387] **4-((7-Methoxy-1,5-naphthyridin-4-yl)oxy)aniline (NA1-6):** MS for $C_{15}H_{13}N_3O_2$: *m/z* 268 (MH+).

[0388] **3-Fluoro-4-((7-fluoro-1,5-naphthyridin-4-yl)oxy)aniline (NA1-7):** MS for $C_{14}H_9F_2N_3O$: *m/z* 274 (MH+).

[0389] **Methyl 8-(4-amino-2-fluorophenoxy)-1,5-naphthyridine-3-carboxylate (NA1-8):** MS for $C_{16}H_{12}FN_3O_3$: *m/z* 314 (MH+).

[0390] **4-((6-Bromo-7-methoxy-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-9):** MS for $C_{15}H_{11}BrFN_3O_2$: *m/z* 364/366 (MH+).

[0391] **3-Fluoro-4-((6-methoxy-1,5-naphthyridin-4-yl)oxy)aniline (NA1-10):** MS for $C_{15}H_{12}FN_3O_2$: *m/z* 286.0 (MH+).

[0392] **4-((7-Bromo-1,5-naphthyridin-4-yl)oxy)aniline (NA1-11):** MS for $C_{14}H_{10}BrN_3O$: *m/z* 316/318 (MH+).

[0393] **4-((7-(Trifluoromethyl)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-12):** MS for $C_{15}H_{10}F_3N_3O$: *m/z* 306 (MH+).

[0394] **3-Fluoro-4-((7-(trifluoromethyl)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-13):** MS for $C_{15}H_9F_4N_3O$: *m/z* 324 (MH+).

[0395] **4-((7-Bromo-6-methyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-14):** MS for $C_{15}H_{12}BrN_3O$: *m/z* 330/332 (MH+).

[0396] **4-((7-Bromo-6-methyl-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-15):** MS for $C_{15}H_{11}BrFN_3O$: *m/z* 348/350 (MH+).

[0397] **4-((6-Methoxy-1,5-naphthyridin-4-yl)oxy)aniline (NA1-17):** MS for $C_{15}H_{13}N_3O_2$: *m/z* 268 (MH+).

[0398] **3-Fluoro-4-((6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-20):** MS for $C_{15}H_{11}F_2N_3O$: *m/z* 288 (MH+).

[0399] **4-((1,5-Naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-21):** MS for $C_{14}H_{10}FN_3O$: *m/z* 256 (MH+).

[0400] **3-Fluoro-4-((6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-26):** MS for $C_{16}H_{14}FN_3O_2$: *m/z* 300 (MH+).

[0401] **3-Fluoro-4-((6-methyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-33):** MS for $C_{15}H_{12}FN_3O$: *m/z* 270 (MH+).

[0402] **4-((6-Methyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-34):** MS for $C_{15}H_{13}N_3O$: *m/z* 252 (MH+).

[0403] **4-((6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy)-3,5-difluoroaniline (NA1-44):** MS for $C_{16}H_{13}F_2N_3O_3$: *m/z* 333.9 (MH+).

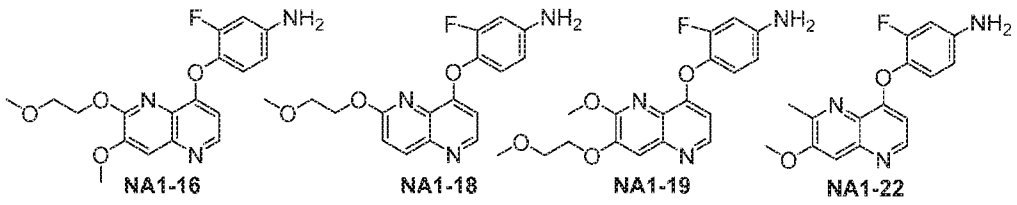
[0404] **4-((6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy)-2,5-difluoroaniline (NA1-45):** MS for $C_{16}H_{13}F_2N_3O_3$: *m/z* 334.0 (MH+).

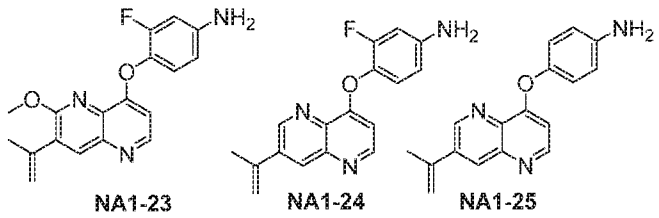
[0405] **4-((6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy)-2,3-difluoroaniline (NA1-46):** MS for $C_{16}H_{13}F_2N_3O_3$: *m/z* 333.9 (MH+).

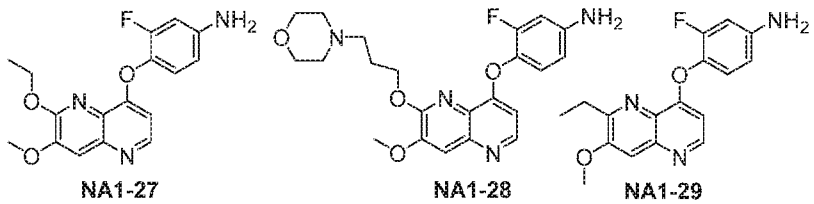
[0406] **3-Chloro-4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)aniline (NA1-47):** MS for $C_{16}H_{14}ClN_3O_3$: *m/z* 331.9 (MH+).

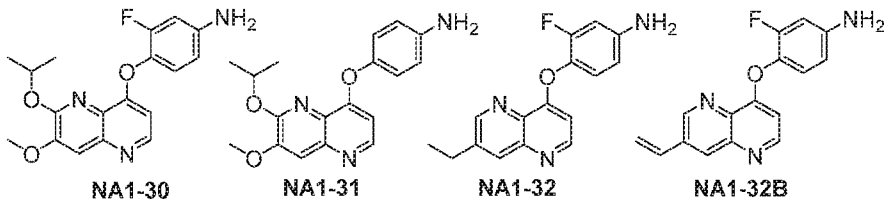
[0407] **4-((6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy)-2-fluoroaniline (NA1-48):** MS for $C_{16}H_{14}FN_3O_3$: *m/z* 316.0 (MH+).

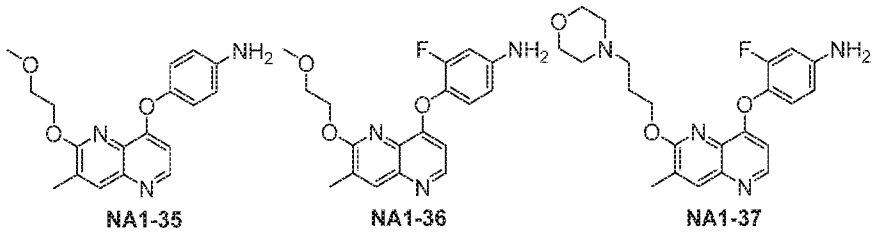
[0408] The following additional intermediates have been made using the synthetic methods detailed in **Examples 61 -71**:

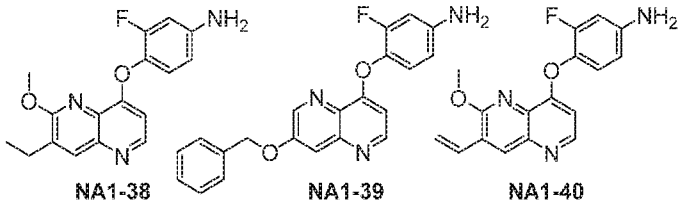


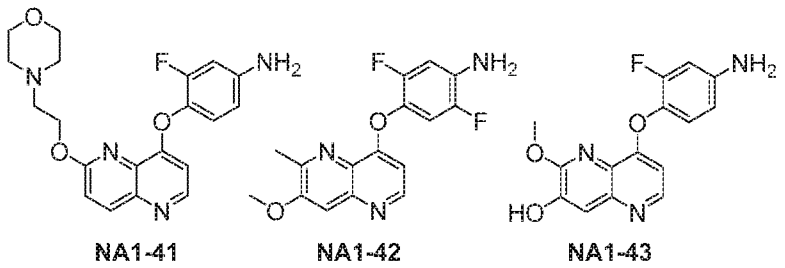


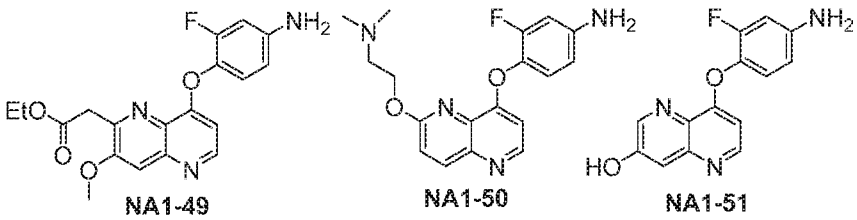




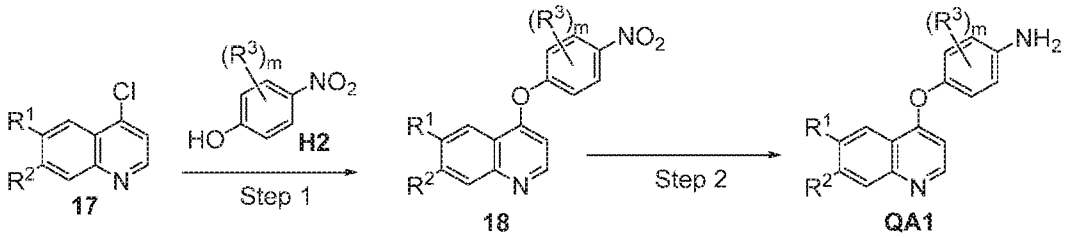








General Procedure H: 4-(Quinolin-4-yloxy)aniline (QA1)



[0409] **Step 1:** To a mixture of Compound **17** (44.7 mmol, 1 eq) and Compound **H2** (62.5 mmol, 1.4 eq) in 2,6-dimethylpyridine (50 mL) was added DMAP (1.10 g, 9.0 mmol, 0.2 eq). The mixture was stirred at 140 °C for 36 h. The reaction was cooled to room temperature, MeOH (32 g) was added, followed by aq. K_2CO_3 (4 g in water (62 g)). The resulting mixture was stirred at 0 °C for 2 h. The resulting mixture was filtered and washed with water (200 mL) to give the Compound **18**.

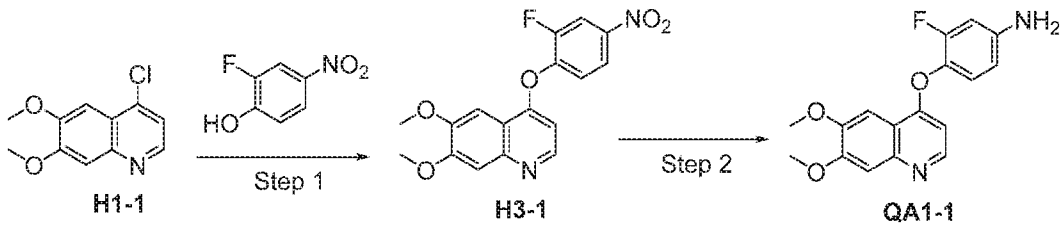
[0410] Step 1 can also be performed as follows: A mixture of Compound **17** (1 eq) and Compound **H2** (1.2-1.4 eq) in an appropriate solvent such as, but not limited to, 2,6-dimethylpyridine or diphenyl ether (1.1-2.2 mL/mmol of **17**) was stirred at 140 °C for typically 36-66 h. DMAP (0.2 eq) can also be optionally added as a catalyst. Upon completion of the reaction as monitored by LC-MS and/or TLC, the reaction mixture was allowed to cool to room temperature and typically worked up by one of the following methods or a similar variation. Method 1: MeOH (0.9 mL/mmol of **17** used) was added,

followed by aq. 6.5% K_2CO_3 (1.4 mL/mmol of **17** used). The resulting mixture was stirred at 0 °C for 2 h. The resulting mixture was filtered and washed with water (4.5 mL/mmol of **17** used) to give Compound **18**. Method 2: The mixture was diluted with MTBE (2.2 mL/mmol of **17** used) and filtered. The resulting solid was washed with MTBE (0.4 mL/mmol of **17** used) and dried under vacuum to give Compound **18**. Regardless of the method of work up, the crude Compound **18** was generally used in subsequent reactions without further purification.

[0411] **Step 2:** To a mixture of Compound **18** (6.1 mmol, 1 eq) in EtOH (40 mL) and water (8 mL) was added Fe (1.71 g, 30.6 mmol, 5.0 eq) and NH_4Cl (2.62 g, 49.0 mmol, 8.0 eq). The mixture was stirred at 85 °C for 3 h. The reaction was filtered, and the filtrate was dried over anhyd. Na_2SO_4 and concentrated to give crude product. To this crude product was added EtOAc (150 mL) and DCM (150 mL). The resulting mixture was filtered, and the filtrate was concentrated to give Compound **QA1**.

[0412] Step 2 can also be performed as follows: To a mixture of Compound **18** (1 eq) in EtOH (4.5-6.5 mL/mmol of **18**) and water (1.1-1.3 mL/mmol of **18**) was added Fe (5.0 eq) and NH_4Cl (8-10 eq). The mixture was stirred at 85 °C for 3-4 h. Upon completion of the reaction as monitored by LC-MS and/or TLC, the reaction mixture was allowed to cool to room temperature and typically worked up by one of the following methods or a similar variation. Method 1: The reaction was filtered, and the filtrate was dried over anhyd. Na_2SO_4 and concentrated to give crude product. To this crude product was added EtOAc (25 mL/mmol of **18** used) and DCM (25 mL/mmol of **18** used). The resulting mixture was filtered, and the filtrate was concentrated to give Compound **QA1**. Method 2: The mixture was filtered through Celite, the filtrate was concentrated under vacuum and the residue was dissolved in EtOAc (11.2 mL/mmol of **18** used). The organic layer was washed with aq. saturated $NaHCO_3$ (6.7 mL/mmol of **18** used), washed with water (6.7 mL/mmol of **18** used), washed with aq. saturated NaCl (6.7 mL/mmol of **18** used), dried over anhyd. Na_2SO_4 and concentrated under vacuum to give Compound **QA1**. Regardless of the method of work up, the crude Compound **QA1** was generally used in subsequent reactions without further purification.

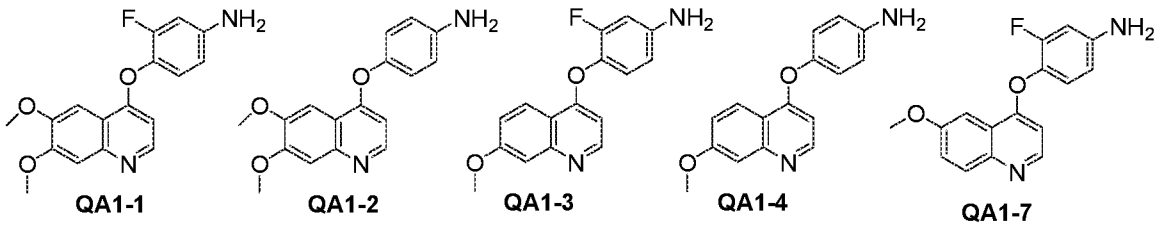
Example of General Procedure H: 4-((6,7-Dimethoxyquinolin-4-yl)oxy)-3-fluoroaniline (QA1-1)



[0413] **Step 1: 4-(2-Fluoro-4-nitrophenoxy)-6,7-dimethoxyquinoline (H3-1):** A suspension of Compound **H1-1** (10 g, 45 mmol, 1 eq) and 2-fluoro-4-nitro-phenol (8.4 g, 54 mmol, 1.2 eq) in Ph_2O (100 mL) was heated and stirred at 140 °C for 66 h. After cooling to room temperature, the mixture was diluted with MTBE (100 mL) and filtered. The filtered cake was washed with MTBE (20 mL) and dried under vacuum to give Compound **H3-1,** which was used in subsequent steps without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (d, 1H), 8.56 (dd, 1H), 8.35-8.27 (m, 1H), 7.89 (t, 1H), 7.79-7.71 (m, 2H), 7.17 (d, 1H), 4.04 (d, 6H); MS for $C_{17}H_{13}FN_2O_5$: *m/z* 344.9 (MH+).

[0414] **Step 2: 4-((6,7-Dimethoxyquinolin-4-yl)oxy)-3-fluoroaniline (QA1-1):** Fe (12.5 g, 223 mmol, 5 eq) was added to a mixture of Compound **H3-1** (16.2 g, 45 mmol, 1 eq) and NH_4Cl (23.9 g, 447 mmol, 10 eq) in EtOH (200 mL) and water (50 mL). The mixture was heated and stirred at 85 °C for 3.5 h. After cooling to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under vacuum and the residue was dissolved in EtOAc (500 mL). The organic layer was washed with aq. $NaHCO_3$ (300 mL), washed with water (300 mL), washed with aq. saturated NaCl (300 mL), dried over anhyd. Na_2SO_4 and concentrated under vacuum to give Compound **QA1-1,** which was used in subsequent reactions without further purification. MS for $C_{17}H_{15}FN_2O_3$: *m/z* 315.0 (MH+).

[0415] The following intermediates were made following **General Procedure H** for the synthesis of 4-(quinolin-4-yloxy)anilines **QA1**:



[0416] **4-((6,7-Dimethoxyquinolin-4-yl)oxy)-3-fluoroaniline (QA1-1):** MS for $C_{17}H_{15}FN_2O_3$: *m/z* 315 (MH+).

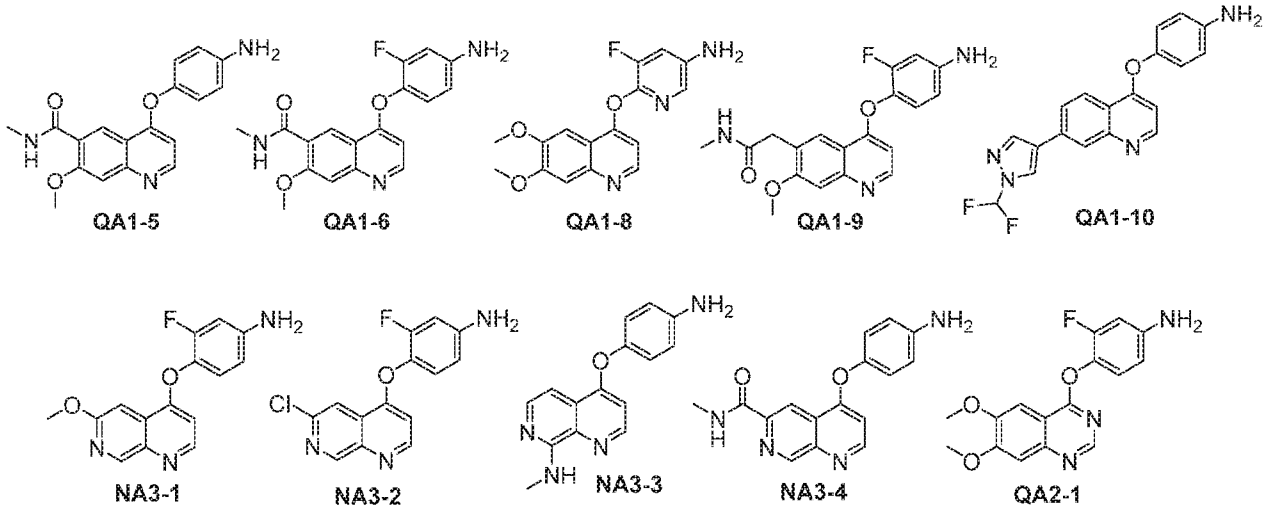
[0417] **4-((6,7-Dimethoxyquinolin-4-yl)oxy)aniline (QA1-2):** MS for $C_{17}H_{16}N_2O_3$: *m/z* 297.2 (MH+).

[0418] **3-Fluoro-4-((7-methoxyquinolin-4-yl)oxy)aniline (QA1-3):** MS for $C_{16}H_{13}FN_2O_2$: *m/z* 285 (MH+).

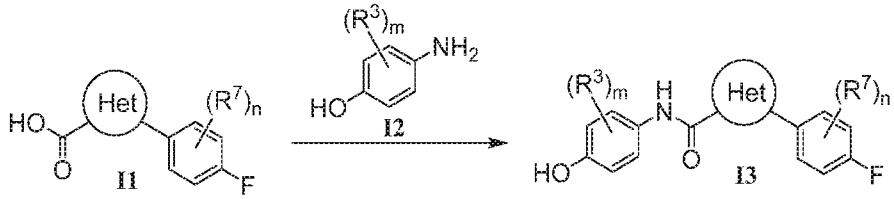
[0419] **4-((7-Methoxyquinolin-4-yl)oxy)aniline (QA1-4):** MS for $C_{16}H_{14}N_2O_2$: *m/z* 267 (MH+).

[0420] **3-Fluoro-4-((6-methoxyquinolin-4-yl)oxy)aniline (QA1-7):** MS for $C_{16}H_{13}FN_2O_2$, *m/z* 285 (MH+).

[0421] The following additional intermediates have been made using the synthetic methods detailed in **Examples 72 -80**:

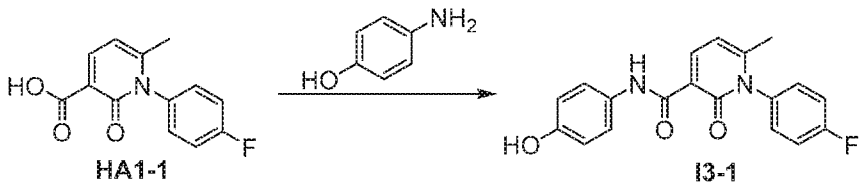


General Procedure I: 4-Hydroxyphenyl carboxamides (I3)



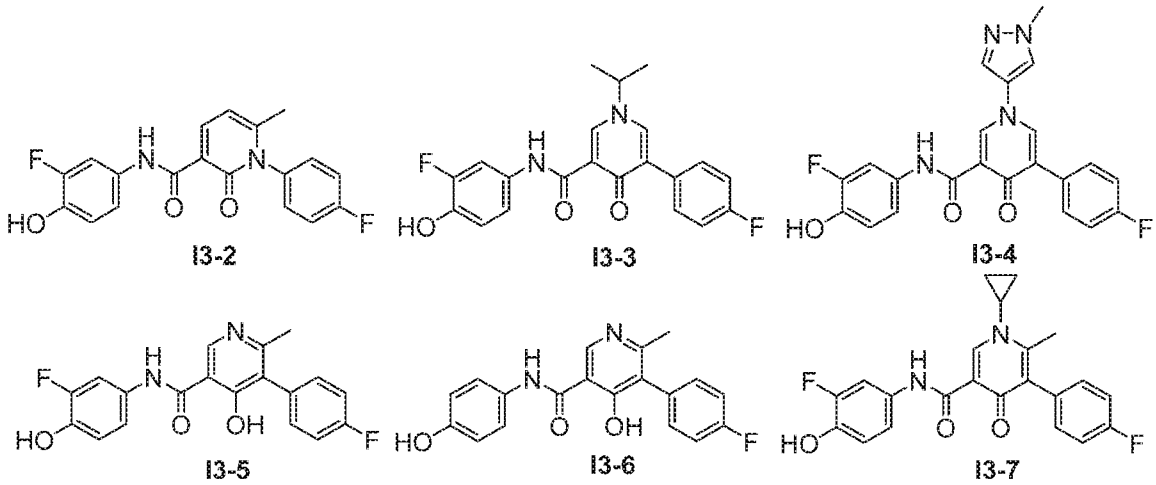
[0422] Compound **I1** can be any of the heterocyclic acids described herein (i.e. **PA-Br**, **PA-Ph**, **PA1**, **PA2**, **PA3**, **PA4**, **PA5**, **PA6**, **PA7**, **HA1**, **HA2**, **HA3**, **HA4**, and the like). The hydroxyl of Compound **I2** can optionally be protected with a benzyl group, which is then removed after the coupling reaction by standard hydrogenation techniques. To a mixture of Compound **I2** (1 eq) and Compound **I1** (1.1 eq) in DMF (2.2 mL/mmol of **I2**) was added HATU (1.1 eq) and DIEA (3 eq). The resulting solution was stirred at 25 °C for 12-15 h. The reaction mixture was diluted with EtOAc (54 mL/mmol of **I2** used) and washed with a 1:1 mixture of water:aq. saturated NaCl (4 x 108 mL/mmol of **I2** used). The organic layer was dried over anhyd. Na_2SO_4 and concentrated. The resulting residue was purified by silica gel column chromatography to give Compound **I3**.

Example of General Procedure I: 1-(4-fluorophenyl)-N-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (I3-1)



[0423] **1-(4-fluorophenyl)-N-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (I3-1):** To a mixture of 4-aminophenol (100 mg, 0.92 mmol, 0.14 mL, 1 eq) and Compound **HA1-1** (249 mg, 1.0 mmol, 1.1 eq) in DMF (2 mL) was added HATU (383 mg, 1.0 mmol, 1.1 eq) and DIEA (355 mg, 2.8 mmol, 0.48 mL, 3 eq). The resulting solution was stirred at 25 °C for 15 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with a 1:1 mixture of water:aq. saturated NaCl (4 x 100 mL). The organic layer was dried over anhyd. Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel column chromatography (DCM:MeOH) to give Compound **I3-1**. MS for $C_{19}H_{15}FN_2O_3$: *m/z* 339.1 (MH+).

[0424] The following compounds were made using **General Procedure I** to form compounds of formula **I3**:



[0425] N-(3-Fluoro-4-hydroxyphenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (I3-2): The 4-aminophenol was replaced with 4-amino-2-fluorophenol. MS for $C_{19}H_{14}F_2N_2O_3$: *m/z* 357 (MH+).

[0426] N-(3-Fluoro-4-hydroxyphenyl)-5-(4-fluorophenyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxamide (I3-3): Compound **HA1-1** was replaced with **PA1-3**. The 4-aminophenol was replaced with 4-amino-2-fluorophenol.

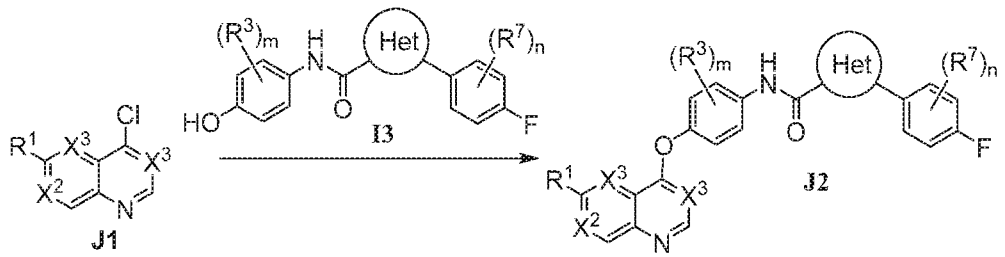
[0427] N-(3-Fluoro-4-hydroxyphenyl)-5-(4-fluorophenyl)-1-(1-methyl-1H-pyrazol-4-yl)-4-oxo-1,4-dihydropyridine-3-carboxamide (I3-4): Compound **HA1-1** was replaced with **PA1-11**. The 4-aminophenol was replaced with 4-amino-2-fluorophenol.

[0428] N-(3-Fluoro-4-hydroxyphenyl)-5-(4-fluorophenyl)-4-hydroxy-6-methylnicotinamide (I3-5): Compound **HA1-1** was replaced with **PA3-1**. The 4-aminophenol was replaced with 4-amino-2-fluorophenol. MS for $C_{19}H_{14}F_2N_2O_3$: *m/z* 357 (MH+).

[0429] 5-(4-Fluorophenyl)-4-hydroxy-N-(4-hydroxyphenyl)-6-methylnicotinamide (I3-6): Compound **HA1-1** was replaced with **PA3-1**. MS for $C_{19}H_{15}FN_2O_3$: *m/z* 339 (MH+).

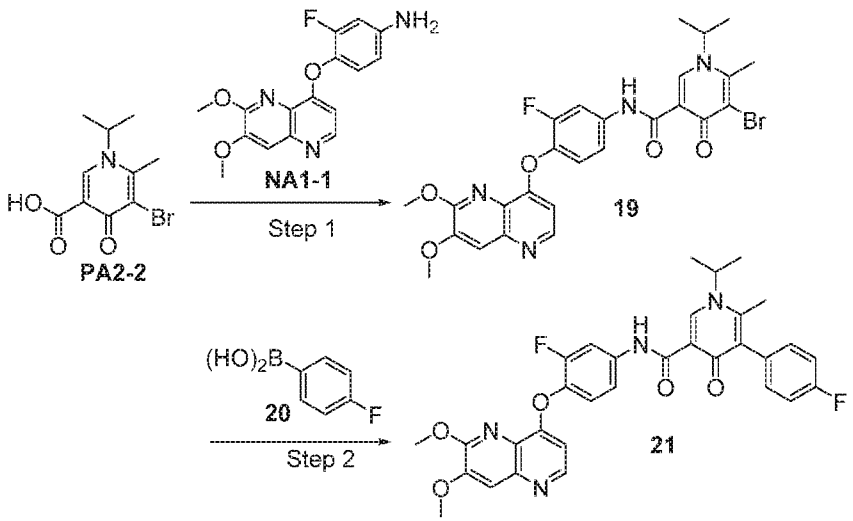
[0430] 1-Cyclopropyl-N-(3-fluoro-4-hydroxyphenyl)-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (I3-7): Compound **HA1-1** was replaced with **PA7-35**. The 4-aminophenol was replaced with 4-(benzyloxy)-3-fluoroaniline to initially form N-(4-(benzyloxy)-3-fluorophenyl)-1-cyclopropyl-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide which was subsequently subject to standard hydrogenation techniques to give Compound **I3-7**. MS for $C_{22}H_{18}F_2N_2O_3$: *m/z* 397 (MH+).

General Procedure J: SNAr Reaction with I3 (J2)



[0431] To a solution of Compound **J1** (1 eq) and Compound **I3** (0.9-1.1 eq) in an appropriate solvent such as, but not limited to DMF or THF (2.7-5.0 mL/mmol of **J1**) was added Cs_2CO_3 (2-6 eq). The reaction mixture was heated to 60-80 °C until the reaction was complete as determined by LC-MS and/or TLC. The reaction mixture was diluted with water and extracted with EtOAc (3 x 135 mL/mmol of **J1** used). The combined organic layers were washed with aq. saturated NaCl (270 mL/mmol of **J1** used), dried over anhyd. Na_2SO_4 and concentrated. Alternatively, the reaction mixture can be diluted with EtOAc and filtered. The filtrate is then washed with water (2x), dried over anhyd. Na_2SO_4 and concentrated. In a modification of the reaction, a mixture of Compound **J1** (1 eq), Compound **I3** (1 eq), DIEA (4.8 eq) and DMSO (16 mL/mmol of **J1**) was heated at 100 °C until the reaction was complete as determined by LC-MS and/or TLC. The reaction mixture was diluted with water (167 mL/mmol of **J1** used), sonicated, filtered and the resulting solid was washed with water. Regardless of which reaction or work up was used, the resulting residue/solid was purified by prep-HPLC to give Compound **J2**.

Example 1: N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (21)



[0432] **Step 1: 5-Bromo-N-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-1-isopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (19).** To a mixture of Compound **NA1-1** (360 mg, 1.14 mmol), Compound **PA2-2** (360 mg, 1.31 mmol) and HATU (1.15 g, 3.03 mmol) in DMF (4 mL) was added DIEA (1.0 mL, 5.7 mmol) and the reaction was stirred at room temperature until reaction completion as monitored by LC-MS or TLC. Aq. saturated $NaHCO_3$ (10 mL) and water (10 mL) were added and resulting suspension was filtered. The resulting material was washed with water and dried to give crude Compound **19** which was used in the next step without further purification. MS for $C_{26}H_{24}BrFN_4O_5$: *m/z* 571/573 (MH+).

[0433] **Step 2: N-(4-((6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-isopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (21):** A mixture of Compound **19** (57 mg, 0.10 mmol), Compound **20** (70 mg, 0.50 mmol), K_3PO_4, (64 mg, 0.30 mmol), XPhos Pd G2 (20 mg, 0.1 mmol), water (0.5 mL) and dioxane (3.0 mL) was degassed with nitrogen for 3 minutes and then stirred at 90 °C for 5h. The mixture was extracted with EtOAc (2x) and the combined

extracts concentrated. The residue was purified by silica gel column chromatography, eluted with EtOAc and further purified by Prep HPLC to give Compound **21**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 8.63 (d, 1H), 8.48 (d, 1H), 7.94 (dd, 1H), 7.58 (s, 1H), 7.34 (d, 1H), 7.40 – 7.15 (m, 5H), 6.76 (d, 1H), 4.72 (q, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.22 (s, 3H), 1.44 (d, 6H); MS for $C_{32}H_{28}F_2N_4O_5$: *m/z* 587 (MH+).

[0434] The following compounds were made following a method analogous that used to synthesize Compound **21** in Example 1 in two steps from Compounds **NA1-1** and **PA2-2**. Where HCl salts are indicated, the target compounds were general converted to the HCl salts by first dissolving the compound in 20% MeOH in DCM, passing it through an Agilent PL-HCO3 ion exchange column and concentrating under reduced pressure (alternatively, the compound was dissolved in DCM and washed with aq. saturated sodium bicarbonate and then concentrated). Secondly, HCl (4 M in Dioxane, 0.5 mL; or 1 M aqueous, 1 mL) was added and the volatile solvents were removed under reduced pressure and the resulting residue dried under high vacuum to give the desired final product as the hydrochloride salt.

[0435] **N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (22):** Compound **NA1-1** was replaced with Compound **QA1-1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (s, 1H), 8.64 (s, 1H), 8.41 (d, 1H), 7.98 (dd, 1H), 7.44 – 7.10 (m, 8H), 6.42 (d, 1H), 4.72 (p, 1H), 3.88 (s, 6H), 2.22 (s, 3H), 1.45 (d, 6H); MS for $C_{33}H_{29}F_2N_3O_5$: *m/z* 586 (MH+).

[0436] **5-(3,4-Dichlorophenyl)-N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (23):** Compound **NA1-1** was replaced with Compound **QA1-1**. Compound **20** was replaced with (3,4-dichlorophenyl)boronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.78 – 8.57 (m, 2H), 8.05 (d, 1H), 7.75 – 7.59 (m, 2H), 7.47 (dd, 4H), 7.18 (d, 1H), 6.84 (d, 1H), 4.74 (p, 1H), 3.96 (d, 6H), 2.25 (s, 3H), 1.45 (d, 6H); MS for $C_{33}H_{28}Cl_2FN_3O_5$: *m/z* 636 (MH+).

[0437] **5-(3-Chloro-4-fluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (24):** Compound **20** was replaced with (3-chloro-4-fluorophenyl)boronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (s, 1H), 8.64 (s, 1H), 8.48 (d, 1H), 7.94 (dd, 1H), 7.58 (s, 1H), 7.49 – 7.07 (m, 5H), 6.77 (d, 1H), 4.72 (p, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.24 (s, 3H), 1.44 (d, 6H); MS for $C_{32}H_{27}ClF_2N_4O_5$: *m/z* 621 (MH+).

[0438] **5-(3,4-Dichlorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (25):** Compound **20** was replaced with (3,4-dichlorophenyl)boronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 8.64 (s, 1H), 8.48 (d, 1H), 7.95 (d, 1H), 7.66 (d, 1H), 7.58 (s, 1H), 7.47 (d, 1H), 7.35 (d, 1H), 7.29 – 7.12 (m, 2H), 6.77 (d, 1H), 4.82 – 4.62 (m, 1H), 3.90 (s, 3H), 3.86 (d, 3H), 2.25 (s, 3H), 1.44 (d, 6H); MS for $C_{32}H_{27}Cl_2FN_4O_5$: *m/z* 637 (MH+).

[0439] **N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (26):** Compound **PA2-2** was replaced with Compound

PA2-3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.58 (d, 1H), 8.48 (d, 1H), 7.94 (d, 1H), 7.58 (d, 1H), 7.33 (d, 1H), 7.22 (dd, 5H), 6.77 (t, 1H), 4.83 (t, 1H), 3.90 (d, 3H), 3.86 (d, 3H), 2.30 – 2.10 (m, 5H), 1.74 (d, 6H). MS for $C_{34}H_{30}F_2N_4O_5$: *m/z* 613 (MH+).

[0440] 5-(3-Chloro-4-fluorophenyl)-1-cyclopentyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxopyridine-3-carboxamide (27): Compound **PA2-2** was replaced with Compound **PA2-3.** Compound **20** was replaced with (3-chloro-4-fluorophenyl)boronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.57 (s, 1H), 8.48 (d, 1H), 7.94 (d, 1H), 7.58 (s, 1H), 7.52 – 7.11 (m, 5H), 6.76 (d, 1H), 4.94 – 4.73 (m, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 2.25 (s, 3H), 2.25 – 2.10 (m, 2H), 1.90 – 1.60 (m, 6H); MS for $C_{34}H_{29}ClF_2N_4O_5$: *m/z* 647 (MH+).

[0441] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (28): Compound **PA2-2** was replaced with Compound **PA2-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.09 (s, 1H), 12.54 (s, 1H), 8.51 – 8.36 (m, 2H), 7.94 (dd, 1H), 7.58 (s, 1H), 7.34 (ddd, 1H), 7.28 – 7.07 (m, 5H), 6.75 (dd, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 2.11 (s, 3H); MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545 (MH+).

[0442] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-5-phenyl-1-propan-2-ylpyridine-3-carboxamide hydrochloride (29): Compound **20** was replaced with phenylboronic acid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.89 (s, 1H), 8.74 (d, 1H), 8.11 (dd, 1H), 7.61 (s, 1H), 7.57 – 7.35 (m, 6H), 7.25 (ddd, 2H), 4.92 (t, 1H), 4.19 (s, 3H), 4.16 (s, 3H), 2.37 (s, 3H), 1.63 (dd, 6H); MS for $C_{32}H_{29}FN_4O_5$: *m/z* 569.3 (MH+).

[0443] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide hydrochloride (30): Compound **20** was replaced with (3-fluorophenyl)boronic acid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.89 (s, 1H), 8.74 (d, 1H), 8.11 (dd, 1H), 7.60 (s, 1H), 7.58 – 7.38 (m, 2H), 7.28 – 7.11 (m, 2H), 7.11 – 6.98 (m, 2H), 6.71 – 6.43 (m, 1H), 4.92 (q, 1H), 4.19 (s, 3H), 4.16 (s, 3H), 2.38 (s, 3H), 1.63 (d, 6H); MS for $C_{32}H_{28}F_2N_4O_5$: *m/z* 587.3 (MH+).

[0444] N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-methoxyphenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide hydrochloride (31): Compound **20** was replaced with (4-methoxyphenyl)boronic acid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.75 (s, 1H), 8.62 (d, 1H), 7.99 (d, 1H), 7.51 (s, 1H), 7.37 (dt, 2H), 7.12 (d, 1H), 7.07 (dd, 2H), 6.98 – 6.91 (m, 2H), 4.86 – 4.77 (m, 1H), 4.07 (s, 3H), 4.04 (s, 3H), 3.76 (s, 3H), 2.27 (d, 3H), 1.56 – 1.43 (m, 6H); MS for $C_{33}H_{31}FN_4O_6$: *m/z* 599.3 (MH+).

[0445] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide hydrochloride (32): Compound **20** was replaced with (4-fluoro-2-methylphenyl)boronic acid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.91 (s, 1H), 8.74 (d, 1H), 8.11 (dd, 1H), 7.63 (s, 1H), 7.57 – 7.40 (m, 2H), 7.23 (d, 1H), 7.19 – 6.99 (m, 3H), 4.92 (q, 1H), 4.19 (s, 3H), 4.16 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H), 1.63 (d, 6H); MS for $C_{33}H_{30}F_2N_4O_5$: *m/z* 601.3 (MH+).

[0446] N-**[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide hydrochloride (33):** Compound **33** can be made by replacing Compound **PA2-2** with Compound **PA4-1** and replacing Compound **20** with phenylboronic acid. Compound **33** was also made using the method exemplified in Example 2 where Compound **PA1-2** was replaced with Compound **PA3-8**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.75 (dd, 2H), 8.13 (dd, 1H), 8.04 (d, 1H), 7.70 – 7.61 (m, 3H), 7.58 – 7.36 (m, 5H), 7.24 (dd, 1H), 4.20 (s, 3H), 4.16 (s, 3H), 4.00 (s, 3H); MS for $C_{29}H_{23}FN_4O_5$: *m/z* 527.1 (MH+).

[0447] N-**[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-methoxyphenyl)-1-methyl-4-oxopyridine-3-carboxamide hydrochloride (34):** Compound **34** can be made by replacing Compound **PA2-2** with Compound **PA4-1** and replacing Compound **20** with (3-fluorophenyl)boronic acid. Compound **34** was also made using the method exemplified in Example 2 where Compound **PA1-2** was replaced with Compound **PA3-9.** ^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (d, 1H), 8.70 (d, 1H), 8.12 (dd, 1H), 7.98 (d, 1H), 7.68 – 7.55 (m, 3H), 7.56 – 7.42 (m, 2H), 7.22 (d, 1H), 7.10 – 7.00 (m, 2H), 4.19 (s, 3H), 4.16 (s, 3H), 3.98 (s, 3H), 3.86 (s, 3H); MS for $C_{30}H_{25}FN_4O_6$: *m/z* 557.1 (MH+).

[0448] **N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide hydrochloride (35):** Compound **35** can be made by replacing Compound **PA2-2** with Compound **PA4-1** and replacing Compound **20** with (4-methoxyphenyl)boronic acid. Compound **35** was also made using the method exemplified in Example 2 where Compound **PA1-2** was replaced with **Compound PA3-10**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (d, 1H), 8.67 (d, 1H), 8.15 – 8.03 (m, 2H), 7.61 (s, 1H), 7.56 – 7.36 (m, 5H), 7.21 – 7.04 (m, 2H), 4.15 (s, 3H), 4.12 (s, 3H), 4.00 (s, 3H); MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545.1 (MH+).

[0449] **N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1,6-dimethyl-4-oxo-5-phenylpyridine-3-carboxamide hydrochloride (36):** Compound **QA1-1** was replaced with Compound **NA1-1**. Compound **PA2-2** was replaced with Compound **PA2-7.** Compound **20** was replaced with phenylboronic acid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.80 (s, 1H), 8.74 (d, 1H), 8.10 (dd,1H), 7.62 (s, 1H), 7.48 (ddt, 5H), 7.31 – 7.24 (m, 2H), 7.22 (dd, 1H), 4.19 (s, 3H), 4.16 (s, 3H), 3.96 (s, 3H), 2.30 (s, 3H); MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541.2 (MH+).

[0450] **N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide hydrochloride (37):** Compound **QA1-1** was replaced with Compound **NA1-1**. Compound **PA2-2** was replaced with Compound **PA2-7.** Compound **20** was replaced with (3-fluorophenyl)boronic acid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.81 (s, 1H), 8.74 (d, 1H), 8.10 (dd, 1H), 7.61 (s, 1H), 7.58 – 7.39 (m, 3H), 7.27 – 7.13 (m, 2H), 7.14 – 7.01 (m, 2H), 4.19 (s, 3H), 4.16 (s, 3H), 3.96 (s, 3H), 2.32 (s, 3H); MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0451] **5-(4-Chlorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-methyl-4-oxopyridine-3-carboxamide hydrochloride (38):** Compound **38** can be made by replacing Compound **PA2-2** with Compound **PA4-1** and replacing Compound **20** with (4-chlorophenyl)boronic acid. Compound **38** was also made using the method exemplified in Example 2 where Compound **PA1-2**

was replaced with Compound **PA3-11**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.77 – 8.70 (m, 2H), 8.14 (dd, 1H), 8.07 (d, 1H), 7.67 (d, 2H), 7.61 (s, 1H), 7.58 – 7.43 (m, 4H), 7.24 (dd, 1H), 4.20 (s, 3H), 4.17 (s, 3H), 4.00 (s, 3H); MS for $C_{29}H_{22}ClFN_4O_5$: *m/z* 561 (MH+).

[0452] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide hydrochloride (39): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **39** can be made by replacing Compound **PA2-2** with Compound **PA4-1** and replacing Compound **20** with phenylboronic acid**.** Compound **39** was also made using the method exemplified in Example 2 where Compound **PA1-2** was replaced with Compound **PA3-8**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.75 (d, 1H), 8.70 (d, 1H), 8.04 (d, 1H), 8.00 – 7.91 (m, 2H), 7.69 – 7.61 (m, 2H), 7.60 (s, 1H), 7.54 – 7.39 (m, 3H), 7.39 – 7.30 (m, 2H), 7.15 (d, 1H), 4.22 (s, 3H), 4.16 (s, 3H), 4.01 (s, 3H); MS for $C_{29}H_{24}N_4O_5$: *m/z* 509.2 (MH+).

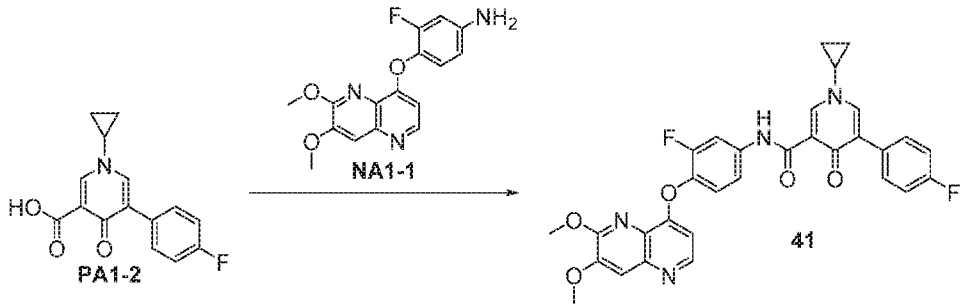
[0453] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide hydrochloride (40): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **40** can be made by replacing Compound **PA2-2** with Compound **PA4-1** and replacing Compound **20** with phenylboronic acid**.** Compound **40** was also made using the method exemplified in Example 2 where Compound PA1-2 was replaced with Compound PA3-8. ^{1}H NMR (400 MHz, CD_3OD) δ 9.04 – 8.96 (m, 2H), 8.76 (d, 1H), 8.17 (dd, 1H), 8.05 (d, 1H), 7.81 (d, 1H), 7.69 – 7.61 (m, 2H), 7.61 – 7.37 (m, 5H), 7.27 (dd, 1H), 4.19 (s, 3H), 4.01 (s, 3H); MS for $C_{28}H_{21}FN_4O_4$: *m/z* 497.2(MH+).

[0454] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2,6-dimethylphenyl)-1-methyl-4-oxopyridine-3-carboxamide (268): Compound **PA2-2** was replaced with Compound **PA4-1**. Compound **20** was replaced with (4-fluoro-2,6-dimethylphenyl)boronic acid. MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0455] N-[3-Fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (501): Compound **NA1-1** was replaced with Compound **NA3-1**. Compound **PA2-2** was replaced with Compound **C4-A**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.41 (s, 1H), 11.48 (s, 1H), 9.18 (s, 1H), 8.65 (d, 1H), 8.04 (d, 1H), 7.48 – 7.40 (m, 3H), 7.34 – 7.21 (m, 4H), 6.75 (d, 1H), 5.05 (s, 2H), 4.02 (s, 3H), 3.50 (d, 3H), 2.24 (s, 3H); MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0456] N-[4-[(6-Chloro-1,7-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (502): Compound **NA1-1** was replaced with Compound **NA3-2**. Compound **PA2-2** was replaced with Compound **C4-A**. MS for $C_{29}H_{21}ClF_2N_4O_4$: *m/z* 563.0 (MH+).

Example 2: 1-Cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (41)



[0457] 1-Cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (41). Compound **NA1-1** was coupled to Compound **PA1-2** using standard HATU coupling procedures similar to that used in **Step 1** of **Example 1** for coupling Compound **NA1-1** to Compound **PA2-2**. After the reaction was complete and the reaction mixture was poured into the aq. saturated $NaHCO_3$ and the resulting suspension was filtered, the recovered material was purified by silica gel column chromatography or prep-HPLC to give Compound **41**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 8.57 (s, 1H), 8.49 (d, 1H), 8.07 (s, 1H), 7.96 (d, 1H), 7.67 (d, 2H), 7.59 (s, 1H), 7.39 (d, 1H), 7.24 (dt, 3H), 6.78 (d, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.81 (t, 1H), 1.18 (s, 2H), 1.01 (d, 2H); MS for $C_{31}H_{24}F_2N_4O_5$: *m/z* 571 (MH+).

[0458] The following compounds were made following a method analogous to that used to synthesize Compound **41** in Example 2 in one step from Compounds **NA1-1** and **PA1-2**. Where HCl salts are indicated, the target compounds were generally converted to the HCl salts by first dissolving the compound in 20% MeOH in DCM, passing it through an Agilent PL-HCO3 ion exchange column and concentrating under reduced pressure (alternatively, the compound was dissolved in DCM and washed with aq. saturated sodium bicarbonate and then concentrated). Secondly, HCl (4 M in Dioxane, 0.5 mL; or 1 M aqueous, 1 mL) was added and the volatile solvents were removed under reduced pressure and the resulting residue dried under high vacuum to give the desired final product as the hydrochloride salt.

[0459] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide (42): Compound **PA1-2** was replaced with Compound **PA1-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (s, 1H), 12.61 (t, 1H), 8.56 (d, 1H), 8.49 (d, 1H), 8.03 (d, 1H), 8.01 – 7.93 (m, 1H), 7.64 (dd, 2H), 7.59 (s, 1H), 7.38 (d, 1H), 7.23 (dt, 3H), 6.78 (d, 1H), 3.89 (d, 6H); MS for $C_{28}H_{20}F_2N_4O_5$: *m/z* 531 (MH+).

[0460] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide (43): Compound **NA1-1** was replaced with Compound **QA1-1**. Compound **PA1-2** was replaced with Compound **PA1-3.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.17 (s, 1H), 8.71 (d, 1H), 8.42 (d, 1H), 8.21 (d, 1H), 8.00 (dd, 1H), 7.67 (dd, 2H), 7.49 – 7.32 (m, 4H), 7.22 (t, 2H), 6.43 (d, 1H), 4.58 (p, 1H), 3.88 (s, 6H), 1.45 (d, 6H); MS for $C_{32}H_{27}F_2N_3O_5$: *m/z* 572 (MH+).

[0461] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide (44): Compound **PA1-2** was replaced with Compound

PA1-3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 8.70 (d, 1H), 8.48 (d, 1H), 8.21 (d, 1H), 8.01 – 7.92 (m, 1H), 7.66 (dd, 2H), 7.58 (s, 1H), 7.38 (d, 1H), 7.24 (dt, 3H), 6.77 (d, 1H), 4.61 – 4.54 (m, 1H), 3.92 – 3.85 (m, 6H), 1.45 (d, 6H); MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0462] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (45): Compound **PA1-2** was replaced with Compound **PA1-4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (s, 1H), 8.63 (d, 1H), 8.48 (d, 1H), 8.09 (d, 1H), 7.96 (dd, 1H), 7.71 – 7.61 (m, 2H), 7.58 (s, 1H), 7.38 (dt, 1H), 7.31 – 7.17 (m, 3H), 6.76 (d, 1H), 3.90 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H); MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545 (MH+).

[0463] 1-Cyclopentyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (46): Compound **PA1-2** was replaced with Compound **PA1-6**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.16 (s, 1H), 8.74 (s, 1H), 8.56 (d, 1H), 8.22 (d, 1H), 8.05 (d, 1H), 7.74 (dd, 2H), 7.66 (s, 1H), 7.46 (d, 1H), 7.32 (dt, 3H), 6.85 (d, 1H), 4.78 (t, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 2.24 (s, 2H), 1.92 (d, 4H), 1.68 (s, 2H); MS for $C_{33}H_{28}F_2N_4O_5$: *m/z* 599 (MH+).

[0464] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(oxetan-3-yl)-4-oxopyridine-3-carboxamide (47): Compound **PA1-2** was replaced with Compound **PA1-7**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 8.78 (d, 1H), 8.49 (t, 1H), 8.30 (d, 1H), 7.97 (d, 1H), 7.79 – 7.63 (m, 2H), 7.59 (d, 1H), 7.40 (d, 1H), 7.26 (dt, 3H), 6.77 (d, 1H), 5.52 (q, 1H), 4.90 (dt, 4H), 4.01 – 3.81 (m, 6H); MS for $C_{31}H_{24}F_2N_4O_6$: *m/z* 587 (MH+).

[0465] 1-tert-Butyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (48): Compound **PA1-2** was replaced with Compound **PA1-8**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.09 (s, 1H), 8.96 (d, 1H), 8.53 (d, 1H), 8.07 (d, 2H), 7.84 (d, 1H), 7.58 (dd, 2H), 7.53 – 7.37 (m, 1H), 7.22 (m, 3H), 6.92 (s, 1H), 4.20 (s, 3H), 4.14 (s, 3H), 1.76 (s, 9H); MS for $C_{32}H_{28}F_2N_4O_5$: *m/z* 587 (MH+).

[0466] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide (49): Compound **PA1-2** was replaced with Compound **PA1-9**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.52 (s, 1H), 8.56 (d, 1H), 8.44 (d, 1H), 7.90 (d, 1H), 7.78 (s, 1H), 7.46 (q, 3H), 7.32 (d, 1H), 7.11 (q, 3H), 6.76 (d, 1H), 4.47 (q, 2H), 4.07 (d, 3H), 4.00 (s, 3H); MS for $C_{30}H_{21}F_5N_4O_5$: *m/z* 613 (MH+).

[0467] 1-Cyclobutyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (50): Compound **PA1-2** was replaced with Compound **PA1-10**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.62 (d, 1H), 8.48 (d, 1H), 8.17 (d, 1H), 7.96 (dd, 1H), 7.71 – 7.61 (m, 2H), 7.58 (s, 1H), 7.38 (ddd, 1H), 7.33 – 7.10 (m, 3H), 6.77 (d, 1H), 4.84 (p, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 2.53 – 2.29 (m, 4H), 1.88 – 1.55 (m, 2H); MS for $C_{32}H_{26}F_2N_4O_5$: *m/z* 585 (MH+).

[0468] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide (51): Compound **PA1-2** was replaced with Compound **PA1-11**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 8.74 (d, 1H), 8.56 (d, 1H), 8.49 (s,

1H), 8.34 (d, 1H), 8.08 (d, 1H), 8.07 – 7.97 (m, 1H), 7.86 – 7.71 (m, 2H), 7.66 (s, 1H), 7.55 – 7.43 (m, 1H), 7.43 – 7.22 (m, 3H), 6.86 (d, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.92 (s, 3H); MS for $C_{32}H_{24}F_2N_6O_5$: *m/z* 611 (MH+).

[0469] N-[4-[(6,7-Dmethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylazetidin-3-yl)-4-oxopyridine-3-carboxamide (52): Compound **PA1-2** was replaced with Compound **PA1-25**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 8.92 (d, 1H), 8.48 (d, 1H), 8.28 (d, 1H), 7.97 (dd, 1H), 7.72 – 7.61 (m, 2H), 7.59 (s, 1H), 7.39 (ddd, 1H), 7.32 – 7.13 (m, 3H), 6.77 (d, 1H), 4.93 (tt, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.64 – 3.41 (m, 4H), 2.27 (s, 3H). MS for $C_{32}H_{27}F_2N_5O_5$: *m/z* 600 (MH+).

[0470] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-3-yl)-4-oxopyridine-3-carboxamide (53): Compound **PA1-2** was replaced with Compound **PA1-12**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 9.07 (d, 1H), 8.49 (d, 1H), 8.43 (d, 1H), 7.98 (dd, 1H), 7.86 (d, 1H), 7.75 – 7.63 (m, 2H), 7.59 (s, 1H), 7.42 (ddd, 1H), 7.26 (dt, 3H), 6.87 (d, 1H), 6.82 – 6.74 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H); MS for $C_{32}H_{24}F_2N_6O_5$: *m/z* 611 (MH+).

[0471] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(3-methyloxetan-3-yl)-4-oxopyridine-3-carboxamide (54): Compound **PA1-2** was replaced with Compound **PA1-27**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.81 (s, 1H), 8.50 (d, 1H), 8.37 (d, 1H), 7.98 (s, 1H), 7.93 (q, 1H), 7.46 (m, 2H), 7.35 (m, 1H), 7.28 (d, 1H), 7.17 (t, 2H), 7.08 (t, 1H), 6.81 (d, 1H), 5.06 (d, 2H), 4.65 (d, 2H), 4.09 (s, 3H), 4.02 (s, 3H), 1.93 (s, 3H); MS for $C_{32}H_{26}F_2N_4O_6$: *m/z* 601.2 (MH+).

[0472] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-1-(3-methyloxetan-3-yl)-4-oxopyridine-3-carboxamide (55): Compound **NA1-1** was replaced with Compound **QA1-1**. Compound **PA1-2** was replaced with Compound **PA1-27.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (s, 1H), 8.40 (d, 1H), 8.37 (d, 1H), 7.90 (q, 1H), 7.51 (s, 1H), 7.46 (m, 2H), 7.35 (m, 2H), 7.26 (d, 1H), 7.13 (m, 3H), 6.38 (d, 1H), 5.06 (d, 2H), 4.65 (d, 2H), 3.98 (d, 3H), 3.40 (s, 3H), 1.93 (s, 3H); MS for $C_{33}H_{27}F_2N_3O_6$: *m/z* 600.2 (MH+).

[0473] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-hydroxy-2-methylpropan-2-yl)-4-oxopyridine-3-carboxamide (56): Compound **PA1-2** was replaced with Compound **PA1-28**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.89 (s, 1H), 8.78 (d, 1H), 8.35 (d, 1H), 7.87 (q, 1H), 7.75 (d, 1H), 7.40 (m, 3H), 7.25 (m, 1H), 7.18 (s, 1H), 7.07 (m, 3H), 6.64 (d, 1H), 4.03 (s, 3H), 3.93 (s, 3H), 3.77 (s, 2H), 1.63 (s, 6H); MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603.3 (MH+).

[0474] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-hydroxy-2-methylpropan-2-yl)-4-oxopyridine-3-carboxamide (57): Compound **NA1-1** was replaced with Compound **QA1-1**. Compound **PA1-2** was replaced with Compound **PA1-28.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.88 (s, 1H), 8.78 (d, 1H), 8.25 (d, 1H), 7.91 (dd, 1H), 7.71 (d, 1H), 7.49 (s, 1H), 7.35 – 7.29 (m, 2H), 7.27 (s, 1H), 7.18 (s, 1H), 7.14 (t, 1H), 7.01 (t, 2H), 6.30 (dd, 1H), 3.98 (s, 3H), 3.96 (d, 1H), 3.94 (s, 3H), 3.79 (s, 2H), 1.63 (s, 6H); MS for $C_{33}H_{29}F_2N_3O_6$: *m/z* 602.3 (MH+).

[0475] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (58): Compound **PA1-2** was replaced with Compound **PA3-7**. ^{1}H NMR (400 MHz, CD_3OD) δ 13.11 (s, 1H), 8.79 (s, 1H), 8.70 (d, 1H), 8.19 – 8.00 (m, 2H), 7.58 (s, 1H), 7.52 – 7.36 (m, 2H), 7.35 – 7.20 (m, 3H), 7.17 (d, 1H), 4.17 (s, 3H), 4.14 (s, 3H), 3.96 (s, 3H), 2.31 (s, 3H); MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0476] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-[1-(trifluoromethyl)cyclopropyl]pyridine-3-carboxamide (59): Compound **PA1-2** was replaced with Compound **PA1-15**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (s, 1H), 8.62 (d, 1H), 8.49 (d, 1H), 8.27 (d, 1H), 7.96 (dd, 1H), 7.69 – 7.60 (m, 2H), 7.58 (s, 1H), 7.40 (dd, 1H), 7.25 (dt, 3H), 6.78 (d, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 1.86 (s, 2H), 1.75 – 1.52 (m, 2H). MS for $C_{32}H_{23}F_5N_4O_5$: *m/z* 639 (MH+).

[0477] 1-[1-(Difluoromethyl)pyrazol-4-yl]-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (60): Compound **PA1-2** was replaced with Compound **PA1-16**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 9.03 (s, 1H), 8.78 (d, 1H), 8.49 (d, 1H), 8.44 (s, 1H), 8.37 (d, 1H), 8.24 – 7.78 (m, 2H), 7.78 – 7.65 (m, 2H), 7.59 (s, 1H), 7.42 (dd, 1H), 7.26 (dt, 3H), 6.78 (d, 1H), 3.90 (s, 3H), 3.87 (d, 3H). MS for $C_{32}H_{22}F_4N_6O_5$: *m/z* 647 (MH+).

[0478] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(1H-pyrazol-3-yl)pyridine-3-carboxamide (61): Compound **PA1-2** was replaced with Compound **PA1-14**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 12.78 (s, 1H), 9.11 (d, 1H), 8.55 – 8.44 (m, 2H), 7.98 (dd, 1H), 7.95 – 7.89 (m, 1H), 7.79 – 7.65 (m, 2H), 7.59 (s, 1H), 7.48 – 7.35 (m, 1H), 7.26 (dt, 3H), 6.91 (t, 1H), 6.79 (d, 1H), 3.90 (s, 3H), 3.87 (d, 3H). MS for $C_{31}H_{22}F_2N_6O_5$: *m/z* 597 (MH+).

[0479] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(1H-pyrazol-4-yl)pyridine-3-carboxamide (62): Compound **PA1-2** was replaced with Compound **PA1-13**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.34 (s, 1H), 12.98 (s, 1H), 8.78 (d, 1H), 8.61 – 8.49 (m, 2H), 8.37 (d, 1H), 8.15 (d, 1H), 8.06 (dd, 1H), 7.83 – 7.74 (m, 2H), 7.66 (s, 1H), 7.49 (ddd, 1H), 7.42 – 7.22 (m, 3H), 6.86 (d, 1H), 3.98 (s, 3H), 3.95 (s, 3H). MS for $C_{31}H_{22}F_2N_6O_5$: *m/z* 597 (MH+).

[0480] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (63): Compound **PA1-2** was replaced with Compound **PA3-4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 8.78 (s, 1H), 8.55 (d, 1H), 8.01 (dd, 1H), 7.66 (s, 1H), 7.42 (dd, 1H), 7.39 – 7.19 (m, 5H), 6.83 (d, 1H), 4.28 (q, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 2.26 (s, 3H), 1.40 (t, 3H); MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0481] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (64): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA3-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (s, 1H), 12.56 (s, 1H), 8.76 (d, 1H), 8.71 (d, 1H), 8.57 (s, 1H), 8.06 (dd, 1H), 7.81 (d, 1H), 7.54 – 7.17 (m, 6H), 6.75 (dd, 1H), 4.01 (s, 3H), 2.19 (s, 3H); MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515 (MH+).

[0482] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (65): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA3-7.** ^{1}H NMR (400 MHz, CD_3OD) δ 8.90 (s, 1H), 8.70 (d, 1H), 7.93 (d, 2H), 7.62 (s, 1H), 7.39 – 7.22 (m, 6H), 7.14 (d, 1H), 4.21 (s, 3H), 4.16 (s, 3H), 4.00 (s, 3H), 2.34 (s, 3H); MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541.2 (MH+).

[0483] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (66): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA5-2.** ^{1}H NMR (400 MHz, CD_3OD) δ 9.00 (d, 1H), 8.96 (d, 1H), 8.11 (d, 1H), 7.78 (d, 1H), 7.50 (d, 2H), 7.33 (dd, 2H), 7.25 (t, 3H), 4.19 (s, 3H), 2.83 (s, 3H), 2.27 (s, 3H); MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529.2 (MH+).

[0484] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (67): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA5-2.** ^{1}H NMR (DMSO-d_6) δ: 13.35 (s, 1H), 11.96 (s, 1H), 8.63 (d, 1H), 8.29 (d, 1H), 8.00 (dd, 1H), 7.38 (dd, 1H), 7.35 – 7.20 (m, 6H), 6.96 (d, 1H), 3.94 (s, 3H), 2.75 (s, 3H), 2.15 (s, 3H); MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529.2 (MH+).

[0485] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (68): Compound **NA1-1** was replaced with Compound **NA1-16**. Compound **PA1-2** was replaced with Compound **PA3-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.2 (s, 1H), 12.6 (s, 1H), 8.56 (s, 1H), 8.55 (d, 1H), 8.01 (dd, 1H), 7.66 (s, 1H), 7.40 (dd, 1H), 7.36 – 7.22 (m, 5H), 6.86 (d, 1H), 4.46 (t, 2H), 3.98 (s, 3H), 3.65 (t, 2H), 3.28 (s, 3H), 2.18 (s, 3H); MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589 (MH+).

[0486] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (69): Compound **PA1-2** was replaced with Compound **PA7-1**. MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559 (MH+).

[0487] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (70): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA7-2.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0488] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(hydroxymethyl)pyridine-3-carboxamide (71): Compound **PA1-2** was replaced with Compound **PA7-3**. Compound **71** may also be obtained by replacing Compound **PA1-2** with Compound **PA7-3a** with subsequent hydrolysis of the acetyl group to give the hydroxyl using standard methods such as stirring in the presence of LiOH in a mixture of water and THF at room temperature. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (s, 1H), 12.30 (s, 1H), 8.58 (s, 1H), 8.55 (dd, 1H), 8.01 (dd, 1H), 7.66 (d, 1H), 7.42 (d, 1H), 7.37 – 7.22 (m, 5H), 6.83 (d, 1H), 5.97 (s, 1H), 4.34 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H); MS for $C_{29}H_{22}F_2N_4O_6$: *m/z* 561 (MH+).

[0489] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide (72): Compound **PA1-2** was replaced with Compound **PA7-4**. MS for $C_{30}H_{24}F_2N_4O_6$: *m/z* 575 (MH+).

[0490] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide (74): Compound **PA1-2** was replaced with Compound **PA7-6**. MS for $C_{31}H_{23}F_5N_4O_5$: *m/z* 627 (MH+).

[0491] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (75): Compound **PA1-2** was replaced with Compound **PA7-7**. MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0492] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(trifluoromethyl)pyridine-3-carboxamide (79): Compound **PA1-2** was replaced with Compound **PA7-11**. MS for $C_{29}H_{19}F_5N_4O_5$: *m/z* 599 (MH+).

[0493] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide (80): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-12.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 12.34 (d, 1H), 8.77 (t, 1H), 8.74 – 8.65 (m, 1H), 8.04 (dd, 1H), 7.94 (d, 1H), 7.81 (t, 1H), 7.75 – 7.59 (m, 2H), 7.54 – 7.41 (m, 1H), 7.39 (d, 1H), 7.26 (td, 2H), 6.76 (d, 1H), 4.02 (s, 3H), 2.67 (s, 3H); MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515 (MH+).

[0494] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide (81): Compound **PA1-2** was replaced with Compound **PA7-13**. MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559 (MH+).

[0495] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide (82): Compound **PA1-2** was replaced with Compound **PA7-14**. MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0496] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (83): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (s, 1H), 8.74 (d, 1H), 8.70 (d, 1H), 8.51 (d, 1H), 8.05 (dd, 1H), 7.79 (d, 1H), 7.55 – 7.35 (m, 6H), 6.73 (t, 2H), 4.00 (s, 3H), 2.09 (s, 3H); MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515.2 (MH+).

[0497] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (84): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA1-1**. MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515 (MH+).

[0498] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxopyridine-3-carboxamide (85): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA1-2**. MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529 (MH+).

[0499] 5-Acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (86): Compound **PA1-2** was replaced with Compound **HA1-3**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 8.94 (s, 1H), 8.55 (d, 1H), 8.02 (dd, 1H), 7.64 (s, 1H), 7.53 - 7.44 (m, 5H), 7.34 - 7.29 (m, 1H), 6.84 (d, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 2.63 (s, 3H), 2.31 (s, 3H); MS for $C_{31}H_{24}F_2N_4O_6$: *m/z* 587.3 (MH+).

[0500] 5-Cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (87): Compound **87** can be made by replacing Compound **PA1-2** with Compound **HA1-4**. Alternatively, Compound **87** was made from Compound **366** as detailed in Example **85**. MS for $C_{30}H_{21}F_2N_5O_5$: *m/z* 570.1 (MH+).

[0501] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (88): Compound **PA1-2** was replaced with Compound **HA2-1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.14 (s, 1H), 12.70 (s, 1H), 8.57 (d, 1H), 8.02 (d, 1H), 7.66 (s, 1H), 7.48 (d, 1H), 7.42 (t, 2H), 7.34 (dt, 3H), 6.86 (d, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 2.29 (s, 3H); MS for $C_{28}H_{21}F_2N_5O_5$: *m/z* 546.2 (MH+).

[0502] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (89): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA2-1.** MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516.2 (MH+).

[0503] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (90): Compound **PA1-2** was replaced with Compound **HA2-2**. MS for $C_{29}H_{23}F_2N_5O_5$: *m/z* 560 (MH+).

[0504] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide (91): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA2-3.** MS for $C_{29}H_{24}FN_5O_5$: *m/z* 542 (MH+).

[0505] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide (92): Compound **PA1-2** was replaced with Compound **HA2-3**. MS for $C_{29}H_{23}F_2N_5O_5$: *m/z* 560 (MH+).

[0506] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide (93): Compound **PA1-2** was replaced with Compound **HA3-1**. MS for $C_{28}H_{21}F_2N_5O_5$: *m/z* 546.1 (MH+).

[0507] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide (94): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA3-1.** MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516.1 (MH+).

[0508] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-5,6-dimethyl-3-oxopyrazine-2-carboxamide (95): Compound **PA1-2** was replaced with Compound **HA3-2**. MS for $C_{29}H_{23}F_2N_5O_5$: *m/z* 560.0 (MH+).

[0509] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-5-hydroxypyrimidine-4-carboxamide (96): Compound **PA1-2** was replaced with Compound **HA4-1**. MS for $C_{27}H_{19}F_2N_5O_5$: *m/z* 532.1 (MH+).

[0510] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide (97): Compound **PA1-2** was replaced with Compound **HA4-2**. MS for $C_{28}H_{21}F_2N_5O_5$: *m/z* 546 (MH+).

[0511] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methyl-6-oxopyrimidine-5-carboxamide (98): Compound **PA1-2** was replaced with Compound **HA4-3**. MS for $C_{28}H_{21}F_2N_5O_5$: *m/z* 546 (MH+).

[0512] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-(methylamino)-6-oxopyrimidine-5-carboxamide (99): Compound **PA1-2** was replaced with Compound **HA4-4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.73 (s, 1H), 8.55 (d, 1H), 7.98 (dd, 1H), 7.65 (s, 1H), 7.5 – 7.35 (m, 5H), 7.29 (t, 1H), 7.05 (d, 1H), 6.81 (d, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 2.85 (d, 3H); MS for $C_{28}H_{22}F_2N_6O_5$: *m/z* 561 (MH+).

[0513] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(dimethylamino)-1-(4-fluorophenyl)-6-oxopyrimidine-5-carboxamide (100): Compound **PA1-2** was replaced with Compound **HA4-5**. MS for $C_{29}H_{24}F_2N_6O_5$: *m/z* 575.2 (MH+).

[0514] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyrimidine-5-carboxamide (101): Compound **PA1-2** was replaced with Compound **HA4-6**. MS for $C_{29}H_{23}F_2N_5O_5$: *m/z* 560 (MH+).

[0515] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-2,4-dioxo-1H-pyrimidine-5-carboxamide (102): Compound **PA1-2** was replaced with Compound **HA4-7**. MS for $C_{27}H_{19}F_2N_5O_6$: *m/z* 548.2 (MH+).

[0516] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-3-(4-fluorophenyl)-2,4-dioxo-1H-pyrimidine-5-carboxamide (103): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA4-7**. MS for $C_{26}H_{17}F_2N_5O_5$: *m/z* 518.2 (MH+).

[0517] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-4-oxo-2-sulfanylidene-1H-pyrimidine-5-carboxamide (104): Compound **PA1-2** can be replaced with Compound **HA4-8**.

[0518] N-[3-Fluoro-4-(7-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (105): Compound **NA1-1** was replaced with Compound **QA1-3**. Compound **PA1-2** was replaced with Compound **PA3-1.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.98 (s, 1H), 8.69 – 8.56 (m, 3H), 8.35 (d, 1H), 8.00 (dd, 1H), 7.53 (d, 1H), 7.43 – 7.27 (m, 2H), 7.27 – 7.13 (m, 4H), 6.58 (d, 1H), 4.02 (s, 3H), 3.03 (br. s, 1H), 2.24 (s, 3H); MS for $C_{29}H_{21}F_2N_3O_4$: *m/z* 514.2 (MH+).

[0519] N-[3-Fluoro-4-(7-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (106): Compound **NA1-1** was replaced with Compound **QA1-3**. Compound **PA1-2** was replaced with Compound **PA3-2.** MS for $C_{32}H_{27}F_2N_3O_4$: *m/z* 556.2 (MH+).

[0520] 1-Ethyl-N-[3-fluoro-4-(7-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (107): Compound **NA1-1** was replaced with Compound **QA1-3**. Compound **PA1-2** was replaced with Compound **PA3-4.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.29 (s, 1H), 8.98 (d, 1H), 8.80 (s, 1H), 8.51 (d, 1H), 8.13 (dd, 1H), 7.79 (d, 1H), 7.59 (tdd, 3H), 7.28 (d, 4H), 7.01 (d, 1H), 4.29 (q, 2H), 4.04 (s, 3H), 2.27 (s, 3H), 1.40 (t, 3H); MS for $C_{31}H_{25}F_2N_3O_4$: *m/z* 542.2 (MH+).

[0521] 5-(4-Fluorophenyl)-4-hydroxy-N-[4-(7-methoxyquinolin-4-yl)oxyphenyl]-6-methylpyridine-3-carboxamide (108): Compound **NA1-1** was replaced with Compound **QA1-4**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{29}H_{22}FN_3O_4$: *m/z* 496.2 (MH+).

[0522] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (109): Compound **NA1-1** was replaced with Compound **QA1-1**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{30}H_{23}F_2N_3O_5$: *m/z* 544.2 (MH+).

[0523] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (110): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA3-2.** MS for $C_{31}H_{26}F_2N_4O_4$: *m/z* 557.2 (MH+).

[0524] 5-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridine-3-carboxamide (111): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA3-7.** MS for $C_{29}H_{23}FN_4O_4$: *m/z* 511 (MH+).

[0525] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (112): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA1-4.** MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515 (MH+).

[0526] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (113): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA3-7.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529 (MH+).

[0527] tert-Butyl 3-[3-[[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]carbamoyl]-5-(4-fluorophenyl)-4-oxopyridin-1-yl]azetidine-1-carboxylate (114): Compound **PA1-2** was replaced with Compound **PA1-26.** MS for $C_{36}H_{33}F_2N_5O_7$: *m/z* 686 (MH+).

[0528] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (115): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA3-2.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 8.63 (s, 1H), 8.54 (d, 1H), 7.75 – 7.64 (m, 2H), 7.58 (s, 1H), 7.28 – 7.06 (m, 6H), 6.81 (d, 1H), 4.70 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.22 (s, 3H), 1.44 (d, 6H); MS for $C_{32}H_{29}FN_4O_5$: *m/z* 569 (MH+).

[0529] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (116): Compound **PA1-2** was replaced with Compound **PA1-5.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559 (MH+).

[0530] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-oxopyridine-3-carboxamide (117): Compound **PA1-2** was replaced with Compound **PA1-17.** MS for $C_{30}H_{24}F_2N_4O_6$: *m/z* 575 (MH+).

[0531] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide (118): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA1-1.** MS for $C_{28}H_{21}FN_4O_5$: *m/z* 513 (MH+).

[0532] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (119): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA3-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 12.56 (s, 1H), 8.54 (t, 2H), 7.82 – 7.69 (m, 2H), 7.64 (s, 1H), 7.35 – 7.23 (m, 4H), 7.21 – 7.08 (m, 2H), 6.80 (d, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 2.18 (s, 3H); MS for $C_{29}H_{23}FN_4O_5$: *m/z* 527 (MH+).

[0533] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide (120): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA1-1.** MS for $C_{27}H_{18}F_2N_4O_4$: *m/z* 501 (MH+).

[0534] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (121): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA3-2.** MS for $C_{31}H_{26}F_2N_4O_4$: *m/z* 557 (MH+).

[0535] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide (122): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA1-3.** MS for $C_{31}H_{27}FN_4O_5$: *m/z* 555 (MH+).

[0536] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide (123): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA1-3.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0537] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-pyridin-2-ylpyridine-3-carboxamide (124): Compound **PA1-2** was replaced with Compound **PA1-18.** MS for $C_{33}H_{23}F_2N_5O_5$: *m/z* 608 (MH+).

[0538] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-pyridin-3-ylpyridine-3-carboxamide (125): Compound **PA1-2** was replaced with Compound **PA1-19.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 9.07 (d, 1H), 8.85 (d, 1H), 8.76 (dd, 1H), 8.57 (d, 1H), 8.50 (d, 1H), 8.32 (dt, 1H), 8.07 (dd, 1H), 7.89 – 7.79 (m, 2H), 7.72 – 7.61 (m, 2H), 7.51 (d, 1H), 7.34 (dt, 3H), 6.86 (d, 1H), 3.98 (s, 3H), 3.95 (s, 3H); MS for $C_{33}H_{23}F_2N_5O_5$: *m/z* 608 (MH+).

[0539] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methoxy-4-oxopyridine-3-carboxamide (126): Compound **PA1-2** was replaced with Compound **PA1-20.** MS for $C_{29}H_{22}F_2N_4O_6$: *m/z* 561 (MH+).

[0540] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methoxy-4-oxopyridine-3-carboxamide (127): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA1-20.** MS for $C_{29}H_{23}FN_4O_6$: *m/z* 543 (MH+).

[0541] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methoxy-4-oxopyridine-3-carboxamide (128): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA1-20.** MS for $C_{28}H_{20}F_2N_4O_5$: *m/z* 531 (MH+).

[0542] N-[4-[(7-Bromo-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide (129): Compound **NA1-1** was replaced with Compound **NA1-4**. Compound **PA1-2** was replaced with Compound **PA1-1.** MS for $C_{27}H_{17}BrF_2N_4O_4$: *m/z* 579/581 (MH+).

[0543] N-[4-[(7-Bromo-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (130): Compound **NA1-1** was replaced with Compound **NA1-4**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{28}H_{19}BrF_2N_4O_4$: *m/z* 593/595 (MH+).

[0544] N-[4-[(7-Bromo-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide (131): Compound **NA1-1** was replaced with Compound **NA1-4**. Compound **PA1-2** was replaced with Compound **PA1-3.** MS for $C_{30}H_{23}BrF_2N_4O_4$: *m/z* 621/623 (MH+).

[0545] N-[4-[(7-Bromo-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (132): Compound **NA1-1** was replaced with Compound **NA1-4**. Compound **PA1-2** was replaced with Compound **PA3-2.** MS for $C_{31}H_{25}BrF_2N_4O_4$: *m/z* 635/637 (MH+).

[0546] N-[4-[(7-Bromo-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (133): Compound **NA1-1** was replaced with Compound **NA1-5**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{27}H_{17}BrF_2N_4O_3$: *m/z* 563/565 (MH+).

[0547] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-hydroxy-4-oxopyridine-3-carboxamide (134): Compound **PA1-2** was replaced with Compound **PA1-21.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.41 (s, 1H), 13.19 (s, 1H), 8.65 (d, 1H), 8.56 (d, 1H), 8.38 (d, 1H), 8.03 (dd, 1H), 7.79 – 7.69 (m, 2H), 7.66 (s, 1H), 7.45 (dd, 1H), 7.32 (dt, 3H), 6.85 (d, 1H), 3.98 (s, 3H), 3.95 (s, 3H); MS for $C_{28}H_{20}F_2N_4O_6$: *m/z* 547 (MH+).

[0548] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(methylamino)-4-oxopyridine-3-carboxamide (135): Compound **PA1-2** was replaced with Compound **PA1-22.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (s, 1H), 8.72 (d, 1H), 8.56 (d, 1H), 8.23 (d, 1H), 8.04 (dd, 1H), 7.80 – 7.70 (m, 2H), 7.66 (s, 1H), 7.51 – 7.41 (m, 1H), 7.32 (dt, 3H), 7.13 (d, 1H), 6.85 (d, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 2.90 (d, 3H); MS for $C_{29}H_{23}F_2N_5O_5$: *m/z* 560 (MH+).

[0549] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(dimethylamino)-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (136): Compound **PA1-2** was replaced with Compound **PA1-23.** MS for $C_{30}H_{25}F_2N_5O_5$: *m/z* 574 (MH+).

[0550] 1-[bis(Dimethylamino)methylideneamino]-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (137): Compound **PA1-2** was replaced with Compound **PA1-24.** MS for $C_{33}H_{31}F_2N_7O_5$: *m/z* 644 (MH+).

[0551] Methyl 8-[2-fluoro-4-[[5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carbonyl]amino]phenoxy]-1,5-naphthyridine-3-carboxylate (138): Compound **NA1-1** was replaced with Compound **NA1-8**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{29}H_{20}F_2N_4O_5$: *m/z* 543 (MH+).

[0552] 1-tert-Butyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (139): Compound **PA1-2** was replaced with Compound **PA3-5.** MS for $C_{33}H_{30}F_2N_4O_5$: *m/z* 601 (MH+).

[0553] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide (140): Compound **PA1-2** was replaced with Compound **PA3-6.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 8.55 (d, 1H), 8.47 (s, 1H), 8.26 (s, 1H), 8.00 (dd, 1H), 7.85 (s, 1H), 7.66 (s, 1H), 7.45 (dt, 1H), 7.39 – 7.21 (m, 5H), 6.83 (d, 1H), 3.97 (s, 3H), 3.94 (s, 6H), 2.01 (s, 3H); MS for $C_{33}H_{26}F_2N_6O_5$: *m/z* 625 (MH+).

[0554] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide (141): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA3-6.** MS for $C_{33}H_{27}FN_6O_5$: *m/z* 607 (MH+).

[0555] N-[4-[(6-Bromo-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (142): Compound **NA1-1** was replaced with Compound **NA1-9**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{28}H_{19}BrF_2N_4O_4$: *m/z* 593/595 (MH+).

[0556] N-[4-[(6-Bromo-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (143): Compound **NA1-1** was replaced with Compound **NA1-9**. Compound **PA1-2** was replaced with Compound **PA3-2.** MS for $C_{31}H_{25}BrF_2N_4O_4$: *m/z* 635/637 (MH+).

[0557] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (144): Compound **NA1-1** was replaced with Compound **NA1-16**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603 (MH+).

[0558] 5-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-oxo-1-propan-2-ylpyridine-3-carboxamide (145): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA1-3.** MS for $C_{30}H_{25}FN_4O_4$: *m/z* 525 (MH+).

[0559] 5-(4-Fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide (146): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA1-1.** MS for $C_{27}H_{19}FN_4O_4$: *m/z* 483 (MH+).

[0560] 5-(4-Fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (147): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{28}H_{21}FN_4O_4$: *m/z* 497 (MH+).

[0561] 5-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (148): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA3-2.** MS for $C_{31}H_{27}FN_4O_4$: *m/z* 538.2 (MH+).

[0562] N-[4-[(7-Bromo-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (149): Compound **NA1-1** was replaced with Compound **NA1-11**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{27}H_{18}FN_4O_3$: *m/z* 545 (MH+).

[0563] 5-(4-Fluorophenyl)-4-hydroxy-6-methyl-N-[4-[[7-(trifluoromethyl)-1,5-naphthyridin-4-yl]oxy]phenyl]pyridine-3-carboxamide (150): Compound **NA1-1** was replaced with Compound **NA1-12.** Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{28}H_{18}F_4N_4O_3$: *m/z* 535 (MH+).

[0564] 5-(4-Fluorophenyl)-N-[3-fluoro-4-[[7-(trifluoromethyl)-1,5-naphthyridin-4-yl]oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide (151): Compound **NA1-1** was replaced with Compound **NA1-13**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{28}H_{17}F_5N_4O_3$: *m/z* 553 (MH+).

[0565] 5-(4-Fluorophenyl)-N-[3-fluoro-4-[[7-(trifluoromethyl)-1,5-naphthyridin-4-yl]oxy]phenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (152): Compound **NA1-1** was replaced with Compound **NA1-13**. Compound **PA1-2** was replaced with Compound **PA3-2.** MS for $C_{31}H_{23}F_5N_4O_3$: *m/z* 595 (MH+).

[0566] N-[4-[(7-Bromo-6-methyl-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (153): Compound **NA1-1** was replaced with Compound **NA1-15**. Compound **PA1-2** was replaced with Compound **PA3-2.** MS for $C_{31}H_{25}BrF_2N_4O_3$: *m/z* 619 (MH+).

[0567] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (154): Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0568] 6-tert-Butyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide (155): Compound **PA1-2** was replaced with Compound **PA5-3.** MS for $C_{32}H_{28}F_2N_4O_5$: *m/z* 587.3 (MH+).

[0569] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (156): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA3-7.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529.2 (MH+).

[0570] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(2-morpholin-4-ylethyl)-4-oxopyridine-3-carboxamide (157): Compound **PA1-2** was replaced with Compound **PA6-1.** MS for $C_{34}H_{31}F_2N_5O_6$: *m/z* 644.1 (MH+).

[0571] 5-(4-Fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2,6-dimethylpyridine-3-carboxamide (158): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA5-2.** ^{1}H NMR (400 MHz, CD_3OD) δ 8.98 (d, 1H), 8.92 (d, 1H), 8.01 – 7.88 (m, 2H), 7.78 (d, 1H), 7.47 – 7.32 (m, 4H), 7.28 (t, 2H), 7.18 (d, 1H), 4.19 (s, 3H), 2.81 (s, 3H), 2.31 (s, 3H); MS for $C_{29}H_{23}FN_4O_4$: *m/z* 511.2 (MH+).

[0572] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(2-imidazol-1-ylethyl)-4-oxopyridine-3-carboxamide (159): Compound **PA1-2** was replaced with Compound **PA6-2.** MS for $C_{33}H_{26}F_2N_6O_5$: *m/z* 625.2 (MH+).

[0573] N-[3-Fluoro-4-[(7-fluoro-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (160): Compound **NA1-1** was replaced with Compound **NA1-7**. Compound **PA1-2** was replaced with Compound **PA3-1.** ^{1}H NMR (400 MHz, CD_3OD) δ 9.00 (d, 1H), 8.80 (d, 1H), 8.63 (s, 1H), 8.18 (dd, 1H), 8.06 (dd, 1H), 7.53 – 7.38 (m, 2H), 7.33 (dd, 2H), 7.24 (t, 2H), 6.92 (d, 1H), 2.27 (s, 3H); MS for $C_{27}H_{17}F_3N_4O_3$: *m/z* 503.2 (MH+).

[0574] N-[3-Fluoro-4-[(7-fluoro-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide (161): Compound **NA1-1** was replaced with Compound **NA1-7**. Compound **PA1-2** was replaced with Compound **PA1-3.** MS for $C_{29}H_{21}F_3N_4O_3$: *m/z* 531.2 (MH+).

[0575] N-[3-Fluoro-4-[(7-fluoro-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (162): Compound **NA1-1** was replaced with Compound **NA1-7**. Compound **PA1-2** was replaced with Compound **PA3-2.** MS for $C_{30}H_{23}F_3N_4O_3$: *m/z* 545.2 (MH+).

[0576] 1-Ethyl-5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide (163): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA3-4.** ^{1}H NMR (400 MHz, CD_3OD) δ 8.81 (s, 1H), 8.72 (d, 1H), 8.68 (d, 1H), 7.87 (d, 2H), 7.76 (d, 1H), 7.36 – 7.20 (m, 6H), 6.81 (d, 1H), 4.32 (q, 2H), 4.08 (s, 3H), 2.34 (s, 3H), 1.54 (t, 3H); MS for $C_{30}H_{25}FN_4O_4$: *m/z* 525.2 (MH+).

[0577] 1-Ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (164): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA3-4.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543.2 (MH+).

[0578] 1-tert-Butyl-5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide (165): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA3-5.** MS for $C_{32}H_{29}FN_4O_4$: *m/z* 553.2 (MH+).

[0579] 1-tert-Butyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (166): Compound **NA1-1** was replaced with

Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA3-5.** MS for $C_{32}H_{28}F2N_4O_4$: *m/z* 571.2 (MH+).

[0580] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (167): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA1-5.** MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541.2 (MH+).

[0581] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (168): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA3-4.** MS for $C_{31}H_{27}FN_4O_5$: *m/z* 555.2 (MH+).

[0582] 1-Ethyl-5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-oxopyridine-3-carboxamide (169): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA1-5.** MS for $C_{29}H_{23}FN_4O_4$: *m/z* 511.2 (MH+).

[0583] 1-Ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (170): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA1-5.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529.2 (MH+).

[0584] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (171): Compound **NA1-1** was replaced with Compound **QA1-2**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{30}H_{24}FN_3O_5$: *m/z* 526 (MH+).

[0585] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (172): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515.2 (MH+).

[0586] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (173): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541.2 (MH+).

[0587] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (174): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541 (MH+).

[0588] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (175): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529 (MH+).

[0589] 5-(4-Fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (176): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{29}H_{23}FN_4O_4$: *m/z* 511 (MH+).

[0590] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (177): Compound **PA1-2** was replaced with Compound **PA7-2.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0591] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (178): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-2.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0592] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-ethyl-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (179): Compound **PA1-2** was replaced with Compound **PA5-7.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0593] 2-Ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (180): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA5-7.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0594] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (181): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-7.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0595] 2-Ethyl-N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (182): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA5-7.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0596] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (183): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA7-7.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0597] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (184): Compound **PA1-2** was replaced with Compound **PA5-11.** MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589 (MH+).

[0598] 5-(4-Fluorophenyl)-4-hydroxy-2-(methoxymethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (185): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA5-11.** MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541 (MH+).

[0599] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (186): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA5-11.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559 (MH+).

[0600] 5-(4-Fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridine-3-carboxamide (187): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA7-7.** MS for $C_{30}H_{25}FN_4O_4$: *m/z* 525 (MH+).

[0601] 2-Ethyl-5-(4-fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (188): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA5-7.** MS for $C_{30}H_{25}FN_4O_4$: *m/z* 525 (MH+).

[0602] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (189): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA5-11.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559 (MH+).

[0603] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (190): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA5-11.** MS for $C_{31}H_{27}FN_4O_6$: *m/z* 571 (MH+).

[0604] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (191): Compound **PA1-2** was replaced with Compound **PA5-5.** MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603 (MH+).

[0605] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (192): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA5-5.** MS for $C_{32}H_{29}FN_4O_6$: *m/z* 585 (MH+).

[0606] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (193): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA5-5.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0607] 5-(4-Fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (194): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA5-5.** ^{1}H NMR (400 MHz, CD_3OD) δ 9.01 – 8.91 (m, 2H), 8.02 – 7.95 (m, 2H), 7.86 (d, 1H), 7.48 – 7.40 (m, 2H), 7.32 – 7.11 (m, 4H), 5.0 (s, 2H), 4.20 (d, 3H), 3.58 (d, 3H), 2.38 (d, 3H), 2.20 (s, 3H); MS for $C_{31}H_{27}FN_4O_5$: *m/z* 555 (MH+).

[0608] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (195): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA5-5.** ^{1}H NMR (400 MHz, CD_3OD) δ 8.89 (d, 1H), 8.45 (d, 1H), 8.14 – 8.06 (m, 1H), 7.66 (d, 1H), 7.59 – 7.47

(m, 2H), 7.40 (d, 1H), 7.20 (q, 2H), 7.11 (dd, 1H), 5.02 (s, 2H), 4.19 (s, 3H), 3.61 (s, 3H), 2.31 (s, 3H), 2.19 (s, 3H); MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0609] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (196): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA7-7.** MS for $C_{31}H_{27}FN_4O_5$: *m/z* 555 (MH+).

[0610] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-ethyl-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (197): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA5-7.** MS for $C_{31}H_{27}F_2N_4O_5$: *m/z* 555 (MH+).

[0611] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (198): Compound **NA1-1** was replaced with Compound **NA1-16**. Compound **PA1-2** was replaced with Compound **PA3-7.** MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603 (MH+).

[0612] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (199): Compound **NA1-1** was replaced with Compound **NA1-16**. Compound **PA1-2** was replaced with Compound **PA5-11.** MS for $C_{33}H_{30}F_2N_4O_7$: *m/z* 633 (MH+).

[0613] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (200): Compound **NA1-1** was replaced with Compound **NA1-16**. Compound **PA1-2** was replaced with Compound **PA7-7.** MS for $C_{33}H_{30}F_2N_4O_6$: *m/z* 617 (MH+).

[0614] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (201): Compound **NA1-1** was replaced with Compound **NA1-16**. Compound **PA1-2** was replaced with Compound **PA5-5.** MS for $C_{34}H_{32}F_2N_4O_7$: *m/z* 647 (MH+).

[0615] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-ethyl-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (202): Compound **PA1-2** was replaced with Compound **PA5-8.** MS for $C_{32}H_{28}F_2N_4O_5$: *m/z* 587 (MH+).

[0616] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-ethyl-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (203): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA5-8.** MS for $C_{32}H_{29}FN_4O_5$: *m/z* 569 (MH+).

[0617] 2-Ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (204): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA5-8.** MS for $C_{31}H_{26}F_2N_4O_4$: *m/z* 557 (MH+).

[0618] 2-Ethyl-5-(4-fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (205): Compound **NA1-1** was replaced with

Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA5-8.** ^{1}H NMR (400 MHz, CD_3OD) δ 9.00 – 8.94 (m, 2H), 8.02 (d, 2H), 7.91 (d, 1H), 7.45 (d, 2H), 7.34 – 7.11 (m, 4H), 4.20 (s, 3H), 3.12 – 3.02 (m, 2H), 2.39 (s, 3H), 2.21 (s, 3H), 1.49 (t, 3H); MS for $C_{31}H_{27}FN_4O_4$: *m/z* 539 (MH+).

[0619] 2-Ethyl-N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (206): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA5-8.** MS for $C_{31}H_{26}F_2N_4O_4$: *m/z* 557 (MH+).

[0620] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (207): Compound **NA1-1** was replaced with Compound **NA1-16**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603 (MH+).

[0621] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (208): Compound **NA1-1** was replaced with Compound **NA1-16**. Compound **PA1-2** was replaced with Compound **PA7-2.** MS for $C_{33}H_{30}F_2N_4O_6$: *m/z* 617 (MH+).

[0622] 5-(2,4-Difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (209): Compound **PA1-2** was replaced with Compound **PA5-4.** MS for $C_{30}H_{23}F_3N_4O_5$: *m/z* 577 (MH+).

[0623] 5-(2,4-Difluorophenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (210): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA5-4.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (s, 1H), 12.05 (s, 1H), 8.77 – 8.67 (m, 2H), 8.02 (d, 1H), 7.79 (d, 1H), 7.37 (dq, 4H), 7.16 (t, 1H), 6.73 (d, 1H), 4.00 (d, 3H), 2.76 (d, 3H), 2.13 (s, 3H); MS for $C_{29}H_{21}F_3N_4O_4$: *m/z* 547 (MH+).

[0624] 5-(2,4-Difluorophenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (211): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA5-6.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.24 (s, 1H), 11.59 (s, 1H), 8.77 – 8.64 (m, 2H), 8.11 – 7.88 (m, 1H), 7.80 (d, 1H), 7.37 (dq, 4H), 7.17 (t, 1H), 6.73 (d, 1H), 5.05 (s, 2H), 4.00 (d, 3H), 3.50 (d, 3H), 2.22 (s, 3H); MS for $C_{30}H_{23}F_3N_4O_5$: *m/z* 577 (MH+).

[0625] 5-(2,4-Difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (212): Compound **PA1-2** was replaced with Compound **PA5-6.** MS for $C_{31}H_{25}F_3N_4O_6$: *m/z* 607 (MH+).

[0626] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(ethoxymethyl)-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (213): Compound **PA1-2** was replaced with Compound **PA5-9.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.70 (s, 1H), 11.39 (s, 1H), 8.54 (d, 1H), 7.98 (dd, 1H), 7.65 (s, 1H), 7.36 (dd, 1H), 7.32 – 7.19 (m, 5H), 6.79 (d, 1H), 5.02 (s, 2H), 3.96 (d, 6H), 3.66 (q, 2H), 2.20 (s, 3H), 1.23 (t, 3H); MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603 (MH+).

[0627] 2-(Ethoxymethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (214): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA5-9.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0628] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(ethoxymethyl)-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (215): Compound **PA1-2** was replaced with Compound **PA5-10.** MS for $C_{33}H_{30}F_2N_4O_6$: *m/z* 617 (MH+).

[0629] 1-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-2-oxopyridine-3-carboxamide (216): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{28}H_{21}FN_4O_4$: *m/z* 497.2 (MH+).

[0630] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(hydroxymethyl)pyridine-3-carboxamide (217): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-3a** with subsequent hydrolysis of the acetyl group to give the hydroxyl using standard methods such as stirring in the presence of LiOH in a mixture of water and THF at room temperature. MS for $C_{28}H_{20}F_2N_4O_5$: *m/z* 531.2 (MH+).

[0631] 5-(4-Fluorophenyl)-4-hydroxy-6-(hydroxymethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide (218): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA7-3.** In this particular case, the HATU coupling method was replaced with standard amide coupling techniques using T_3P and DIEA in DCM with stirring at room temperature, followed by heating at 45 °C. MS for $C_{28}H_{21}FN_4O_5$: *m/z* 513.2 (MH+).

[0632] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxopyridine-3-carboxamide (219): Compound **PA1-2** was replaced with Compound **HA1-2.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559 (MH+).

[0633] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxopyridine-3-carboxamide (220): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-2.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529.2 (MH+).

[0634] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide (221): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA7-4.** MS for $C_{30}H_{25}FN_4O_6$: *m/z* 557.2 (MH+).

[0635] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide (222): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-4.** MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545.2 (MH+).

[0636] 5-(4-Fluorophenyl)-6-(hydroxymethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-methyl-4-oxopyridine-3-carboxamide (223): Compound **NA1-1** was replaced with

Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA7-4.** MS for $C_{29}H_{23}FN_4O_5$: *m/z* 527.2 (MH+).

[0637] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide (224): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA7-4.** MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545.2 (MH+).

[0638] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxopyridine-3-carboxamide (225): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-2.** MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541.2 (MH+).

[0639] 1-(4-Fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-2-oxopyridine-3-carboxamide (226): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA1-2.** MS for $C_{29}H_{23}FN_4O_4$: *m/z* 511 (MH+).

[0640] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (227): Compound **NA1-1** was replaced with Compound **NA1-16**. Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589.2 (MH+).

[0641] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide (228): Compound **NA1-1** was replaced with Compound **NA1-16**. Compound **PA1-2** was replaced with Compound **PA7-4.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 8.81 (s, 1H), 8.56 (d, 1H), 8.01 (d, 1H), 7.66 (s, 1H), 7.42 (d, 1H), 7.34 – 7.26 (m, 5H), 6.86 (d, 1H), 5.65 (s, 1H), 4.48 – 4.44 (m, 2H), 4.32 (s, 2H), 4.05 (s, 3H), 3.98 (s, 3H), 3.65 (s, 2H), 3.30 – 3.25 (m, 3H); MS for $C_{32}H_{28}F_2N_4O_7$: *m/z* 619.2 (MH+).

[0642] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (229): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{29}H_{23}FN_4O_5$: *m/z* 527.2 (MH+).

[0643] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (230): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA2-2.** MS for $C_{28}H_{21}F_2N_5O_4$: *m/z* 530 (MH+).

[0644] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(hydroxymethyl)pyridine-3-carboxamide (231): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA7-3a** with subsequent hydrolysis of the acetyl group to give the hydroxyl using standard methods such as stirring in the presence of LiOH in a mixture of water and THF at room temperature. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (s, 1H), 8.62 (d, 1H), 8.58 (s, 1H), 8.29 (d, 1H), 8.03 (d, 1H), 7.43 (d, 1H), 7.31 (tt, 7H), 6.97 (d, 1H), 6.07 (s, 1H), 4.34 (s, 2H), 3.94 (s, 3H); MS for $C_{28}H_{20}F_2N_4O_5$: *m/z* 531 (MH+).

[0645] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide (232): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA4-2.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 9.08 (d, 1H), 8.60 (dd, 1H), 8.22 (dd, 1H), 7.92 (dt, 1H), 7.41 – 7.25 (m, 5H), 7.23 – 7.13 (m, 2H), 6.86 (d, 1H), 4.03 (d, 3H), 2.37 (d, 3H); MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516 (MH+).

[0646] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyrimidine-5-carboxamide (233): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA4-6.** MS for $C_{28}H_{21}F_2N_5O_4$: *m/z* 530 (MH+).

[0647] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4-methyl-6-oxopyrimidine-5-carboxamide (234): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA4-3.** MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516 (MH+).

[0648] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide (235): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA7-12.** MS for $C_{29}H_{23}FN_4O_5$: *m/z* 527 (MH+).

[0649] 5-(4-Fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methylpyridine-3-carboxamide (236): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA7-12.** MS for $C_{28}H_{21}FN_4O_4$: *m/z* 497 (MH+).

[0650] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide (237): Compound **PA1-2** was replaced with Compound **PA7-12.** MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545 (MH+).

[0651] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide (238): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA7-13.** MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541 (MH+).

[0652] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide (239): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-13.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529 (MH+).

[0653] 1-Ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide (240): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-14.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0654] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(trifluoromethyl)pyridine-3-carboxamide (241): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-11.** MS for $C_{28}H_{17}F_5N_4O_4$: *m/z* 569 (MH+).

[0655] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide (242): Compound **NA1-1** was replaced with Compound

NA1-10. Compound **PA1-2** was replaced with Compound **PA7-12.** MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515.2 (MH+).

[0656] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide (243): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA7-13.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529.2 (MH+).

[0657] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide (244): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA7-14.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.44 (d, 1H), 8.01 (s, 1H), 7.79 – 7.66 (m, 4H), 7.57 (s, 1H), 7.25 – 7.05 (m, 4H), 6.67 (d, 1H), 4.04 (q, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.25 (s, 4H), 1.29 (t, 3H); MS for $C_{31}H_{27}FN_4O_5$: *m/z* 555.2 (MH+).

[0658] 5-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (245): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA2-1.** MS for $C_{27}H_{20}FN_5O_4$: *m/z* 498 (MH+).

[0659] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (246): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA2-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.16 (s, 1H), 12.74 (s, 1H), 8.95 – 8.63 (m, 2H), 8.05 (d, 1H), 7.81 (s, 1H), 7.63 – 7.22 (m, 6H), 6.78 (d, 1H), 4.02 (s, 3H), 2.29 (s, 3H); MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516 (MH+).

[0660] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (247): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA2-2.** MS for $C_{29}H_{24}FN_5O_5$: *m/z* 542 (MH+).

[0661] 5-(4-Fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (248): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA2-2.** MS for $C_{28}H_{22}FN_5O_4$: *m/z* 512 (MH+).

[0662] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide, racemate (249A): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA2-2.** MS for $C_{28}H_{21}F_2N_5O_4$: *m/z* 530 (MH+).

[0663] The following two atropisomers were recovered from the chiral SFC separation of Compound **249A**. Absolute stereochemistry was not determined:

[0664] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridazine-3-carboxamide, atropisomer 1 (249B): MS for $C_{28}H_{21}F_2N_5O_4$: *m/z* 530.1 (MH+). Analytical chiral SFC (Chiralcel OJ-3, 100 x 4.6 mm, 3 μm; Mobile phase: A = CO_2, B = EtOH (0.05% DEA), Gradient 5-40% B in 4 min and hold at 40% for 2.5 min, flow rate = 2.8 mL/min) retention time = 3.375 min.

[0665] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridazine-3-carboxamide, atropisomer 2 (249C): MS for

$C_{28}H_{21}F_2N_5O_4$: *m/z* 530.1 (MH+). Analytical chiral SFC (Chiralcel OJ-3, 100 x 4.6 mm, 3 μm; Mobile phase: A = CO_2, B = EtOH (0.05% DEA), Gradient 5-40% B in 4 min and hold at 40% for 2.5 min, flow rate = 2.8 mL/min) retention time = 4.303 min.

[0666] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide (250): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA2-3.** MS for $C_{28}H_{21}F_2N_5O_4$: *m/z* 530 (MH+).

[0667] 5-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridazine-3-carboxamide (251): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA2-3.** MS for $C_{28}H_{22}FN_5O_4$: *m/z* 512 (MH+).

[0668] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (252): Compound **NA1-1** was replaced with Compound **NA1-16**. Compound **PA1-2** was replaced with Compound **HA2-2.** MS for $C_{31}H_{27}F_2N_5O_6$: *m/z* 604 (MH+).

[0669] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (253): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA2-1.** MS for $C_{28}H_{22}FN_5O_5$: *m/z* 528 (MH+).

[0670] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (254): Compound **PA1-2** was replaced with Compound **HA1-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.54 (d, 1H), 8.49 (d, 1H), 7.99 (d, 1H), 7.64 (s, 1H), 7.46 (m, 5H), 7.30 (m, 1H), 6.81 (d, 1H), 6.72 (d, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 2.08 (s, 3H); MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545 (MH+).

[0671] 1-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-methyl-6-oxopyrimidine-5-carboxamide (255): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA4-3.** MS for $C_{27}H_{20}FN_5O_4$: *m/z* 498 (MH+).

[0672] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4-methyl-6-oxopyrimidine-5-carboxamide (256): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA4-3.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.74 (d, 1H), 8.72 – 8.65 (m, 1H), 8.52 (s, 1H), 7.94 (dd, 1H), 7.79 (d, 1H), 7.58 (dd, 2H), 7.53 – 7.35 (m, 4H), 6.76 (d, 1H), 4.00 (s, 3H), 2.38 (s, 3H); MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516 (MH+).

[0673] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyrimidine-5-carboxamide (257): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA4-6.** MS for $C_{28}H_{21}F_2N_5O_4$: *m/z* 530 (MH+).

[0674] 1-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2,4-dimethyl-6-oxopyrimidine-5-carboxamide (258): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA4-6.** MS for $C_{28}H_{22}FN_5O_4$: *m/z* 512 (MH+).

[0675] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide (259): Compound **NA1-1** was replaced with

Compound **QA1-1**. Compound **PA1-2** was replaced with Compound **PA7-6.** MS for $C_{32}H_{24}F_5N_3O_5$: *m/z* 626 (MH+).

[0676] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide (260): Compound **NA1-1** was replaced with Compound **QA1-2**. Compound **PA1-2** was replaced with Compound **PA7-6.** MS for $C_{32}H_{25}F_4N_3O_5$: *m/z* 608 (MH+).

[0677] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide (261): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-6.** MS for $C_{30}H_{21}F_5N_4O_4$: *m/z* 597 (MH+).

[0678] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide (262): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA3-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.38 (s, 1H), 8.54 (d, 1H), 7.81 (d, 2H), 7.74 (s, 1H), 7.64 (s, 1H), 7.56 - 7.44 (m, 4H), 7.20 (d, 2H), 6.80 (d, 1H), 3.98 - 3.95 (m, 3H), 3.93 (s, 3H), 2.04 (s, 3H); MS for $C_{28}H_{22}FN_5O_5$: *m/z* 528.1 (MH+).

[0679] 4-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-methyl-3-oxopyrazine-2-carboxamide (263): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA3-1.** MS for $C_{27}H_{20}FN_5O_4$: *m/z* 498.2 (MH+).

[0680] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide (264): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA3-1.** MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516.1 (MH+).

[0681] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide (265): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA4-2.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.29 (s, 1H), 8.84 (s, 1H), 8.74 (d, 1H), 8.70 (d, 1H), 8.03 (dd, 1H), 7.80 (d, 1H), 7.61 (dd, 2H), 7.55 (br d, 1H), 7.48 (t, 2H), 7.41 (t, 1H), 6.74 (d, 1H), 4.00 (s, 3H), 2.23 (s, 3H); MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516.1 (MH+).

[0682] 1-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methyl-6-oxopyrimidine-5-carboxamide (266): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA4-2.** MS for $C_{27}H_{20}FN_5O_4$: *m/z* 498.1 (MH+).

[0683] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide (267): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA4-2.** ^{1}H NMR (400 MHz, CD_3OD) δ 8.92 (s, 1H), 8.80 (d, 1H), 7.70 - 7.58 (m, 7H), 7.41 (d, 1H), 7.11 (t, 2H), 4.15 (d, 6H), 2.41 (s, 3H); MS for $C_{28}H_{22}FN_5O_5$: *m/z* 528.2 (MH+).

[0684] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-(methoxymethyl)-1-methyl-4-oxopyridine-3-carboxamide (269): Compound **PA1-2** was replaced with Compound **PA7-26.** MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589.2 (MH+).

[0685] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-(methoxymethyl)-1-methyl-4-oxopyridine-3-carboxamide (270): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-26.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0686] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide (271): Compound **PA1-2** was replaced with Compound **PA7-28.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 8.82 (s, 1H), 8.55 (d, 1H), 8.02 (dd, 1H), 7.66 (s, 1H), 7.47 – 7.40 (m, 1H), 7.37 – 7.24 (m, 5H), 6.83 (d, 1H), 5.70 (t, 1H), 4.41 (q, 2H), 4.32 (d, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 1.47 (t, 3H); MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589.2 (MH+).

[0687] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-5-(4-fluorophenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide (272): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA7-28.** MS for $C_{31}H_{27}FN_4O_6$: *m/z* 571.2 (MH+).

[0688] 1-Ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide (273): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-28.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0689] 1-Ethyl-5-(4-fluorophenyl)-6-(hydroxymethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-oxopyridine-3-carboxamide (274): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **PA7-28.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.81 (s, 1H), 8.74 (d, 1H), 8.70 (d, 1H), 7.83 (d, 2H), 7.79 (d, 1H), 7.38 – 7.22 (m, 6H), 6.75 (d, 1H), 5.69 (t, 1H), 4.41 (d, 2H), 4.32 (d, 2H), 4.01 (s, 3H), 1.47 (t, 3H); MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541.2 (MH+).

[0690] 1-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-phenylmethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-2-oxopyridine-3-carboxamide (275): Compound **NA1-1** was replaced with Compound **NA1-39**. Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{34}H_{24}F_2N_4O_4$: *m/z* 591.2 (MH+).

[0691] 1-(4-Fluoro-2-methylphenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-2-oxopyridine-3-carboxamide (276): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **HA1-2.** MS for $C_{29}H_{23}FN_4O_4$: *m/z* 511.2 (MH+).

[0692] 5-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-phenylmethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (277): Compound **NA1-1** was replaced with Compound **NA1-39**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{35}H_{26}F_2N_4O_4$: *m/z* 605.2 (MH+).

[0693] 1-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-phenylmethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2,4-dimethyl-6-oxopyrimidine-5-carboxamide (278): Compound **NA1-1** was replaced with

Compound **NA1-39**. Compound **PA1-2** was replaced with Compound **HA4-6.** MS for $C_{34}H_{25}F_2N_5O_4$: *m/z* 606.2 (MH+).

[0694] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (279): Compound **PA1-2** was replaced with Compound **HA1-5.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0695] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (280): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-5.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529.2 (MH+).

[0696] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (281): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA1-5.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529.2 (MH+).

[0697] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide (282): Compound **PA1-2** was replaced with Compound **PA7-30.** MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589.2 (MH+).

[0698] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluoro-2-methylphenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide (283): Compound **PA1-2** was replaced with Compound **PA7-36.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 8.83 (s, 1H), 8.56 (d, 1H), 8.02 (d, 1H), 7.66 (d, 1H), 7.44 (d, 1H), 7.33 (t, 1H), 7.18 (d, 1H), 7.14 – 7.06 (m, 2H), 6.84 (s, 1H), 5.62 (s, 1H), 4.41 (d, 2H), 4.31 (d, 1H), 4.17 (d, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 2.06 (s, 3H), 1.47 (t, 3H); MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603.2 (MH+).

[0699] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-5-(4-fluoro-2-methylphenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide (284): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA7-36.** MS for $C_{32}H_{29}FN_4O_6$: *m/z* 585.2 (MH+).

[0700] 1-Ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-(hydroxymethyl)-4-oxopyridine-3-carboxamide (285): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-36.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573.2 (MH+).

[0701] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide (286): Compound **PA1-2** was replaced with Compound **HA1-16.** MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545.2 (MH+).

[0702] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide (287): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA1-16.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.61 (dd, 1H), 8.30 (dd, 1H), 7.96 (d, 1H), 7.75 (d, 1H), 7.56 – 7.30 (m, 7H), 6.95 (d, 1H), 6.39 (d, 1H), 3.97 (d, 3H), 2.32 (d, 3H); MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515 (MH+).

[0703] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (288): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-5.** MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541.2 (MH+).

[0704] 1-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4,6-dimethyl-2-oxopyridine-3-carboxamide (289): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA1-5.** MS for $C_{29}H_{23}FN_4O_4$: *m/z* 511.2 (MH+).

[0705] 1-(4-Fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4,6-dimethyl-2-oxopyridine-3-carboxamide (290): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **HA1-5.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.59 (dd, 1H), 8.28 (dd, 1H), 7.79 (dd, 2H), 7.45 – 7.34 (m, 4H), 7.31 (dd, 1H), 7.25 – 7.17 (m, 2H), 6.90 (dd, 1H), 6.38 (s, 1H), 3.95 (d, 3H), 2.38 (d, 3H), 1.98 (s, 3H); MS for $C_{29}H_{23}FN_4O_4$: *m/z* 511.2 (MH+).

[0706] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide (291): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-19.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 1H), 8.81 – 8.75 (m, 1H), 8.72 (d, 1H), 8.61 (d, 1H), 8.15 (d, 1H), 8.07 (d, 1H), 7.84 – 7.78 (m, 1H), 7.67 – 7.59 (m, 2H), 7.53 (d, 1H), 7.48 – 7.38 (m, 3H), 6.79 – 6.71 (m, 2H), 4.01 (s, 3H); MS for $C_{27}H_{18}F_2N_4O_4$: *m/z* 501.2 (MH+).

[0707] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide (292): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA1-19.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 8.63 (d, 1H), 8.60 (d, 1H), 8.30 (d, 1H), 8.18 – 8.11 (m, 1H), 8.04 (d, 1H), 7.62 (dd, 2H), 7.54 – 7.29 (m, 5H), 6.99 (d, 1H), 6.75 (dd, 1H), 3.93 (s, 3H); MS for $C_{27}H_{18}F_2N_4O_4$: *m/z* 501.2 (MH+).

[0708] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide (293): Compound **PA1-2** was replaced with Compound **HA1-19.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 8.64 – 8.58 (m, 1H), 8.56 (d, 1H), 8.14 (dd, 1H), 8.03 (d, 1H), 7.68 – 7.58 (m, 3H), 7.45 (q, 3H), 7.33 (t, 1H), 6.85 (d, 1H), 6.74 (s, 1H), 3.98 (s, 3H), 3.94 (s, 3H); MS for $C_{28}H_{20}F_2N_4O_5$: *m/z* 531.2 (MH+).

[0709] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide (294): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-16.** MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515.2 (MH+).

[0710] N-[3-Fluoro-4-(1,5-naphthyridin-4-yloxy)phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (295): Compound **NA1-1** was replaced with Compound **NA1-21**. Compound **PA1-2** was replaced with Compound **HA1-5.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 9.03 (dd, 1H), 8.79 (dd, 1H), 8.46 (dd, 1H), 8.00 (d, 1H), 7.88 (dd, 1H), 7.51 (d, 1H), 7.46 – 7.35 (m, 5H), 6.92 (d, 1H), 6.40 (s, 1H), 2.39 (d, 3H), 1.99 (s, 3H); MS for $C_{28}H_{20}F_2N_4O_3$: *m/z* 499.2 (MH+).

[0711] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (296): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA1-15.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543.2 (MH+).

[0712] N-[3-Fluoro-4-[(6-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (297): Compound **NA1-1** was replaced with Compound **NA1-33**. Compound **PA1-2** was replaced with Compound **HA1-5.** MS for $C_{29}H_{22}F_2N_4O_3$: *m/z* 513.2 (MH+).

[0713] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (298): Compound **PA1-2** was replaced with Compound **HA1-15.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 8.46 (d, 1H), 7.87 (d, 1H), 7.58 (s, 1H), 7.38 (d, 1H), 7.30 – 7.11 (m, 4H), 6.72 (d, 1H), 6.35 (s, 1H), 3.92 – 3.89 (m, 3H), 3.89 (s, 3H), 2.33 (s, 3H), 1.97 (s, 3H), 1.85 (s, 3H); MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573.2 (MH+).

[0714] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide (299): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-16.** MS for $C_{29}H_{23}FN_4O_5$: *m/z* 527.2 (MH+).

[0715] 1-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-methyl-2-oxopyridine-3-carboxamide (300): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA1-16.** MS for $C_{28}H_{21}FN_4O_4$: *m/z* 497.2 (MH+).

[0716] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(methoxymethyl)pyridine-3-carboxamide (301): Compound **PA1-2** was replaced with Compound **PA7-17.** MS for $C_{30}H_{24}F_2N_4O_6$: *m/z* 575.2 (MH+).

[0717] N-[3-Fluoro-4-(1,5-naphthyridin-4-yloxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (302): Compound **NA1-1** was replaced with Compound **NA1-21**. Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{27}H_{18}F_2N_4O_3$: *m/z* 485.2 (MH+).

[0718] N-[3-Fluoro-4-(1,5-naphthyridin-4-yloxy)phenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide (303): Compound **NA1-1** was replaced with Compound **NA1-21**. Compound **PA1-2** was replaced with Compound **HA1-16.** MS for $C_{27}H_{18}F_2N_4O_3$: *m/z* 485.2 (MH+).

[0719] N-[3-Fluoro-4-(1,5-naphthyridin-4-yloxy)phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide (304): Compound **NA1-1** was replaced with Compound **NA1-21**. Compound **PA1-2** was replaced with Compound **HA1-19.** MS for $C_{26}H_{16}F_2N_4O_3$: *m/z* 471.2 (MH+).

[0720] 5-Bromo-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (305): Compound **PA1-2** was replaced with Compound **HA1-6.** MS for $C_{30}H_{23}BrF_2N_4O_5$: *m/z* 639.2 (MH+).

[0721] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4,5,6-trimethyl-2-oxopyridine-3-carboxamide (306): Compound **PA1-2** was replaced with Compound **HA1-8.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 8.52 (d, 1H), 7.92 (dd, 1H), 7.65 (s, 1H), 7.50 –

7.43 (m, 1H), 7.43 – 7.24 (m, 5H), 6.78 (d, 1H), 4.03 – 3.93 (m, 6H), 2.23 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H); MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573.2 (MH+).

[0722] 5-Chloro-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (307): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-7.** MS for $C_{30}H_{24}ClFN_4O_5$: *m/z* 575.2 (MH+).

[0723] 5-Chloro-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (308): Compound **PA1-2** was replaced with Compound **HA1-7.** MS for $C_{30}H_{23}ClF_2N_4O_5$: *m/z* 593.2 (MH+).

[0724] 5-Chloro-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (309): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-7.** MS for $C_{29}H_{21}ClF_2N_4O_4$: *m/z* 563.2 (MH+).

[0725] 5-Chloro-1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4,6-dimethyl-2-oxopyridine-3-carboxamide (310): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA1-7.** MS for $C_{29}H_{22}ClFN_4O_4$: *m/z* 545.2 (MH+).

[0726] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-4-methyl-2-oxopyridine-3-carboxamide (311): Compound **PA1-2** was replaced with Compound **HA1-17.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0727] 5-Bromo-1-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4,6-dimethyl-2-oxopyridine-3-carboxamide (312): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA1-6.** MS for $C_{29}H_{22}BrFN_4O_4$: *m/z* 591 (MH+).

[0728] 5-Bromo-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (313): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-6.** MS for $C_{30}H_{24}BrFN_4O_5$: *m/z* 621.2 (MH+).

[0729] 5-Bromo-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (314): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-6.** MS for $C_{29}H_{21}BrF_2N_4O_4$: *m/z* 609.2 (MH+).

[0730] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,5,6-trimethyl-2-oxopyridine-3-carboxamide (315): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-8.** MS for $C_{31}H_{27}FN_4O_5$: *m/z* 555 (MH+).

[0731] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,5,6-trimethyl-2-oxopyridine-3-carboxamide (316): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-8.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.74 (d, 1H), 8.69 (d, 1H), 7.95 (dd, 1H), 7.79 (d, 1H), 7.50 (dd, 1H), 7.40 (td, 3H), 7.33 – 7.25 (m, 2H), 6.74 (d, 1H), 4.00 (s, 3H), 2.24 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H); MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0732] 1-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4,5,6-trimethyl-2-oxopyridine-3-carboxamide (317): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA1-8.** MS for $C_{30}H_{25}FN_4O_4$: *m/z* 525 (MH+).

[0733] 5-N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyridine-3,5-dicarboxamide (318): Compound **PA1-2** was replaced with Compound **HA1-10.** MS for $C_{31}H_{25}F_2N_5O_6$: *m/z* 602.2 (MH+).

[0734] 5-N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyridine-3,5-dicarboxamide (319): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-10.** MS for $C_{31}H_{26}FN_5O_6$: *m/z* 584.2 (MH+).

[0735] 5-Cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (320): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-9.** MS for $C_{31}H_{24}FN_5O_5$: *m/z* 566.2 (MH+).

[0736] 5-Acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (321): Compound **PA1-2** was replaced with Compound **HA1-11.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H), 8.52 (d, 1H), 7.91 (dd, 1H), 7.65 (s, 1H), 7.49 – 7.31 (m, 6H), 6.78 (d, 1H), 3.97 (d, 6H), 2.54 (s, 3H), 2.15 (s, 3H), 1.90 (s, 3H); MS for $C_{32}H_{26}F_2N_4O_6$: *m/z* 601.2 (MH+).

[0737] 5-Acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (322): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-11.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.44 (d, 1H), 7.69 (d, 2H), 7.57 (s, 1H), 7.39 – 7.25 (m, 4H), 7.12 (d, 2H), 6.68 (d, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 2.47 (s, 3H), 2.08 (s, 3H), 1.83 (s, 3H); MS for $C_{32}H_{27}FN_4O_6$: *m/z* 583.2 (MH+).

[0738] 5-Acetyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (323): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-11.** MS for $C_{31}H_{24}F_2N_4O_5$: *m/z* 571.2 (MH+).

[0739] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-fluoro-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (324): Compound **PA1-2** was replaced with Compound **HA1-14.** MS for $C_{30}H_{23}F_3N_4O_5$: *m/z* 577.2 (MH+).

[0740] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-fluoro-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (325): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-14.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.52 (d, 1H), 7.76 (d, 2H), 7.64 (s, 1H), 7.47 – 7.36 (m, 4H), 7.19 (d, 2H), 6.76 (d, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 2.34 (d, 3H), 1.96 (d, 3H); MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0741] 5-Fluoro-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (326): Compound **NA1-1** was replaced

with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-14.** MS for $C_{29}H_{21}F_3N_4O_4$: *m/z* 547.2 (MH+).

[0742] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-ethenyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (327): Compound **PA1-2** was replaced with Compound **HA1-12.** MS for $C_{32}H_{26}F_2N_4O_5$: *m/z* 585.2 (MH+).

[0743] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-ethenyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (328): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-12.** MS for $C_{32}H_{27}FN_4O_5$: *m/z* 567.2 (MH+).

[0744] 5-Ethenyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (329): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-12.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H), 8.75 (d, 1H), 8.69 (d, 1H), 7.95 (dd, 1H), 7.80 (d, 1H), 7.50 (d, 1H), 7.41 (t, 3H), 7.34 (dd, 2H), 6.75 (d, 1H), 6.61 (dd, 1H), 5.63 (dd, 1H), 5.38 – 5.29 (m, 1H), 4.01 (s, 3H), 2.21 (s, 3H), 2.01 (s, 3H); MS for $C_{31}H_{24}F_2N_4O_4$: *m/z* 555.2 (MH+).

[0745] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-ethyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (330): Compound **PA1-2** was replaced with Compound **HA1-13.** MS for $C_{32}H_{28}F_2N_4O5$: *m/z* 587.2 (MH+).

[0746] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-ethyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (331): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-13.** MS for $C_{32}H_{29}FN_4O_5$: *m/z* 569.2 (MH+).

[0747] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-4-methyl-2-oxopyridine-3-carboxamide (332): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-17.** MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541.2 (MH+).

[0748] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-ethoxy-5-(4-fluorophenyl)-6-methylpyridine-3-carboxamide (333): Compound **PA1-2** was replaced with Compound **PA7-38.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 571 [M-H]-.

[0749] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-4-methyl-2-oxopyridine-3-carboxamide (334): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-17.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 8.75 (d, 1H), 8.70 (d, 1H), 7.97 (dd, 1H), 7.80 (d, 1H), 7.63 (d, 1H), 7.51 (dd, 1H), 7.42 (t, 1H), 7.31 (dd, 2H), 7.20 (td, 1H), 6.76 (d, 1H), 6.39 (d, 1H), 4.01 (s, 3H), 2.35 (s, 3H), 2.12 (s, 3H); MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529 (MH+).

[0750] 5-Ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (335): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA1-13.** MS for $C_{31}H_{26}F_2N_4O_4$: *m/z* 557 (MH+).

[0751] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-2-(methoxymethyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (336): Compound **PA1-2** was replaced with Compound **PA6-4.** MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603.2 (MH+).

[0752] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-fluoro-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (337): Compound **PA1-2** was replaced with Compound **HA1-18.** MS for $C_{29}H_{21}F_3N_4O_5$: *m/z* 563.1 (MH+).

[0753] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-fluoro-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (338): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-18.** MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545.1 (MH+).

[0754] 3-(4-Fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2,4-dioxo-1H-pyrimidine-5-carboxamide (339): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **HA4-7.** MS for $C_{26}H_{18}FN_5O_5$: *m/z* 500 (MH+).

[0755] 5-(4-Fluorophenyl)-4-hydroxy-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2,6-dimethylpyridine-3-carboxamide (340): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{29}H_{23}FN_4O_4$: *m/z* 511 (MH+).

[0756] 5-(4-Fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (341): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **PA3-2.** MS for $C_{31}H_{27}FN_4O_4$: *m/z* 539 (MH+).

[0757] 5-(4-Fluorophenyl)-4-hydroxy-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (342): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{28}H_{21}FN_4O_4$: *m/z* 497 (MH+).

[0758] 1-(4-Fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-2-oxopyridine-3-carboxamide (343): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{28}H_{21}FN_4O_4$: *m/z* 497 (MH+).

[0759] tert-Butyl N-[5-[[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]carbamoyl]-1-(4-fluorophenyl)-6-oxopyrimidin-2-yl]carbamate (344): Compound **PA1-2** was replaced with Compound **HA4-9.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.43 (s, 1H), 10.86 (s, 1H), 8.55 (d, 1H), 7.92 – 7.84 (m, 1H), 7.57 (s, 1H), 7.27 (s, 6H), 7.18 (t, 1H), 6.78 (d, 1H), 4.11 (d, 3H), 4.05 (s, 3H), 1.46 (s, 9H); MS for $C_{32}H_{28}F_2N_6O_7$: *m/z* 647 (MH+).

[0760] N-[3-Fluoro-4-(6-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (345): Compound **NA1-1** was replaced with Compound **QA1-7**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{30}H_{23}F_2N_3O_4$: *m/z* 528 (MH+).

[0761] N-[3-Fluoro-4-(6-methoxyquinolin-4-yl)oxyphenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (346): Compound **NA1-1** was replaced with Compound **QA1-7**. Compound **PA1-2** was replaced with Compound **HA1-1.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 8.65 (d, 1H), 8.55 (d, 1H), 8.03 – 7.95 (m, 2H), 7.63 (d, 1H), 7.45 – 7.16 (m, 7H), 6.55 – 6.49 (m, 2H), 3.99 (s, 3H), 2.14 (s, 3H); MS for $C_{29}H_{21}F_2N_3O_4$: *m/z* 514 (MH+).

[0762] N-[3-Fluoro-4-(6-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (347): Compound **NA1-1** was replaced with Compound **QA1-7**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{29}H_{21}F_2N_3O_4$: *m/z* 514 (MH+).

[0763] N-[3-Fluoro-4-[[6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (348): Compound **NA1-1** was replaced with Compound **NA1-18**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559 (MH+).

[0764] N-[3-Fluoro-4-[[6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (349): Compound **NA1-1** was replaced with Compound **NA1-18**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0765] N-[3-Fluoro-4-[[6-(2-morpholin-4-ylethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (350): Compound **NA1-1** was replaced with Compound **NA1-18**. Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559 (MH+).

[0766] N-[3-Fluoro-4-[[6-(2-morpholin-4-ylethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (351): Compound **NA1-1** was replaced with Compound **NA1-41**. Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{33}H_{29}F_2N_5O_5$: *m/z* 614 (MH+).

[0767] N-[4-[[6-[2-(Dimethylamino)ethoxy]-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (352): Compound **NA1-1** was replaced with Compound **NA1-41**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{33}H_{29}F_2N_5O_5$: *m/z* 614 (MH+).

[0768] N-[4-[[6-[2-(Dimethylamino)ethoxy]-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (353): Compound **NA1-1** was replaced with Compound **NA1-50.** Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{31}H_{27}F_2N_5O_4$: *m/z* 572 (MH+).

[0769] N-[3-Fluoro-4-[[6-(2-morpholin-4-ylethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (354): Compound **NA1-1** was replaced with Compound **NA1-50.** Compound **PA1-2** was replaced with Compound **PA5-2.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.33 (s, 1H), 11.13 (s, 1H), 8.51 (d, 1H), 8.44 (s, 1H), 8.15 (d, 1H), 7.80 (d, 1H), 7.24 (d, 1H), 7.08 (dtt, 6H), 6.78 (d, 1H), 4.62 (t, 2H), 3.07 (d, 2H), 2.77 (s, 3H), 2.57 (s, 5H), 2.06 (s, 3H); MS for $C_{32}H_{29}F_2N_5O_4$: *m/z* 586 (MH+).

[0770] 5-(4-Fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridine-3-carboxamide (355): Compound **NA1-1** was replaced with Compound **NA1-41**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{34}H_{31}F_2N_5O_5$: *m/z* 628 (MH+).

[0771] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-(hydroxymethyl)-2-oxopyridine-3-carboxamide (356): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **PA3-7.** MS for $C_{29}H_{23}FN_4O_4$: *m/z* 511 (MH+).

[0772] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-(methoxymethyl)-2-oxopyridine-3-carboxamide (357): Compound **PA1-2** was replaced with Compound **HA1-25.** MS for $C_{29}H_{22}F_2N_4O_6$: *m/z* 561 (MH+).

[0773] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-(methoxymethyl)-2-oxopyridine-3-carboxamide (358): Compound **PA1-2** was replaced with Compound **HA1-26.** MS for $C_{30}H_{24}F_2N_4O_6$: *m/z* 575 (MH+).

[0774] 5-Acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide (359): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-24.** MS for $C_{30}H_{23}FN_4O_6$: *m/z* 555.1 (MH+).

[0775] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-3,8-dioxo-6,7-dihydro-5H-isoquinoline-4-carboxamide (360): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-29.** MS for $C_{32}H_{25}FN_4O_6$: *m/z* 581.2 (MH+).

[0776] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-oxopyridine-3-carboxamide (361): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA1-19.** MS for $C_{28}H_{21}FN_4O_5$: *m/z* 513.0 (MH+).

[0777] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-8-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-6-carboxamide (362): Compound **PA1-2** was replaced with Compound **PA7-27.** MS for $C_{31}H_{24}F_2N_4O_5$: *m/z* 571.1 (MH+).

[0778] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-oxo-6,7,8,9-tetrahydroquinolizine-3-carboxamide (363): Compound **PA1-2** was replaced with Compound **PA7-34.** MS for $C_{32}H_{26}F_2N_4O_5$: *m/z* 585.1 (MH+).

[0779] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridazine-3-carboxamide (364): Compound **PA1-2** was replaced with Compound **HA2-5.** MS for $C_{31}H_{27}F_2N_5O_5$: *m/z* 588.2 (MH+).

[0780] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-ethoxy-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (365): Compound **PA1-2** was replaced with Compound **PA7-19.** MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589.2 (MH+).

[0781] 5-Bromo-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (366): Compound **PA1-2** was replaced with Compound **HA1-20.** MS for $C_{29}H_{21}BrF_2N_4O_5$: *m/z* 625.1 (MH+).

[0782] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-5-prop-1-en-2-ylpyridine-3-carboxamide (367): Compound **PA1-2** was replaced with

Compound **HA1-21.** ^{1}H NMR (400 MHz, CD_3OD) δ 12.24 (s, 1H), 8.68 (d, 1H), 8.48 (s, 1H), 8.06 (dd, 1H), 7.57 (s, 1H), 7.45-7.37 (m, 6H), 7.14 (d, 1H), 5.41-5.39 (m, 1H), 5.04 (s, 1H), 4.14 (s, 3H), 4.12 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H); MS for $C_{32}H_{26}F_2N_4O_5$: *m/z* 585.1 (MH+).

[0783] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-5-propan-2-ylpyridine-3-carboxamide (368): Compound **PA1-2** was replaced with Compound **HA1-22.** MS for $C_{32}H_{28}F_2N_4O_5$: *m/z* 587.1 (MH+).

[0784] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-ethoxy-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (369): Compound **PA1-2** was replaced with Compound **PA7-37.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.80 (d, 1H), 7.99 (d, 1H), 7.90-7.79 (m, 1H), 7.59-7.46 (m, 2H), 7.38-7.25 (m, 4H), 7.21-7.11 (m, 1H), 4.40 (q, 2H), 4.07 (s, 3H), 4.05 (s, 3H), 3.50 (s, 3H), 2.19 (s, 3H), 1.30 (t, 3H); MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603.1 (MH+).

[0785] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-5,6-dimethyl-2-oxopyridine-3-carboxamide (370): Compound **PA1-2** was replaced with Compound **HA1-23.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.3 (MH+).

[0786] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-ethoxy-1-(4-fluorophenyl)-5-methyl-2-oxopyridine-3-carboxamide (371): Compound **PA1-2** was replaced with Compound **HA1-27.** MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589.1 (MH+).

[0787] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methoxy-5-methyl-2-oxopyridine-3-carboxamide (372): Compound **PA1-2** was replaced with Compound **HA1-28.** MS for $C_{30}H_{24}F_2N_4O_6$: *m/z* 575.2 (MH+).

[0788] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3,5,6-tetrahydro-1H-indolizine-8-carboxamide, racemate (373): Compound **PA1-2** was replaced with Compound **PA7-41.** ^{1}H NMR (400 MHz, CD_3OD) δ = 8.65 (d, 1H), 7.98-7.89 (m, 1H), 7.57 (s, 1H), 7.37-7.27 (m, 4H), 7.14-7.05 (m, 3H), 4.16 (s, 3H), 4.11 (s, 3H), 3.98-3.89 (m, 2H), 3.88-3.65 (m, 3H), 3.55 (br t, 2H), 2.25-2.14 (m, 2H); MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573.1 (MH+).

[0789] The following two compounds were recovered from the chiral separation of Compound **373**. Absolute stereochemistry was not determined:

[0790] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3,5,6-tetrahydro-1H-indolizine-8-carboxamide, enantiomer 1 (374): MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573.2 (MH+). Analytical chiral SFC (Chiralcel OD-3, 50 x 4.6 mm, 3 μm; Mobile phase: A = CO_2, B = EtOH (0.05% DEA), Isocratic 40%, flow rate = 4.0 mL/min) retention time = 1.345 min.

[0791] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3,5,6-tetrahydro-1H-indolizine-8-carboxamide, enantiomer 2 (375): MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573.1 (MH+). Analytical chiral SFC (Chiralcel OD-3, 50 x 4.6 mm, 3 μm; Mobile phase: A = CO_2, B = EtOH (0.05% DEA), Isocratic 40%, flow rate = 4.0 mL/min) retention time = 4.971 min.

[0792] N-[3-Fluoro-4-[7-methoxy-6-[2-(methylamino)-2-oxoethyl]quinolin-4-yl]oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (376): Compound **NA1-1** was replaced

with Compound **QA1-9**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{32}H_{26}FN_4O_5$: *m/z* 585.1 (MH+).

[0793] N-[4-[7-[1-(Difluoromethyl)pyrazol-4-yl]quinolin-4-yl]oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (377): Compound **NA1-1** was replaced with Compound **QA1-10**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{32}H_{22}F_3N_5O_3$: *m/z* 582.1 (MH+).

[0794] 4-(4-Fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-methyl-3-oxopyrazine-2-carboxamide (378): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **HA3-1.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (s, 1H), 8.57 (d, 1H), 8.20 (d, 1H), 7.87 - 7.79 (m, 3H), 7.41 - 7.31 (m, 2H), 7.29 (br s, 1H), 7.25 (br s, 1H), 7.16 (dd, 3H), 6.86 (d, 1H), 4.02 (s, 3H), 2.16 (s, 3H); MS for $C_{27}H_{20}FN_5O_4$: *m/z* 498.1 (MH+).

[0795] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-3-oxopyrazine-2-carboxamide (379): Compound **PA1-2** was replaced with Compound **HA3-3.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.29 (s, 1H), 8.55 (d, 1H), 8.04 - 7.93 (m, 2H), 7.67 - 7.60 (m, 4H), 7.53 (br d, 1H), 7.45 (br t, 2H), 7.37 (br t, 1H), 6.84 (br d, 1H), 3.97 (s, 3H), 3.95 (s, 3H); MS for $C_{27}H_{19}F_2N_5O_5$: *m/z* 532.1 (MH+).

[0796] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-3-oxopyrazine-2-carboxamide (380): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA3-3.** MS for $C_{26}H_{17}F_2N_5O_4$: *m/z* 502.0 (MH+).

[0797] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-3-oxopyrazine-2-carboxamide (381): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA3-3.** MS for $C_{26}H_{17}F_2N_5O_4$: *m/z* 502.1 (MH+).

[0798] 4-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-3-oxopyrazine-2-carboxamide (382): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA3-3.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.73 (d, 1H), 8.70 (d, 1H), 7.98 (d, 1H), 7.85 (d, 2H), 7.79 (d, 1H), 7.67 - 7.62 (m, 3H), 7.45 (t, 2H), 7.28 (d, 2H), 6.76 (d, 1H), 4.00 (s, 3H); MS for $C_{26}H_{18}FN_5O_4$: *m/z* 484.1 (MH+).

[0799] 4-(4-Fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-3-oxopyrazine-2-carboxamide (383): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **HA3-3.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 8.61 (d, 1H), 8.28 (d, 1H), 7.97 (d, 1H), 7.82 (d, 2H), 7.70-7.60 (m, 3H), 7.44 (t, 2H), 7.30 (d, 1H), 7.24 (d, 2H), 6.94 (d, 1H), 3.93 (s, 3H); MS for $C_{26}H_{18}FN_5O_4$: *m/z* 484.0 (MH+).

[0800] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-3-oxopyrazine-2-carboxamide (384): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA3-3.** MS for $C_{27}H_{20}FN_5O_5$: *m/z* 514.1 (MH+).

[0801] 1-(4-Fluorophenyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methyl-6-oxopyrimidine-5-carboxamide (385): Compound **NA1-1** was replaced with Compound **NA1-17**.

Compound **PA1-2** was replaced with Compound **HA4-2.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.82 (s, 1H), 8.61 (d, 1H), 8.27 (d, 1H), 7.80 (d, 2H), 7.61 (dd, 2H), 7.47 (t, 2H), 7.29 (d, 1H), 7.21 (d, 2H), 6.94 (d, 1H), 3.91 (s, 3H), 2.22 (s, 3H); MS for $C_{27}H_{20}FN_5O_4$: *m/z* 498.0 (MH+).

[0802] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(4-fluorophenyl)-3-oxopyridazine-4-carboxamide (386): Compound **PA1-2** was replaced with Compound **HA2-16.** ^{1}H NMR (400 MHz, CD_3OD) δ 12.00 (s, 1H), 8.73 (d, 1H), 8.37 (d, 1H), 8.32 (d, 1H), 8.12 (dd, 1H), 7.71-7.65 (m, 2H), 7.60 (s, 1H), 7.59-7.54 (m, 1H), 7.48 (t, 1H), 7.30 (t, 2H), 7.23 (d, 1H), 4.17 (s, 3H), 4.14 (s, 3H). MS for $C_{27}H_{19}F_2N_5O_5$: *m/z* 532.1 (MH+).

[0803] 5-(4-Fluorophenyl)-4-hydroxy-6-methyl-N-[4-[[8-(methylamino)-1,7-naphthyridin-4-yl]oxy]phenyl]pyridine-3-carboxamide (387): Compound **NA1-1** was replaced with Compound **NA3-3**. Compound **PA1-2** was replaced with Compound **PA3-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 12.75 (d, 1H), 10.03 (d, 1H), 8.76 (d, 1H), 8.53 (d, 1H), 7.86 (d, 2H), 7.75 (d, 1H), 7.38 (d, 1H), 7.33-7.24 (m, 6H), 7.07 (d, 1H), 3.18 (d, 3H), 2.18 (s, 3H); MS for $C_{28}H_{22}FN_5O_3$: *m/z* 496.0 (MH+).

[0804] N-[3-Chloro-4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (388): Compound **NA1-1** was replaced with Compound **NA1-47**. Compound **PA1-2** was replaced with Compound **PA3-7.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (br s, 1H), 8.78 (br s, 2H), 8.24 (br s, 1H), 7.85 (br s, 1H), 7.65 (br s, 1H), 7.51 - 6.98 (m, 6H), 4.03 (br s, 6H), 3.66 - 3.63 (m, 3H), 2.21 (br s, 3H); MS for $C_{30}H_{24}ClFN_4O_5$: *m/z* 575.1 (MH+).

[0805] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-2-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (389): Compound **NA1-1** was replaced with Compound **NA1-48**. Compound **PA1-2** was replaced with Compound **PA3-7.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0806] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-2,3-difluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (390): Compound **NA1-1** was replaced with Compound **NA1-46**. Compound **PA1-2** was replaced with Compound **PA3-7.** MS for $C_{30}H_{23}F_3N_4O_5$: *m/z* 577.1 (MH+).

[0807] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-2,5-difluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (391): Compound **NA1-1** was replaced with Compound **NA1-45**. Compound **PA1-2** was replaced with Compound **PA3-7.** MS for $C_{30}H_{23}F_3N_4O_5$: *m/z* 577.1 (MH+).

[0808] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3,5-difluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (392): Compound **NA1-1** was replaced with Compound **NA1-44**. Compound **PA1-2** was replaced with Compound **PA3-7.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.91 (s, 1H), 8.62 (s, 1H), 8.53 (d, 1H), 7.56-7.48 (m, 3H), 7.20 (d, 4H), 6.78 (d, 1H), 4.09 (s, 3H), 4.02 (s, 3H), 3.86 (s, 3H), 2.28 (s, 3H); MS for $C_{30}H_{23}F_3N_4O_5$: *m/z* 577.1 (MH+).

[0809] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluoro-2-methylphenyl)-5-methyl-3-oxopyrazine-2-carboxamide (393): Compound **PA1-2** was replaced with Compound **HA3-4.** MS for $C_{29}H_{23}F_2N_5O_5$: *m/z* 560.1 (MH+).

[0810] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluoro-2-methylphenyl)-5-methyl-3-oxopyrazine-2-carboxamide (394): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA3-4.** ^{1}H NMR (400 MHz, CD_3OD) δ 8.92 - 8.81 (m, 1H), 8.49 - 8.38 (m, 1H), 8.13 (br d, 1H), 7.86 (br s, 1H), 7.70 - 7.54 (m, 2H), 7.50 (br t, 1H), 7.43 - 7.26 (m, 3H), 7.22 (m, 1H), 4.15 (br s, 3H), 2.13 (br s, 6H); MS for $C_{28}H_{21}F_2N_5O_4$: *m/z* 530.3 (MH+).

[0811] 5-(2,4-Difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-6-methylpyridine-3-carboxamide (395): Compound **PA1-2** was replaced with Compound **PA7-22.** MS for $C_{29}H_{21}F_3N_4O_5$: *m/z* 563.0 (MH+).

[0812] 5-(2,4-Difluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridine-3-carboxamide (396): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA3-13.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.79 (s, 1H), 8.53 (d, 1H), 7.77 (br d, 2H), 7.63 (s, 1H), 7.39 - 7.26 (m, 2H), 7.18 (br d, 3H), 6.79 (d, 1H), 3.97 - 3.89 (m, 9H), 2.21 (s, 3H); MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.1 (MH+).

[0813] 4-[4-[[1-(4-Fluorophenyl)-6-methyl-2-oxopyridine-3-carbonyl]amino]phenoxy]-N-methyl-1,7-naphthyridine-6-carboxamide (397): Compound **NA1-1** was replaced with Compound **NA3-4**. Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{29}H_{22}FN_5O_4$: *m/z* 524.1 (MH+).

[0814] 4-[4-[[5-(4-Fluorophenyl)-4-hydroxy-6-methylpyridine-3-carbonyl]amino]phenoxy]-N-methyl-1,7-naphthyridine-6-carboxamide (398): Compound **NA1-1** was replaced with Compound **NA3-4**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{29}H_{22}FN_5O_4$: *m/z* 524.1 (MH+).

[0815] 1-Cyclopropyl-N-[6-(6,7-dimethoxyquinolin-4-yl)oxy-5-fluoropyridin-3-yl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (399): Compound **NA1-1** was replaced with Compound **QA1-8**. MS for $C_{31}H_{24}F_2N_4O_5$: *m/z* 571 (MH+).

[0816] N-[6-(6,7-Dimethoxyquinolin-4-yl)oxy-5-fluoropyridin-3-yl]-5-(4-fluorophenyl)-1-(1-methylazetidin-3-yl)-4-oxopyridine-3-carboxamide (400): Compound **NA1-1** was replaced with Compound **QA1-8**. Compound **PA1-2** was replaced with Compound **PA1-25.** MS for $C_{32}H_{27}F_2N_5O_5$: *m/z* 600 (MH+).

[0817] N-[6-(6,7-Dimethoxyquinolin-4-yl)oxy-5-fluoropyridin-3-yl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide (401): Compound **NA1-1** was replaced with Compound **QA1-8**. Compound **PA1-2** was replaced with Compound **PA1-11.** MS for $C_{32}H_{24}F_2N_6O_5$: *m/z* 611 (MH+).

[0818] N-[6-(6,7-Dimethoxyquinolin-4-yl)oxy-5-fluoropyridin-3-yl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-3-yl)-4-oxopyridine-3-carboxamide (402): Compound **NA1-1** was replaced with Compound **QA1-8**. Compound **PA1-2** was replaced with Compound **PA1-12.** MS for $C_{32}H_{24}F_2N_6O_5$: *m/z* 611 (MH+).

[0819] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-ethoxy-5-(4-fluorophenyl)-2-methylpyridine-3-carboxamide (403): Compound **PA1-2** was replaced with Compound **PA7-40.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0820] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carboxamide (404): Compound **PA1-2** was replaced with Compound **PA7-25.** MS for $C_{31}H_{24}F_2N_4O_5$: *m/z* 571 (MH+).

[0821] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carboxamide (405): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-25.** MS for $C_{30}H_{22}F_2N_4O_4$: *m/z* 541 (MH+).

[0822] N-[4-(6,7-Dimethoxyquinazolin-4-yl)oxy-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carboxamide (406): Compound **NA1-1** was replaced with Compound **QA2-1**. Compound **PA1-2** was replaced with Compound **PA7-25.** MS for $C_{31}H_{24}F_2N_4O_5$: *m/z* 571 (MH+).

[0823] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carboxamide (407): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA7-25.** MS for $C_{31}H_{25}FN_4O_5$: *m/z* 553 (MH+).

[0824] 4-[2-Fluoro-4-[[6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carbonyl]amino]phenoxy]-7-methoxy-N-methylquinoline-6-carboxamide (408): Compound **NA1-1** was replaced with Compound **QA1-6**. Compound **PA1-2** was replaced with Compound **PA7-25.** MS for $C_{33}H_{26}F_2N_4O_5$: *m/z* 597 (MH+).

[0825] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-6-(4-fluorophenyl)-7-oxo-2,3-dihydro-1H-indolizine-8-carboxamide (409): Compound **NA1-1** was replaced with Compound **QA1-1**. Compound **PA1-2** was replaced with Compound **PA7-25.** MS for $C_{32}H_{25}F_2N_3O_5$: *m/z* 570 (MH+).

[0826] 1-Ethyl-N-[3-fluoro-4-[(7-hydroxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (410): Compound **NA1-1** was replaced with Compound **NA1-51**. Compound **PA1-2** was replaced with Compound **PA3-4.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.2 (s, 1H), 11.3 (s, 1H), 8.80 (s, 1H), 8.76 (d, 2H), 8.08 (d, 1H), 7.64 (d, 1H), 7.51 (d, 1H), 7.45 (t, 1H), 7.29 (d, 4H), 6.83 (s, 1H), 4.29 (q, 2H), 2.27 (s, 3H), 1.40 (t, 3H); MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529 (MH+).

[0827] 6-Chloro-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (411): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-29.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (s, 1H), 8.96 (s, 1H), 8.76 (d, 1H), 8.72 (s, 1H), 8.05 (dd, 1H), 7.81 (d, 1H), 7.54 – 7.47 (m, 1H), 7.47 – 7.27 (m, 5H), 6.76 (dd, 1H), 4.01 (s, 6H); MS for $C_{28}H_{19}ClF_2N_4O_4$: *m/z* 549 (MH+).

[0828] 6-Chloro-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (412): Compound **PA1-2** was replaced with Compound **PA7-29.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (s, 1H), 8.95 (s, 1H), 8.56 (d, 1H), 8.01 (dd,

1H), 7.66 (s, 1H), 7.45 (d, 1H), 7.39 – 7.27 (m, 5H), 6.84 (d, 1H), 4.01 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H); MS for $C_{29}H_{21}ClF_2N_4O_5$: *m/z* 579 (MH+).

[0829] 5-(4-Fluorophenyl)-4-hydroxy-N-[4-[(7-methoxy-6-propan-2-yloxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (413): Compound **NA1-1** was replaced with Compound **NA1-31**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{31}H_{27}FN_4O_5$: *m/z* 555 (MH+).

[0830] 5-(4-Fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(7-methoxy-6-propan-2-yloxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (414): Compound **NA1-1** was replaced with Compound **NA1-31**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{32}H_{29}FN_4O_5$: *m/z* 569 (MH+).

[0831] N-[3-Fluoro-4-[(7-methoxy-6-propan-2-yloxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (415): Compound **NA1-1** was replaced with Compound **NA1-30**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0832] N-[3-Fluoro-4-[(7-methoxy-6-propan-2-yloxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (416): Compound **NA1-1** was replaced with Compound **NA1-30**. Compound **PA1-2** was replaced with Compound **PA7-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (s, 1H), 12.6 (s, 1H), 8.57 (s, 1H), 8.56 (s, 1H), 8.00 (dd, 1H), 7.62 (s, 1H), 7.35 (d, 1H), 7.27 – 7.03 (m, 4H), 6.92 (d, 1H), 5.29 (p, 1H), 3.95 (s, 3H), 2.06 (s, 6H), 1.27 (dd, 6H); MS for $C_{32}H_{28}F_2N_4O_5$: *m/z* 587 (MH+).

[0833] 5-(4-Fluoro-2,6-dimethylphenyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide (417): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA7-20.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0834] N-[4-[(7-Ethyl-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (418): Compound **NA1-1** was replaced with Compound **NA1-32**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{29}H_{22}F_2N_4O_3$: *m/z* 513 (MH+).

[0835] N-[4-[(7-Ethyl-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (419): Compound **NA1-1** was replaced with Compound **NA1-32**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{30}H_{24}F_2N_4O_3$: *m/z* 527 (MH+).

[0836] N-[4-[(7-Ethyl-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (420): Compound **NA1-1** was replaced with Compound **NA1-38**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0837] N-[4-[(7-Ethyl-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (421): Compound **NA1-1** was replaced

with Compound **NA1-38**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{31}H_{26}F_2N_4O_4$: *m/z* 557 (MH+).

[0838] N-[4-[(7-Ethenyl-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (422): Compound **NA1-1** was replaced with Compound **NA1-40**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{30}H_{22}F_2N_4O_4$: *m/z* 541 (MH+).

[0839] N-[4-[(7-Ethenyl-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (423): Compound **NA1-1** was replaced with Compound **NA1-40**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{31}H_{24}F_2N_4O_4$: *m/z* 555 (MH+).

[0840] N-[3-Fluoro-4-[[7-methoxy-6-(3-morpholin-4-ylpropoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (424): Compound **NA1-1** was replaced with Compound **NA1-28**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{35}H_{33}F_2N_5O_6$: *m/z* 658 (MH+).

[0841] N-[3-Fluoro-4-[[7-methoxy-6-(3-morpholin-4-ylpropoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (425): Compound **NA1-1** was replaced with Compound **NA1-28**. Compound **PA1-2** was replaced with Compound **PA7-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 12.64 (s, 1H), 8.60 – 8.53 (m, 2H), 8.01 (d, 1H), 7.64 (s, 1H), 7.38 (d, 1H), 7.27 (t, 1H), 7.17 (d, 1H), 7.12 – 7.05 (m, 2H), 6.88 (d, 1H), 4.34 (t, 2H), 3.97 (s, 3H), 3.49 (t, 4H), 2.40 – 2.27 (m, 6H), 2.07 (s, 6H), 1.87 (m, 2H); MS for $C_{36}H_{35}F_2N_5O_6$: *m/z* 672 (MH+).

[0842] N-[3-Fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (426): Compound **NA1-1** was replaced with Compound **NA1-20**. Compound **PA1-2** was replaced with Compound **PA3-1** MS for $C_{28}H_{19}F_3N_4O_3$: *m/z* 517 (MH+).

[0843] N-[3-Fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (427): Compound **NA1-1** was replaced with Compound **NA1-20**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{29}H_{21}F_3N_4O_3$: *m/z* 531 (MH+).

[0844] N-[3-Fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (428): Compound **NA1-1** was replaced with Compound **NA1-20**. Compound **PA1-2** was replaced with Compound **PA7-2.** MS for $C_{30}H_{23}F_3N_4O_3$: *m/z* 545 (MH+).

[0845] N-[3-Fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (429): Compound **NA1-1** was replaced with Compound **NA1-20**. Compound **PA1-2** was replaced with Compound **PA7-7.** MS for $C_{30}H_{23}F_3N_4O_3$: *m/z* 545 (MH+).

[0846] N-[3-Fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridazine-3-carboxamide (430): Compound **NA1-1** was replaced with Compound **NA1-20**. Compound **PA1-2** was replaced with Compound **HA2-2.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.21 (s, 1H), 12.83 (s, 1H), 8.74 (d, 1H), 8.49 (d, 1H), 8.06 (d, 1H), 7.54 (d, 1H), 7.46 (t, 1H), 7.25 – 7.07 (m, 3H), 6.92 (d, 1H), 2.49 (s, 3H), 2.16 (s, 3H), 2.11 (s, 3H); MS for $C_{28}H_{20}F_3N_5O_3$: *m/z* 532 (MH+).

[0847] N-[3-Fluoro-4-[(7-hydroxy-6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (431): Compound **NA1-1** was replaced with Compound **NA1-43**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545 (MH+).

[0848] N-[3-Fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (432): Compound **NA1-1** was replaced with Compound **NA1-19**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603 (MH+).

[0849] 1-Cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (433): Compound **PA1-2** was replaced with Compound **PA7-35.** MS for $C_{32}H_{26}F_2N_4O_5$: *m/z* 585 (MH+).

[0850] 1-Cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (434): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA7-35.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.60 (s, 1H), 8.54 (dd, 1H), 7.77 (d, 2H), 7.65 (d, 1H), 7.34 – 7.25 (m, 4H), 7.18 (d, 2H), 6.81 (dd, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 2.43 (m, 1H), 2.37 (s, 3H), 1.26 – 1.18 (m, 4H); MS for $C_{32}H_{27}FN_4O_5$: *m/z* 567 (MH+).

[0851] 1-Cyclopropyl-N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (435): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA7-35.** MS for $C_{31}H_{24}F_2N_4O_4$: *m/z* 555 (MH+).

[0852] N-[3-Fluoro-4-[[6-(2-methoxyethoxy)-7-methyl-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (436): Compound **NA1-1** was replaced with Compound **NA1-36**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0853] 5-(4-Fluorophenyl)-4-hydroxy-N-[4-[[6-(2-methoxyethoxy)-7-methyl-1,5-naphthyridin-4-yl]oxy]phenyl]-6-methylpyridine-3-carboxamide (437): Compound **NA1-1** was replaced with Compound **NA1-35**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{31}H_{27}FN_4O_5$: *m/z* 555 (MH+).

[0854] N-[3-Fluoro-4-[[7-methyl-6-(3-morpholin-4-ylpropoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (438): Compound

NA1-1 was replaced with Compound **NA1-37**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{35}H_{33}F_2N_5O_5$: *m/z* 642 (MH+).

[0855] 1-Cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide (439): Compound **PA1-2** was replaced with Compound **PA7-32.** MS for $C_{33}H_{28}F_2N_4O_5$: *m/z* 599 (MH+).

[0856] 1-Cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide (440): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA7-32.** MS for $C_{33}H_{29}FN_4O_5$: *m/z* 581 (MH+).

[0857] 1-Cyclopropyl-N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxopyridine-3-carboxamide (441): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA7-32.** MS for $C_{32}H_{26}F_2N_4O_4$: *m/z* 569 (MH+).

[0858] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methoxy-2-methylpyridine-3-carboxamide (442): Compound **PA1-2** was replaced with Compound **PA7-16.** MS for $C_{30}H_{24}F_2N_4O_6$: *m/z* 575 (MH+).

[0859] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4,6-dihydroxy-2-methylpyridine-3-carboxamide (443): Compound **PA1-2** was replaced with Compound **PA7-15.** MS for $C_{29}H_{22}F_2N_4O_6$: *m/z* 561 (MH+).

[0860] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4,6-dimethoxy-2-methylpyridine-3-carboxamide (444): Compound **PA1-2** was replaced with Compound **PA7-39.** MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589 (MH+).

[0861] N-[3-Fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (445): Compound **NA1-1** was replaced with Compound **NA1-20**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{29}H_{21}F_3N_4O_3$: *m/z* 531 (MH+).

[0862] N-[3-Fluoro-4-[(6-fluoro-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (446): Compound **NA1-1** was replaced with Compound **NA1-20**. Compound **PA1-2** was replaced with Compound **PA5-11.** MS for $C_{30}H_{23}F_3N_4O_4$: *m/z* 561 (MH+).

[0863] N-[4-[(6-Ethoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methyl-2-oxopyridine-3-carboxamide (447): Compound **NA1-1** was replaced with Compound **NA1-27**. Compound **PA1-2** was replaced with Compound **HA1-16.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559 (MH+).

[0864] 5-(4-Fluoro-2-methylphenyl)-4-hydroxy-6-methyl-N-[4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide (448): Compound **NA1-1** was replaced with

Compound **NA1-25**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{31}H_{25}FN_4O_3$: *m/z* 521 (MH+).

[0865] N-[3-Fluoro-4-[(6-methoxy-7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (449): Compound **NA1-1** was replaced with Compound **NA1-23**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{32}H_{26}F_2N_4O_4$: *m/z* 569 (MH+).

[0866] 5-(4-Fluoro-2-methylphenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide (450): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{31}H_{24}F_2N_4O_3$: *m/z* 539 (MH+).

[0867] 5-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (451): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **PA5-2.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.4 (s, 1H), 11.6 (s, 1H), 9.19 (s, 1H), 8.71 (d, 1H), 8.30 (s, 1H), 7.96 (d, 1H), 7.33 (m, 2H), 7.18 (m, 4H), 6.79 (d, 1H), 5.81 (s, 1H), 5.37 (s, 1H), 2.68 (s, 3H), 2.22 (s, 3H), 2.08 (s, 3H); MS for $C_{31}H_{24}F_2N_4O_3$: *m/z* 539 (MH+).

[0868] N-[3-Fluoro-4-[(6-methoxy-7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (452): Compound **NA1-1** was replaced with Compound **NA1-23**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{31}H_{24}F_2N_4O_4$: *m/z* 555 (MH+).

[0869] N-[3-Fluoro-4-[(6-methoxy-7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (453): Compound **NA1-1** was replaced with Compound **NA1-23**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{32}H_{26}F_2N_4O_4$: *m/z* 569 (MH+).

[0870] 5-(4-Fluorophenyl)-4-hydroxy-6-methyl-N-[4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide (454): Compound **NA1-1** was replaced with Compound **NA1-25**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{30}H_{23}FN_4O_3$: *m/z* 507 (MH+).

[0871] 5-(4-Fluorophenyl)-4-hydroxy-2,6-dimethyl-N-[4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide (455): Compound **NA1-1** was replaced with Compound **NA1-25**. Compound **PA1-2** was replaced with Compound **PA5-2.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.4 (s, 1H), 11.9 (s, 1H), 9.25 (s, 1H), 8.77 (d, 1H), 8.37 (s, 1H), 7.81 (d, 2H), 7.25 (m, 6H), 6.85 (d, 1H), 5.88 (s, 1H), 5.44 (s, 1H), 2.75 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H); MS for $C_{31}H_{25}FN_4O_3$: *m/z* 521 (MH+).

[0872] 5-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide (456): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{30}H_{22}F_2N_4O_3$: *m/z* 525 (MH+).

[0873] 1-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4,6-dimethyl-2-oxopyridine-3-carboxamide (457): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **HA1-5.** MS for $C_{31}H_{24}F_2N_4O_3$: *m/z* 539 (MH+).

[0874] N-[3-Fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (458): Compound **NA1-1** was replaced with Compound **NA1-26.** Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529 (MH+).

[0875] N-[3-Fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (459): Compound **NA1-1** was replaced with Compound **NA1-26**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0876] N-[3-Fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (460): Compound **NA1-1** was replaced with Compound **NA1-26**. Compound **PA1-2** was replaced with Compound **PA7-1.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0877] 5-(4-Fluoro-2-methylphenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (461): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **PA7-2.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.6 (s, 1H), 12.0 (s, 1H), 9.26 (s, 1H), 8.78 (d, 1H), 8.37 (s, 1H), 8.03 (dd, 1H), 7.39 (m, 2H), 7.15 (d, 1H), 7.06 (m, 2H), 6.86 (d, 1H), 5.88 (s, 1H), 5.44 (s, 1H), 2.79 (s, 3H), 2.29 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H); MS for $C_{32}H_{26}F_2N_4O_3$: *m/z* 553 (MH+).

[0878] 1-(4-Fluorophenyl)-2-methyl-6-oxo-N-[4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyrimidine-5-carboxamide (462): Compound **NA1-1** was replaced with Compound **NA1-25**. Compound **PA1-2** was replaced with Compound **HA4-2.** MS for $C_{29}H_{22}FN_5O_3$: *m/z* 508 (MH+).

[0879] 5-(4-Fluoro-2-methylphenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (463): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **HA2-2.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.2 (s, 1H), 12.9 (s, 1H), 9.27 (s, 1H), 8.79 (d, 1H), 8.38 (s, 1H), 8.06 (dd, 1H), 7.52 (d, 1H), 7.45 (m, 1H), 7.19 (m, 2H), 7.10 (m, 1H), 6.91 (d, 1H), 5.89 (s, 1H), 5.44 (s, 1H), 2.99 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H); MS for $C_{30}H_{23}F_2N_5O_3$: *m/z* 540 (MH+).

[0880] 5-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (464): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **HA2-1.** MS for $C_{29}H_{21}F_2N_5O_3$: *m/z* 526 (MH+).

[0881] 1-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methyl-6-oxopyrimidine-5-carboxamide (465): Compound **NA1-1** was replaced with Compound

NA1-24. Compound **PA1-2** was replaced with Compound **HA4-2.** MS for $C_{29}H_{21}F_2N_5O_3$: *m/z* 526 (MH+).

[0882] 1-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-2,4-dimethyl-6-oxopyrimidine-5-carboxamide (466): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **HA4-6.** MS for $C_{30}H_{23}F_2N_5O_3$: *m/z* 540 (MH+).

[0883] 1-(4-Fluorophenyl)-2,4-dimethyl-6-oxo-N-[4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyrimidine-5-carboxamide (467): Compound **NA1-1** was replaced with Compound **NA1-25**. Compound **PA1-2** was replaced with Compound **HA4-6.** MS for $C_{30}H_{24}FN_5O_3$: *m/z* 522 (MH+).

[0884] N-[3-Fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyrimidine-5-carboxamide (468): Compound **NA1-1** was replaced with Compound **NA1-26.** Compound **PA1-2** was replaced with Compound **HA4-6.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.9 (s, 1H), 8.58 (d, 1H), 8.13 (s, 1H), 8.01 (dd, 1H), 7.46 (dd, 1H), 7.34 (m, 1H), 7.15 (m, 4H), 6.94 (d, 1H), 3.93 (s, 3H), 2.35 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H); MS for $C_{29}H_{23}F_2N_5O_4$: *m/z* 544 (MH+).

[0885] N-[3-Fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (469): Compound **NA1-1** was replaced with Compound **NA1-26**. Compound **PA1-2** was replaced with Compound **PA5-11.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0886] N-[3-Fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (470): Compound **NA1-1** was replaced with Compound **NA1-26**. Compound **PA1-2** was replaced with Compound **PA5-5.** MS for $C_{32}H_{28}F_2N_4O_5$: *m/z* 587 (MH+).

[0887] N-[3-Fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (471): Compound **NA1-1** was replaced with Compound **NA1-26**. Compound **PA1-2** was replaced with Compound **PA7-2.** MS for $C_{31}H_{26}F_2N_4O_4$: *m/z* 557 (MH+).

[0888] N-[3-Fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (472): Compound **NA1-1** was replaced with Compound **NA1-26**. Compound **PA1-2** was replaced with Compound **HA2-1.** MS for $C_{28}H_{21}F_2N_5O_4$: *m/z* 530 (MH+).

[0889] N-[3-Fluoro-4-[(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (473): Compound **NA1-1** was replaced with Compound **NA1-26**. Compound **PA1-2** was replaced with Compound **HA2-2.** MS for $C_{29}H_{23}F_2N_5O_4$: *m/z* 544 (MH+).

[0890] 5-(4-Fluoro-2-methylphenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2-methylpyridine-3-carboxamide (474): Compound **NA1-1** was replaced

with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **PA7-23.** MS for $C_{31}H_{24}F_2N_4O_3$: *m/z* 539 (MH+).

[0891] 1-Ethyl-5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridazine-3-carboxamide (475): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **HA2-4A.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (s, 1H), 9.27 (s, 1H), 8.79 (d, 1H), 8.38 (s, 1H), 8.05 (d, 1H), 7.51 (d, 1H), 7.45 (m, 1H), 7.34 (m, 4H), 6.88 (d, 1H), 5.88 (s, 1H), 5.44 (s, 1H), 4.41 (q, 2H), 2.37 (s, 3H), 2.29 (s, 3H), 1.46 (t, 3H); MS for $C_{31}H_{25}F_2N_5O_3$: *m/z* 554 (MH+).

[0892] 4-Ethoxy-5-(4-fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridazine-3-carboxamide (476): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **HA2-4B.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.7 (s, 1H), 9.27 (s, 1H), 8.79 (d, 1H), 8.39 (s, 1H), 7.95 (d, 1H), 7.52 (d, 2H), 7.46 (m, 2H), 7.29 (t, 2H), 6.94 (d, 1H), 5.89 (s, 1H), 5.45 (s, 1H), 4.47 (q, 2H), 2.29 (s, 3H), 2.28 (s, 3H), 1.57 (t, 3H); MS for $C_{31}H_{25}F_2N_5O_3$: *m/z* 554 (MH+).

[0893] 5-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridazine-3-carboxamide (477): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **HA2-3.** MS for $C_{30}H_{23}F_2N_5O_3$: *m/z* 540 (MH+).

[0894] 5-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-prop-1-en-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-methoxy-6-methylpyridazine-3-carboxamide (478): Compound **NA1-1** was replaced with Compound **NA1-24**. Compound **PA1-2** was replaced with Compound **HA2-3B.** MS for $C_{30}H_{23}F_2N_5O_3$: *m/z* 540 (MH+).

[0895] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-methylpyridine-3-carboxamide (479): Compound **PA1-2** was replaced with Compound **PA7-23.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0896] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2-methylpyridine-3-carboxamide (480): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA7-23.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529.2 (MH+).

[0897] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide (481): Compound **PA1-2** was replaced with Compound **PA7-33.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (s, 1H), 8.53 (d, 1H), 7.98 – 7.91 (m, 1H), 7.89 (s, 1H), 7.65 (s, 1H), 7.47 – 7.42 (m, 1H), 7.34 (t, 1H), 7.20 – 6.99 (m, 3H), 6.78 (d, 1H), 3.97 (s, 3H), 3.97 (s, 3H), 3.74 (s, 3H), 2.54 (s, 3H), 2.19 (s, 3H); MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573.2 (MH+).

[0898] N-[3-Fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (482): Compound

NA1-1 was replaced with Compound **NA1-19**. Compound **PA1-2** was replaced with Compound **PA5-11.** MS for $C_{33}H_{30}F_2N_4O_7$: *m/z* 633.2 (MH+).

[0899] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide (483): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **PA7-33.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543.2 (MH+).

[0900] N-[3-Fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (484): Compound **NA1-1** was replaced with Compound **NA1-19**. Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589.2 (MH+).

[0901] N-[3-Fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (485): Compound **NA1-1** was replaced with Compound **NA1-19**. Compound **PA1-2** was replaced with Compound **HA1-5.** MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603.2 (MH+).

[0902] N-[3-Fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide (486): Compound **NA1-1** was replaced with Compound **NA1-19**. Compound **PA1-2** was replaced with Compound **PA3-7.** MS for $C_{32}H_{28}F_2N_4O_6$: *m/z* 603.2 (MH+).

[0903] N-[3-Fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (487): Compound **NA1-1** was replaced with Compound **NA1-19**. Compound **PA1-2** was replaced with Compound **PA7-2.** MS for $C_{33}H_{30}F_2N_4O_6$: *m/z* 617.2 (MH+).

[0904] 4-Chloro-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxamide (488): Compound **PA1-2** was replaced with Compound **HA2-11.** MS for $C_{28}H_{20}ClF_2N_5O_4$: *m/z* 564.2 (MH+).

[0905] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-methoxy-6-methylpyridazine-3-carboxamide (489): Compound **PA1-2** was replaced with Compound **HA2-6B.** MS for $C_{30}H_{25}F_2N_5O_5$: *m/z* 574.1 (MH+).

[0906] 5-Bromo-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2-methylpyridine-3-carboxamide (490): Compound **PA1-2** was replaced with Compound **PA7-24.** MS for $C_{23}H_{18}BrFN_4O_5$: *m/z* 531.0 (MH+).

[0907] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-8-(4-fluorophenyl)-2-methyl-7-oxo-[1,3]oxazolo[3,2-a]pyridine-6-carboxamide (491): Compound **PA1-2** was replaced with Compound **PA7-31.** MS for $C_{31}H_{22}F_2N_4O_6$: *m/z* 585.1 (MH+).

[0908] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (492): Compound **PA1-2** was replaced with Compound **E3-1.** MS for $C_{25}H_{23}FN_4O_6$: *m/z* 495.1 (MH+).

[0909] 5-(4-Fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-methylpyridine-3-carboxamide (493): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **PA7-23.** MS for $C_{29}H_{23}FN_4O_4$: *m/z* 511.2 (MH+).

[0910] N-[3-Fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (494): Compound **NA1-1** was replaced with Compound **NA3-1**. Compound **PA1-2** was replaced with Compound **HA1-1.** MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515.2 (MH+).

[0911] N-[4-[(6-Chloro-1,7-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (496): Compound **NA1-1** was replaced with Compound **NA3-2**. Compound **PA1-2** was replaced with Compound **HA1-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 9.25 (s, 1H), 8.80 (d, 1H), 8.44 (d, 1H), 8.23 (d, 1H), 8.03 (dd, 1H), 7.56 – 7.22 (m, 5H), 6.87 (d, 1H), 6.66 (d, 2H), 2.02 (s, 3H); MS for $C_{27}H_{17}ClF_2N_4O_3$: *m/z* 519.0 (MH+).

[0912] N-[4-[(6-Chloro-1,7-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide (497): Compound **NA1-1** was replaced with Compound **NA3-2**. Compound **PA1-2** was replaced with Compound **HA4-2.** MS for $C_{26}H_{16}ClF_2N_5O_3$: *m/z* 520.0 (MH+).

[0913] N-[4-[(6-Chloro-1,7-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide (498): Compound **NA1-1** was replaced with Compound **NA3-2**. Compound **PA1-2** was replaced with Compound **HA3-1.** MS for $C_{26}H_{16}ClF_2N_5O_3$: *m/z* 520.0 (MH+).

[0914] N-[3-Fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide (499): Compound **NA1-1** was replaced with Compound **NA3-1**. Compound **PA1-2** was replaced with Compound **HA4-2.** MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516.0 (MH+).

[0915] N-[3-Fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide (500): Compound **NA1-1** was replaced with Compound **NA3-1**. Compound **PA1-2** was replaced with Compound **HA3-1.** MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516.0 (MH+).

[0916] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1-methyl-4-oxopyridine-3-carboxamide (503): Compound **PA1-2** was replaced with Compound **PA3-12.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0917] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-ethyl-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide (504): Compound **PA1-2** was replaced with Compound **PA7-18.** MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[0918] 5-(4-Fluoro-2-methylphenyl)-N-[3-fluoro-4-(1,5-naphthyridin-4-yloxy)phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (505): Compound **NA1-1** was replaced with Compound **NA1-21**. Compound **PA1-2** was replaced with Compound **PA7-2.** MS for $C_{29}H_{22}F_2N_4O_3$: *m/z* 513 (MH+).

[0919] N-[3-Fluoro-4-[(6-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (506): Compound **NA1-1** was replaced with

Compound **NA1-33**. Compound **PA1-2** was replaced with Compound **PA7-2.** MS for $C_{30}H_{24}F_2N_4O_3$: *m/z* 527 (MH+).

[0920] 5-(4-Fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethyl-N-[4-[(6-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide (507): Compound **NA1-1** was replaced with Compound **NA1-34**. Compound **PA1-2** was replaced with Compound **PA7-2.** MS for $C_{30}H_{25}FN_4O_3$: *m/z* 509 (MH+).

[0921] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide (508): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **PA6-5.** MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[0922] 2-Ethyl-5-(4-fluorophenyl)-4-hydroxy-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (509): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **PA5-7.** MS for $C_{30}H_{25}FN_4O_4$: *m/z* 525 (MH+).

[0923] 5-(4-Fluorophenyl)-4-hydroxy-2-(methoxymethyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (510): Compound **NA1-1** was replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **PA5-11.** MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541 (MH+).

[0924] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide (511): Compound **PA1-2** was replaced with Compound **PA6-5.** MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[0925] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide (512): Compound **PA1-2** was replaced with Compound **HA2-6A.** MS for $C_{30}H_{25}F_2N_5O_5$: *m/z* 574 (MH+).

[0926] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide (513): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA2-6A.** ^{1}H NMR (400 MHz, CD_3OD) δ 9.04 – 8.96 (m, 2H), 8.16 – 8.08 (m, 1H), 7.80 (d, 1H), 7.59 (dt, 2H), 7.27 (d, 1H), 7.21 – 7.05 (m, 3H), 4.59 (s, 3H), 4.19 (s, 3H), 2.26 (s, 3H), 2.20 (s, 3H); MS for $C_{29}H_{23}F_2N_5O_4$: *m/z* 544 (MH+).

[0927] 5-(4-Fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1,6-dimethyl-4-oxopyridazine-3-carboxamide (514): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA2-6A.** ^{1}H NMR (400 MHz, CD_3OD) δ 9.02 – 8.90 (m, 2H), 8.00 (dd, 2H), 7.78 (d, 1H), 7.49 – 7.42 (m, 2H), 7.22 – 7.06 (m, 4H), 4.58 (d, 3H), 4.19 (d, 3H), 2.33 – 2.19 (m, 6H); MS for $C_{29}H_{24}FN_5O_4$: *m/z* 526 (MH+).

[0928] 5-(4-Fluorophenyl)-4-methoxy-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridazine-3-carboxamide (515): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA2-3B.** MS for $C_{28}H_{22}FN_5O_4$: *m/z* 512 (MH+).

[0929] 5-(4-Fluoro-2-methylphenyl)-4-hydroxy-2-(methoxymethyl)-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (516): Compound **NA1-1** was

replaced with Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **PA5-5.** MS for $C_{31}H_{27}FN_4O_5$: *m/z* 555 (MH+).

[0930] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide (517): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA2-6A.** MS for $C_{30}H_{26}FN_5O_5$: *m/z* 556 (MH+).

[0931] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-[4-fluoro-2-(hydroxymethyl)phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (518): Compound **PA1-2** was replaced with Compound **PA7-21.** MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589 (MH+).

[0932] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(4-fluorophenyl)-6-methyl-3-oxopyridazine-4-carboxamide (519): Compound **PA1-2** was replaced with Compound **HA2-12.** MS for $C_{28}H_{21}F_2N_5O_5$: *m/z* 546 (MH+).

[0933] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-6-methyl-3-oxopyridazine-4-carboxamide (520): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA2-12.** MS for $C_{28}H_{22}FN_5O_5$: *m/z* 528 (MH+).

[0934] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-6-methyl-3-oxopyridazine-4-carboxamide (521): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA2-12.** ^{1}H NMR (400 MHz, CD_3OD) δ 12.13 (s, 1H), 8.86 (s, 1H), 8.81 (d, 1H), 8.33 (s, 1H), 8.08 (d, 1H), 7.74 (d, 1H), 7.63 (dd, 2H), 7.53 (d, 1H), 7.44 (t, 1H), 7.28 (t, 2H), 6.99 (d, 1H), 4.12 (s, 3H), 2.55 (s, 3H); MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516 (MH+).

[0935] 2-(4-Fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-3-oxopyridazine-4-carboxamide (522): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA2-12.** ^{1}H NMR (400 MHz, CD_3OD) δ 12.08 (s, 1H), 8.98 (d, 1H), 8.92 (d, 1H), 8.34 (s, 1H), 8.01 (d, 2H), 7.78 (d, 1H), 7.68 (dd, 2H), 7.43 (d, 2H), 7.31 (t, 2H), 7.18 (d, 1H), 4.19 (s, 3H), 2.54 (s, 3H); MS for $C_{27}H_{20}FN_5O_4$: *m/z* 498 (MH+).

[0936] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,2,6-trimethyl-4-oxopyridine-3-carboxamide (523): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **PA6-5.** MS for $C_{31}H_{27}FN_4O_5$: *m/z* 555 (MH+).

[0937] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(4-fluorophenyl)-5,6-dimethyl-3-oxopyridazine-4-carboxamide (524): Compound **PA1-2** was replaced with Compound **HA2-15.** MS for $C_{29}H_{23}F_2N_5O_5$: *m/z* 560 (MH+).

[0938] N-[3-Fluoro-4-(6-methoxyquinolin-4-yl)oxyphenyl]-5-(4-fluorophenyl)-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (525): Compound **NA1-1** was replaced with Compound **QA1-7**. Compound **PA1-2** was replaced with Compound **PA5-11.** MS for $C_{31}H_{25}F_2N_3O_5$: *m/z* 558 (MH+).

[0939] 2-Ethyl-5-(4-fluoro-2-methylphenyl)-4-hydroxy-N-[4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (526): Compound **NA1-1** was replaced with

Compound **NA1-17**. Compound **PA1-2** was replaced with Compound **PA5-8.** MS for $C_{31}H_{27}FN_4O_4$: *m/z* 539 (MH+).

[0940] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(4-fluoro-2-methylphenyl)-3-oxopyridazine-4-carboxamide (527): Compound **PA1-2** was replaced with Compound **HA2-13.** MS for $C_{28}H_{21}F_2N_5O_5$: *m/z* 546 (MH+).

[0941] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluoro-2-methylphenyl)-3-oxopyridazine-4-carboxamide (528): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA2-13.** MS for $C_{28}H_{22}FN_5O_5$: *m/z* 528 (MH+).

[0942] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluoro-2-methylphenyl)-3-oxopyridazine-4-carboxamide (529): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA2-13.** MS for $C_{27}H_{19}F_2N_5O_4$: *m/z* 516 (MH+).

[0943] 2-(4-Fluoro-2-methylphenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-3-oxopyridazine-4-carboxamide (530): Compound **NA1-1** was replaced with Compound **NA1-6**. Compound **PA1-2** was replaced with Compound **HA2-13.** MS for $C_{27}H_{20}FN_5O_4$: *m/z* 498 (MH+).

[0944] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-methoxy-6-methylpyridazine-3-carboxamide (531): Compound **PA1-2** was replaced with Compound **HA2-3B.** MS for $C_{29}H_{23}F_2N_5O_5$: *m/z* 560 (MH+).

[0945] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-5-(methoxymethyl)-3-oxopyridazine-4-carboxamide (532): Compound **NA1-1** was replaced with Compound **NA1-3**. Compound **PA1-2** was replaced with Compound **HA2-14.** ^{1}H NMR (400 MHz, CD_3OD) δ 11.90 (s, 1H), 8.83 (d, 1H), 8.69 (d, 1H), 8.58 (s, 1H), 8.01 (dd, 1H), 7.82 (s, 1H), 7.65 – 7.56 (m, 2H), 7.49 – 7.41 (m, 1H), 7.34 (t, 1H), 7.28 – 7.22 (m, 2H), 6.70 (d, 1H), 4.52 (s, 2H), 4.05 (s, 3H), 3.52 (s, 3H); MS for $C_{28}H_{21}F_2N_5O_5$: *m/z* 546 (MH+).

[0946] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(4-fluorophenyl)-5-(methoxymethyl)-3-oxopyridazine-4-carboxamide (533): Compound **PA1-2** was replaced with Compound **HA2-14.** ^{1}H NMR (400 MHz, CD_3OD) δ 11.85 (s, 1H), 8.60 – 8.52 (m, 2H), 7.97 (dd, 1H), 7.69 (s, 1H), 7.64 – 7.56 (m, 2H), 7.43 – 7.35 (m, 1H), 7.30 – 7.18 (m, 3H), 6.82 (d, 1H), 4.52 (s, 2H), 4.09 (d, 6H), 3.51 (s, 3H); MS for $C_{29}H_{23}F_2N_5O_6$: *m/z* 576 (MH+).

[0947] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-methoxy-6-methylpyridazine-3-carboxamide (534): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA2-3B.** MS for $C_{29}H_{24}FN_5O_5$: *m/z* 542 (MH+).

[0948] 5-Bromo-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-hydroxy-2-(methoxymethyl)-6-methylpyridine-3-carboxamide (535): Compound **PA1-2** was replaced with Compound **C4-A.** MS for $C_{25}H_{22}BrFN_4O_6$: *m/z* 573 (MH+).

[0949] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-1H-pyridazine-3-carboxamide (536): Compound **PA1-2** was replaced with Compound **HA2-7.** MS for $C_{22}H_{18}FN_5O_5$: *m/z* 452 (MH+).

[0950] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-(4-fluorophenyl)-5-(methoxymethyl)-3-oxopyridazine-4-carboxamide (537): Compound **NA1-1** was replaced with Compound **NA1-2**. Compound **PA1-2** was replaced with Compound **HA2-14.** MS for $C_{29}H_{24}FN_5O_6$: *m/z* 558 (MH+).

[0951] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-methoxy-6-methylpyridazine-3-carboxamide (538): Compound **NA1-1** was replaced with Compound **NA1-10**. Compound **PA1-2** was replaced with Compound **HA2-3B.** MS for $C_{28}H_{21}F_2N_5O_4$: *m/z* 530 (MH+).

[0952] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxyphenyl]-1-(4-fluorophenyl)-6-oxo-2-propan-2-ylsulfanylpyrimidine-5-carboxamide (539): Compound **NA1-1** was replaced with Compound **QA1-2**. Compound **PA1-2** was replaced with Compound **HA4-10.** MS for $C_{31}H_{27}FN_4O_5S$: *m/z* 587 (MH+).

[0953] 4-[4-[[5-(4-Fluorophenyl)-4-hydroxy-6-methylpyridine-3-carbonyl]amino]phenoxy]-7-methoxy-N-methylquinoline-6-carboxamide (540): Compound **NA1-1** was replaced with Compound **QA1-5**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{31}H_{25}FN_4O_5$: *m/z* 553 (MH+).

[0954] N-[3-Fluoro-4-[(7-methoxy-6-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (541): Compound **NA1-1** was replaced with Compound **NA1-22**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{29}H_{22}F_2N_4O_4$: *m/z* 529 (MH+).

[0955] N-[2,5-Difluoro-4-[(7-methoxy-6-methyl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (542): Compound **NA1-1** was replaced with Compound **NA1-42**. Compound **PA1-2** was replaced with Compound **PA3-1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.48 (s, 1H), 12.67 (s, 1H), 8.70 – 8.47 (m, 3H), 7.70 (s, 1H), 7.62 (dd, 1H), 7.39 – 7.15 (m, 4H), 6.79 (dd, 1H), 4.01 (s, 3H), 2.59 (s, 3H), 2.18 (s, 3H); MS for $C_{29}H_{21}F_3N_4O_4$: *m/z* 547 (MH+).

[0956] 1-(4-Fluorophenyl)-2-methyl-N-[4-[[8-(methylamino)-1,7-naphthyridin-4-yl]oxy]phenyl]-6-oxopyrimidine-5-carboxamide (543): Compound **NA1-1** was replaced with Compound **NA3-3**. Compound **PA1-2** was replaced with Compound **HA4-2.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.82 (d, 1H), 8.55 (dd, 1H), 7.97 (dd, 1H), 7.90 – 7.75 (m, 2H), 7.73 – 7.53 (m, 3H), 7.47 (td, 2H), 7.33 – 7.16 (m, 2H), 7.07 (dd, 1H), 6.77 (dd, 1H), 2.99 (d, 3H), 2.23 (s, 3H); MS for $C_{27}H_{21}FN_6O_3$: *m/z* 497 (MH+).

[0957] [5-[[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]carbamoyl]-3-(4-fluorophenyl)-4-hydroxypyridin-2-yl]methyl acetate (544): Compound **PA1-2** was replaced with Compound **PA7-3a.** MS for $C_{31}H_{24}F_2N_4O_7$: *m/z* 603.2 (MH+).

[0958] Ethyl 2-(8-(2-fluoro-4-(5-(4-fluorophenyl)-4-hydroxy-6-methylnicotinamido)-phenoxy)-3-methoxy-1,5-naphthyridin-2-yl)acetate (545): Compound **NA1-1** was replaced with Compound **NA1-49**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{32}H_{26}F_2N_4O_6$: *m/z* 601.1 (MH+).

[0959] N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (546): Compound **NA1-1** was replaced with Compound **QA1-1**. Compound **PA1-2** was replaced with Compound **HA2-1.** MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545.1 (MH+).

[0960] N-(4-((7-Bromo-6-methoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (547): Compound **NA1-1** was replaced with Compound **NA1-4**. Compound **PA1-2** was replaced with Compound **PA5-2.** MS for $C_{29}H_{21}BrF_2N_4O_4$: *m/z* 609 (MH+).

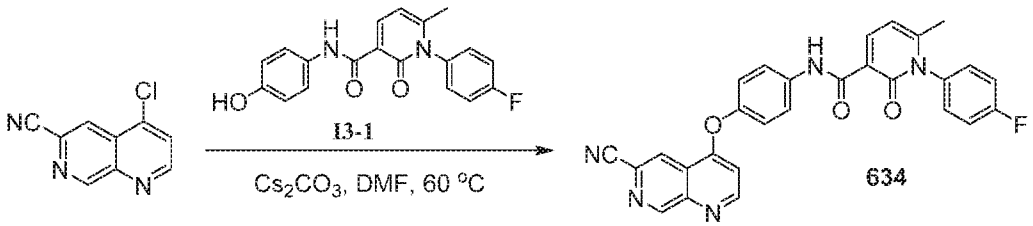
[0961] N-(4-((7-Bromo-6-methyl-1,5-naphthyridin-4-yl)oxy)phenyl)-5-(4-fluorophenyl)-1-isopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (548): Compound **NA1-1** was replaced with Compound **NA1-14**. Compound **PA1-2** was replaced with Compound **PA3-2.** MS for $C_{31}H_{26}BrFN_4O_3$: *m/z* 601 (MH+).

[0962] N-(4-((7-Bromo-6-methyl-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-4-hydroxy-6-methylnicotinamide (549): Compound **NA1-1** was replaced with Compound **NA1-15**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{28}H_{19}BrF_2N_4O_3$: *m/z* 608 (MH+). *m/z* 577 (MH+).

[0963] N-(4-((7-Bromo-6-methyl-1,5-naphthyridin-4-yl)oxy)phenyl)-5-(4-fluorophenyl)-4-hydroxy-6-methylnicotinamide (550): Compound **NA1-1** was replaced with Compound **NA1-14**. Compound **PA1-2** was replaced with Compound **PA3-1.** MS for $C_{28}H_{20}BrFN_4O_3$: *m/z* 608 (MH+). *m/z* 559 (MH+).

[0964] Additional compounds were made through synthetic modifications made to select compounds listed under **Examples 1** and **2**. The syntheses of those compounds are detailed in Examples 81-104.

Example 3: N-[4-[(6-Cyano-1,7-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (634)



[0965] N-[4-[(6-Cyano-1,7-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (634): Compound **634** was made by **General Procedure J**. Specifically, to a solution of 4-chloro-1,7-naphthyridine-6-carbonitrile (70 mg, 0.37 mmol, 1 eq) and Compound **I3-1** (137 mg, 0.41 mmol, 1.1 eq) in DMF (1 mL) was added Cs_2CO_3 (240 mg, 0.74 mmol, 2 eq). The reaction mixture was heated at 60 °C for 12 h. The reaction mixture was diluted with water and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with aq. saturated NaCl (100 mL),

dried over anhyd. Na_2SO_4 and concentrated. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80 * 30mm * 3um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 43% - 73%, 9 min) to give Compound **634**. ^{1}H NMR (400 MHz, CD_3OD) δ 9.42 (s, 1H), 8.92 (d, 1H), 8.82 (s, 1H), 8.58 (d, 1H), 7.86 (d, 2H), 7.44 - 7.36 (m, 4H), 7.31 (d, 2H), 6.99 (d, 1H), 6.70 (d, 1H), 2.16 (s, 3H); MS for $C_{28}H_{18}FN_5O_3$: *m/z* 492.1 (MH+).

[0966] The following compounds were made using **General Procedure J** to form compounds of formula **J2:**

[0967] N-[4-(6,7-Dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (635): 4-Chloro-1,7-naphthyridine-6-carbonitrile was replaced with 4-chloro-6,7-dimethoxypyrido[3,2-d]pyrimidine (which can be synthesized according to methods known in the art (see, e.g., WO 2019/148036 A1)). Compound **I3-1** was replaced with Compound **I3-2**. MS for $C_{28}H_{21}F_2N_5O_5$: *m/z* 546 (MH+).

[0968] N-[4-(6,7-Dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide (636): 4-Chloro-1,7-naphthyridine-6-carbonitrile was replaced with 4-chloro-6,7-dimethoxypyrido[3,2-d]pyrimidine (which can be synthesized according to methods known in the art (see, e.g., WO 2019/148036 A1)). Compound **I3-1** was replaced with Compound **I3-3**. MS for $C_{30}H_{25}F_2N_5O_5$: *m/z* 574.0 (MH+).

[0969] N-[4-(6,7-Dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide (637): 4-Chloro-1,7-naphthyridine-6-carbonitrile was replaced with 4-chloro-6,7-dimethoxypyrido[3,2-d]pyrimidine (which can be synthesized according to methods known in the art (see, e.g., WO 2019/148036 A1)). Compound **I3-1** was replaced with Compound **I3-4**. MS for $C_{31}H_{23}F_2N_7O_5$: *m/z* 612.4 (MH+).

[0970] N-[3-Fluoro-4-[6-methoxy-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (638): 4-Chloro-1,7-naphthyridine-6-carbonitrile was replaced with 4-chloro-6-methoxy-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidine (which can be synthesized according to methods known in the art (see, e.g., WO 2019/148036 A1)). Compound **I3-1** was replaced with Compound **I3-2**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.1 (s, 1H), 8.59 (s,1H), 8.51 (d, 1H), 7.98 (m, 1H), 7.68 (s, 1H), 7.50 (m, 2H), 7.44 (m, 4H), 6.72 (d, 1H), 4.38 (t, 2H), 4.10 (s, 3H), 3.76 (t, 2H), 3.34 (s, 3H), 2.09 (s, 3H); MS for $C_{30}H_{25}F_2N_5O_6$: *m/z* 590 (MH+).

[0971] N-[3-Fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (639): 4-Chloro-1,7-naphthyridine-6-carbonitrile was replaced with 4-chloro-6-methoxy-1,7-naphthyridine. Compound **I3-1** was replaced with Compound **I3-5**. MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515 (MH+).

[0972] 1-Cyclopropyl-N-[3-fluoro-4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (640): 4-Chloro-1,7-naphthyridine-6-carbonitrile was replaced with 4-chloro-6-methoxy-1,7-naphthyridine. Compound **I3-1** was replaced with Compound **I3-7**. MS for $C_{31}H_{24}F_2N_4O_4$: *m/z* 555.0 (MH+).

[0973] N-[4-[(6-Chloro-1,7-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (641): 4-Chloro-1,7-naphthyridine-6-carbonitrile was replaced with 4,6-dichloro-1,7-naphthyridine. Compound **I3-1** was replaced with Compound **I3-5**. MS for $C_{27}H_{17}ClF_2N_4O_3$: *m/z* 519.0 (MH+).

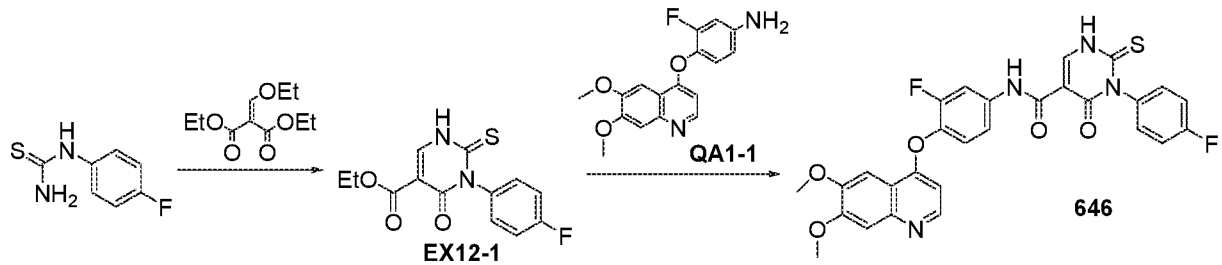
[0974] N-[3-Fluoro-4-(1,7-naphthyridin-4-yloxy)phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (642): 4-Chloro-1,7-naphthyridine-6-carbonitrile was replaced with 4-chloro-1,7-naphthyridine. Compound **I3-1** was replaced with Compound **I3-5**. MS for $C_{27}H_{18}F_2N_4O_3$: *m/z* 485 (MH+).

[0975] 5-(4-Fluorophenyl)-4-hydroxy-6-methyl-N-[4-(1,7-naphthyridin-4-yloxy)phenyl]pyridine-3-carboxamide (643): 4-Chloro-1,7-naphthyridine-6-carbonitrile was replaced with 4-chloro-1,7-naphthyridine. Compound **I3-1** was replaced with Compound **I3-6**. MS for $C_{27}H_{19}FN_4O_3$: *m/z* 467.0 (MH+).

[0976] 5-(4-Fluorophenyl)-4-hydroxy-N-[4-[(6-methoxy-1,7-naphthyridin-4-yl)oxy]phenyl]-6-methylpyridine-3-carboxamide (644): 4-Chloro-1,7-naphthyridine-6-carbonitrile was replaced with 4-chloro-6-methoxy-1,7-naphthyridine. Compound **I3-1** was replaced with Compound **I3-6**. MS for $C_{28}H_{21}FN_4O_4$: *m/z* 497 (MH+).

[0977] N-[3-Fluoro-4-[(6-methyl-1,7-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (645): 4-Chloro-1,7-naphthyridine-6-carbonitrile was replaced with 4-chloro-6-methyl-1,7-naphthyridine. Compound **I3-1** was replaced with Compound **I3-5**. MS for $C_{28}H_{20}F_2N_4O_3$: *m/z* 499 (MH+).

Example 4: N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-3-(4-fluorophenyl)-4-oxo-2-sulfanylidene-1H-pyrimidine-5-carboxamide (646)



[0978] Step 1: Ethyl 3-(4-fluorophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (EX12-1). A mixture of diethyl 2-(ethoxymethylene)malonate (3.2 mL, 13.8 mmol), 1-(4-fluorophenyl)-thiourea (2.54 g, 15 mmol), and HCl (36% aq., 3.2 mL) in EtOH was refluxed for 6 h. The reaction was cooled to room temperature and filtered. The resulting solid was washed with EtOH and dried to give the Compound **EX12-1**. MS for $C_{13}H_{11}FN_2O_3S$: *m/z* 295 (MH+).

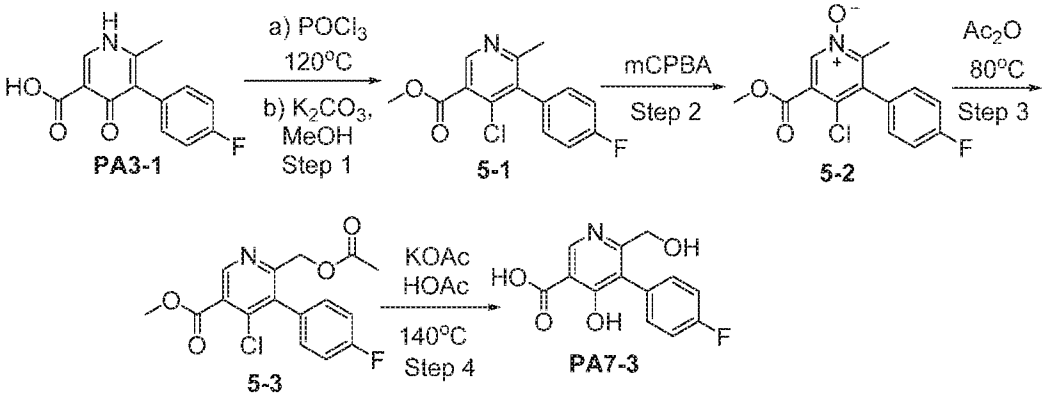
[0979] Step 2: N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-3-(4-fluorophenyl)-4-oxo-2-sulfanylidene-1H-pyrimidine-5-carboxamide (646). To a mixture of Compound **EX12-1** (50 mg, 0.17 mmol) and Compound **QA1-1** (50 mg, 0.16 mmol) in THF, was added $Li[N(SiMe_3)_2]$ (2 M in THF, 0.4 mL, 0.8 mmol). The reaction was stirred at room temperature overnight, quenched with aq. saturated $NaHCO_3$ and extracted with EtOAc. The organic extract was concentrated, and the residue purified by

silica gel chromatography to give the Compound **646** (83 mg, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.59 (b, 1H), 10.97 (s, 1H), 8.49 (d, 1H), 8.31 (s, 1H), 8.02 (d, 1H), 7.60 – 7.30 (m, 8H), 6.48 (d, 1H), 3.96 (s, 6H). MS for $C_{28}H_{20}F_2N_4O_5S$: *m/z* 563 (MH+).

[0980] The following compound was made by the same method as Compound **646** in Example 4:

[0981] **N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-4-oxo-2-sulfanylidene-1H-pyrimidine-5-carboxamide (104):** Compound **QA1-1** was replaced with Compound **NA1-1**. MS for $C_{27}H_{19}F_2N_5O_5S$: *m/z* 564 (MH+).

Example 5: 5-(4-Fluorophenyl)-4-hydroxy-6-(hydroxymethyl)nicotinic acid (PA7-3)



[0982] **Step 1: Methyl 4-chloro-5-(4-fluorophenyl)-6-methylnicotinate (5-1).** A mixture of Compound **PA3-1** (2.33 g, 9.42 mmol, 1 eq) and $POCl_3$ (6.7 mL) was heated to 120 °C under microwave irradiation for 25 min. The resulting solution was diluted with DCM and added over 15 min to a mixture of MeOH and K_2CO_3 at -10 °C. The reaction was allowed to warm to room temperature and then concentration in vacuo. The resulting residue was partitioned between and EtOAc (125 mL) and water (125 mL). The organic layer was washed with water (125 mL), washed with aq saturated NaCl (125 mL), dried over anhyd Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (0 to 50% EtOAc in hexanes) to give Compound **5-1** (2.78g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.26 – 7.14 (m, 4H), 3.99 (s, 3H), 2.38 (s, 3H); MS for $C_{14}H_{11}ClFNO_2$: *m/z* 280 (MH+).

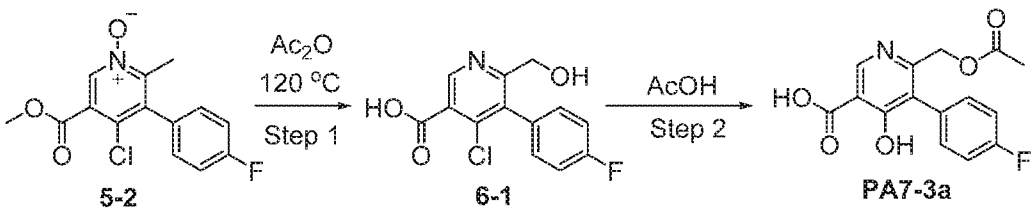
[0983] **Step 2: 4-Chloro-3-(4-fluorophenyl)-5-(methoxycarbonyl)-2-methylpyridine 1-oxide (5-2).** A solution of mCPBA (3.9 g, 16.9 mmol, 1.5 eq) in DCM (26 mL) was added to Compound **5-1** (3.3 g, 11.8 mmol, 1.0 eq) in DCM (26 mL) over 5 min. After the reaction was complete the reaction mixture was adsorbed onto Celite and purified by silica gel chromatography (0 to 100% EtOAc in hexanes) to give Compound **5-2** (2.8g, 981% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.28 – 7.15 (m, 4H), 4.00 (s, 3H), 2.35 (s, 3H); MS for $C_{14}H_{11}ClFNO_3$: *m/z* 296 (MH+).

[0984] **Step 3: Methyl 6-(acetoxymethyl)-4-chloro-5-(4-fluorophenyl)nicotinate (5-3).** A mixture of Compound **5-2** (2.8 g, 9.5 mmol, 1 eq) and acetic anhydride (13 g) was heated at 40 °C for 5 h, 60 °C for 1 h, 80 °C for 1 h, then 40 °C for an additional 12 h. The reaction mixture was adsorbed onto Celite and purified by silica gel Chromatography (0 to 40% EtOAc in hexanes) to give Compound **5-3** (1.8 g,

90% by mass, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.27 – 7.17 (m, 4H), 4.95 (s, 2H), 4.01 (s, 3H), 2.09 (s, 3H); MS for $C_{16}H_{13}ClFNO_4$: *m/z* 338 (MH+).

[0985] Step 4: 5-(4-Fluorophenyl)-4-hydroxy-6-(hydroxymethyl)nicotinic acid (PA7-3). A mixture of Compound **5-3** (0.94 g, 2.5 mmol, 1 eq), KOAc (0.80 g, 8.1 mmol, 3.2 eq) and acetic acid (1.8 g, 30 mmol, 24 eq) was heated to 140 °C for 1 h, 160 °C for 1 h and 180 °C for 30 min. The reaction mixture was transferred to a separatory funnel, basified with 1M NaOH (pH ~ 13) and washed with EtOAc. The aqueous phase was acidified to pH ~ 2. A precipitate formed and aq saturated NaCl was added to the resulting suspension and further precipitation was observed. The precipitate was isolated via filtration and the mother liquid was extracted with EtOAc (2X). The combined extracts were concentrated and the resulting solid combined with the filtered precipitate to give Compound **PA7-3** (0.43 g, 90% by mass, 59% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (s, 1H), 8.49 (d, 1H), 7.39 – 7.24 (m, 4H), 6.11 (s, 1H), 4.39 (s, 2H); MS for $C_{13}H_{10}FNO_4$: *m/z* 264 (MH+).

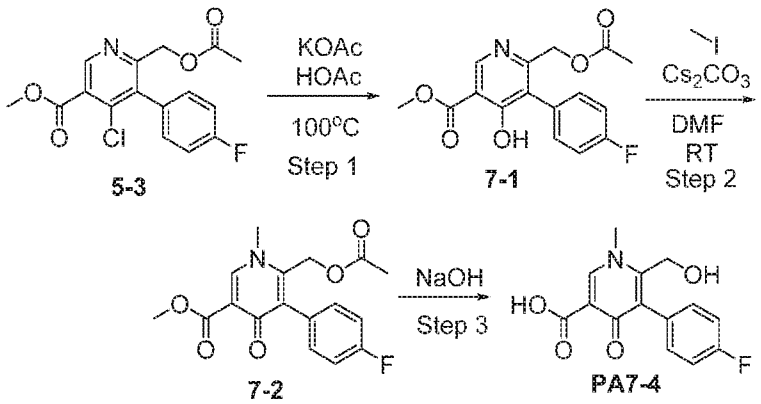
Example 6: 6-(Acetoxymethyl)-5-(4-fluorophenyl)-4-hydroxynicotinic acid (PA7-3a)



[0986] Step 1: 4-Chloro-5-(4-fluorophenyl)-6-(hydroxymethyl)nicotinic acid (6-1). To a solution of Compound **5-2** (3 g, 10.2 mmol, 1 eq) was added acetic anhydride (21.8 g, 213 mmol, 20 mL, 21 eq). The mixture was stirred at 120 °C for 2 h. The reaction mixture was concentrated under reduced pressure. To the resulting residue was added aq $NaHCO_3$ (200 mL) until a pH of 9-10 was attained. The resulting aq solution was washed with DCM (3 x 200 mL). The aqueous phase was acidified with 1 N HCl to pH=2 and extracted with DCM (3 x 200 mL). Both the aqueous phase and combined organic extracts were concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 3/1) to give Compound **6-1** (2 g, 70% yield). MS for $C_{13}H_9ClFNO_3$: *m/z* 281.8 (MH+).

[0987] Step 2: 6-(Acetoxymethyl)-5-(4-fluorophenyl)-4-hydroxynicotinic acid (PA7-3a). A mixture of Compound **6-1** (2 g, 7.1 mmol, 1 eq) in acetic acid (100 mL) was stirred at 120 °C for 16 h under an atmosphere of nitrogen. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, DCM:MeOH = 100/1 to 50/1) to give Compound **PA7-3a** (230 mg, 10.6% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 7.44-7.22 (m, 5H), 4.89 (s, 2H), 2.03 (s, 3H); MS for $C_{15}H_{12}FNO_5$: *m/z* 305.9 (MH+).

Example 7: 5-(4-Fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-4)



[0988] Step 1: Methyl 6-(acetoxymethyl)-5-(4-fluorophenyl)-4-hydroxynicotinate (7-1). A mixture of Compound **5-3** (1.4 g, 4.15 mmol, 1 eq), KOAc (2.8 g, 28.6 mmol, 6.9 eq) and acetic acid (5 mL) was heated to 100 °C for 14 h. The contents were subsequently cooled and diluted with water (100 mL). Filtration of the resulting precipitate gave Compound **7.1** (1.2 g, 80% by mass, 69% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.31 (s, 1H), 7.25 (s, 2H), 7.23 (s, 2H), 4.76 (s, 2H), 3.74 (s, 3H), 2.03 (s, 3H); MS for $C_{16}H_{14}FNO_5$: *m/z* 320 (MH+).

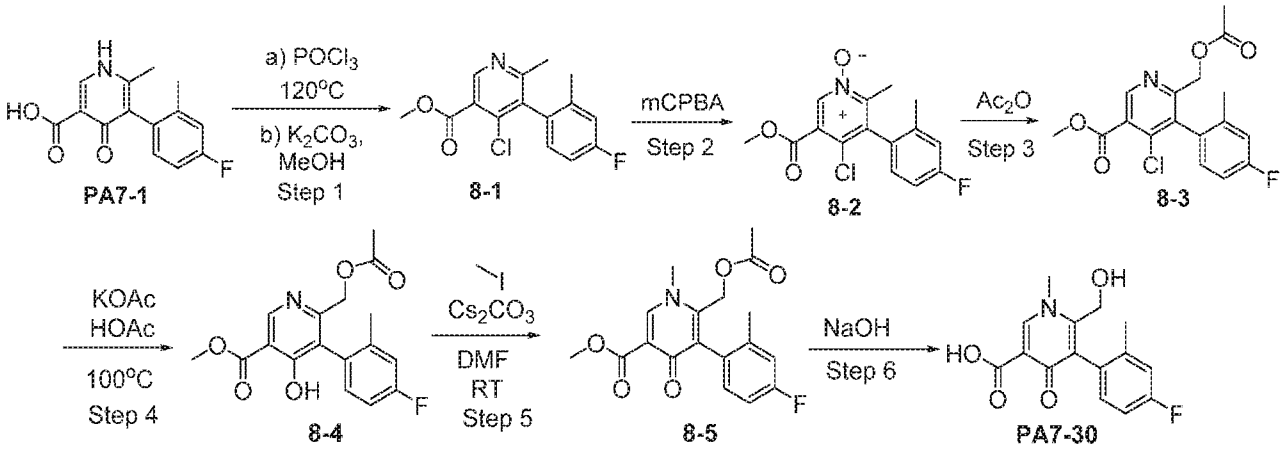
[0989] Step 2: Methyl 6-(acetoxymethyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (7-2). A mixture of Compound **7-1** (0.24 g, 0.75 mmol, 1 eq), Cs_2CO_3 (0.33 g, 1.0 mmol, 1.3 eq), DMF (3.0 mL) and methyl iodide (0.12 mL, 1.9 mL, 2.5 eq) was stirred at ambient temperature in a sealed vial. The reaction was allowed to proceed overnight, and then the contents were diluted with aq saturated NaCl (50 mL) and extracted with EtOAc (2 x 20 mL). The combined extracts were concentrated, and the residue was purified by silica gel chromatography (0% to 100% EtOAc then 0 to 5% MeOH in EtOAc gradient) to give Compound **7-2** (0.16 g, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.18 (ddd, 2H), 7.10 (t, 2H), 4.87 (s, 2H), 3.90 (s, 3H), 3.78 (s, 3H), 2.15 (s, 3H); MS for $C_{17}H_{16}FNO_5$: *m/z* 334.2 (MH+).

[0990] Step 3: 5-(4-Fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-4). Compound **7-2** was converted to Compound **PA7-4** using a modification of the ester hydrolysis procedure used in Step 3 of **General Procedure A**. In this particular case the reaction mixture was heated to reflux for 2 h prior to work up. ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1H), 7.35 (ddd, 2H), 7.28 – 7.18 (m, 2H), 4.49 (s, 2H), 4.15 (s, 3H); MS for $C_{14}H_{12}FNO_4$: *m/z* 278 (MH+).

[0991] The following compound was made by the same three step procedure as Compound **PA7-4** in **Example 7**:

[0992] 1-Ethyl-5-(4-fluorophenyl)-6-(hydroxymethyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-28): ^{1}H NMR (400 MHz, DMSO-d_6) δ 16.34 (s, 1H), 8.86 (s, 1H), 7.39 – 7.25 (m, 4H), 5.79 (t, 1H), 4.44 (q, 2H), 4.35 (d, 2H), 1.46 (t, 3H); MS for $C_{15}H_{14}FNO_4$: *m/z* 292 (MH+).

Example 8: 5-(4-Fluoro-2-methylphenyl)-6-(hydroxymethyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-30)



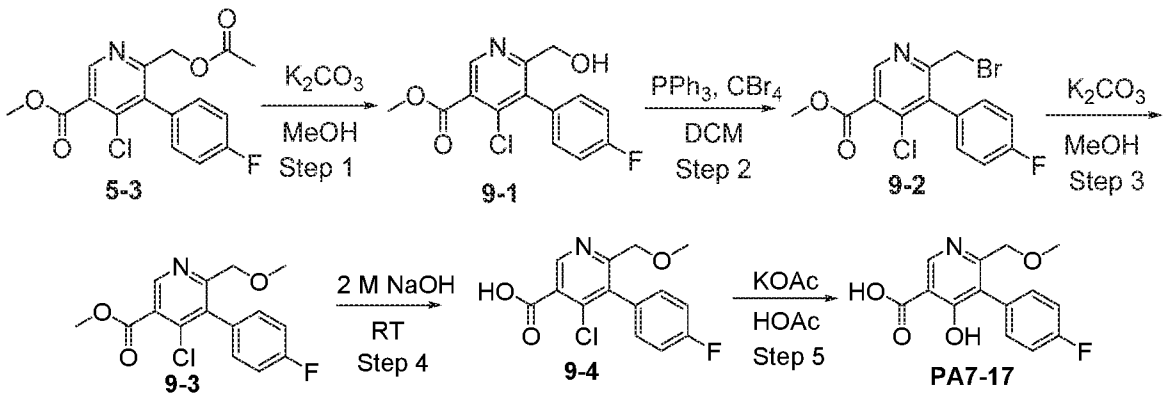
[0993] Steps 1-3: Methyl 6-(acetoxymethyl)-4-chloro-5-(4-fluoro-2-methylphenyl)nicotinate (8-3). Compound **8-3** was made in three steps from Compound **PA7-1** following the same procedure that Compound **5-3** was made from Compound **PA3-1** in Steps 1-3 in **Example 5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.12 – 6.99 (m, 3H), 4.88 (s, 2H), 4.01 (s, 3H), 2.11 – 2.06 (m, 6H); MS for $C_{17}H_{15}ClFNO_4$: *m/z* 352 (MH+).

[0994] Steps 4-6: 5-(4-Fluoro-2-methylphenyl)-6-(hydroxymethyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-30). Compound **PA7-30** was made in three steps from Compound **8-3** following the same procedure that Compound **PA7-4** was made from Compound **5-3** in Steps 1-3 of **Example 7**. MS for $C_{15}H_{14}FNO_4$: *m/z* 292 (MH+).

[0995] The following compound was made by the same six step procedure as Compound **PA7-30** in **Example 8**:

[0996] 1-Ethyl-5-(4-fluoro-2-methylphenyl)-6-(hydroxymethyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-36): MS for $C_{16}H_{16}FNO_4$: *m/z* 306 (MH+).

Example 9: 5-(4-Fluorophenyl)-4-hydroxy-6-(methoxymethyl)nicotinic acid (PA7-17)



[0997] Steps 1: Methyl 4-chloro-5-(4-fluorophenyl)-6-(hydroxymethyl)nicotinate (9-1). A mixture of Compound **5-3** (0.60 g, 1.8 mmol, 1 eq), MeOH (5 mL) and K_2CO_3 (0.40 g, 2.9 mmol, 1.6 eq) was stirred at ambient temperature for 24 h. The reaction was subsequently diluted with EtOAc, filtered

and concentrated. The resulting residue was purified by silica gel chromatography (0% to 100% EtOAc in hexanes) to give Compound **9-1** (0.20 g, 038% yield). MS for $C_{14}H_{11}ClFNO_3$: *m/z* 296 (MH+).

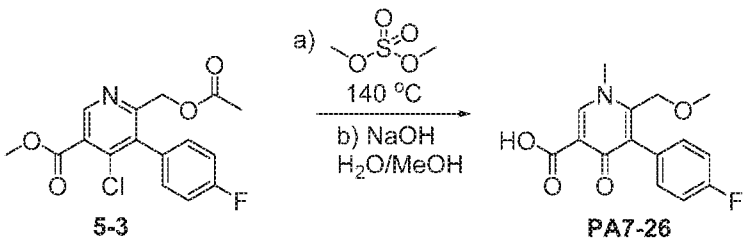
[0998] Steps 2: Methyl 6-(bromomethyl)-4-chloro-5-(4-fluorophenyl)nicotinate (9-2). To a stirring mixture of Compound **9-1** (0.20 g, 0.68 mmol, 1 eq), DCM (3 mL) and CBr_4 (0.65 g, 2.0 mmol, 3 eq) was added PPh_3 (0.52 g, 2.0 mmol, 3 eq). After 1 h the crude reaction was purified by silica gel chromatography (0% to 100% EtOAc in hexanes) to give Compound **9-2** (54 mg, 22% yield). MS for $C_{14}H_{10}BrClFNO_2$: *m/z* 360 (MH+).

[0999] Steps 3: Methyl 4-chloro-5-(4-fluorophenyl)-6-(methoxymethyl)nicotinate (9-3). A mixture of Compound **9-2** (54 mg, 0.15 mmol, 1 eq), MeOH (1 mL) and K_2CO_3 (0.10 g , 0.31 mmol, 2.1 eq) was stirred at ambient temperature for 1 h. The reaction was subsequently concentrated, diluted with EtOAc, and filtered to give Compound **9-3** which was used in the subsequent step without further purification. MS for $C_{15}H_{13}ClFNO_3$: *m/z* 310 (MH+).

[01000] Steps 4: 4-Chloro-5-(4-fluorophenyl)-6-(methoxymethyl)nicotinic acid (9-4). Compound **9-3** was converted to Compound **9-4** using a modification of the ester hydrolysis procedure used in Step 3 of **General Procedure A**. MS for $C_{14}H_{11}ClFNO_3$: *m/z* 296 (MH+).

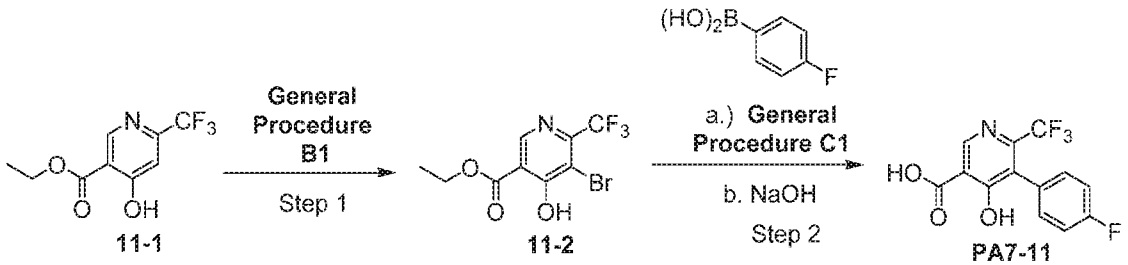
[01001] Steps 5: 5-(4-Fluorophenyl)-4-hydroxy-6-(methoxymethyl)nicotinic acid (PA7-17). Compound **PA7-17** was made from Compound **9-4** in the same manner that Compound **PA7-3** was made from Compound **5-3** in Step 4 of **Example 5**. MS for $C_{14}H_{12}FNO_4$: *m/z* 278 (MH+).

Example 10: 5-(4-Fluorophenyl)-6-(methoxymethyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-26)



[01002] 5-(4-Fluorophenyl)-6-(methoxymethyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-26). Compound **5-3** (0.50 g, 1.5 mmol, 1 eq) and dimethyl sulfate (0.66 g, 5.3 mmol, 3.6 mmol) were heated at 140 °C under microwave irradiation for 5 min. Aq 25% NaOH (4 mL) was added to the reaction and the vial contents were heated to 80 °C. After 48 h the reaction was cooled, acidified with 1 M HCl to pH ~2 and extracted with EtOAc (3x). The combined organic extracts were concentrated, and the resulting residue was purified prep HPLC (C18, 20% to 40% ACN in H_2O (+FA)) to give Compound **PA7-26** (37 mg, 9% yield). MS for $C_{15}H_{14}FNO_4$: *m/z* 292 (MH+).

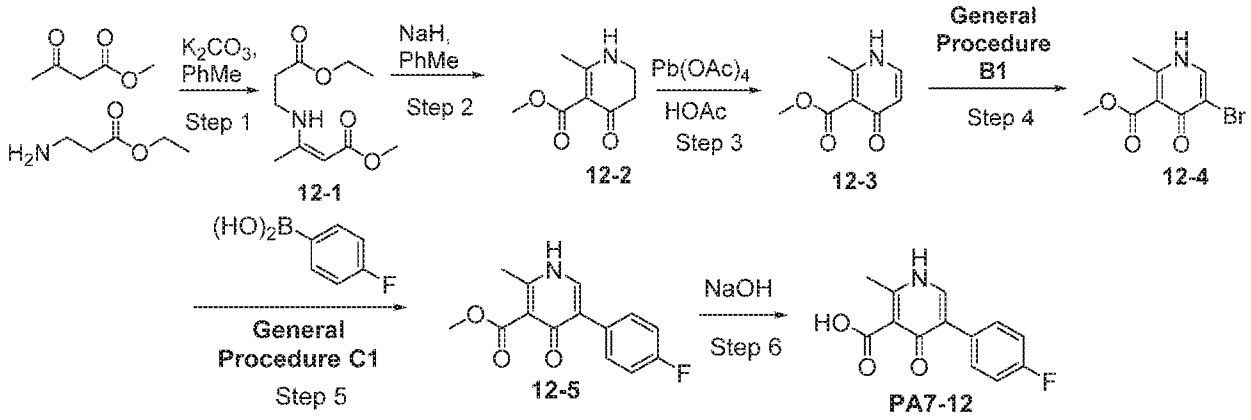
Example 11: 5-(4-Fluorophenyl)-4-hydroxy-6-(trifluoromethyl)nicotinic acid (PA7-11)



[01003] Step 1: Ethyl 5-bromo-4-hydroxy-6-(trifluoromethyl)nicotinate (11-2). Compound **11-2** was synthesized from Compound **11-1** using **General Procedure B1**. MS for $C_9H_7BrF_3NO_3$: *m/z* 314/316 (MH+).

[01004] Step 2: 5-(4-Fluorophenyl)-4-hydroxy-6-(trifluoromethyl)nicotinic acid (PA7-11). The ethyl ester of Compound **PA7-11** was synthesized from Compound **11-2** using **General Procedure C1**. Specifically in this case, a mixture of Compound **11-2** (250 mg, 0.80 mmol), (4-fluorophenyl)boronic acid (270 mg, 1.93 mmol), $Pd(PPh_3)_4$ (50 mg, 0.043 mmol) and K_2CO_3 (600 mg, 4.34 mmol) in dioxane (3 mL) and water (1.5 mL) was degassed with nitrogen for 2 min, followed by stirring at 90 °C overnight forming the ethyl ester of Compound **PA7-11**. After cooling to room temperature, the ethyl ester was subsequently hydrolyzed by adding NaOH (2 M, 5 mL) to the reaction mixture. The resulting mixture was stirred at room temperature until ester hydrolysis was complete. The mixture was washed with EtOAc (2x) and the aqueous phase was acidified to pH 2-3 and extracted with EtOAc (2x). The combined EtOAc extracts were dried over anhyd Na_2SO_4, and concentrated. The resulting residue was suspended in a mixture solvent of DCM/hexane (7.5/7.5 mL), sonicated for 2 min, and filtered to give Compound **PA7-11** (244 mg, 100% yield). MS for $C_{13}H_7F_4NO_3$: *m/z* 302.2 (MH+).

Example 12: 5-(4-Fluorophenyl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-12)



[01005] Step 1: Methyl 3-((3-ethoxy-3-oxopropyl)amino)but-2-enoate (12-1): A mixture of 3-aminopropionic acid ethyl ester hydrochloride (15.6 g, 101 mmol), methyl 3-oxobutanoate (10.8mL, 101 mmol) and anhyd K_2CO_3 (28.0 g, 203 mmol) in toluene (200 mL) was refluxed with a Dean-Stark trap overnight. The reaction mixture was cooled and diluted with EtOAc (150 mL), filtered and the filtrate was concentrated under reduced pressure to give crude Compound **12-1** (21 g), which was used in the next step without further purification.

[01006] Step 2: Methyl 2-methyl-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (12-2): To a solution of crude Compound **12-1** (21 g, 95 mmol) in 200 mL of toluene was added sodium hydride (6.0 g, 60 % dispersion in oil, 150 mmol) and the resulting yellow suspension was refluxed overnight. The mixture was concentrated to remove solvent and the residue was treated carefully with water (100 mL), acidified to pH 2 with 6 M HCl and then washed with Et_2O (3x). The aqueous phase was basified with $NaHCO_3$ and extracted with EtOAc (5x). The combined EtOAc extracts were dried over anhyd Na_2SO_4, and concentrated to give Compound **12-2** (7.6 g, 46% yield) which was used without further purification. MS for $C_8H_{11}NO_3$: *m/z* 170 (MH+).

[01007] Step 3: Methyl 2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (12-3): A mixture of Compound **12-2** (3.6 g, 21 mmol) and lead tetraacetate (20 g, 58 mmol) in 30 mL of acetic acid was stirred at 100 °C overnight and concentrated under reduced pressure to remove acetic acid. The resulting residue was purified by silica gel chromatography (5 – 15% MeOH in DCM) to give Compound **12-3** (2.0 g, 56%). MS for $C_8H_9NO_3$: *m/z* 168 (MH+).

[01008] Step 4: Methyl 5-bromo-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (12-4): Compound **12-4** was synthesized from Compound **12-3** using **General Procedure B1**. MS for $C_8H_8BrNO_3$: *m/z* 246/248 (MH+).

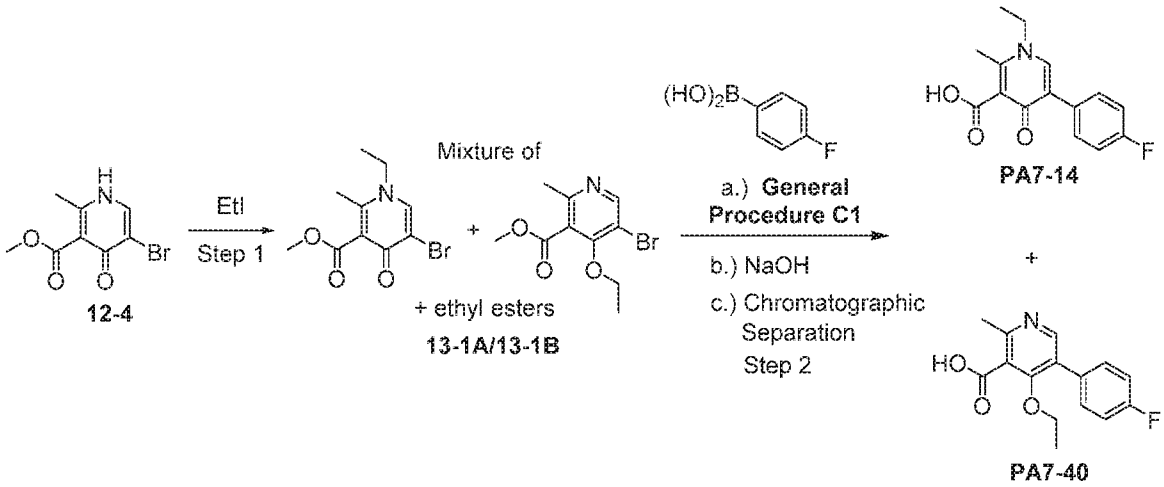
[01009] Step 5: Methyl 5-(4-fluorophenyl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (12-5): Compound **12-5** was synthesized from Compound **12-4** using **General Procedure C1**. MS for $C_{14}H_{12}FNO_3$: *m/z* 262 (MH+).

[01010] Step 6: 5-(4-Fluorophenyl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-12). Compound **12-5** was converted to Compound **PA7-12** by the ester hydrolysis procedure used in Step 3 of **General Procedure A**. MS for $C_{13}H_{10}FNO_3$: *m/z* 248 (MH+).

[01011] The following compounds were made using the same procedure used to synthesize Compound **PA7-12** in **Example 12**:

[01012] 5-(4-Fluoro-2-methylphenyl)-4-hydroxy-2-methylnicotinic acid (PA7-23): MS for $C_{14}H_{12}FNO_3$: *m/z* 262.0 (MH+).

Example 13: 1-Ethyl-5-(4-fluorophenyl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-14) and 4-Ethoxy-5-(4-fluorophenyl)-2-methylnicotinic acid (PA7-40)



[01013] Step 1: Mixture 13-1A/13-1B. To a suspension of Compound **12-4** (180 mg, 0.73 mmol) and Cs_2CO_3 (600 mg, 1.84 mmol) in DMF (4 mL), was added EtI (0.5 mL, 6.25 mmol). The resulting mixture was stirred at room temperature for 2 h and then partitioned between DCM and water. The DCM phase was washed with aq saturated NaCl and concentrated to give the mixture **13-1A/13-1B** (248 mg). MS for methyl esters $C_{10}H_{12}BrNO_3$: *m/z* 274/276 (MH+).

[01014] Step 2: 1-Ethyl-5-(4-fluorophenyl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-14) and 4-Ethoxy-5-(4-fluorophenyl)-2-methylnicotinic acid (PA7-40): A mixture of Compound **PA7-14** and Compound **PA7-40** was made from the mixture of Compounds **13-1A/13-1B** by the same method used to make Compound **PA7-11** from Compound **11-2** in Step 2 of **Example 11**. The mixture of Compound **PA7-14** and Compound **PA7-40** was subsequently separated by silica gel chromatography (5-15% MeOH in EtOAc) to give pure Compound **PA7-14** (46% yield in two steps from Compound **12-4**) and pure Compound **PA7-40** (26% yield in two steps from Compound **12-4**). Compound **PA7-14:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.77 – 7.69 (m, 2H), 7.31 (td, 2H), 4.30 (q, 2H), 2.96 (s, 3H), 1.39 (t, 3H); MS for $C_{15}H_{14}FNO_3$: *m/z* 276.3 (MH+). Compound **PA7-40:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.57 (dd, 2H), 7.30 (t, 2H), 3.80 (q, 2H), 2.42 (s, 3H), 1.05 (t, 3H); MS for $C_{15}H_{14}FNO_3$: *m/z* 276.3 (MH+).

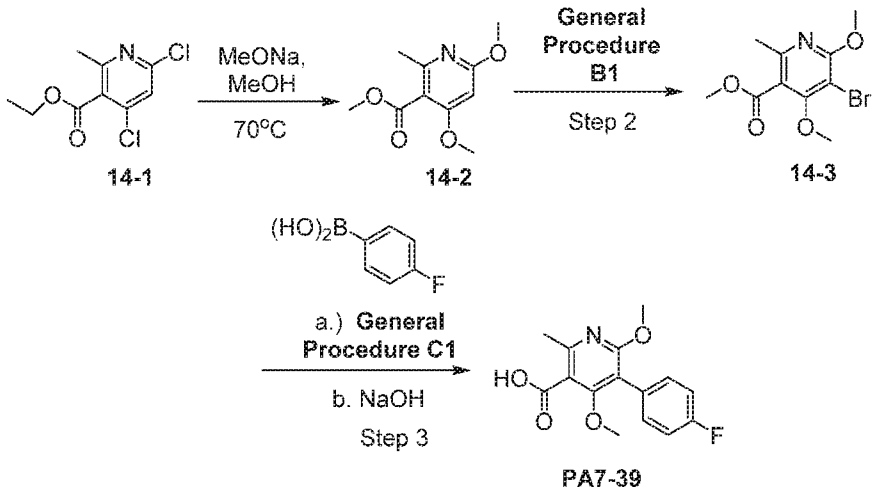
[01015] The following compounds was made using the same method used to make Compound **PA7-14** and/or Compound **PA7-40** in Example 13:

[01016] 5-(4-Fluorophenyl)-1,2-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-13): MS for $C_{14}H_{12}FNO_3$: *m/z* 262.3 (MH+).

[01017] 5-(4-Fluoro-2-methylphenyl)-1,2-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-33): MS for $C_{15}H_{14}FNO_3$: *m/z* 276.2 (MH+).

[01018] 4-Ethoxy-5-(4-fluorophenyl)-6-methylnicotinic acid (PA7-38): MS for $C_{15}H_{14}FNO_3$: *m/z* 276.1 (MH+).

Example 14: 5-(4-Fluorophenyl)-4,6-dimethoxy-2-methylnicotinic acid (PA7-39)

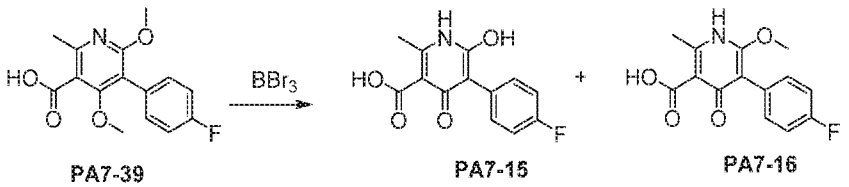


[01019] Step 1: Methyl 4,6-dimethoxy-2-methylnicotinate (14-2). A mixture of Compound **14-1** (3.6 g, 15.4 mmol) and NaOMe (1.8M, 30 mL, 54 mmol) was stirred at 70 °C until the reaction was complete and concentrated to remove MeOH. To the resulting residue was added water and the resulting suspension was filtered. The solid was washed with water and dried under vacuum to give Compound **14-2** (3.3 g, 100% yield). MS for $C_{10}H_{13}NO_4$: *m/z* 212 (MH+).

[01020] Step 2: Methyl 5-bromo-4,6-dimethoxy-2-methylnicotinate (14-3): Compound **14-3** was synthesized from Compound **14-2** using **General Procedure B1**. MS for $C_{10}H_{12}BrNO_4$: *m/z* 290/292 (MH+).

[01021] Step 3: 5-(4-Fluorophenyl)-4,6-dimethoxy-2-methylnicotinic acid (PA7-39): Compound **PA7-39** was made from Compound **14-3** by the same method used to make Compound **PA7-11** from Compound **11-2** in Step 2 of **Example 11**. MS for $C_{15}H_{14}FNO_4$: *m/z* 292 (MH).

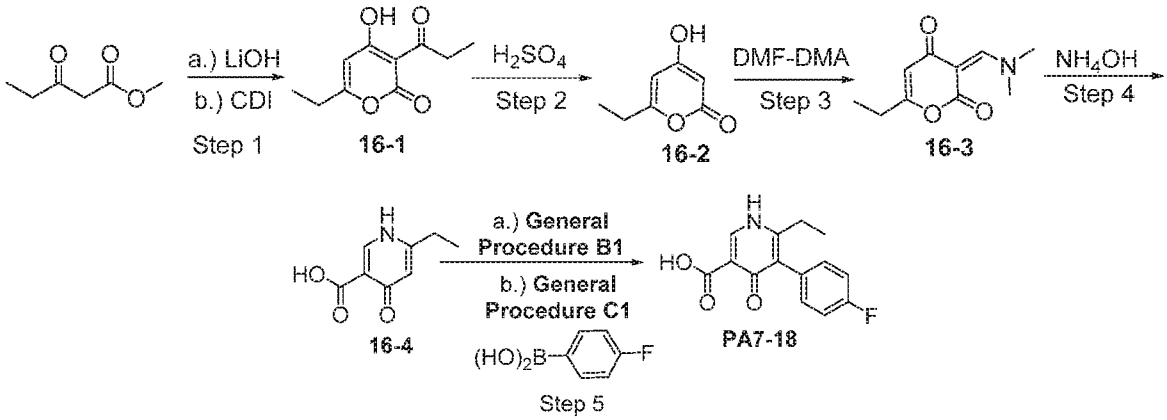
Example 15: 5-(4-Fluorophenyl)-6-hydroxy-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-15) and 5-(4-Fluorophenyl)-6-methoxy-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-16)



[01022] 5-(4-Fluorophenyl)-6-hydroxy-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-15) and 5-(4-Fluorophenyl)-6-methoxy-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-16). A mixture of Compound **PA7-39** (550 mg, 1.89 mmol) and BBr_3 (2 mL, 21.4 mmol) in DCM (6 mL) was stirred at room temperature for 1 h, quenched with water and concentrated in vacuo to remove DCM. To the resulting residue was added 2 M HCl (10 mL) and MeOH (10 mL). The resulting mixture was stirred at room temperature for 4 h and then concentrated to remove MeOH. The resulting residue was extracted with EtOAc (3x) and the combined extracts were concentrated in vacuo. The resulting residue was purified by silica gel chromatography (0-10% MeOH in DCM) to give Compound

PA7-15 (82 mg, 15% yield), MS for $C_{13}H_{10}FNO_4$: *m/z* 264 (MH+) and Compound **PA7-16** (176 mg, 33% yield), MS for $C_{14}H_{12}FNO_4$: *m/z* 278 (MH+).

Example 16: 6-Ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-18)



[01023] Step 1: 6-ethyl-4-hydroxy-3-propionyl-2H-pyran-2-one (16-1). A solution of methyl 3-oxopentanoate (5g, 38.46 mmol) in MeOH (20 mL) was charged with 1 M LiOH (10 eq). The resulting mixture was stirred at room temperature for 1 h. MeOH was removed in vacuo and the aqueous layer was washed with EtOAc (3x). The aqueous layer was acidified using 6 N HCl to pH 2-3 and extracted with EtOAc (3x). The combined organic extracts were washed with aq saturated NaCl, dried over anhyd Na_2SO_4 and concentrated. The resulting residue was dissolved in THF (50 mL) and to the resulting solution was added 1,1'-carbonyldiimidazole (1.1 eq). The resulting mixture was stirred at room temperature overnight. The crude reaction mixture was diluted with EtOAc, washed with 1 M HCl, washed with aq saturated NaCl, dried over anhyd Na_2SO_4 and concentrated to give Compound **16-1** (3.47 g, 46% yield). MS for $C_{10}H_{12}O_4$: *m/z* 197 (MH+).

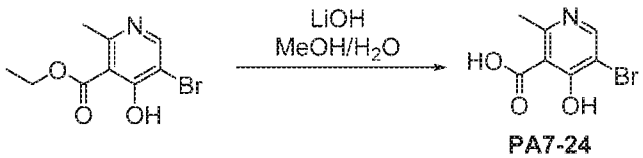
[01024] Step 2: 6-Ethyl-4-hydroxy-2H-pyran-2-one (16-2): Concentrated H_2SO_4 (5 mL) was added to Compound **16-1** (3.47g, 17.7 mmol) and heated to 130 °C for 30 min. The reaction mixture was allowed to cool to room temperature and poured onto ice. The resulting aqueous mixture was neutralized with 3 N NaOH, extracted with EtOAc, washed with aq saturated NaCl, dried over anhyd Na_2SO_4 and concentrated to give Compound **16-2**. MS for $C_7H_8O_3$: *m/z* 141 (MH)

[01025] Step 3: (Z)-3-((Dimethylamino)methylene)-6-ethyl-2H-pyran-2,4(3H)-dione (16-3): To Compound **16-2** (1.76 g, 7.69 mmol) in dioxane (20 mL) was added DMF-DMA (2.9 mL). The resulting mixture was stirred at room temperature for 30 min and then concentrated in vacuo to give crude Compound **16-3** which was used in the next step without further purification. MS for $C_{10}H_{13}NO_3$: *m/z* 196 (MH)

[01026] Step 4: 6-Ethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (16-4): To crude Compound **16-3** (1.5 g, 7.69 mmol) in water (11 mL) was added ammonium hydroxide (6 eq). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then chilled to 0 °C and acidified using 6 N HCl to pH 4. The resulting mixture was extracted with EtOAc (4x). The combined organic extracts were washed with aq saturated NaCl, dried over anhyd Na_2SO_4 and concentrated to give Compound **16-4** which was used in the next step without further purification. MS for $C_8H_9NO_3$: *m/z* 168 (MH)

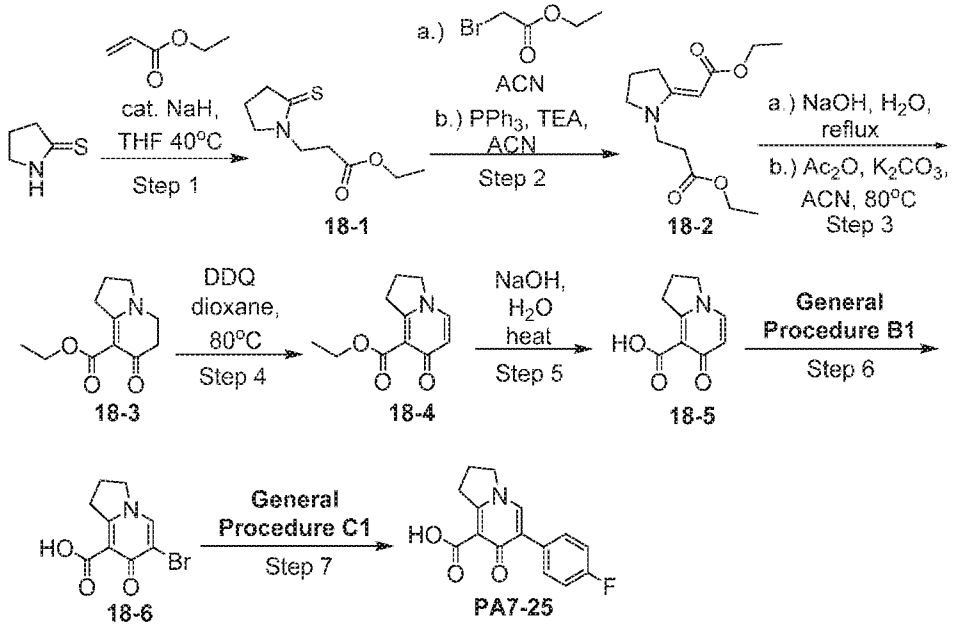
[01027] Step 5: 6-Ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-18): Compound **PA7-18** was made in two steps from Compound **16-4.** Compound **16-4** was first brominated using **General Procedure B1**. The resulting bromide was converted to Compound **PA7-18** through **General Procedure C1**. MS for $C_{14}H_{12}FNO_3$: *m/z* 262 (MH)

Example 17: 5-Bromo-4-hydroxy-2-methylnicotinic acid (PA7-24)



[01028] 5-Bromo-4-hydroxy-2-methylnicotinic acid (PA7-24): Ethyl 5-bromo-4-hydroxy-2-methyl-pyridine-3-carboxylate can be made in the same manner as the corresponding methyl ester Compound **12-4** in **Example 12**. To a 20 mL vial equipped with a magnetic stir bar and a pressure relief septum was added ethyl 5-bromo-4-hydroxy-2-methyl-pyridine-3-carboxylate (1.50 g, 5.77 mmol, 1.00 eq), MeOH (10 mL), and water (3 mL). LiOH hydrate (800 mg, 19.07 mmol, 3.31 eq) was added in a single portion, and the reaction was heated to 65 °C for 3 h. The solution was then concentrated to remove most of the MeOH, and the solution was acidified to pH = 3 with 6 M HCl. The resulting precipitate was collected by vacuum filtration to give Compound **PA7-24** (1.22 g, 91% yield). MS for $C_7H_6BrNO_3$: *m/z* 232.0 (MH+).

Example 18: 6-(4-Fluorophenyl)-7-oxo-1,2,3,7-tetrahydroindolizine-8-carboxylic acid (PA7-25)



[01029] Step 1: Ethyl 3-(2-thioxopyrrolidin-1-yl)propanoate (18-1): To a stirred solution of pyrrolidine-2-thione (500 mg, 4.95 mmol) in dry THF (10 mL) was added a catalytic amount of NaH (60% dispersion in oil, 18 mg, 0.95 mmol) followed by the dropwise addition of ethyl acrylate (0.6 mL, d 0.94 g/mL, 0.56 mmol). The mixture was stirred at 40 °C overnight. The reaction mixture was evaporated to remove the solvent in vacuo. The resulting residue was partitioned between EtOAc and aq $NaHCO_3$ (1 M). The organic phase was separated, washed with aq saturated NaCl and concentrated. The resulting residue was purified by silica gel chromatography (0-50% of EtOAc in hexane) to give

Compound **18-1** (0.9 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (q, 2H), 4.03 (t, 2H), 3.83 (t, 2H), 3.04 (t, 2H), 2.80 (t, 2H), 2.08 (q, 2H), 1.29 (t, 3H); MS for $C_9H_{15}NO_2S$: *m/z* 202 (MH+).

[01030] Step 2: Ethyl (E)-3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoate (18-2): Ethyl bromoacetate (0.6 mL, d 1.51 g/ML, 5.42 mmol) was added dropwise to a stirred solution of Compound **18-1** (0.9 g, 4.48 mmol) in dry ACN (10 mL). The resulting solution was stirred at room temperature overnight. The volatiles were removed *in vacuo*, and the residue was thoroughly dried under vacuum. This salt was then re-dissolved in dry ACN (10 mL) to which was added triphenylphosphine (1.42 g, 5.42 mmol) and TEA (0.77 mL, 5.5 mmol). The resulting solution was stirred at room for 3 days and concentrated. The residue was partitioned between water and DCM. The organic phase was separated, washed with aq saturated NaCl and evaporated in vacuo. The resulting residue was purified by silica gel chromatography (DCM first to remove Ph_3P/Ph_3PS, and then with 0-40% EtOAc in hexane) to give Compound **18-2** (1.09 g, 95% yield). MS for $C_{13}H_{21}NO_4$: *m/z* 256 (MH+).

[01031] Step 3: Ethyl 7-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (18-3): A mixture of Compound **18-2** (1.09 g, 4.27 mmol) and NaOH (172 mg, 4.3 mmol) in water (10 mL) was refluxed until hydrolysis was complete followed by cooling to room temperature. The resulting mixture was acidified to pH 3 and extracted with EtOAc (3x). The combined extracts were dried over anhyd Na_2SO_4 and concentrated. This crude acid was then mixed with K_2CO_3 (1.2 g, 8.7 mmol) and acetic anhydride (0.5 mL, 5.40 mmol) in ACN (20 mL). The mixture was stirred at 80 °C overnight, cooled to room temperature, quenched with water and extracted with DCM (3x). The combined DCM extracts were dried with Na_2SO_4 and concentrated to give crude Compound **18-3** (880 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (q, 2H), 3.80 (t, 2H), 3.73 (t, 2H), 3.37 (t, 2H), 2.83 (t, 2H), 2.23 (q, 2H), 1.37 (t, 3H); MS for $C_{11}H_{15}NO_3$: *m/z* 210 (MH+).

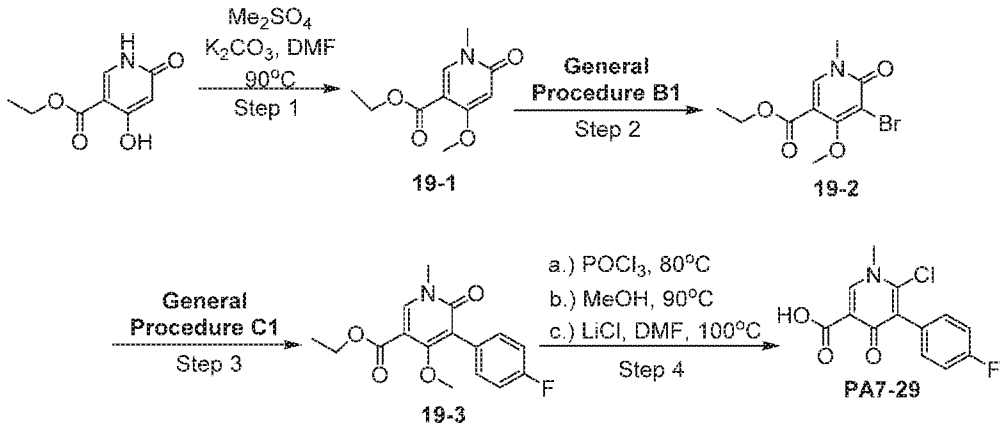
[01032] Step 4: Ethyl 7-oxo-1,2,3,7-tetrahydroindolizine-8-carboxylate (18-4): Compound **18-3** (790 mg, 3.78 mmol) was mixed with DDQ (990 mg, 4.36 mmol) in dioxane (8 mL) and the reaction mixture stirred at 80 °C overnight. After cooling to room temperature, the mixture was partitioned between EtOAc and aq $NaHCO_3$. The aqueous phase was extracted twice with EtOAc, and the combined organic phases were dried over anhyd Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (0-10% MeOH in DCM) to give Compound **18-4** (560 mg, 72%). MS for $C_{11}H_{13}NO_3$: *m/z* 208 (MH+).

[01033] Step 5: 7-oxo-1,2,3,7-tetrahydroindolizine-8-carboxylic acid (18-5). Compound **18-4** was converted to Compound **18-5** by a modification of the ester hydrolysis procedure used in Step 3 of **General Procedure A**. In this case the reaction was heated at 80 °C overnight, followed by 90 °C for an additional 4 h prior to the usual work-up. MS for $C_9H_9NO_3$: *m/z* 180 (MH+).

[01034] Step 6: 6-Bromo-7-oxo-1,2,3,7-tetrahydroindolizine-8-carboxylic acid (18-6): Compound **18-6** was synthesized from Compound **18-5** using **General Procedure B1**. MS for $C_9H_8BrNO_3$: *m/z* 258/260 (MH+).

[01035] Step 7: 6-(4-Fluorophenyl)-7-oxo-1,2,3,7-tetrahydroindolizine-8-carboxylic acid (PA7-25): Compound **PA7-25** was synthesized from Compound **18-6** using **General Procedure C1**. MS for $C_{15}H_{12}FNO_3$: *m/z* 274 (MH+).

Example 19: 6-Chloro-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-29)



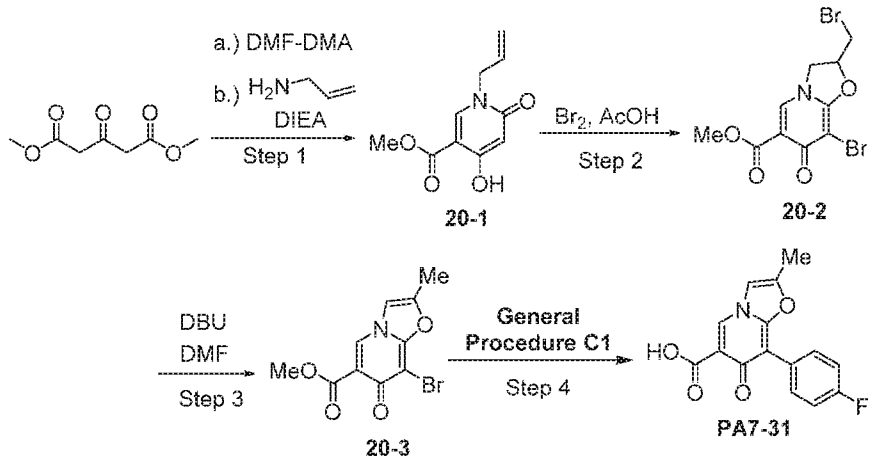
[01036] Step 1: Ethyl 4-methoxy-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (19-1): A mixture of ethyl 4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (3.2 g, 1.75 mmol), dimethyl sulfate (2.1 mL, 2.22 mmol), K_2CO_3 (7.0 g, 5.1 mmol) in DMF (30 mL) was stirred at 90 °C. Upon completion of the reaction as monitored by LC-MS, the mixture was cooled to room temperature and partitioned between EtOAc and water. The phases were separated and the aqueous was further extracted with EtOAc. The combined organic phases were dried over anhyd Na_2SO_4 and concentrated to give Compound **19-1** which was used without further purification. MS for $C_{10}H_{13}NO_4$: *m/z* 212 (MH+).

[01037] Step 2: Ethyl 5-bromo-4-methoxy-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylated (19-2): Compound **19-2** was synthesized from Compound **19-1** using **General Procedure B1**. MS for $C_{10}H_{12}BrNO_4$: *m/z* 290/292 (MH+).

[01038] Step 3: Ethyl 5-(4-fluorophenyl)-4-methoxy-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (19-3): Compound **19-3** was synthesized from Compound **19-2** using **General Procedure C1**. MS for $C_{16}H_{16}FNO_4$: *m/z* 306 (MH+).

[01039] Step 4: 6-Chloro-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-29): A mixture of Compound **19-3** (2.02 g, 6.62 mmol) and $POCl_3$ (10 mL) was stirred at 80 °C for 4 h and then evaporated to dryness. To the resulting residue was added MeOH (5 mL) and the resulting mixture stirred at 90 °C for 1 h and then evaporated to dryness. The resulting residue was mixed with LiCl (3.0 g, 70.8 mmol) in DMF (3 mL) and the resulting mixture stirred at 100 °C for 4 h, cooled to room temperature, quenched with NaOH (1M) to pH>12 and washed with EtOAc (2x). The aqueous phase was acidified to pH 2 with 6 M HCl and extracted with EtOAc (2x). The combined extracts were dried over anhyd Na_2SO_4 and concentrated to give crude Compound **PA7-29** (620 mg, 33% yield), which was used without further purification. MS for $C_{13}H_9FNO_3$: *m/z* 282 (MH+).

Example 20: 8-(4-Fluorophenyl)-2-methyl-7-oxo-7H-oxazolo[3,2-a]pyridine-6-carboxylic acid (PA7-31)



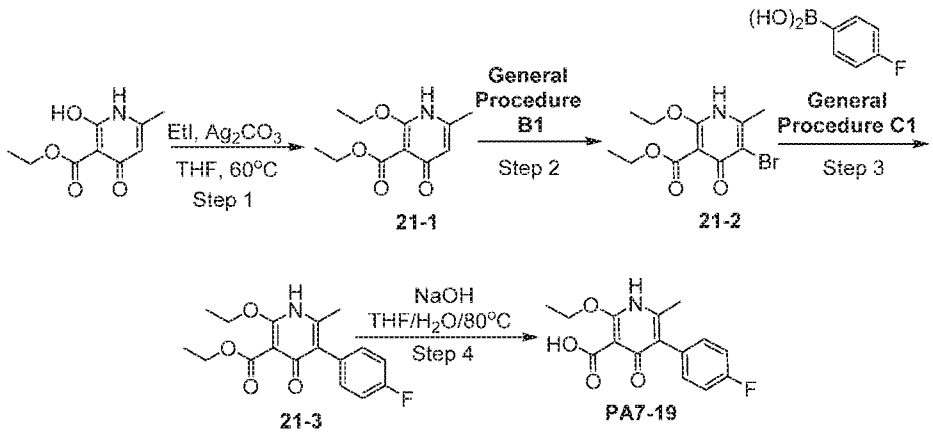
[01040] Step 1: Methyl 1-allyl-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (20-1): To a 40 mL vial equipped with a magnetic stir bar and a pressure relief septum was added dimethyl 3-oxopentanedioate (5.0 mL, 35 mmol, 1.1 eq) and DMF-DMA (5.5 mL, 41 mmol, 1.3 eq). The mixture was stirred in open air vigorously for 1.5 h at 100 °C. The vial was cooled to room temperature and allylamine hydrochloride (3.0 g, 32 mmol, 1.0 eq) was added in a single portion followed by DIEA(10 mL, 56.2 mmol, 1.8 eq). The resulting solution was then heated to 80 °C for 4 h, cooled to room temperature, concentrated and purified by silica gel chromatography (0 - 100% EtOAc in hexanes) to give Compound **20-1** (2.1 g, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (d, 1H), 8.11 (s, 1H), 6.08 – 5.80 (m, 2H), 5.43 – 5.17 (m, 2H), 4.58 (dd, 2H), 3.93 (d, 3H). MS for $C_{10}H_{11}NO_4$: *m/z* 210.0 (MH+).

[01041] Step 2: Methyl 8-bromo-2-(bromomethyl)-7-oxo-2,3-dihydro-7H-oxazolo[3,2-a]pyridine-6-carboxylate (20-2): To a 100 mL round bottom flask equipped with a magnetic stir bar was added Compound **20-1** (1.0 g, 4.8 mmol) in acetic acid (5.0 mL). Bromine (1.0 mL, 19 mmol, 4.1 equiv.) was added dropwise, and the reaction was heated to 60 °C for 4 h. The reaction was allowed to cool to room temperature and the resulting suspension was filtered to give Compound **20-2** (780 mg, 44% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 5.53 – 5.40 (m, 1H), 4.64 (dd, Hz, 1H), 4.28 (dd, 1H), 3.98 (qd, 2H), 3.72 (s, 3H); MS for $C_{10}H_9Br_2NO_4$: *m/z* 367.8 (MH+).

[01042] Step 3: Methyl 8-bromo-2-methyl-7-oxo-7H-oxazolo[3,2-a]pyridine-6-carboxylate (20-3): To a 20-mLvial equipped with a magnetic stir bar and a pressure relief septum was added Compound **20-2** (700 mg, 1.91 mmol) in DMF (5 mL). DBU (1 mL, 6.70 mmol, 3.51 equiv.) was added in a single portion at room temperature and the reaction was stirred at room temperature for 3 h. The reaction was then concentrated, loaded onto silica gel, and purified by silica gel chromatography (gradient 0 to 100% EtOAc in hexanes) to give Compound **20-3** (130 mg, 23.8% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 7.75 (s, 1H), 3.76 (s, 3H), 2.37 (s, 3H).

[01043] Step 4: 8-(4-Fluorophenyl)-2-methyl-7-oxo-7H-oxazolo[3,2-a]pyridine-6-carboxylic acid (PA7-31): Compound **PA7-31** was synthesized from Compound **20-3** using **General Procedure C1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.97 (s, 1H), 7.73 (dd, 2H), 7.33 (t, 2H), 2.40 (s, 3H).

Example 21: 2-Ethoxy-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-19)



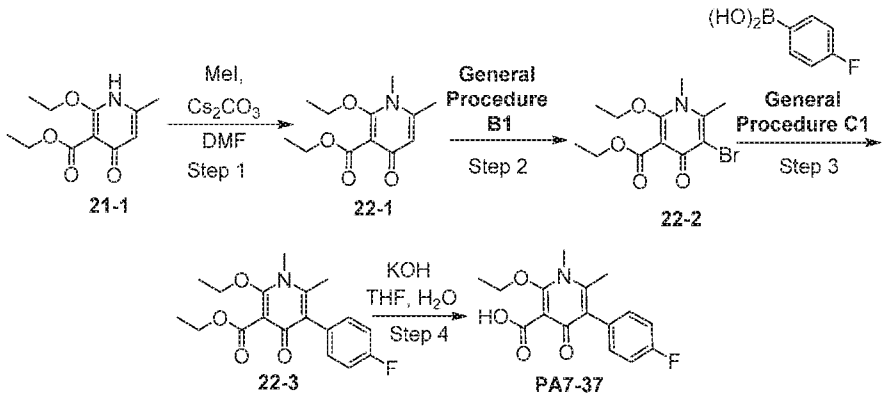
[01044] Step 1: Ethyl 2-ethoxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (21-1): To a mixture of ethyl 2,4-dihydroxy-6-methyl-pyridine-3-carboxylate (1.2 g, 6.1 mmol, 1 eq) and Ag_2CO_3 (840 mg, 3.05 mmol, 0.5 eq) in THF (10 mL) was added iodoethane (7.50 mmol, 0.6 mL, 1.2 eq). The mixture was stirred at 60 °C for 12 h. The mixture was concentrated, and the resulting residue was purified by flash silica gel chromatography (0~10% EtOAc/Petroleum ether) to give Compound **21-1** (638 mg, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.20 (s, 1H), 6.36 (s, 1H), 4.47-4.31 (m, 4H), 2.34 (s, 3H), 1.46-1.36 (m, 6H); MS for $C_{11}H_{15}NO_4$: *m/z* 226 (MH+).

[01045] Step 2: Ethyl 5-bromo-2-ethoxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (21-2): Compound **21-2** was synthesized from Compound **21-1** using **General Procedure B1**. MS for $C_{11}H_{14}BrNO_4$: *m/z* 305.7 (MH+).

[01046] Step 3: Ethyl 2-ethoxy-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (21-3): Compound **21-3** was synthesized from Compound **21-2** using **General Procedure C1**. MS for $C_{17}H_{18}FNO_4$: *m/z* 320.0 (MH+).

[01047] Step 4: 2-Ethoxy-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-19): Compound **21-3** was converted to Compound **PA7-19** using a modification of the ester hydrolysis procedure used in Step 3 of **General Procedure A**. In this particular case the reaction mixture was heated to 80 °C prior to work up. MS for $C_{15}H_{14}FNO_4$: *m/z* 291.9 (MH+).

Example 22: 2-Ethoxy-5-(4-fluorophenyl)-1,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-37)



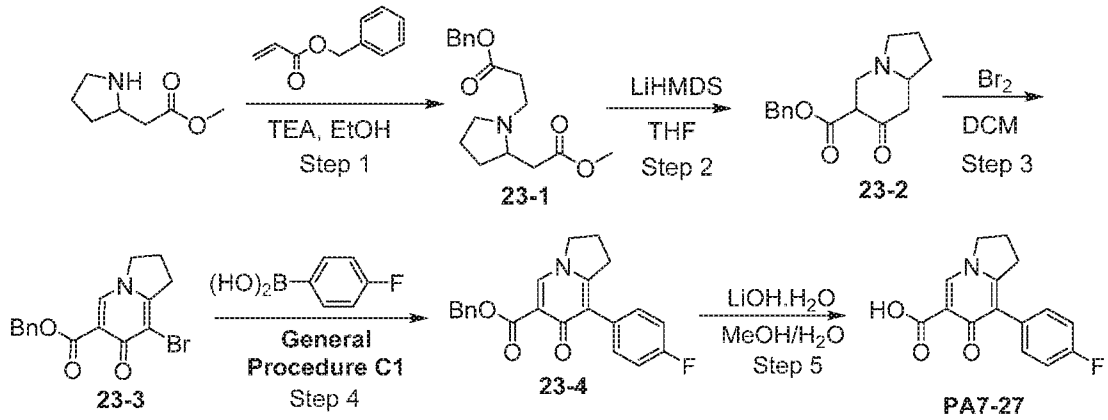
[01048] Step 1: Ethyl 2-ethoxy-1,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylate (22-1): To a mixture of Compound **21-1** (154 mg, 0.68 mmol, 1 eq) in DMF (2 mL) was added Cs_2CO_3 (267.32 mg, 0.82 mmol, 1.2 eq) and MeI (1.03 g, 7.3 mmol, 0.45 mL, 11 eq). The mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with aq saturated NaCl (15 mL), dried over anhyd Na_2SO_4, concentrated and purified by flash silica gel chromatography (0~10% EtOAc/Petroleum ether) to give Compound **22-1** (163 mg, 99.6% yield). MS for $C_{12}H_{17}NO_4$: *m/z* 240.2 (MH+).

[01049] Step 2: Ethyl 5-bromo-2-ethoxy-1,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylate (22-2): Compound **22-2** was synthesized from Compound **22-1** using **General Procedure B1**. MS for $C_{12}H_{16}BrNO_4$: *m/z* 319.8 (MH+).

[01050] Step 3: Ethyl 2-ethoxy-5-(4-fluorophenyl)-1,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylate (22-3): Compound **22-3** was synthesized from Compound **22-2** using **General Procedure C1**. MS for $C_{18}H_{20}FNO_4$: *m/z* 333.9 (MH+).

[01051] Step 4: 2-Ethoxy-5-(4-fluorophenyl)-1,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (PA7-37): Compound **21-3** was converted to Compound **PA7-19** using a modification of the ester hydrolysis procedure used in Step 3 of **General Procedure A**. In this particular case the NaOH was replaced with KOH and the reaction mixture was heated to 100 °C prior to work up. MS for $C_{16}H_{16}FNO_4$: *m/z* 305.9 (MH+).

Example 23: 8-(4-Fluorophenyl)-7-oxo-1,2,3,7-tetrahydroindolizine-6-carboxylic acid (PA7-27)



[01052] Step 1: Benzyl 3-(2-(2-methoxy-2-oxoethyl)pyrrolidin-1-yl)propanoate (23-1): To a mixture of methyl 2-pyrrolidin-2-ylacetate (1.04 g, 7.3 mmol, 1 eq) and benzyl prop-2-enoate (1.77 g, 11 mmol, 1.5 eq) in EtOH (15 mL) was added TEA (3.67 g, 36 mmol, 5.1 mL, 5 eq) in one portion at 20 °C. The mixture was stirred at 20 °C for 16 h. The mixture was concentrated then diluted with water (300 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with aq saturated NaCl (10 mL), dried over anhyd Na_2SO_4, concentrated and the resulting residue was purified by flash silica gel chromatography (0~10% MeOH/DCM) to give Compound **23-1** (1.2 g, 54% yield). MS for $C_{17}H_{23}NO_4$: *m/z* 306.1 (MH+).

[01053] Step 2: Benzyl 7-oxooctahydroindolizine-6-carboxylate (23-2): To a mixture of Compound **23-1** (1.2 g, 4 mmol, 1 eq) in THF (15 mL) was added LiHMDS (1 M, 7.9 mL, 2 eq) slowly in one portion at -78 °C under an atmosphere of nitrogen. The mixture was stirred at -78 °C for 2 h. Conc. HCl (10 mL) and THF (1 mL) was added into the reaction mixture. The mixture was concentrated, then diluted with water (60 mL) and the pH adjust to 8 with the addition of K_2CO_3. The resulting mixture was extracted with EtOAc (2 x 60 mL). The combined organic extracts were washed with aq saturated NaCl (20 mL), dried over anhyd Na_2SO_4, concentrated and purified by silica gel column chromatography (3% MeOH in DCM) to give Compound **23-2** (600 mg, 56% yield). MS for $C_{16}H_{19}NO_3$: *m/z* 274.1 (MH+).

[01054] Step 3: Benzyl 8-bromo-7-oxo-1,2,3,7-tetrahydroindolizine-6-carboxylate (23-3): To a mixture of Compound **23-2** (600 mg, 2.2 mmol, 1 eq) in DCM (10 mL) was added Br_2 (351 mg, 2.2 mmol, 0.11 mL, 1 eq) in one portion at 20 °C. The mixture was stirred at 0-20 °C for 3 h. The mixture was diluted with DCM (50 mL), washed with aq saturated $NaHCO_3$, concentrated and purified by silica gel column chromatography (2% MeOH in DCM) to give Compound **23-3** (170 mg, 22% yield). MS for $C_{16}H_{19}NO_3$: *m/z* 348.0 (MH+).

[01055] Step 4: Benzyl 8-(4-fluorophenyl)-7-oxo-1,2,3,7-tetrahydroindolizine-6-carboxylate (23-4): Compound **23-4** was synthesized from Compound **23-3** using **General Procedure C1**. MS for $C_{22}H_{18}FNO_3$: *m/z* 364.1 (MH+).

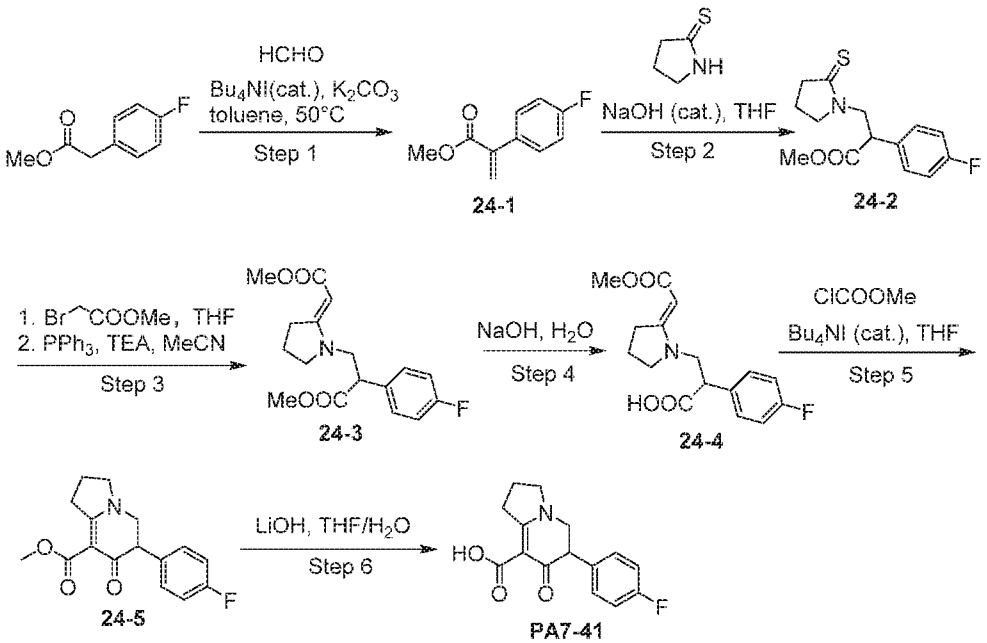
[01056] Step 5: 8-(4-Fluorophenyl)-7-oxo-1,2,3,7-tetrahydroindolizine-6-carboxylic acid (PA7-27): To a mixture of Compound **23-4** (75 mg, 0.21 mmol, 1 eq) in MeOH (6 mL) and water (2 mL) was added LiOH monohydrate (86.61 mg, 2.06 mmol, 10 eq) in one portion at 20 °C under an atmosphere of

nitrogen. The mixture was stirred at 20 °C for 12 h. The pH of the resulting mixture was adjusted to pH 4-5 by the addition of aq 2 N HCl. The mixture was then diluted with water (30mL) and extracted with EtOAc (3 x 50 mL). The combined EtOAc extracts were concentrated and purified by silica gel column chromatography (5% MeOH in DCM) to give Compound **PA7-27** (56 mg, 99% yield). MS for $C_{15}H_{12}FNO_3$: *m/z* 274.1 (MH+).

[01057] The following compound was made by the same technique used to make **PA7-27** in **Example 23**:

[01058] 1-(4-Fluorophenyl)-2-oxo-6,7,8,9-tetrahydro-2H-quinolizine-3-carboxylic acid (PA7-34): MS for $C_{16}H_{14}FNO_3$: *m/z* 288.1 (MH+).

Example 24: 6-(4-Fluorophenyl)-7-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylic acid (PA7-41)



[01059] Step 1: Methyl 2-(4-fluorophenyl)acrylate (24-1): Formaldehyde (2.70 g, 33 mmol, 2.5 mL, 2.8 eq), tetrabutylammonium;iodide (175 mg, 0.47 mmol, 0.04 eq) and K_2CO_3 (4.93 g, 36 mmol, 3 eq) were added to a solution of methyl 2-(4-fluorophenyl)acetate (2 g, 12 mmol, 1 eq) in toluene (15 mL). The mixture was warmed and stirred at 50 °C for 17 h. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted with toluene (2 x 50 mL). The organic extracts were dried over anhyd Na_2SO_4, concentrated and the resulting residue was purified by silica gel column chromatography (3% EtOAc in petroleum ether) to give Compound **24-1** (0.61 g, 28% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.35 (m, 2H), 7.09-7.00 (m, 2H), 6.36 (d, 1H), 5.87 (d, 1H), 3.82 (s, 3H).

[01060] Step 2: Methyl 2-(4-fluorophenyl)-3-(2-thioxopyrrolidin-1-yl)propanoate (24-2): Compound **24-1** (610 mg, 3.4 mmol, 1 eq) and pyrrolidine-2-thione (330 mg, 3.3 mmol, 0.96 eq) were dissolved in dry THF (10 mL) followed by the addition of NaOH (20 mg, 0. 500 mmol, 0.15 e*q*). The resulting mixture was stirred at 25-30 °C for 90 h. The mixture was diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were concentrated, and the resulting residue was purified by silica gel column chromatography (20% EtOAc in petroleum ether) to give

Compound **24-2** (624 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 2H), 7.07-6.98 (m, 2H), 4.56 (t, 1H), 4.17 (dd, 1H), 3.97 (dd, 1H), 3.75-3.69 (m, 1H), 3.69 (s, 3H), 3.28-3.20 (m, 1H), 3.00-2.89 (m, 2H), 2.00-1.82 (m, 2H).

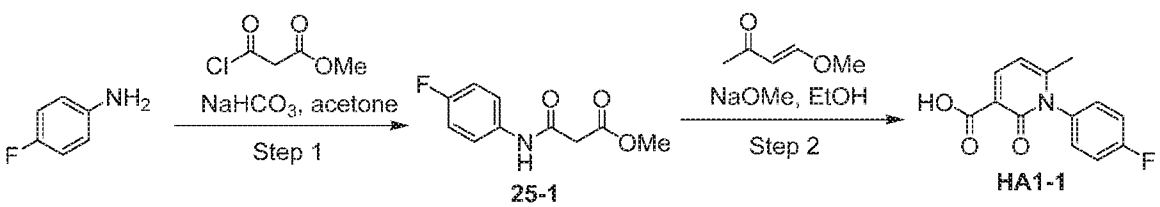
[01061] Step 3: Methyl (E)-2-(4-fluorophenyl)-3-(2-(2-methoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoate (24-3): Methyl 2-bromoacetate (405 mg, 2.6 mmol, 0.25 mL, 1.2 eq) was added to a solution of Compound **24-2** (620 mg, 2.20 mmol, 1 eq) in THF (10 mL) and the mixture was stirred at 20-30 °C for 16 h. The resulting mixture was concentrated under vacuum and the residue was dissolved in ACN (10 mL). PPh_3 (636 mg, 2.4 mmol, 1.1 eq) and TEA (268 mg, 2.6 mmol, 0.37 mL, 1.2 eq) were added. The resulting mixture was stirred at 20-30 °C for another 24 h. The mixture was concentrated under vacuum and the resulting residue was purified by silica gel column chromatography (20% EtOAc in petroleum ether) to give Compound **24-3** (564 mg, 73% yield). MS for $C_{17}H_{20}FNO_4$: *m/z* 321.9 (MH+).

[01062] Step 4: (E)-2-(4-Fluorophenyl)-3-(2-(2-methoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoic acid (24-4): NaOH (65 mg, 1.6 mmol, 1.0 eq) was added to a mixture of Compound **24-3** (560 mg, 1.6 mmol, 1 eq) in water (10 mL). The mixture was heated and stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was lyophilized to give Compound **24-4** (530 mg, 99.8% yield). MS for $C_{16}H_{18}FNO_4$: *m/z* 307.9 (MH+).

[01063] Step 5: Methyl 6-(4-fluorophenyl)-7-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (24-5): Methyl chloroformate (122 mg, 1.3 mmol, 0.1 mL, 1.1 eq) was added to a suspension of Compound **24-4** (400 mg, 1.2 mmol, 1 eq) and tetrabutylammonium;iodide (44 mg, 0.12 mmol, 0.1 eq) in THF (20 mL) under an atmosphere of nitrogen. The mixture was stirred at 20-30 °C for 22 h. The mixture was concentrated under vacuum and the resulting residue was purified by silica gel column chromatography (0-10% EtOH in EtOAc) followed by further purification by prep-HPLC (Venusil ASB Phenyl 150*30mm*5um;mobile phase: [water (0.05% HCl)-ACN]; B%: 30%-60%, 9 min) to give Compound **24-5** (130 mg, 87% yield). MS for $C_{16}H_{16}FNO_3$: *m/z* 289.9 (MH+).

[01064] Step 6: 6-(4-Fluorophenyl)-7-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylic acid (PA7-41): $LiOH.H_2O$ (165 mg, 3.9 mmol, 10 eq) was added to a solution of Compound **24-5** (110 mg, 0.38 mmol, 1 eq) in THF (5 mL) and water (1 mL). The mixture was stirred at 60 °C for 18 h. After cooling to room temperature, the mixture was concentrated under vacuum to remove the organic solvent. The residual aqueous layer was diluted with water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over anhyd Na_2SO_4 and concentrated under vacuum to give crude Compound **PA7-41** (100 mg, 96% yield). MS for $C_{15}H_{14}FNO3$: *m/z* 275.9 (MH+).

Example 25: 1-(4-Fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-1)



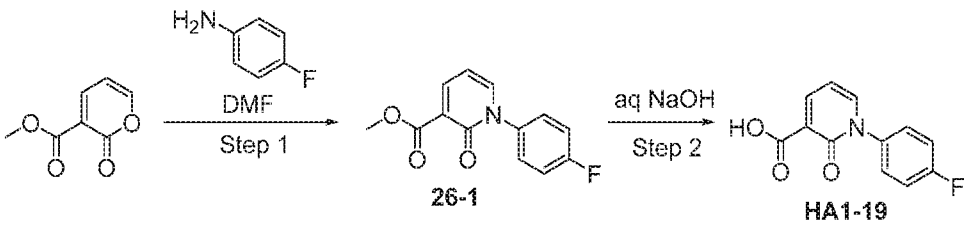
[01065] Step 1: Methyl 3-((4-fluorophenyl)amino)-3-oxopropanoate (25-1): To a mixture of 4-fluoroaniline (50 g, 450 mmol, 43 mL, 1 eq) and $NaHCO_3$ (64 g, 765 mmol, 30 mL, 1.7 eq) in acetone (250 mL) was added methyl 3-chloro-3-oxo-propanoate (92 g, 675 mmol, 72 mL, 1.5 eq) dropwise and the resulting solution was stirred at 20 °C for 12 h. Water (200 mL) was added to the reaction mixture and the mixture was concentrated to remove the acetone. Water (200 mL) was again added and the mixture was stirred to precipitate. The resulting solid was filtered, washed with petroleum ether (2 x 50mL) and dried to give Compound **25-1** (89 g, 94% yield) which was used in subsequent reactions without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.61-7.54 (m, 2H), 7.19-7.12 (m, 2H), 3.65 (s, 3H), 3.46 (s, 2H); MS for $C_{10}H_{10}FNO_3$: *m/z* 212.1 (MH+).

[01066] Step 2: 1-(4-Fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-1): To a solution of Compound **25-1** (1.0 g, 4.7 mmol, 1 eq) in EtOH (10 mL) was added 25% NaOMe in MeOH (2.35 g, 11 mmol, 2.3 eq) followed by the addition of (E)-4-methoxybut-3-en-2-one (521 mg, 5.2 mmol, 0.5 mL, 1.1 eq) and the resulting reaction mixture was stirred at 65 °C for 12 h. The reaction mixture was concentrated to remove the solvent and the pH adjusted 5 with aq HCl solution (3 M). The resulting suspension was filtrated, and the filtrate was concentrated to dryness to give Compound **HA1-1** (550 mg, 47% yield) which was used in subsequent reactions without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.21 (s, 1H), 8.40 (d, 1H), 7.54-7.49 (m, 2H), 7.47-7.41 (m, 2H), 6.80 (d, 1H), 2.09 (s, 3H); MS for $C_{13}H_{10}FNO_3$: *m/z* 248 (MH+).

[01067] The following compounds were made using the same synthetic techniques exemplified in **Example 25**:

[01068] 1-(4-Fluoro-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-2): The NaOMe in step 2 was replaced with NaOEt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.15 (s, 1H), 8.45 (d, 1H), 7.45 (dd, 1H), 7.39 (dd, 1H), 7.28 (td, 1H), 6.85 (d, 1H), 2.07 (s, 3H), 2.00 (s, 3H); MS for $C_{14}H_{12}FNO_3$: *m/z* 262 (MH+).

Example 26: 1-(4-Fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-19)



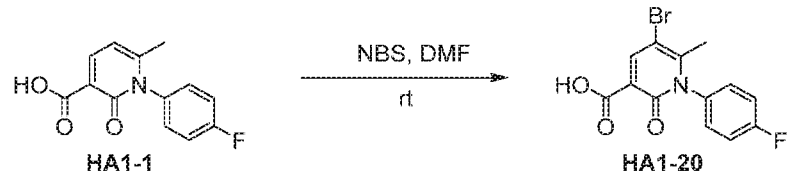
26-1 HA1-19

[01069] Step 1: Methyl 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (26-1): To a solution of methyl 2-oxopyran-3-carboxylate (400 mg, 2.6 mmol, 1 eq) in DMF (5 mL) was added 4-fluoroaniline (317 mg, 2.8 mmol, 0.27 mL, 1.1 eq) dropwise at 0 °C and the resulting mixture was stirred for 2 h at this temperature followed by heating the reaction mixture at 30 °C for 12 h. The resulting solid was filtered, and the filtrate was diluted with DCM (30 mL). The resulting precipitate was filtered and combined with the previously filtered solid. The resulting combined solids were washed with DCM (2 x 5 mL) and dried under vacuum to give Compound **26-1** (550 mg, 68% yield). ^{1}H NMR (400 MHz,

DMSO-d_6) δ 7.97-8.27 (m, 1H), 7.89-7.97 (m, 1H), 7.21-7.29 (m, 4H), 6.97-7.04 (m, 1H), 3.74 (s, 3H); MS for $C_{13}H_{10}FNO_3$: *m/z* 248.0 (MH+).

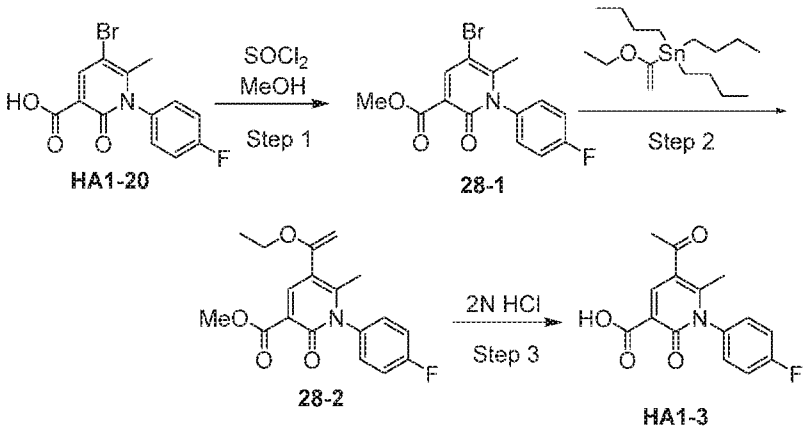
[01070] Step 2: 1-(4-Fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-19): Compound **HA1-19** was made from Compound **26-1** using standard ester hydrolysis conditions such as those used in Step 3 of **Example 7**. MS for $C_{12}H_8FNO_3$: *m/z* 234 (MH+).

Example 27: 5-Bromo-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-20)



[01071] 5-Bromo-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-20): To a mixture of Compound **HA1-1** (550 mg, 2.2 mmol, 1 eq) in DMF (5 mL) was added NBS (475 mg, 2.7 mmol, 1.2 eq) under an atmosphere of nitrogen. The mixture was stirred at 25 °C for 12 h. The mixture was concentrated to remove the solvent and water (30mL) was added and the resulting mixture was extracted with DCM (2 x 20 mL). The combined organic extracts were concentrated to give Compound **HA1-20** (700 mg, 96% yield) which was used in subsequent reactions without further purification. MS for $C_{13}H_9BrFNO_3$: *m/z* 327.9 (MH+).

Example 28: 5-Acetyl-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-3)

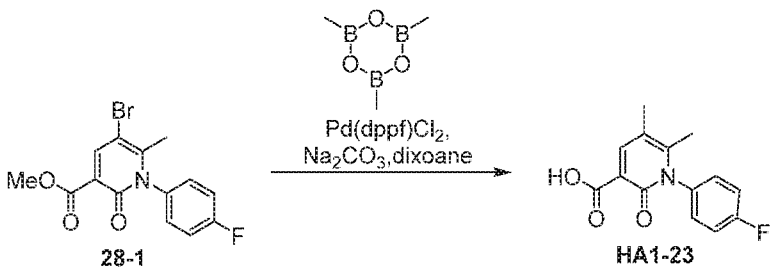


[01072] Step 1: Methyl 5-bromo-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (28-1): To a mixture of Compound **HA1-20** (11.0 g, 33.73 mmol, 1 eq) in MeOH (100 mL) was added thionyl chloride (20 g, 169 mmol, 12.2 mL, 5 eq) at 0 °C and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated to remove the solvent, diluted with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with aq saturated NaCl (30 mL), dried with anhyd Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by flash silica gel chromatography (0~30% EtOAc/petroleum ether) to give Compound **28-1** (11.0 g, 96% yield). MS for $C_{14}H_{11}BrFNO_3$: *m/z* 341.7 (MH+).

[01073] Step 2: Methyl 5-(1-ethoxyvinyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (28-2): To a solution of Compound **28-1** (200 mg, 0.59 mmol, 1 eq) and tributyl(1-ethoxyvinyl)stannane (0.84 g, 2.33 mmol, 0.78 mL, 3.96 eq) in dioxane (5 mL) was added DPPF (32.6 mg, 0.059 mmol, 0.1 eq), $Pd(dppf)Cl_2$ (43 mg, 0.059 mmol, 0.1 eq) and CuI (11.2 mg, 0.059 mmol, 0.1 eq). The reaction mixture was stirred at 100 °C for 12 h under an atmosphere of nitrogen. Aq saturated KF (20 mL) was added and the mixture was stirred at 25 °C for 1 h, then $NH_3.H_2O$ (5 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with aq saturated NaCl (10 mL), dried over Na_2SO_4 and concentrated Compound **28-2** (190 mg, 98% yield) which was used in subsequent reactions without further purification. MS for $C_{18}H_{18}FNO_4$: *m/z* 332.1 (MH+).

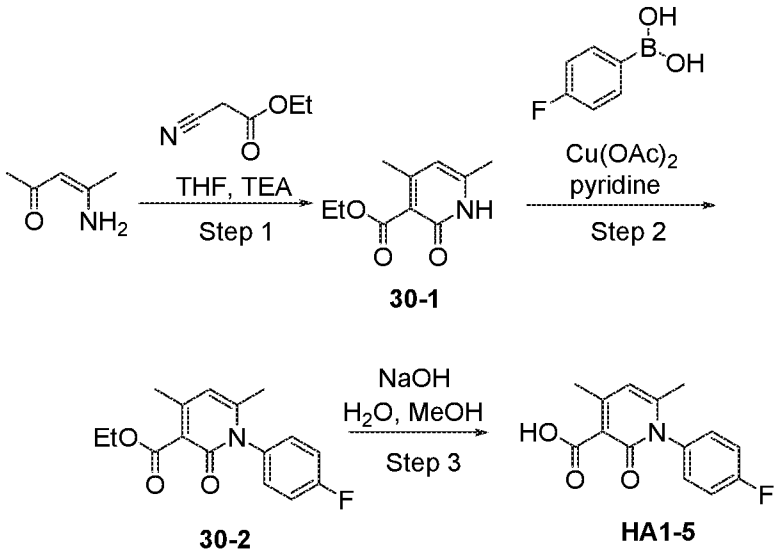
[01074] Step 3: 5-Acetyl-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-3): A mixture of Compound **28-2** (190 mg, 0.57 mmol, 1 eq) in aq HCl (2 M, 5 mL, 17 eq) was stirred at 25 °C for 2 h. The resulting mixture was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over anhyd Na_2SO_4 and concentrated to give Compound **HA1-3** (67 mg, 40% yield) which was used in subsequent reactions without further purification. MS for $C_{15}H_{12}FNO_4$: *m/z* 290.0 (MH+).

Example 29: 1-(4-Fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-23)



[01075] 1-(4-Fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-23): To a solution of 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.48 g, 5.9 mmol, 1.6 mL, 2 eq) and Compound **28-1** (1.0 g, 2.94 mmol, 1 *eq*) in dioxane (10 mL) and water (2 mL) was added Na_2CO_3 (623 mg, 5.9 mmol, 2 eq) and $Pd(dppf)Cl_2$ (108 mg, 0.15 mmol, 0.05 eq) under an atmosphere of nitrogen. The mixture was stirred at 120 °C for 3 h. The reaction mixture was concentrated to remove the solvent, diluted with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic extracts were washed with aq saturated NaCl (10 mL), dried with anhyd Na_2SO_4 and concentrated under vacuum. The resulting residue was purified flash silica gel chromatography (0~10% MeOH/DCM) to give Compound **HA1-23** (200 mg, 26% yield). MS for $C_{14}H_{12}FNO_3$: *m/z* 261.9 (MH+).

Example 30: 1-(4-Fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic (HA1-5)



[01076] Step 1: Ethyl 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate (30-1): (Z)-4-aminopent-3-en-2-one (5.0 g, 50 mmol, 1 eq) and ethyl 2-cyanoacetate (5.8 g, 51 mmol, 1.02 eq) were added to a stirring solution of THF (56 mL) and TEA (2.0 g, 20 mmol, 0.4 eq). After heating for 48 h, the reaction was cooled to ambient temperature and allowed to sit for 4 days. The resulting mixture was filtered, and the solids were washed with EtOAc to give Compound **30-1** (2.98 g, 30% yield). MS for $C_{10}H_{13}NO_3$: *m/z* = 196 (MH+).

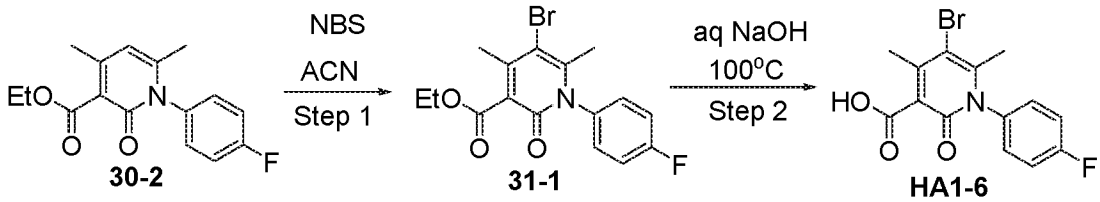
[01077] Step 2: Ethyl 1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate (30-2): Compound **30-1** (9.0 g, 46 mmol, 1 eq), diacetoxycopper hydrate (10 g, 50 mmol, 1.1 eq), (4-fluorophenyl)boronic acid (16 g, 110 mmol, 2.4 eq), 1,2-dichloroethane (15 mL) and pyridine (40 mL) were heated to 45 °C under an atmosphere of oxygen (1 atm). After overnight reaction the contents were cooled to ambient temperature, diluted with EtOAc and filtered through a short plug of silica gel. The crude product was concentrated onto Celite and purified by silica gel chromatography (220 g, 0% to 2% MeOH in DCM) to give Compound **30-2** (4.2 g, 31% yield). MS for $C_{16}H_{16}FNO_3$: *m/z* = 290 (MH+).

[01078] Step 3: 1-(4-Fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic (HA1-5): Compound **HA1-5** was made from Compound **30-2** using standard ester hydrolysis conditions such as those used in Step 3 of **Example 7**. MS for $C_{14}H_{12}FNO_3$: *m/z* 262 (MH+).

[01079] The following compound was made using the same method used to make Compound **HA1-5** in **Example 30:**

[01080] 1-(4-Fluoro-2-methylphenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-15): MS for $C_{15}H_{14}FNO_3$: *m/z* 276 (MH+).

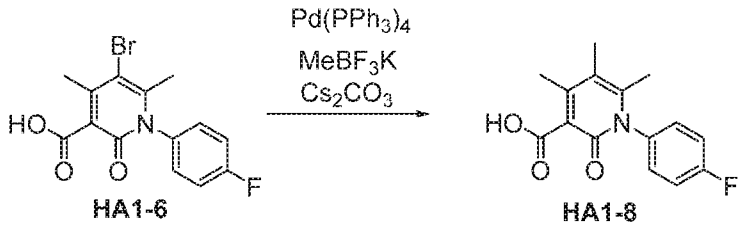
Example 31: 5-Bromo-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-6)



[01081] Step 1: Ethyl 5-bromo-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate (31-1): To a stirring solution of Compound **30-2** (1.0 g, 3.5 mmol, 1 eq) in ACN (12 mL) at room temperature was added NBS (1.0 g, 5.6 mmol, 1.6 eq) in a single portion. After several hours at room temperature, the reaction was quenched with the addition of aq saturated $Na_2S_2O_3$ (20 mL). The mixture was then diluted with water (80 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were dried with anhyd Na_2SO_4, concentrated and purified by silica gel chromatography (0% to 40% EtOAc in hexanes) to give Compound **31-1** (1.11 g, 87% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 – 7.33 (m, 4H), 4.25 (q, 2H), 2.25 (s, 3H), 2.13 (s, 3H), 1.29 – 1.14 (m, 3H); MS for $C_{16}H_{15}BrFNO_3$: *m/z* 370 (MH+).

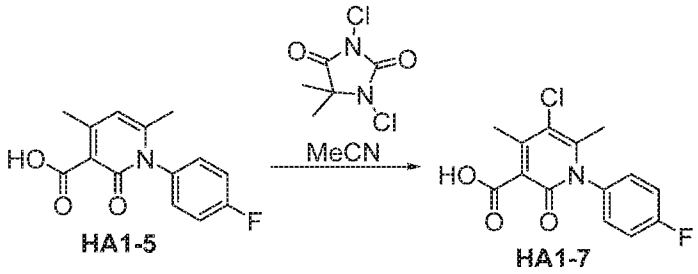
[01082] Step 2: 5-Bromo-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-6): Compound **HA1-6** was made from Compound **31-1** using standard ester hydrolysis conditions such as those used in Step 3 of **Example 7**. MS for $C_{14}H_{11}BrFNO_3$: *m/z* 340 (MH+).

Example 32: 1-(4-Fluorophenyl)-4,5,6-trimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid HA1-8)



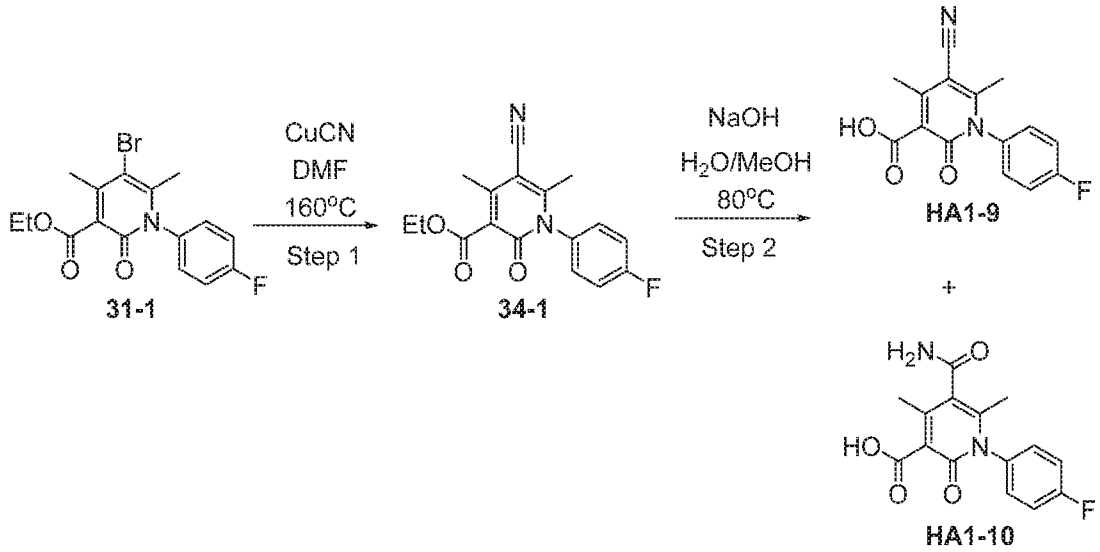
[01083] 1-(4-Fluorophenyl)-4,5,6-trimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-8): A mixture of Compound **HA1-6** (175 mg, 0.51 mmol, 1 eq), potassium methyltrifluoroborate (0.48 g, 3.9 mmol, 7.7 eq), Cs_2CO_3 (0.33 g, 1.0 mmol, 2 eq), tetrakis(triphenylphosphine) palladium(0) (110 mg, 0.095 mmol, 0.19 eq), DMF (0.50 mL), water (0.30 mL) and THF (1.0 mL) was heated to 80 °C under an inert atmosphere. After overnight reaction, the resulting reaction mixture was concentrated, diluted with EtOAc (10 mL) and extracted (2 x Veq) with dilute aq NaOH (pH ~12). The combined aqueous basic extracts were acidified with concentrated HCl (pH 2) and extracted with EtOAc (3 x Veq). The combined organic extracts were purified by prep HPLC (10% to 90% MeCN in water (+FA)) to give Compound **HA1-8** (30 mg, 22% yield). MS for $C_{15}H_{14}FNO_3$: *m/z* 276 (MH+).

Example 33: 5-Chloro-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-7)



[01084] 5-Chloro-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-7): To a solution of Compound **HA1-5** (98 mg, 0.38 mmol, 1 eq) in ACN (1.0 mL) was added a solution of 1,3-dichloro-5,5-dimethylhydantoin (100 mg, 0.5 mmol, 1.3 eq) in ACN (1.0 mL) over 5 min. After 2 h, the reaction was quenched by the addition of an equal volume of aq saturated $Na_2S_2O_5$. The resulting mixture was stirred for 5 min after which water (20 mL) was added and the resulting mixture was extracted with EtOAc (2 x Veq) and concentrated to give Compound **HA1-7** (78 mg, 68% yield). MS for $C_{14}H_{11}ClFNO_3$: *m/z* 296 (MH+).

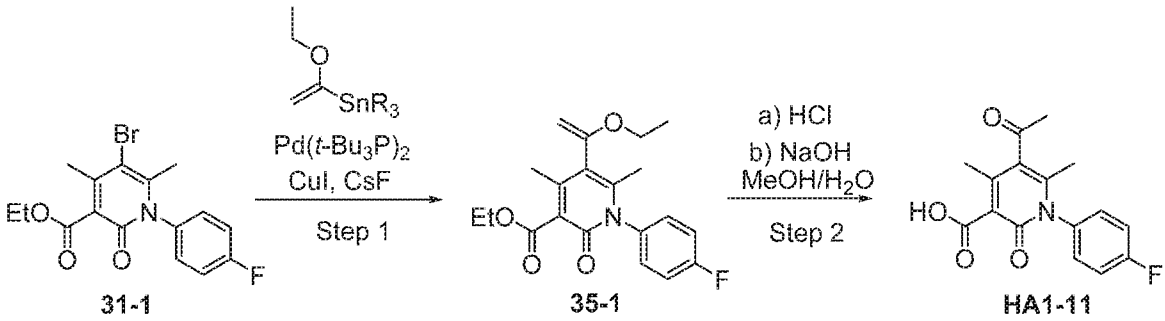
Example 34: 5-Cyano-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-9) and 5-Carbamoyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-10)



[01085] Step 1: Ethyl 5-cyano-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate (34-1): A mixture of Compound **31-1** (286 mg, 0.777 mmol, 1.0 eq), copper(I) cyanide (186 mg, 2.08 mmol, 2.7 eq) and DMF (1.0 mL) were heated to 160 °C for 3 h in a microwave reactor. The resulting mixture was subsequently diluted with water and extracted with EtOAc (3 x Veq). The combined organic extracts were concentrated and purified by silica gel chromatography (0% to 100% EtOAc in hexanes) to give Compound **34-1** (210 mg, 86.0% Yield). MS for $C_{17}H_{15}FN_2O_3$: *m/z* 315 (MH+).

[01086] Step 2: 5-Cyano-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-9) and 5-Carbamoyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-10): Compound **34-1** was subjected to standard ester hydrolysis conditions such as those used in Step 3 of **Example 7** to give 90 mg of a mixture of Compound **HA1-9** (MS for $C_{15}H_{11}FN_2O_3$: *m/z* 287 (MH+) and Compound **HA1-10** (MS for $C_{15}H_{13}FN_2O_4$: *m/z* 305 (MH+). The mixture of **HA1-9** and **HA1-10** was used as is in subsequent reactions without separation or further purification.

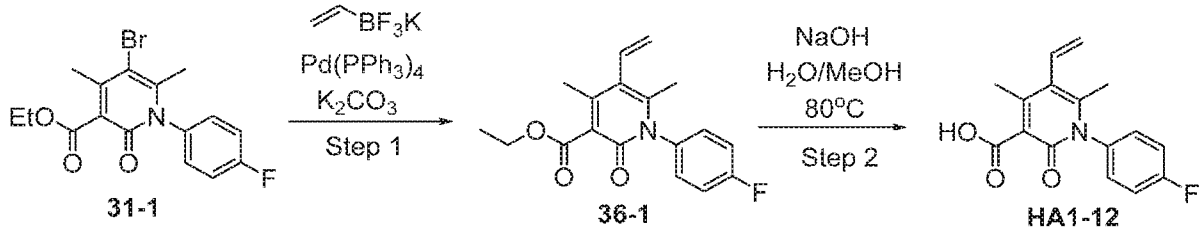
Example 35: 5-Acetyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-11)



[01087] Step 1: Ethyl 5-(1-ethoxyvinyl)-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate (35-1): A mixture of cesium fluoride (290 mg, 1.91 mmol, 2.4 eq), copper(I) iodide (15 mg, 0.079 mmol, 0.10 eq), bis(tri-*tert*-butylphosphine)palladium(0) (45 mg, 0.088 mmol, 0.11 eq), Compound **31-1** (290 mg, 0.788 mmol, 1.0 eq), tributyl(1-ethoxyvinyl)stannane (425 mg, 1.177 mmol, 1.5 eq) and DMF (2 mL) was stirred at 45 °C under an inert atmosphere of argon (1 atm). After overnight reaction, the reaction mixture was diluted with water and extracted with EtOAc (3 x Veq). The combined organic extracts were concentrated and purified by silica gel chromatography (0% to 50% EtOAc in hexanes) to give Compound **35-1** (100 mg, 35% Yield). MS for $C_{20}H_{22}FNO_4$: *m/z* 360.2 (MH+).

[01088] Step 2: 5-Acetyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-11): To a stirring solution Compound **35-1** (100 mg, 0.28 mmol, 1.0 eq) in MeOH (2.0 mL) was added HCl (50.0 mg, 37 mass%, 0.51 mmol, 1.8 eq) in water (2.0 mL). After stirring for several hours at ambient temperature an LC-MS indicated the Compound **35-1** had been consumed to produce the partially hydrolyzed intermediate. NaOH (260 mg, 6.50 mmol, 23 eq) was subsequently added and the reaction was heated to 80 °C for 2 h. The reaction mixture was then acidified (pH ~2) with conc HCl. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x Veq). The combined EtOAc extracts were concentrated and purified by prep HPLC (10% to 60% MeCN in water (FA)) to give Compound **HA1-11** (48 mg, 57% Yield). MS for $C_{16}H_{14}FNO_4$: *m/z* 304 (MH+).

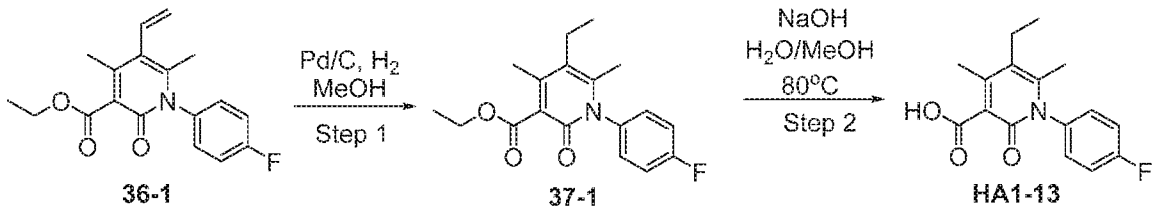
Example 36: 1-(4-Fluorophenyl)-4,6-dimethyl-2-oxo-5-vinyl-1,2-dihydropyridine-3-carboxylic acid (HA1-12)



[01089] Step 1: Ethyl 1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-5-vinyl-1,2-dihydropyridine-3-carboxylate (36-1): A mixture of Compound **31-1** (300 mg, 0.81 mmol, 1.0 eq), potassium vinyltrifluoroborate (300 mg, 2.2 mmol, 2.8 eq), tetrakis(triphenylphosphine)palladium(0) (90 mg, 0.078 mmol, 0.10 eq), K_2CO_3 (250 mg, 1.8 mmol, 2.2 eq), 1,4-dioxane (4.0 mL) and water (1.0 mL) was heated in a microwave reactor for 15 min at 120 °C. The resulting mixture was diluted with water and extracted with an equal volume of EtOAc. The organic extract was concentrated and purified by silica gel chromatography (0% to 50% EtOAc in hexanes) to give Compound **36-1**(0.26 g, 99% yield). MS for $C_{18}H_{18}FNO_3$: *m/z* 316 (MH+).

[01090] Step 2: 1-(4-Fluorophenyl)-4,6-dimethyl-2-oxo-5-vinyl-1,2-dihydropyridine-3-carboxylic acid (HA1-12): Compound **HA1-12** was made from Compound **36-1** using standard ester hydrolysis conditions such as those used in Step 3 of **Example 7**. MS for $C_{16}H_{14}FNO_3$: *m/z* 288 (MH+).

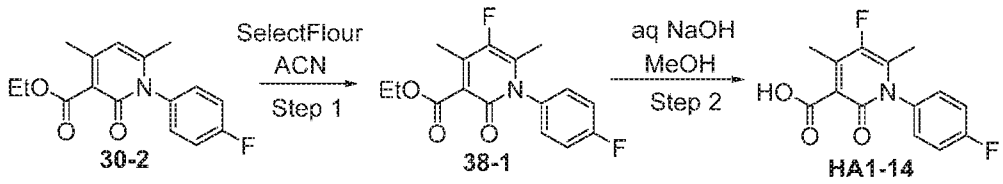
Example 37: 5-Ethyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-13)



[01091] Step 1: Ethyl 5-ethyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate (37-1): A mixture of Compound **36-1** (114 mg, 0.36 mmol, 1.0 eq), palladium on carbon (20 mg, 10% mass) and MeOH (1.0 mL) was stirred overnight under an atmosphere of hydrogen (1 atm). The reaction was then filtered through a pad of Celite and concentrated. The resulting residue was purified by prep HPLC (10% to 60% ACN in water (+FA)) to give Compound **37-1** (50 mg, 40% yield); MS for $C_{18}H_{20}FNO_3$: *m/z* 318 (MH+).

[01092] Step 2: 5-Ethyl-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-13): Compound **HA1-13** was made from Compound **37-1** using standard ester hydrolysis conditions such as those used in Step 3 of **Example 7**. MS for $C_{16}H_{16}FNO_3$: *m/z* 290 (MH+).

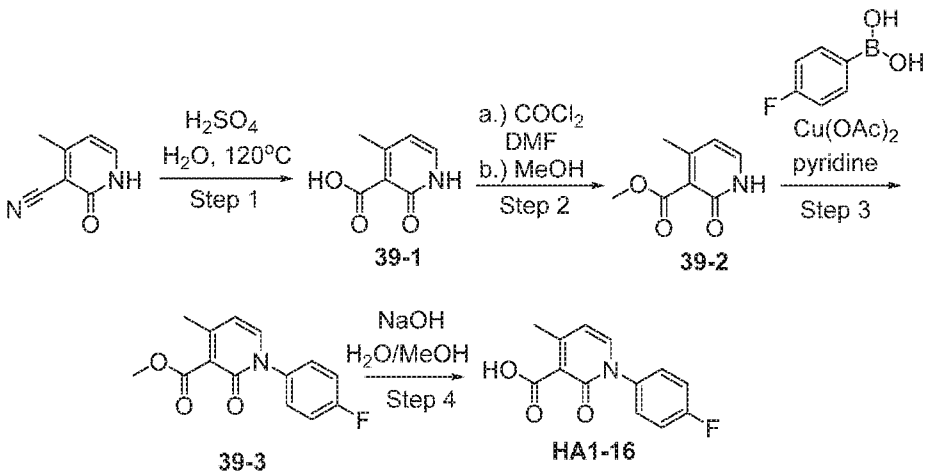
Example 38: 5-Fluoro-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-14)



[01093] Step 1: Ethyl 5-fluoro-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate (38-1): To a stirring solution of Compound **30-2** (500 mg, 1.7 mmol, 1.2 eq) in ACN (6 mL) was added Selectfluor (510 mg, 1.4 mmol, 1.0 eq). After 4 h, the crude reaction mixture was directly purified by silica gel chromatography (0% to 60% EtOAc in hexanes) to give Compound **38-1** (160 mg, 34% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 – 7.32 (m, 4H), 4.25 (q, 2H), 2.17 (d, 3H), 1.89 (d, 3H), 1.25 (t, 3H); MS for $C_{16}H_{15}F_2NO_3$: *m/z* 308 (MH+).

[01094] Step 2: 5-Fluoro-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-14): Compound **HA1-14** was made from Compound **38-1** using standard ester hydrolysis conditions such as those used in Step 3 of **Example 7**. MS for $C_{14}H_{11}F_2NO_3$: *m/z* 280 (MH+).

Example 39: 1-(4-Fluorophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-16)



[01095] Step 1: 4-Methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (39-1): A mixture of 4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1.2 g, 8.9 mmol, 1 eq), water (3.4 mL) and concentrated sulfuric acid (1.9 mL) was heated to 120 °C for 4 h. The reaction was subsequently cooled, basified with 2 M NaOH (pH ~10) and washed with EtOAc (2 x Veq). The aqueous layer was acidified with 6 M HCl (pH ~ 2), diluted with aq saturated NaCl and extracted with EtOAc (3 x Veq). The combined EtOAc extracts were dried over anhyd Na_2SO_4 and concentrated to give Compound **39-1** (0.36 g, 26% yield). MS for $C_7H_7NO_3$: *m/z* 154 (MH+).

[01096] Step 2: Methyl 4-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (39-2): To a mixture of Compound **39-1** (0.36 g, 2.35 mmol, 1 eq), DCM (8 mL) and DMF (0.10 mL) under an atmosphere of nitrogen was added oxalyl chloride (0.55 mL, 6.4 mmol, 2.7 eq). After stirring for 4 h at ambient temperature, anhyd MeOH (1.0 mL) was added to the reaction in a dropwise fashion. One hour after the addition of MeOH, the contents were concentrated and purified by silica gel chromatography (0 to 100%

EtOAc in hexanes followed by 0 to 20% MeOH in EtOAc) to give Compound **39-2**(0.28 g, 71% yield). MS for $C_8H_9NO_3$: *m/z* 168 (MH+).

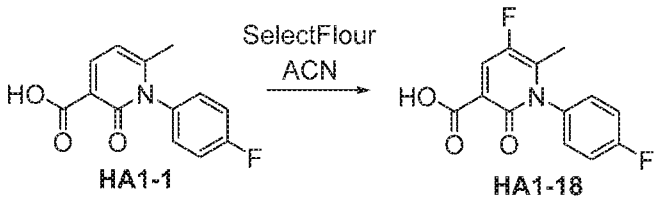
[01097] Step 3: Methyl 1-(4-fluorophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (39-3): Compound **39-3** was made from Compound **39-2** in the same manner Compound **30-2** was made from Compound **30-1** in **Example 30**. MS for $C_{14}H_{12}FNO_3$: *m/z* 262 (MH+).

[01098] Step 4: 1-(4-Fluorophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-16): Compound **HA1-16** was made from Compound **39-3** using standard ester hydrolysis conditions such as those used in Step 3 of **Example 7**. MS for $C_{13}H_{10}FNO_3$: *m/z* 248 (MH+).

[01099] The following compound was made using the same method used to make Compound **HA1-16** in **Example 39**:

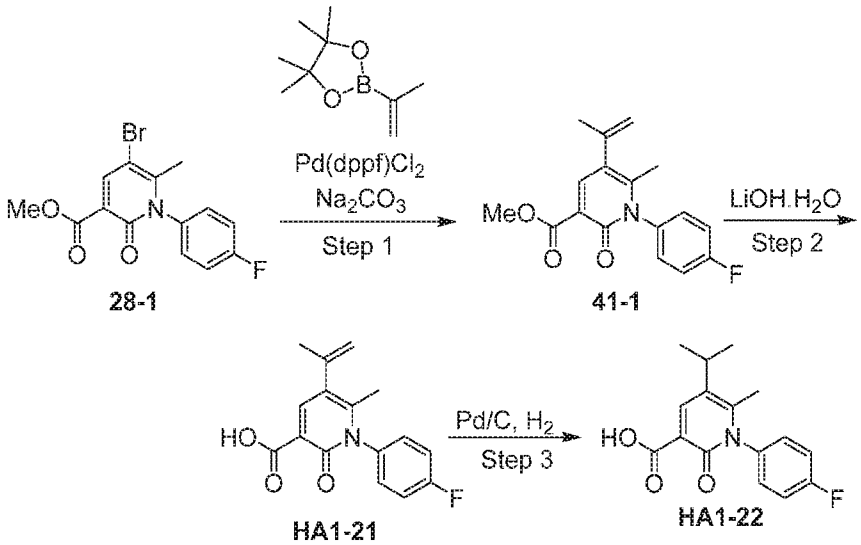
[01100] 1-(4-Fluoro-2-methylphenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-17 MS for $C_{14}H_{12}FNO_3$: *m/z* 262 (MH+).

Example 40: 5-Fluoro-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-18)



[01101] 5-Fluoro-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-18): Compound **HA1-18** was made from Compound **HA1-1** by the same method used to convert Compound **30-2** to Compound **38-1** in Step 1 of **Example 38**. MS for $C_{13}H_9F_2NO_3$: m/z 266 (MH+).

Example 41: 1-(4-Fluorophenyl)-6-methyl-2-oxo-5-(prop-1-en-2-yl)-1,2-dihydropyridine-3-carboxylic acid (HA1-21) and 1-(4-Fluorophenyl)-5-isopropyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-22)



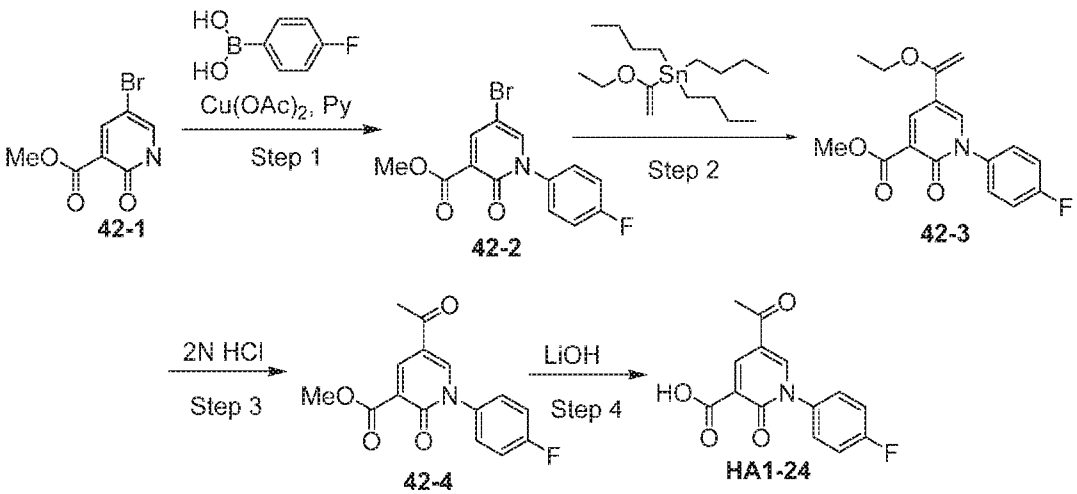
[01102] Step 1: Methyl 1-(4-fluorophenyl)-6-methyl-2-oxo-5-(prop-1-en-2-yl)-1,2-dihydropyridine-3-carboxylate (41-1): To a solution of Compound **28-1** (1.0 g, 2.9 mmol, 1 eq) and 2-

isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (94.0 mg, 2.9 mmol, 1 eq) in dioxane (10 mL) and water (2 mL) was added Na_2CO_3 (935 mg, 8.8 mmol, 3 eq) and $Pd(dppf)Cl_2$ (215 mg, 0.29 mmol, 0.1 eq) under an atmosphere of nitrogen. The mixture was stirred at 120 °C for 2 h under microwave irradiation. Water (30 mL) was added and the reaction mixture was extracted with DCM (3 x 30 mL). The combined organic extracts were washed with aq saturated NaCl (10 mL) concentrated under vacuum to give Compound **41-1** (320 mg, 36% yield). MS for $C_{17}H_{16}FNO_3$: *m/z* 301.9 (MH+).

[01103] Step 2: 1-(4-Fluorophenyl)-6-methyl-2-oxo-5-(prop-1-en-2-yl)-1,2-dihydropyridine-3-carboxylic acid (HA1-21): A mixture of Compound **41-1** (250 mg, 0.83 mmol, 1 eq) and $LiOH.H_2O$ (70 mg, 1.7 mmol, 2 eq) in THF (5 mL) and water (2 mL) was stirred at 50 °C for 3 h. The reaction mixture was acidified with aq 2 M HCl solution to pH ~6, diluted with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic extracts were dried over anhyd Na_2SO_4 and concentrated to give Compound **H1-21** (200 mg, 84% yield). MS for $C_{16}H_{14}FNO_3$: *m/z* 288.1 (MH+).

[01104] 1-(4-Fluorophenyl)-5-isopropyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-22): To a solution of Compound **HA1-21** (150 mg, 0.52 mmol, 1 eq) in MeOH (5 mL) was added 5% Pd/C (10 mg, 0.052 mmol, 0.1 eq) under an atmosphere of nitrogen. The resulting suspension was degassed under vacuum and purged with hydrogen gas several times. The mixture was then stirred under an atmosphere of hydrogen (15 psi) at 25 °C for 12 h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum to give crude Compound **HA1-22** (100 mg, 66% yield) which was used in subsequent reactions without further purification. MS for $C_{16}H_{16}FNO_3$: *m/z* 289.9 (MH+).

Example 42: 5-Acetyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-24)



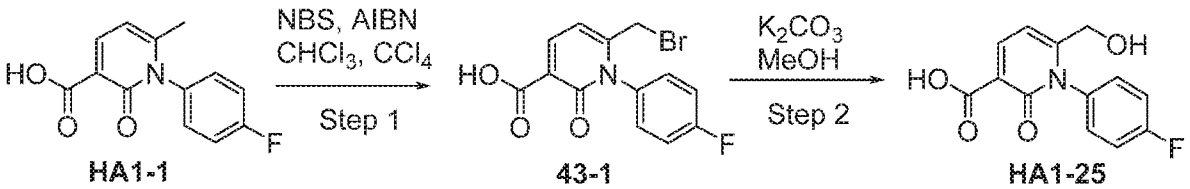
[01105] Step 1: Methyl 5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (42-2): Compound **42-2** was made from Compound **42-1** in the same manner Compound **30-2** was made from Compound **30-1** in **Example 30**. MS for $C_{13}H_9BrFNO_3$: *m/z* 327.8 (MH+).

[01106] Step 2: Methyl 5-(1-ethoxyvinyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (42-3): Compound **42-3** was made from Compound **42-2** in the same manner Compound **28-2** was made from Compound **28-1** in **Example 28**. MS for $C_{17}H_{16}FNO_4$: *m/z* 317.9 (MH+).

[01107] Step 3: Methyl 5-acetyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (42-4): Compound **42-4** was made from Compound **42-3** in the same manner Compound **HA1-3** was made from Compound **28-2** in **Example 28**. MS for $C_{15}H_{12}FNO_4$: *m/z* 289.9 (MH+).

[01108] Step 4: 5-Acetyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-24): Compound **HA1-24** was made from Compound **42-4** in the same manner Compound **HA1-21** was made from Compound **41-1** in **Example 41**. MS for $C_{14}H_{10}FNO_4$: *m/z* 275.9 (MH+).

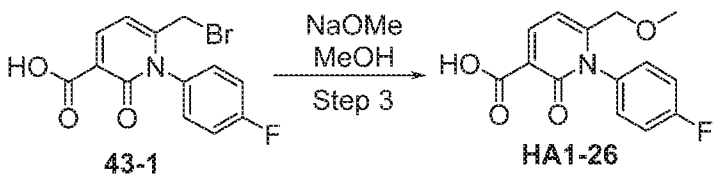
Example 43: 1-(4-Fluorophenyl)-6-(hydroxymethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-25)



[01109] Step 1: 6-(Bromomethyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (43-1): A 50-mL round bottom flask was charged with NBS (441 mg, 2.5 mmol, 1.2 eq), AIBN (104 mg, 0.6 mmol, 0.3 eq), $CHCl_3$ (5 mL) and CCl_4 (15 mL). Compound **HA1-1** (500 mg, 2.0 mmol, 1.0 eq) was added in bulk to the stirring reaction which was sealed with a rubber septum and irradiated with a high wattage lamp overnight. The reaction was diluted with DCM and washed with water. The organic phase was extracted with aq 1 N Na_2CO_3. The aqueous layer was then acidified with 6 N HCl and extracted twice with DCM. The combined organic extracts were washed with aq saturated NaCl, dried over Na_2SO_4 and concentrated to give crude Compound **43-1** which was carried forward without further purification. MS for $C_{13}H_9BrFNO_3$: *m/z* 326 (MH+).

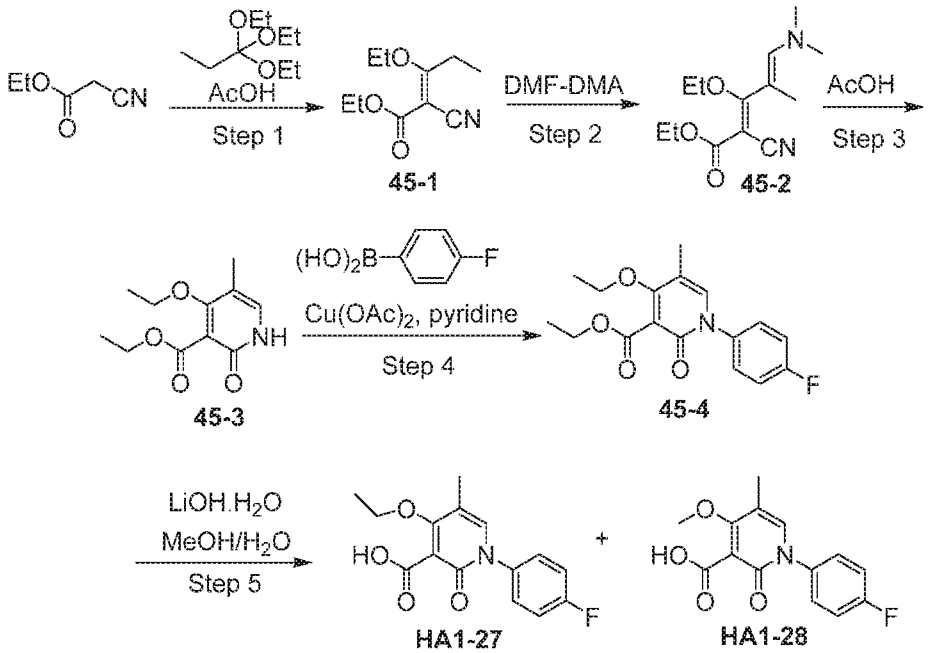
[01110] Step 2: 1-(4-Fluorophenyl)-6-(hydroxymethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-25): A 20-mL scintillation vial bearing crude Compound **43-1** (198 mg, 0.5 mmol) was charged with K_2CO_3 (72.2 mg, 0.52 mmol,1.1 eq) and a Teflon stir bar. MeOH (5 mL) was added and the reaction was stirred at room temperature overnight. The reaction was then heated to 50 °C and stirred for an additional 18 h. The reaction was reduced under vacuum and the resulting residue partitioned between DCM and water. The phases were separated, and the aqueous layer was further basified with 1 N Na_2CO_3 and washed with DCM. The aqueous layer was then carefully acidified with 6 N HCl and extracted with DCM and 15% iPrOH in EtOAc. The organic layers were dried over $Na_2SO_4$and concentrated. The resulting residue was purified by prep HPLC (10-90% MeCN in H_2O (0.1% FA) to give Compound **HA1-25** (9.4 mg, 7% yield over 2-steps): MS for $C_{13}H_{10}FNO_4$: *m/z* 264 (MH+).

Example 44: 1-(4-Fluorophenyl)-6-(methoxymethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-26)



[01111] 1-(4-Fluorophenyl)-6-(methoxymethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-26): A 10 mL round bottom flask was heat dried under vacuum and charged with a Teflon stir bar, sodium methoxide (80 mg, 1.5 mmol, 3 eq) and MeOH (3 mL). Compound **43-1** (155 mg, 0.5 mmol, 1.0 eq) was added in bulk and the resulting mixture stirred at room temperature for 10 min until a precipitate formed. The solids were filtered off and the filtrate was concentrated and was dissolved in water and washed with EtOAc. The aqueous layer was acidified to pH~4 and extracted twice with EtOAc. The combined organic layers were washed with aq saturated NaCl, dried over Na_2SO_4 and concentrated. The resulting residue was purified by prep HPLC (15 - 75% MeCN in H_2O (0.1% FA) to give Compound **HA1-26** (29 mg). MS for $C_{14}H_{12}FNO_4$: *m/z* 278 (MH+).

Example 45: 4-Ethoxy-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-27) and 1-(4-Fluorophenyl)-4-methoxy-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-28)



[01112] Step 1: Ethyl (Z)-2-cyano-3-ethoxypent-2-enoate (45-1): To a solution of ethyl 2-cyanoacetate (5 g, 44 mmol, 4.7 mL, 1 eq) in AcOH (1.3 g, 22 mmol, 1.3 mL, 0.5 eq) was added 1,1,1-triethoxypropane (15.6 g, 88 mmol, 17.6 mL, 2 eq). The colorless solution was stirred at 130 °C for 20 hr. The reaction mixture was concentrated under reduced pressure to give Compound **45-1** (8.7 g, 100% yield) which was used in subsequent reactions without further purification. MS for $C_{10}H_{15}NO_3$: *m/z* 198.0 (MH+).

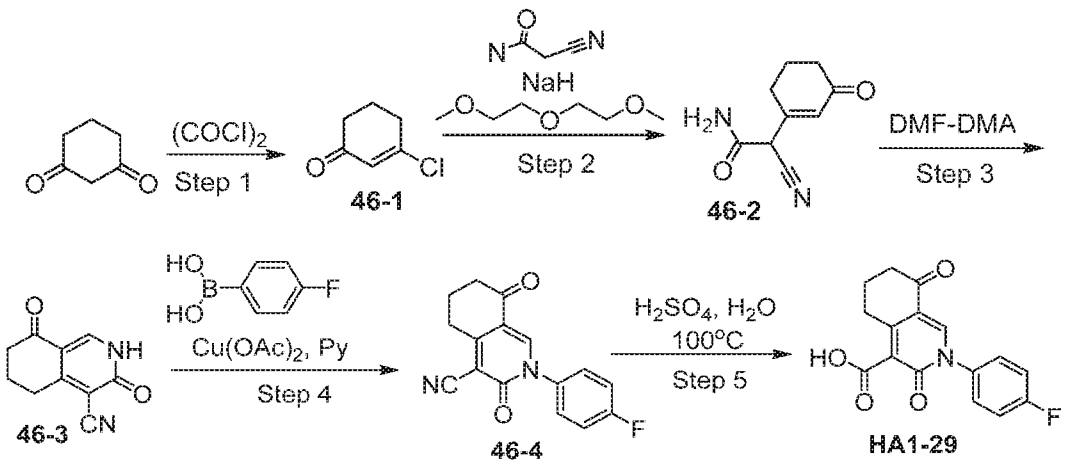
[01113] Step 2: Ethyl (2Z,4E)-2-cyano-5-(dimethylamino)-3-ethoxy-4-methylpenta-2,4-dienoate (45-2): A solution of Compound **45-1** (8.72 g, 44.2 mmol, 1 eq) in DMF-DMA (6.85 g, 57.5 mmol, 7.6 mL, 1.3 eq) was stirred at 70 °C for 16 h. The reaction mixture was concentrated to give Compound **45-2** (11 g, 99% yield) which was used in subsequent reactions without further purification. MS for $C_{13}H_{20}N_2O_3$: *m/z* 253.0 (MH+).

[01114] Step 3: Ethyl 4-ethoxy-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (45-3): A mixture of Compound **45-2** (11 g, 44 mmol, 1 eq) in AcOH (50 mL) was stirred at 130 °C for 16 h. The reaction mixture diluted with water (100 mL) and aq saturated $NaHCO_3$ was added to pH = 8. The resulting aqueous mixture was extracted with EtOAc (2 x 80 mL). The combined organic extracts were concentrated and the resulting residue was purified by silica gel column chromatography (petroleum ether:EtOAc = 3:1 to 1:1 to DCM:MeOH) followed by further purification by silica gel chromatography DCM:MeOH = 1:0 - 20:1) to give Compound **45-3** (2 g, 41% purity). MS for $C_{11}H_{15}NO_4$: *m/z* 226.0 (MH+).

[01115] Step 4: Ethyl 4-ethoxy-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (45-4): Compound **45-4** was made from Compound **45-3** in the same manner Compound **30-2** was made from Compound **30-1** in **Example 30**. MS for $C_{17}H_{18}FNO_4$: *m/z* 320.1 (MH+).

[01116] Step 5: 4-Ethoxy-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-27) and 1-(4-Fluorophenyl)-4-methoxy-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (HA1-28): To a solution of Compound **45-4** (130 mg, 0.41 mmol, 1 eq) in MeOH (5 mL) and water (1 mL) was added $LiOH.H_2O$ (137 mg, 3.3 mmol, 8 eq). The colorless solution was stirred at 20 °C for 15 h. The reaction residue was concentrated under reduced pressure to remove MeOH. The resulting residue was diluted with water (20 mL) and washed with EtOAc (2 x 50 mL). The aqueous layer was acidified with 1 N HCl to pH = 2 and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over anhyd Na_2SO_4 and concentrated to give a mixture of Compound **HA1-27** and **HA1-28** (60 mg) which was used in subsequent reactions without further purification or separation. Compound **HA1-27**: MS for $C_{15}H_{14}FNO_4$: *m/z* 291.9 (MH+). Compound **HA1-28**: MS for $C_{14}H_{12}FNO_4$: *m/z* 277.9 (MH+).

Example 46: 2-(4-Fluorophenyl)-3,8-dioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxylic acid (HA1-29)



[01117] Step 1: 3-Chlorocyclohex-2-en-1-one (46-1): To a solution of cyclohexane-1,3-dione (5 g, 44.6 mmol, 1 eq) in ACN (100 mL) was added oxalyl dichloride (8.49 g, 66.9 mmol, 5.9 mL, 1.5 eq) slowly at 25 °C and the resulting reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated to give Compound **46-1** (5.6 g, 96% yield) which was used in next step directly without

further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (t, 1H), 2.69 (dt, 2H), 2.44-2.36 (m, 2H), 2.14-2.04 (m, 2H).

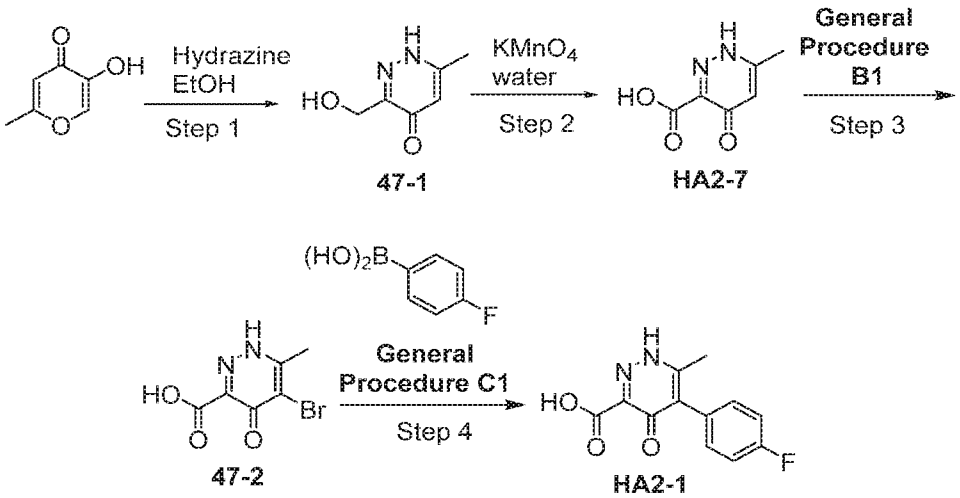
[01118] Step 2: 2-Cyano-2-(3-oxocyclohex-1-en-1-yl)acetamide (46-2): To a solution of 2-cyanoacetamide (3.61 g, 42.9 mmol, 1.0 eq) in diethylene glycol dimethyl ether (100 mL) was added 60% NaH (2.06 g, 51.5 mmol, 1.2 eq) slowly at 0 °C and then Compound **46-1** (5.6 g, 42.9 mmol, 1.0 eq) was added slowly. The reaction mixture was stirred at 25 °C for 15 h. The reaction was diluted with water (300 mL) and extracted with EtOAc (4 x 200 mL). The combined organic extracts were washed with aq saturated NaCl (2 x 500 mL) and dried over anhyd Na_2SO_4. The organic layer was concentrated to about 50 mL, cooled to room temperature and then filtered. The resulting solid was collected and dried in vacuo to give Compound **46-2** (3.1 g, 40% yield). MS for $C_9H_{10}N_2O_2$: *m/z* 178.8 (MH+).

[01119] Step 3: 3,8-Dioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (46-3): To a solution of Compound **46-2** (2.5 g, 14 mmol, 1 eq) in DMF (7 mL) was added DMF-DMA (2.01 g, 17 mmol, 2.24 mL, 1.2 eq) slowly. The reaction mixture was stirred at 25 °C for 60 h. The reaction mixture was diluted with aq 2.5% NaOH (50 mL) and washed DCM (2 x 30 mL2). The aqueous layer was acidified by conc HCl to pH=1. The resulting precipitate was filtered, and the resulting solid was triturated with a mixture of MeOH/water (2/1, 30 mL) and then filtered. The solid was collected and dried in vacuo to give Compound **46-3** (960 mg, 36% yield). MS for $C_{10}H_8N_2O_2$: *m/z* 188.9 (MH+).

[01120] Step 4: 2-(4-Fluorophenyl)-3,8-dioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (46-4): Compound **46-4** was made from Compound **46-3** in the same manner Compound **30-2** was made from Compound **30-1** in **Example 30**. MS for $C_{16}H_{11}FN_2O_2$: *m/z* 282.9 (MH+).

[01121] Step 5: 2-(4-Fluorophenyl)-3,8-dioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxylic acid (HA1-29): To a solution of Compound **46-4** (160 mg, 0.57 mmol, 1 eq) in water (1 mL) was added H_2SO_4 (1 mL) slowly. The reaction mixture was stirred at 100 °C for 8 hr. The reaction mixture was poured into ice water (50 mL) and then extracted with DCM (2 x 20 mL). The combined DCM extracts were extracted with aq 2 N NaOH (2 x 20 mL). The combined aqueous extracts were acidified with conc HCl to pH=1, and then extracted with DCM (2 x 30 mL). The combined organic extracts were washed with aq saturated NaCl (30 mL), dried over anhyd Na_2SO_4 and concentrated to give Compound **HA1-29** (65 mg, 38% yield). MS for $C_{16}H_{12}FNO_4$: *m/z* 301.8 (MH+).

Example 47: 5-(4-Fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (HA1-2) and 6-Methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (HA2-7)



[01122] Step 1: 3-(Hydroxymethyl)-6-methylpyridazin-4(1H)-one (47-1): To a solution of 5-hydroxy-2-methyl-4H-pyran-4-one (2.5 g, 19.8 mmol) in EtOH (80 mL) was added hydrazine (4 mL, 60% in water). The resulting mixture was heated to reflux for 90 min. The reaction mixture was allowed to cool to room temperature. The resulting precipitate was filtered and allowed to dry in the open air to afford Compound **47-1** (1.4 g, 51% yield). MS for $C_6H_8N_2O_2$: *m/z* 141 (MH+).

[01123] Step 2: 6-Methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (HA2-7): To a solution of Compound **47-1** (1.4 g, 10 mmol) in water (56 mL) at 75 °C was added $KMnO_4$ (17.2 mmol, 1.8 eq) in water (84 mL) dropwise over 20 min. The mixture was allowed to cool to room temperature and filtered through a Celite pad. The solvent was partially removed, and the resulting mixture was acidified using 6 M HCl to pH 2. The solution was chilled to 0 °C along with scraping the side of the flask to facilitate precipitation. The resulting solid was filtered and allowed to dry in the open air to afford Compound **HA2-7** (912 mg, 59% yield). MS for $C_6H_6N_2O_3$: *m/z* 155 (MH+).

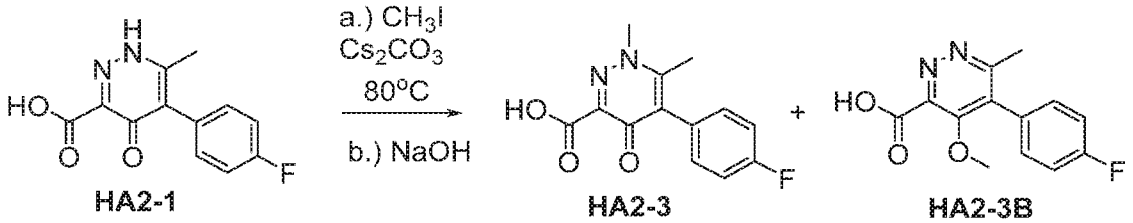
[01124] Step 3: 5-Bromo-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (47-2): Compound **47-2** was synthesized from Compound **HA2-7** using **General Procedure B1**. MS for $C_6H_5BrN_2O_3$: *m/z* 233 (MH+).

[01125] Step 4: 5-(4-Fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (HA1-2): Compound **HA1-2** was synthesized from Compound **47-2** using **General Procedure C1**. MS for $C_{12}H_9FN_2O_3$: *m/z* 249 (MH+).

[01126] The following compound was made using the same method as that used to make Compound **HA2-1** in **Example 47**:

[01127] 5-(4-Fluoro-2-methylphenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (HA2-2): MS for $C_{13}H_{11}FN_2O_3$: *m/z* 263 (MH+).

Example 48: 5-(4-Fluorophenyl)-1,6-dimethyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (HA2-3) and 5-(4-Fluorophenyl)-4-methoxy-6-methylpyridazine-3-carboxylic acid (HA2-3B)



[01128] 5-(4-Fluorophenyl)-1,6-dimethyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (HA2-3) and 5-(4-Fluorophenyl)-4-methoxy-6-methylpyridazine-3-carboxylic acid (HA2-3B): To a solution of Compound **HA2-1** (3 g, 12.1 mmol) in DMF (20 mL) and water (20 mL) was added cesium carbonate (36.3 mmol, 3 eq) and iodomethane (36.3 mmol, 3 eq). The resulting mixture was heated to 80 °C for 3 h. To this reaction mixture was added aq 1 N NaOH and stirring was continued at 80 °C overnight. The reaction mixture was allowed to cool to room temperature. Water was added and the resulting mixture was washed with EtOAc (3x). The aqueous phase was acidified using aq 6 M HCl to pH 2. The resulting solid was filtered and allowed to dry in the open air to give a 1:2 mixture of Compound **HA2-3**:Compound **HA2-3B** (1.85 g). MS for $C_{13}H_{11}FN_2O_3$: *m/z* 263 (MH+). This mixture of Compound **HA2-3** and **HA2-3B** was used in subsequent reactions without separation of the regioisomers.

[01129] The following compounds were made using the same process that was used to make the mixture of Compounds **HA2-3** and **HA2-3B** in **Example 48**. The resulting mixture of regioisomers can either be separated at this stage or used as mixtures in subsequent reactions.

[01130] 1-Ethyl-5-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (HA2-4A): MS for $C_{14}H_{13}FN_2O_3$: *m/z* 277 (MH+).

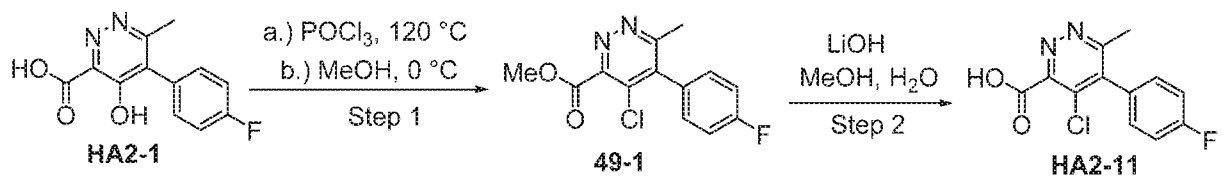
[01131] 4-Ethoxy-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxylic acid (HA2-4B): MS for $C_{14}H_{13}FN_2O_3$: *m/z* 277(MH+).

[01132] 5-(4-Fluorophenyl)-1-isopropyl-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (HA2-5): MS for $C_{15}H_{15}FN_2O_3$: *m/z* 291.0 (MH+).

[01133] 5-(4-Fluoro-2-methylphenyl)-1,6-dimethyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (HA2-6A): MS for $C_{14}H_{13}FN_2O_3$: *m/z* 277 (MH+).

[01134] 5-(4-Fluoro-2-methylphenyl)-4-methoxy-6-methylpyridazine-3-carboxylic acid (HA2-6B): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 – 7.12 (m, 3H), 4.68 (s, 3H), 2.22 (s, 3H), 2.07 (s, 3H); MS for $C_{14}H_{13}FN_2O_3$: *m/z* 277 (MH+).

Example 49: 4-Chloro-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxylic acid (HA2-11)

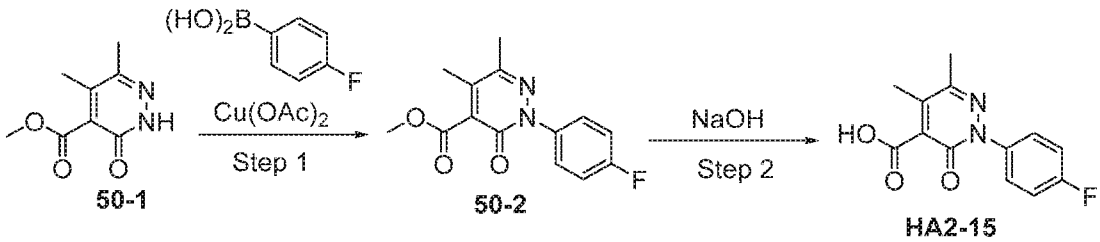


[01135] Step 1: Methyl 4-chloro-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxylate (49-1): To a 5 mL microwave vial equipped with a magnetic stir bar was added Compound **HA2-1** (687 mg, 2.8

mmol) and phosphoryl chloride (3.5 mL, 37 mmol, 13.5 eq). The vial was purged with nitrogen, sealed and placed in the microwave reactor at 120 °C for 30 min. The resulting dark brown solution was slowly added to MeOH (40 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 30 min. The reaction was then concentrated under reduced pressure and purified by silica gel column chromatography (0 - 50% EtOAc in hexanes) to give Compound **49-1** (405 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 4H), 4.09 (s, 3H), 2.58 (s, 3H). MS for $C_{13}H_{10}ClFN_2O_2$: *m/z* 281.0 (MH+).

[01136] Step 2: 4-Chloro-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxylic acid (HA2-11): To a 20-mLvial equipped with a magnetic stir bar and a pressure relief septum was added a solution of Compound **49-1** (256 mg, 0.912 mmol) in MeOH (5 mL) and water (1 mL). $LiOH{\cdot}H_2O$ (60 mg, 1.4 mmol, 1.6 eq) was added in a single portion and the reaction was allowed to proceed at room temperature for 30 min. The resulting solution was adjusted to pH = 3 with aq 6 M HCl and concentrated to near dryness. The resulting mixture was diluted with water (10 mL). The resulting suspension was filtered to give Compound **HA2-11** (223 mg, 92% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 7.63 – 7.25 (m, 4H), 2.44 (s, 3H). MS for $C_{12}H_8ClFN_2O_2$: *m/z* 267.0 (MH+).

Example 50: 2-(4-Fluorophenyl)-5,6-dimethyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (HA2-15)



[01137] Step 1: Methyl 2-(4-fluorophenyl)-5,6-dimethyl-3-oxo-2,3-dihydropyridazine-4-carboxylate (50-2): To a solution of Compound **50-1** (100 mg, 0.55 mmol) in DMA (2 mL) was added (4-fluorophenyl)boronic acid (0.66 mmol, 1.2 eq) and copper (II) acetate (0.66 mmol, 1.2 eq). Oxygen gas was bubbled into the resulting mixture for 5 min and then the mixture was heated to 90 °C under an atmosphere of oxygen for 30 min. The reaction mixture was allowed to cool to room temperature and filtered through a Celite pad. The solvent was removed under reduced pressure and resulting crude residue was purified by flash silica gel chromatography (0-100% EtOAc/hexanes) to give Compound **50-2** (50 mg, 33% yield). MS for $C_{14}H_{13}FN_2O_3$: *m/z* 277 (MH+).

[01138] Step 2: 2-(4-Fluorophenyl)-5,6-dimethyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (HA2-15): Compound **50-2** was converted to Compound **HA2-15** using the ester hydrolysis procedure used in Step 3 of **General Procedure A**. MS for $C_{13}H_{11}FN_2O_3$: *m/z* 263 (MH+).

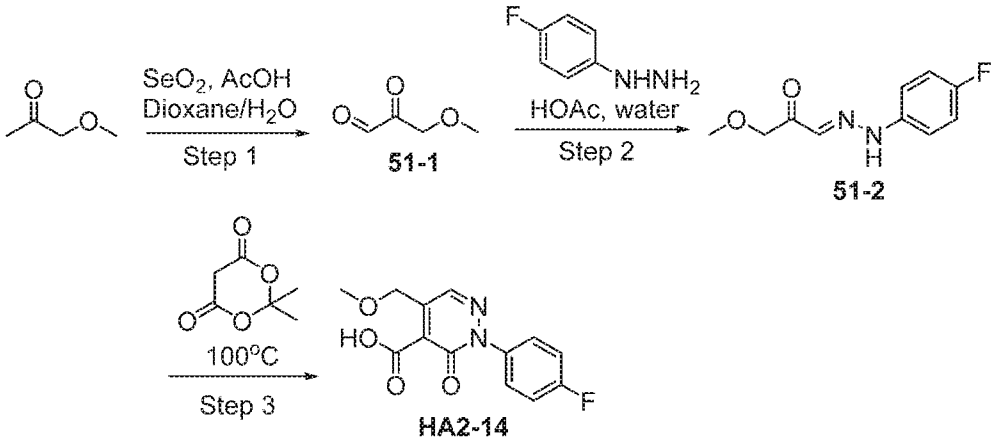
[01139] The following compounds were made using similar techniques to those used to make Compound **HA2-15** in **Example 50**:

[01140] 2-(4-Fluorophenyl)-6-methyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (HA2-12): MS for $C_{12}H_9FN_2O_3$: *m/z* 249(MH+).

[01141] 2-(4-Fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (HA2-16): MS for $C_{11}H_7FN_2O_3$: *m/z* 234.8 (MH+).

[01142] 2-(4-Fluoro-2-methylphenyl)-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (HA2-13): MS for $C_{12}H_9FN_2O_3$: *m/z* 249 (MH+).

Example 51: 2-(4-Fluorophenyl)-5-(methoxymethyl)-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (HA2-14)

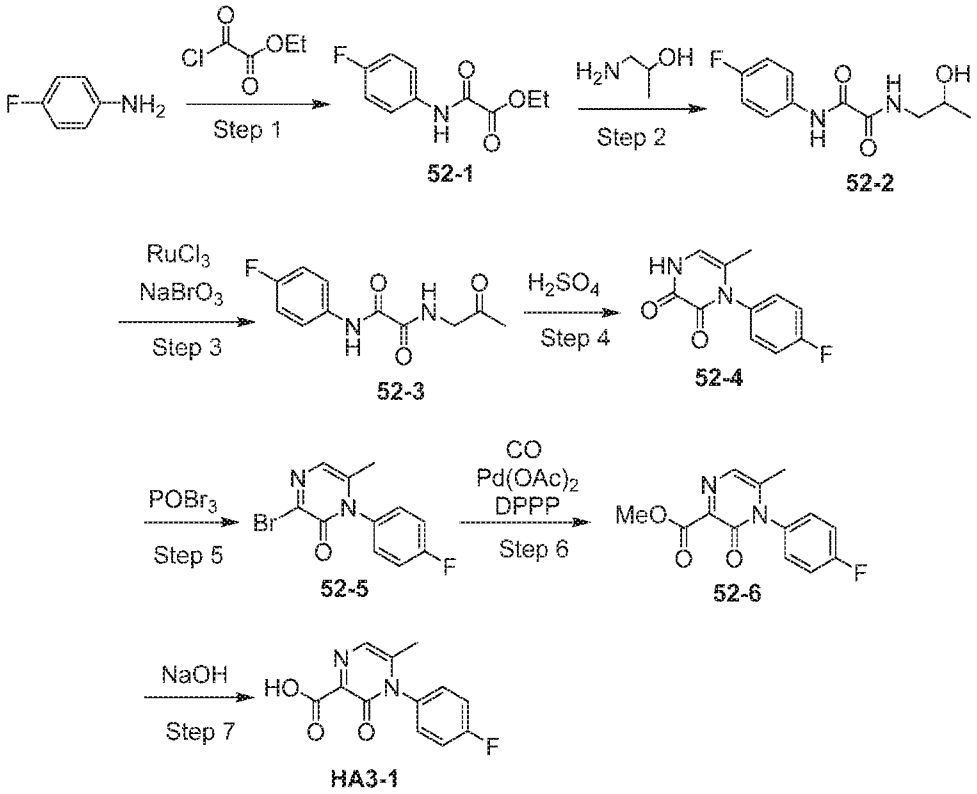


[01143] Step 1: 3-Methoxy-2-oxopropanal (51-1): To a solution of selenium dioxide (2.80 g, 25.2 mmol) in dioxane (14 mL) and AcOH/water (0.5 mL/0.5 mL (1:1 v/v)) was added 1-methoxypropan-2-one (1.86 g, 21 mmol) slowly. The resulting mixture was stirred at 100 °C overnight. The resulting reaction mixture was allowed to cool to room temperature, filtered through a Celite pad to give a solution of Compound **51-1** which was used directly in the next step without further purification.

[01144] Step 2: (E)-1-(2-(4-Fluorophenyl)hydrazineylidene)-3-methoxypropan-2-one (51-2): To the crude solution of Compound **51-1** from step 1 was added water (30 mL), AcOH (1.2 mL) and (4-fluorophenyl)hydrazine (21 mmol, 1 eq). The resulting mixture was stirred at room temperature overnight. The resulting solids were filtered to give Compound **51-2** (3.53 g, 80% yield over 2 steps). MS for $C_{10}H_{11}FN_2O_2$: *m/z* 211 (MH+).

[01145] Step 3: 2-(4-Fluorophenyl)-5-(methoxymethyl)-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (HA2-14): To a solution of Compound **51-2** (3.53 g, 17 mmol) in toluene (20 mL) was added AcOH (0.5 mL) and Meldrum's acid (16.81 mmol, 1 eq). The resulting mixture was heated to 100 °C overnight. Solvent was removed under reduced pressure, aq 1 N NaOH (20 mL) was added and the resulting mixture was washed with EtOAc (3x). The aqueous phase was acidified with aq 6 M HCl to pH 1-2 and extracted with EtOAc (3x). The combined EtOAc extracts were washed with aq saturated NaCl, dried over anhyd Na_2SO_4 and concentrated to give Compound **HA2-14** (1.2 g, 26% yield). MS for $C_{13}H_{11}FN_2O_4$: *m/z* 279 (MH+).

Example 52: 4-(4-Fluorophenyl)-5-methyl-3-oxo-3,4-dihydropyrazine-2-carboxylic acid (HA3-1)



[01146] Step 1: Ethyl 2-((4-fluorophenyl)amino)-2-oxoacetate (52-1): To a solution of 4-fluoroaniline (10 g, 90 mmol, 8.6 mL, 1 eq) and TEA (13.7 g, 135 mmol, 18.8 mL, 1.5 eq) in EtOAc (150 mL) was added ethyl 2-chloro-2-oxo-acetate (14.7 g, 108 mmol, 12 mL, 1.2 eq) at 0 °C dropwise. The resulting white suspension was stirred at 20 °C for 15 h. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with aq saturated NaCl (100 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure to 30 mL. EtOAc (40 mL) and petroleum ether (120 mL) were added and the resulting mixture stirred for 5 min. The resulting solid was filtered, washed with petroleum ether (2 x 30 mL) and dried under vacuum to give Compound **52-1** (16.3 g, 86% yield). MS for $C_{10}H_{10}FNO_3$: *m/z* 211.8 (MH+).

[01147] Step 2: N^1-(4-Fluorophenyl)-N^2-(2-hydroxypropyl)oxalamide (52-2): To a mixture of Compound **52-1** (11.3 g, 53.5 mmol, 1 eq) in EtOH (100 mL) was added 1-aminopropan-2-ol (4.42 g, 58.9 mmol, 4.6 mL, 1.1 eq) at 70 °C dropwise. The mixture was stirred at 80 °C for 3 h. The reaction mixture was concentrated under reduced pressure until 30 mL remained. Petroleum ether (150 mL) was added and the resulting mixture was stirred for 1 h. The resulting solid was filtered, washed with petroleum ether (2 x 30 mL) and dried under vacuum to give Compound **52-2** (12.2 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (br s, 1H), 7.92 (br s, 1H), 7.65 - 7.57 (m, 2H), 7.13 - 7.03 (m, 2H), 4.08 - 3.98 (m, 1H), 3.60-3.50 (m, 1H), 3.35-3.25 (m, 1H), 2.11 (br s, 1H), 1.27 (d, 3H).

[01148] Step 3: N^1-(4-Fluorophenyl)-N^2-(2-oxopropyl)oxalamide (52-3): To a mixture of Compound **52-2** (10.2 g, 42.5 mmol, 1 eq) in ACN (100 mL) was added a solution of $RuCl_3$ (132 mg, 0.64 mmol, 0.015 eq) in water (10 mL) followed by a solution of sodium bromate (7.05 g, 47 mmol, 1.1 eq) in water

(20 mL). The purple mixture was stirred at 20 °C for 19 h. The reaction mixture was concentrated under reduced pressure to remove ACN. To the resulting residue was added water (200 mL) and the mixture was stirred for 2 h. Solids were filtered and washed with water (2 x 50 mL). The filtrate was concentrated under reduced pressure to give Compound **52-3** (9 g, 89% yield) which was used in subsequent reactions without further purification. MS for $C_{11}H_{11}FN_2O_3$: *m/z* 238.9 (MH+).

[01149] Step 4: 1-(4-Fluorophenyl)-6-methyl-1,4-dihydropyrazine-2,3-dione (52-4): A mixture of Compound **52-3** (9 g, 38 mmol, 1 eq) in conc H_2SO_4 (10 mL) was stirred at 55 °C for 1.5 h. The resulting mixture was cooled to 0 °C and water (150 mL) was added slowly. The resulting solids were filtered, washed with water (3 x 30 mL) and dried under vacuum to give Compound **52-4** (7.3 g, 88% yield) which was used in subsequent reactions without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, 4H), 6.11 (s, 1H), 1.65 (s, 3H).

[01150] Step 5: 3-Bromo-1-(4-fluorophenyl)-6-methylpyrazin-2(1H)-one (52-5): To a mixture of Compound **52-4** (7.3 g, 33 mmol, 1 eq) in ACN (70 mL) was added a solution of $POBr_3$ (10.4 g, 36.5 mmol, 1.1 eq) in ACN (30 mL). The mixture was stirred at 65 °C for 6 h. The reaction mixture was added to aq saturated $NaHCO_3$ (200 mL) at 0 °C slowly. The mixture was stirred for 0.5 h, then extracted with EtOAc (2 x 150 mL). The combined organic extracts were dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column (petroleum ether:EtOAc = 30:1 to 1:1) to give Compound **52-5** (6.3 g, 62% yield). MS for $C_{11}H_8BrFN_2O$: *m/z* 282.8 (MH+).

[01151] Step 6: Methyl 4-(4-fluorophenyl)-5-methyl-3-oxo-3,4-dihydropyrazine-2-carboxylate (52-6): To a mixture of Compound **52-5** (2.3 g, 8.1 mmol, 1 eq) in MeOH (30 mL) was added 1,3-bis(diphenylphosphino)propane (DPPP) (36.9 mg, 0.09 mmol, 0.011 eq) and TEA (2.5 g, 24 mmol, 3.4 mL, 3 eq) followed by the addition of $Pd(OAc)_2$ (18.2 mg, 0.08 mmol, 0.01 eq). The mixture was stirred at 70 °C for 60 h under CO (50 Psi). The reaction mixture was concentrated under reduced pressure. The resulting residue was diluted with water (150 mL), then extracted with DCM (2 x 80 mL). The combined organic extracts were dried over anhyd Na_2SO_4, concentrated and purified by silica gel column chromatography (petroleum ether:EtOAc = 3:1 to 0:1) to give Compound **52-6**(1.55 g, 58% yield). MS for $C_{13}H_{11}FN_2O_3$: *m/z* 262.9 (MH+).

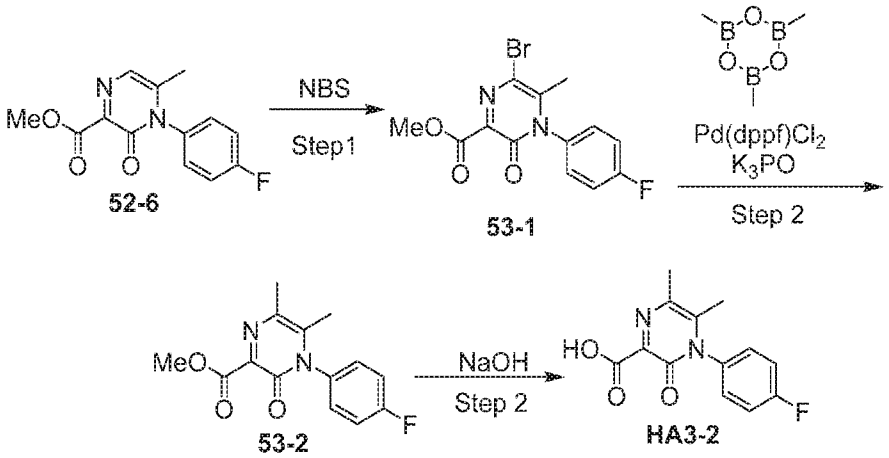
[01152] Step 7: 4-(4-Fluorophenyl)-5-methyl-3-oxo-3,4-dihydropyrazine-2-carboxylic acid (HA3-1): Compound **52-6** was converted to Compound **HA3-1** using the ester hydrolysis procedure used in Step 3 of **General Procedure A**. MS for $C_{12}H_9FN_2O_3$: *m/z* 248.9 (MH+).

[01153] The following compounds were made using techniques similar to those used to make Compound **H3-1** in **Example 52**:

[01154] 4-(4-Fluorophenyl)-3-oxo-3,4-dihydropyrazine-2-carboxylic acid (HA3-3): MS for $C_{11}H_7FN_2O_3$: *m/z* 234.9 (MH+).

[01155] 4-(4-Fluoro-2-methylphenyl)-5-methyl-3-oxo-3,4-dihydropyrazine-2-carboxylic acid (HA3-4): MS for $C_{13}H_{11}FN_2O_3$: *m/z* 262.9 (MH+).

Example 53: 4-(4-Fluorophenyl)-5,6-dimethyl-3-oxo-3,4-dihydropyrazine-2-carboxylic acid (HA3-2)

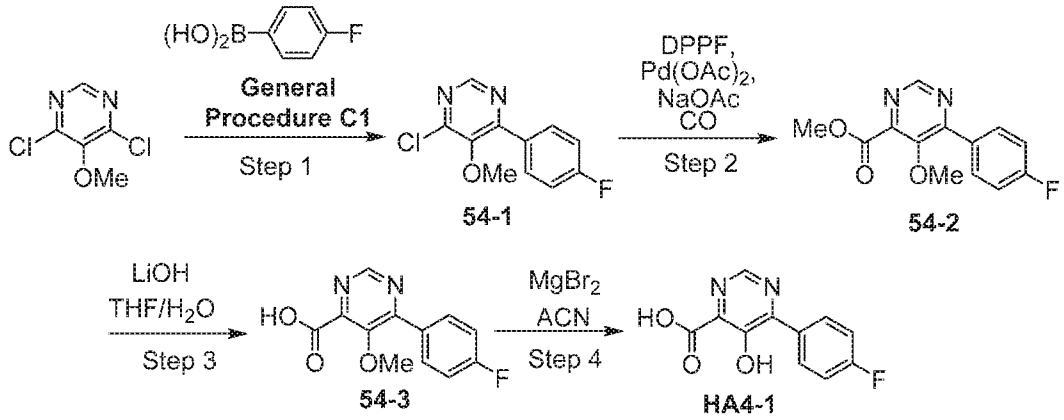


[01156] Step 1: Methyl 6-bromo-4-(4-fluorophenyl)-5-methyl-3-oxo-3,4-dihydropyrazine-2-carboxylate (53-1): To a solution of Compound **52-6** (0.5 g, 1.9 mmol, 1 eq) in DMF (5 mL) was added NBS (339 mg, 1.9 mmol, 1 eq) and the mixture was stirred at 25 °C for 2.5 h. The reaction mixture was diluted with water (80 mL) and stirred for 0.5 h. The mixture was then extracted with DCM (3 x 50 mL). The combined organic extracts were dried over anhyd Na_2SO_4, concentrated under reduced pressure and purified by silica gel column chromatography (petroleum ether:EtOAc = 10:1 to 1:1) to give Compound **53-1** (580 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.21 (m, 2H), 7.17 - 7.12 (m, 2H), 3.93 (s, 3H), 2.21 (s, 3H).

[01157] Step 2: Methyl 4-(4-fluorophenyl)-5,6-dimethyl-3-oxo-3,4-dihydropyrazine-2-carboxylate (53-2): To a mixture of Compound **53-1** (280 mg, 0.82 mmol, 1 eq), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane in (3.5 M in THF) (0.23 mL, 1.6 mmol, 2 eq) and dioxane (4 mL) was added K_3PO_4 (348 mg, 1.6 mmol, 2 eq) followed by $Pd(dppf)Cl_2$ (60 mg, 0.082 mmol, 0.1 eq) under an atmosphere of nitrogen. The mixture was stirred at 90 °C for 15 h under an atmosphere of nitrogen. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over anhyd Na_2SO_4, concentrated under reduced pressure and purified flash silica gel chromatography (0~50% EtOAc gradient) to give Compound **53-2** (150 mg, 56% yield). MS for $C_{14}H_{13}FN_2O_3$: *m/z* 276.9 (MH+).

[01158] Step 3: 4-(4-Fluorophenyl)-5,6-dimethyl-3-oxo-3,4-dihydropyrazine-2-carboxylic acid (HA3-2): Compound **53-2** was converted to Compound **HA3-2** using the ester hydrolysis procedure used in Step 3 of **General Procedure A**. MS for $C_{13}H_{11}FN_2O_3$: *m/z* 262.9 (MH+).

Example 54: 6-(4-Fluorophenyl)-5-hydroxypyrimidine-4-carboxylic acid (HA4-1)



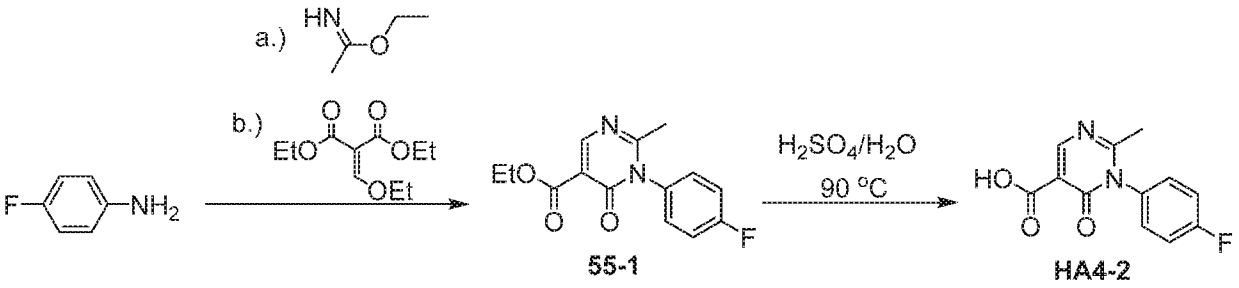
[01159] Step 1: 4-Chloro-6-(4-fluorophenyl)-5-methoxypyrimidine (54-1): Compound **54-1** was synthesized from 4,6-dichloro-5-methoxypyrimidine using **General Procedure C1**. MS for $C_{11}H_8ClFN_2O$: *m/z* 238.9 (MH+).

[01160] Step 2: Methyl 6-(4-fluorophenyl)-5-methoxypyrimidine-4-carboxylate (54-2): To a mixture of Compound **54-1** (635 mg, 2.7 mmol, 1 eq) and MeOH (5.54 g, 172 mmol, 7 mL, 65 eq) in DMF (7 mL) was added cyclopentyl(diphenyl)phosphane; iron (DPPF) (295 mg, 0.53 mmol, 0.2 eq), diacetoxypalladium (61 mg, 0.27 mmol, 0.1 eq) and sodium acetate (656 mg, 8 mmol, 3 eq). The mixture was degassed under vacuum and purged with CO several times. The mixture was stirred at 75 °C for 13 h under CO (50 psi). The mixture was diluted with water (70 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with aq saturated NaCl (30 mL), dried over anhyd Na_2SO_4 and concentrated. The resulting residue was purified by flash silica gel chromatography (0~10% EtOAc gradient in petroleum ether) to give Compound **54-2** (660 mg, 94% yield). MS for $C_{13}H_{11}FN_2O_3$: *m/z* 262.9 (MH+).

[01161] Step 3: 6-(4-Fluorophenyl)-5-methoxypyrimidine-4-carboxylic acid (54-3): Compound **54-3** was made from Compound **54-2** in a manner similar to the way that Compound **HA2-11** was made from Compound **49-1** in **Example 49**. MS for $C_{12}H_9FN_2O_3$: *m/z* 248.9 (MH+).

[01162] Step 4: 6-(4-Fluorophenyl)-5-hydroxypyrimidine-4-carboxylic acid (HA4-1): To a mixture of Compound **54-3** (189 mg, 0.76 mmol, 1 eq) in ACN (4 mL) was added $MgBr_2$ (280 mg, 1.5 mmol, 2 eq). The mixture was stirred at 50 °C for 1 h. The mixture was diluted with water (10 mL), the pH was adjusted to pH = 3 with aq 1.0 M HCl and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with aq saturated NaCl (20 mL), dried over anhyd Na_2SO_4 and concentrated to give Compound **HA4-1** (113 mg, 63% yield) which was used in subsequent reactions without further purification. MS for $C_{11}H_7FN_2O_3$: *m/z* 234.9 (MH+).

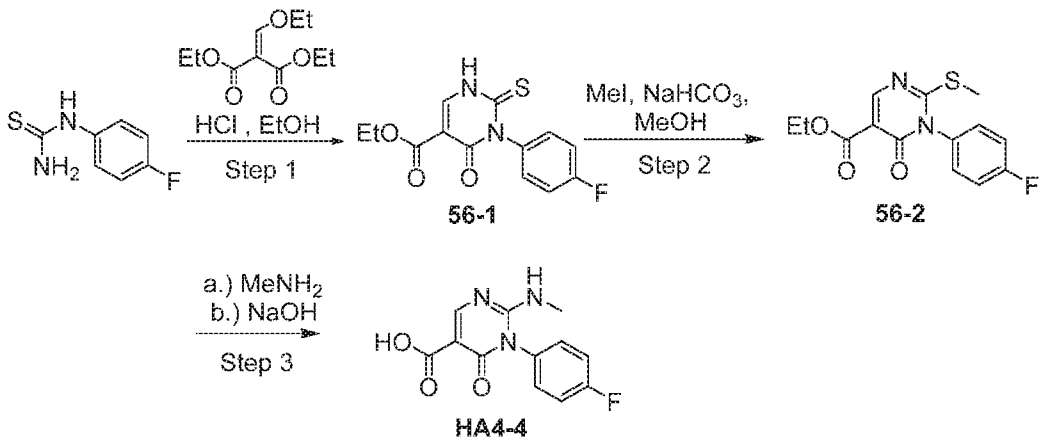
Example 55: 1-(4-Fluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid, Sodium salt (HA4-2)



[01163] Step 1: Ethyl 1-(4-fluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate (55-1): A mixture of 4-fluoroaniline (11 g, 99 mmol, 1 eq), ethyl ethanimidate HCl (12 g, 99 mmol, 1 eq) and TEA (11 g, 109 mmol, 1.1 eq) in EtOH (40 mL) was stirred at 20 °C for 64 h. Diethyl 2-(ethoxymethylene)propanedioate (23.6 g, 109 mmol, 1.1 eq) was then added to the mixture and stirring was continued at 80 °C for 7 h. The reaction mixture was diluted with water (300 mL) and extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with aq saturated NaCl (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 5/1 to 5/4) to give Compound **55-1**(5.0 g, 18 mmol, 18% yield). MS for $C_{14}H_{13}FN_2O_3$: *m/z* 276.9 (MH+).

[01164] Step 2: 1-(4-Fluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (HA4-2): A mixture of Compound **55-1** (1 g, 3.62 mmol, 1 eq), water (500 mg, 28 mmol, 0.5 mL, 7.7 eq) and H_2SO_4 (5 mL) was stirred at 90 °C for 3.5 h. The reaction mixture was added dropwise to ice (300 mL) at 0 °C, and the pH was adjusted to pH = 7-8 slowly with $NaHCO_3$ at 0 °C. The resulting mixture was washed with EtOAc (3 x 20 mL). The aqueous phase was carefully acidified with aq 2 M HCl to pH = 4-5 and then extracted with EtOAc (4 x 50 mL). The combined EtOAc extracts were washed with aq saturated NaCl (15 mL), dried over anhyd Na_2SO_4 and concentrated in vacuo to give crude Compound **HA4-2** (690 mg, 77% yield) which was used into the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.56 (br s, 1H), 8.88 (br s, 1H), 7.44 - 7.13 (m, 4H), 2.34 (br s, 3H).

Example 56: 1-(4-Fluorophenyl)-2-(methylamino)-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (HA4-4)



[01165] Step 1: Ethyl 3-(4-fluorophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (56-1): A mixture of diethyl 2-(ethoxymethylene)malonate (3.2 mL, 13.8 mmol), 1-(4-fluorophenyl)-thiourea (2.54 g, 15 mmol), and HCl (36% aq, 3.2 mL) in EtOH was refluxed for 6 h. The reaction was cooled to room temperature and filtered. The resulting solid was washed with EtOH and dried to give Compound **56-1** (2.6 g, 64% yield). MS for $C_{13}H_{11}FN_2O_3S$: *m/z* 295 (MH+).

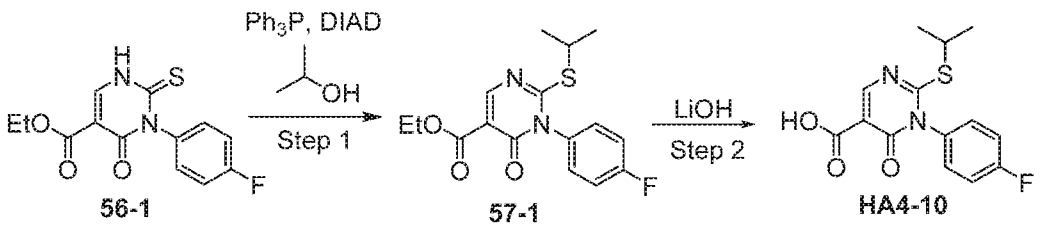
[01166] Step 2: Ethyl 1-(4-fluorophenyl)-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (56-2): To a mixture of Compound **56-1** (1.5 g, 5.1 mmol), aq saturated $NaHCO_3$ (4 mL) and MeOH was added MeI (1.0 mL, 16.1 mmol). The reaction was stirred at room temperature overnight and concentrated to remove MeOH and excess MeI. The resulting solid was filtered, washed with water and dried to give Compound **56-2** (1.51 g, 96% yield). MS for $C_{14}H_{13}FN_2O_3S$: *m/z* 309 (MH+).

[01167] Step 3: 1-(4-Fluorophenyl)-2-(methylamino)-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (HA4-4): A mixture of Compound **56-2** (130 mg, 0.447 mmol) and $MeNH_2$ (8 M solution in EtOH, 1.0 mL) was stirred at 50 °C for 20 min and then concentrated to remove all volatiles. To the resulting residue was added aq NaOH (2 M, 1 mL) and MeOH (2 mL). The resulting mixture was stirred at room temperature for 4 h, concentrated to remove most of the MeOH and acidified with aq HCl (6 M) to pH~2. The resulting solids were filtered, washed with water and dried to give Compound **HA4-4** (70 mg, 63% yield). MS for $C_{12}H_{10}FN_3O_3$: *m/z* 264 (MH+).

[01168] The following compound was made using the same method employed to make Compound **HA4-4** from Compound **56-2** in **Example 56**:

[01169] 2-(Dimethylamino)-1-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (HA4-5): MS for $C_{13}H_{12}FN_3O_3$: *m/z* 278 (MH+).

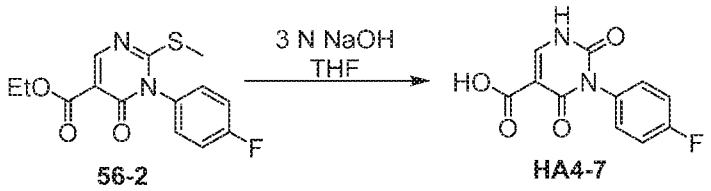
Example 57: 1-(4-Fluorophenyl)-2-(isopropylthio)-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (HA4-10)



[01170] Step 1: Ethyl 1-(4-fluorophenyl)-2-(isopropylthio)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (57-1): Compound **56-1** (294 mg, 1.0 mmol), triphenylphosphine (400 mg, 1.52 mmol) and isopropanol (120 mg, 2.0 mmol) were dissolved in anhydrous DCM (5 mL). The resulting solution was cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD) (202 mg, 1.0 mmol) was added dropwise. The mixture is stirred at 0 °C for 2 h, and then water was added. The resulting mixture was extracted with EtOAc. The combined EtOAc extracts were washed with aq saturated NaCl and concentrated. The resulting residue was purified by flash column chromatography to give Compound **57-1** (270 mg, 80%).

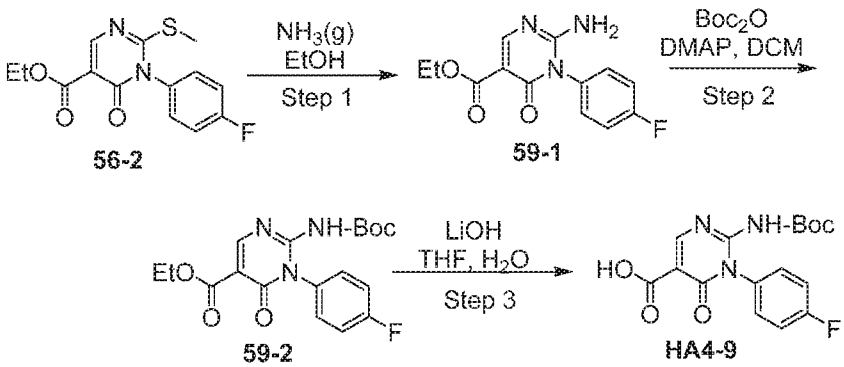
[01171] Step 2: 1-(4-Fluorophenyl)-2-(isopropylthio)-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid: Compound **HA4-10** was made from Compound **57-1** in a manner similar to the way that Compound **HA2-11** was made from Compound **49-1** in **Example 49**.

Example 58: 3-(4-Fluorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (HA4-7)



[01172] 3-(4-Fluorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (HA4-7): A 20-mL scintillation vial was charged with a Teflon stir bar, Compound **56-2** (207 mg, 0.670 mmol) and THF (4.4 mL). Aq 3 N NaOH (2.2 mL) was added and the reaction was stirred at room temperature for 20 h. The reaction was diluted with water and washed with DCM. The aqueous layer was acidified with aq 1 N HCl and extracted twice with EtOAc. The combined EtOAc extracts were washed with aq saturated NaCl, dried over anhyd Na_2SO_4 and concentrated to give Compound **HA4-7**(158 mg, 94% yield). MS for $C_{11}H_7FN_2O_4$: *m/z* 251 (MH+).

Example 59: 2-((tert-Butoxycarbonyl)amino)-1-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (HA4-9)

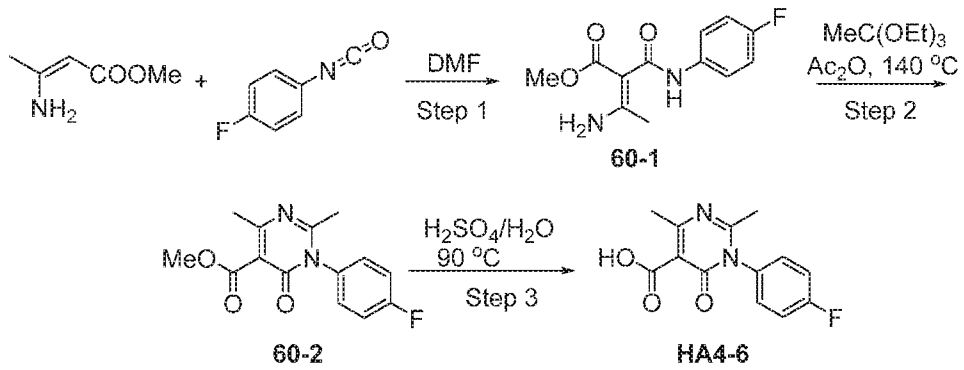


[01173] Step 1: Ethyl 2-amino-1-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (59-1): A sealed tube reaction vessel was charged with a Teflon stir bar and Compound **56-2** (99 mg, 0.32 mmol). The vessel was sealed with a rubber septum and the material was suspended in 5 mL of EtOH. Ammonia gas was bubbled into the solution until all material was dissolved then the vessel was capped and stirred at room temperature overnight. The reaction was concentrated to give Compound **59-1** (88 mg, 99% yield). MS for $C_{13}H_{12}FN_3O_3$: *m/z* 278 (MH+).

[01174] Step 2: Ethyl 2-((tert-butoxycarbonyl)amino)-1-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (59-2): A 4 mL scintillation vial was charged with Compound **59-1** (50 mg, 0.180 mmol), DMAP (5.5 mg, 0.045 mmol, 0.25 eq) and a Teflon stir bar. The material was suspended in DCM and a 1 M solution of Boc_2O in THF (0.27 mL, 0.27 mmol, 1.5 eq) was added to the stirring reaction. The reaction was stirred at room temperature for 3 h then diluted with DCM and MeOH and concentrated in the presence of silica gel (500 mg). The resulting powder was loaded onto a silica gel column and the reaction product was purified by silica gel column chromatography (eluting with 0-50% EtOAc in hexanes) to give Compound **59-2** (34 mg, 50% yield). MS for $C_{18}H_{20}FN_3O_5$: *m/z* 378 (MH+).

[01175] Step 3: 2-((tert-Butoxycarbonyl)amino)-1-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (HA4-9): Compound **HA4-9** was made from Compound **59-2** in a manner similar to the way that Compound **HA2-11** was made from Compound **49-1** in **Example 49**. MS for $C_{16}H_{16}FN_3O_5$: *m/z* 350 (MH+).

Example 60: 1-(4-Fluorophenyl)-2,4-dimethyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (HA4-6)



[01176] Step 1: Methyl (Z)-3-amino-2-((4-fluorophenyl)carbamoyl)but-2-enoate (60-1): To a solution of methyl (Z)-3-aminobut-2-enoate (2.58 g, 22 mmol) in DMF (10 mL) as added slowly a solution of 4-fluorophenyl isocyanate (3.1 g, 22 mmol) in 10 min. The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was then slowly poured into water (350 mL). The precipitate was filtered and dried under vacuum to give Compound **60-1** (4.8 g, 87% yield) which was used in the next step without further purification. MS for $C_{12}H_{13}FN_2O_3$: *m/z* 253 (MH+).

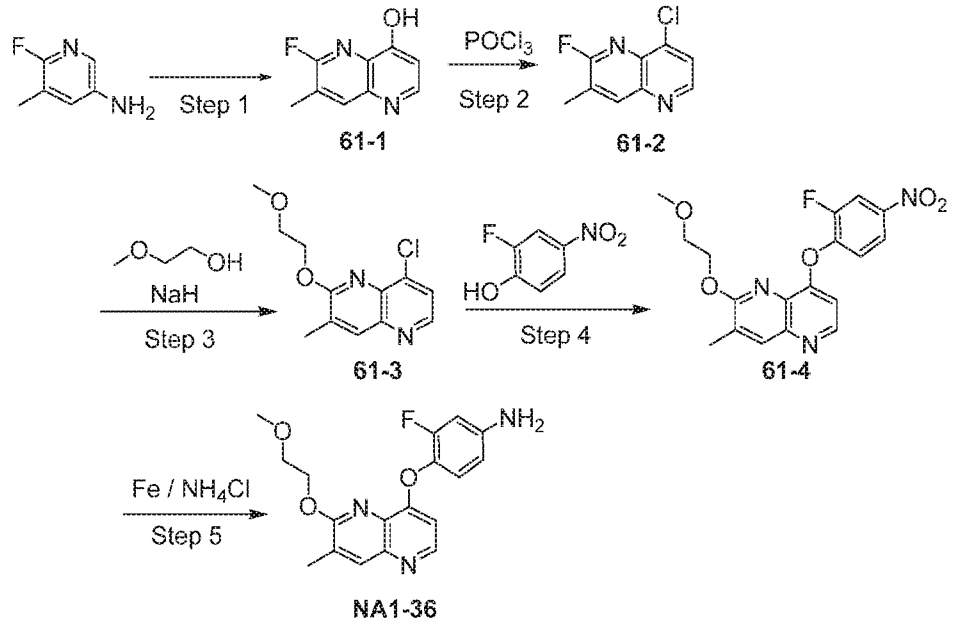
[01177] Step 2: Methyl 1-(4-fluorophenyl)-2,4-dimethyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate (60-2): Compound **60-1** (2.52 g, 10 mmol) was mixed with triethyl orthoacetate (6.6g, 40 mmol) in Ac_2O (2 mL). The resulting mixture was stirred at 140 °C for 12 h. The reaction mixture was then concentrated, and the resulting residue was purified by flash silica gel chromatography to give Compound **60-2** (900 mg, 32% yield). MS for $C_{14}H_{13}FN_2O_3$: *m/z* 277 (MH+).

[01178] Step 2: 1-(4-Fluorophenyl)-2,4-dimethyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (HA4-6): Compound **60-2** (50 mg, 1.81 mmol) was mixed with H_2SO_4 (2 g) and water (135 mg). The resulting mixture was stirred at 90 °C for 4 h. After it was cooled to room temperature, water was slowly added, and the resulting precipitate was filtered and dried under vacuum to give Compound **HA4-6** (250 mg, 52% yield). MS for $C_{13}H_{11}FN_2O_3$: *m/z* 263 (MH+).

[01179] The following compound was made in the same manner as Compound **HA4-6** in **Example 60**:

[01180] Same procedures: **1-(4-Fluorophenyl)-4-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (HA4-3):** MS for $C_{12}H_9FN_2O_3$: *m/z* 249 (MH+).

Example 61: 3-Fluoro-4-((6-(2-methoxyethoxy)-7-methyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-36)



[01181] Step 1: 6-Fluoro-7-methyl-1,5-naphthyridin-4-ol (61-1): Compound **61-1** was made from 6-fluoro-5-methylpyridin-3-amine using Step 1 of **General Procedure G**.

[01182] Step 2: 8-Chloro-2-fluoro-3-methyl-1,5-naphthyridine (61-2): A mixture of Compound **61-1** (560 mg, 3.14 mmol), $POCl_3$ (1.5 g, 9.8 mmol) and DIEA (1.74 mL, 10 mmol) in toluene (10 mL) was stirred at 100 °C for 30 min, then cooled to room temperature and concentrated. The resulting residue was purified by silica gel chromatography (0-70% EtOAc in hexanes) to give Compound **61-2** (586 mg, 94% yield). MS for $C_9H_6ClFN_2$: *m/z* 197 (MH+).

[01183] Step 3: 8-Chloro-2-(2-methoxyethoxy)-3-methyl-1,5-naphthyridine (61-3): To a solution of 2-methoxyethanol (150 mg, 2 mmol) in DMF (4 mL) was added NaH (60%, 90 mg, 2.25 mmol) with stirring at < 20 °C, followed by the addition of Compound **61-2** (256 mg, 1.3 mmol). The resulting mixture was stirred at room temperature for 10 min. The reaction was then quenched with water. The resulting solid was filtered, washed with water and dried to give Compound **62-3** (330 mg, 100% yield). MS for $C_{12}H_{13}ClN_2O_2$: *m/z* 253 (MH+).

[01184] Step 4: 8-(2-Fluoro-4-nitrophenoxy)-2-(2-methoxyethoxy)-3-methyl-1,5-naphthyridine (61-4): Compound **61-4** was made from Compound **61-3** using step 1 of **General Procedure H**.

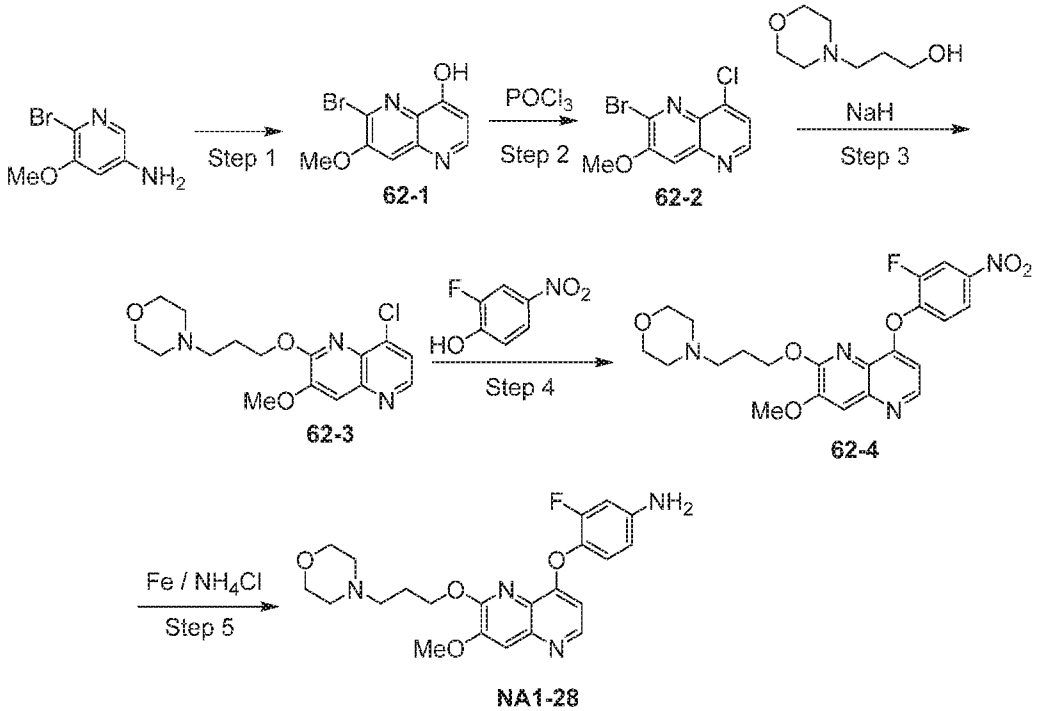
[01185] Step 5: 3-Fluoro-4-((6-(2-methoxyethoxy)-7-methyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-36): Compound **NA1-36** was made from Compound **61-4** using step 3 of **General Procedure G**. MS for $C_{18}H_{18}FN_3O_3$: *m/z* 344 (MH+).

[01186] The following compounds were made in a similar fashion to that of Compound **NA1-36** in **Example 61**.

[01187] 4-((6-(2-Methoxyethoxy)-7-methyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-35): MS for $C_{18}H_{19}N_3O_3$: *m/z* 326 (MH+).

[01188] 3-Fluoro-4-((7-methyl-6-(3-morpholinopropoxy)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-37): MS for $C_{22}H_{25}FN_4O_3$: *m/z* 413 (MH+).

Example 62: 3-Fluoro-4-((7-methoxy-6-(3-morpholinopropoxy)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-28)



[01189] Step 1: 6-Bromo-7-methoxy-1,5-naphthyridin-4-ol (62-1): Compound **62-1** was made from 6-bromo-5-methoxypyridin-3-amine using step 1 of **General Procedure G**. MS for $C_9H_7BrN_2O_2$, found 255/257 (MH+).

[01190] Step 2: 2-Bromo-8-chloro-3-methoxy-1,5-naphthyridine (62-2): Compound **62-2** was made from Compound **62-1** in the same manner that Compound **61-2** was made from Compound **61-1** in **Example 61**. MS for $C_9H_6BrClN_2O$: 275 (MH+).

[01191] Step 3: 4-(3-((8-Chloro-3-methoxy-1,5-naphthyridin-2-yl)oxy)propyl)morpholine (62-3): To a solution of 3-morpholinopropan-1-ol (125 mg, 0.86 mmol) in DMF (2 mL) was slowly added NaH (60% in oil, 38 mg, 0.95 mmol). The resulting suspension was stirred at room temperature for 5 min, followed by addition of Compound **62-2** (110 mg, 0.40 mmol). The mixture was stirred at room temperature for 30 min, quenched with aq $NaHCO_3$ and extracted with EtOAc (2x). The combined extracts were washed with aq saturated NaCl and concentrated. The resulting residue was purified by silica gel chromatography (0-5% MeOH in EtOAc) to give Compound **62-3** (104 mg, 77% yield). MS for $C_{16}H_{20}ClN_3O_3$: 338 (MH+).

[01192] Step 4: 4-(3-((8-(2-Fluoro-4-nitrophenoxy)-3-methoxy-1,5-naphthyridin-2-yl)oxy)propyl)morpholine (62-4): Compound **62-4** was made from Compound **62-3** using step 1 of **General Procedure H**.

[01193] Step 5: 3-Fluoro-4-((7-methoxy-6-(3-morpholinopropoxy)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-28): Compound **NA1-28** was made from Compound **62-4** using step 3 of **General Procedure G**. MS for $C_{22}H_{25}FN_4O_4$: 429 (MH+).

[01194] The following compounds were made in a similar fashion to that of Compound **NA1-28** in **Example 62**.

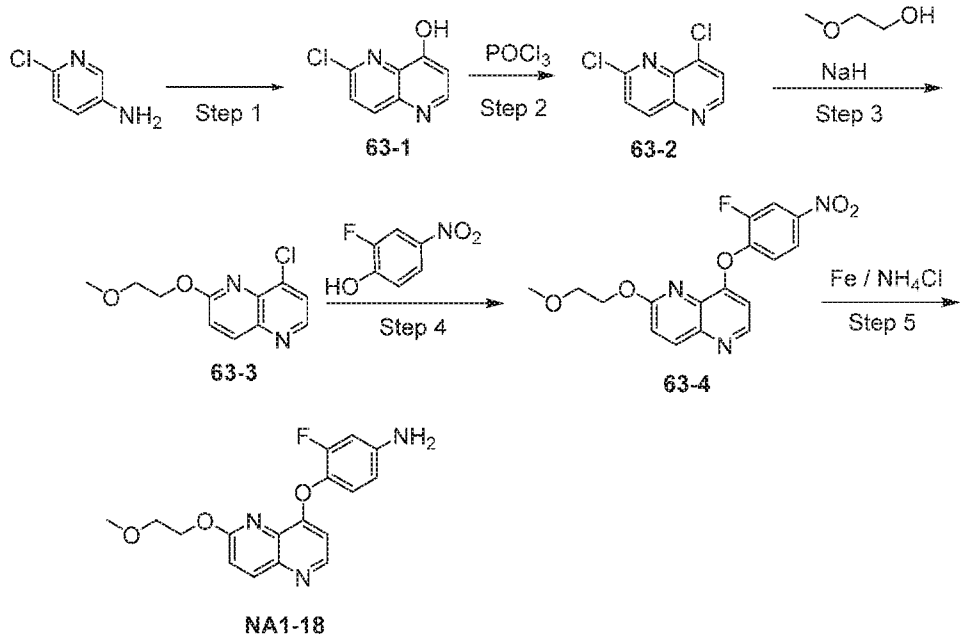
[01195] 3-Fluoro-4-((7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-16): MS for $C_{18}H_{18}FN_3O_4$: 360 (MH+).

[01196] 4-((6-Ethoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-27): MS for $C_{17}H_{16}FN_3O_3$: 330 (MH+).

[01197] 3-Fluoro-4-((6-isopropoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy)aniline (NA1-30): MS for $C_{18}H_{18}FN_3O_3$: 344 (MH+).

[01198] 4-((6-Isopropoxy-7-methoxy-1,5-naphthyridin-4-yl)oxy)aniline (NA1-31): MS for $C_{18}H_{19}N_3O_3$: 326 (MH+).

Example 63: 3-Fluoro-4-((6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-18)



[01199] Step 1: 6-Chloro-1,5-naphthyridin-4-ol (63-1): Compound **63-1** was made from 6-chloropyridin-3-amine using step 1 of **General Procedure G**.

[01200] Step 2: 2,8-Dichloro-1,5-naphthyridine (63-2): Compound **63-2** was made from Compound **63-1** in the same manner that Compound **61-2** was made from Compound **61-1** in **Example 61**. MS for $C_8H_4Cl_2N_2$: 199 (MH+).

[01201] Step 3: 8-Chloro-2-(2-methoxyethoxy)-1,5-naphthyridine (63-3): Compound **63-3** was made from Compound **63-2** in the same manner that Compound **62-3** was made from Compound **62-2** in **Example 61**. MS for $C_{11}H_{11}ClN_2O_2$, found 239 (MH+).

[01202] Step 4: 8-(2-Fluoro-4-nitrophenoxy)-2-(2-methoxyethoxy)-1,5-naphthyridine (63-4): Compound **63-4** was made from Compound **63-3** using step 1 of **General Procedure H**. MS for $C_{17}H_{14}FN_3O_5$, found 360 (MH+).

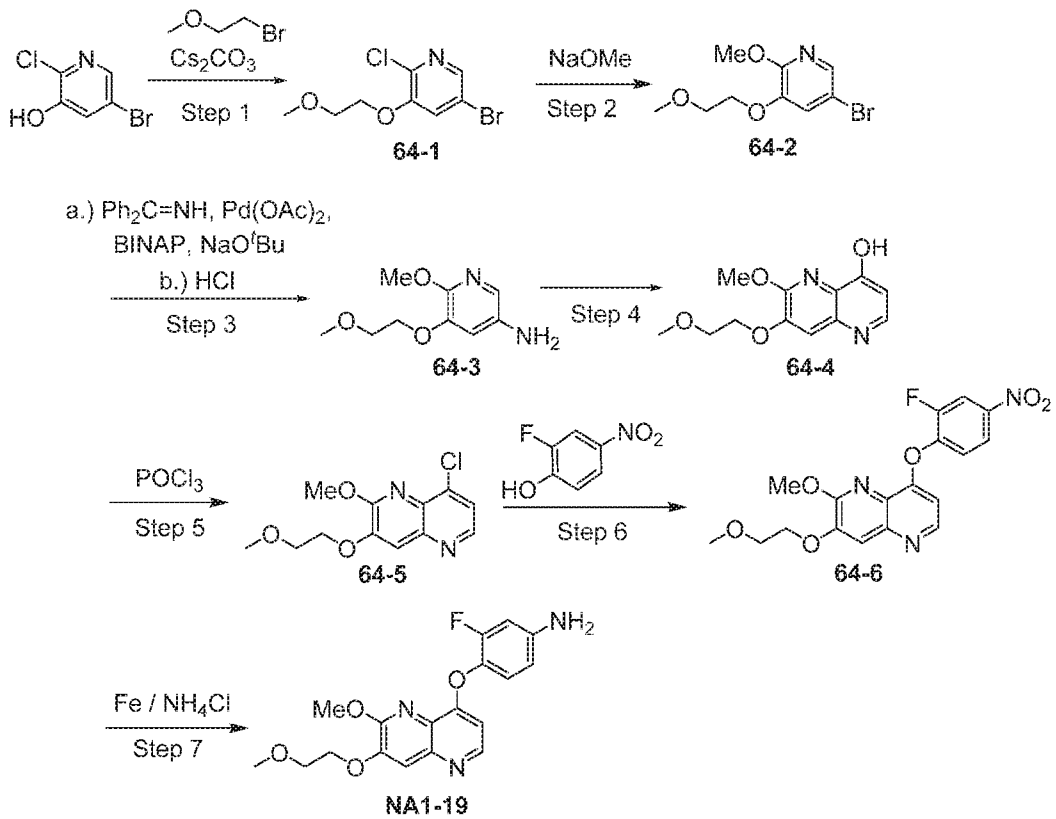
[01203] Step 5: 3-Fluoro-4-((6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-18): Compound **NA1-18** was made from Compound **63-4** using step 3 of **General Procedure G**. MS for $C_{17}H_{16}FN_3O_3$, found 330 (MH+).

[01204] The following compounds were made in a similar fashion to that of Compound **NA1-18** in **Example 63**.

[01205] 3-Fluoro-4-((6-(2-morpholinoethoxy)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-41): MS for $C_{20}H_{21}FN_4O_3$, found 385 (MH+).

[01206] 4-((6-(2-(Dimethylamino)ethoxy)-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-50): MS for $C_{18}H_{19}FN_4O_2$, found 343 (MH+).

Example 64: 3-Fluoro-4-((6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-19)



[01207] Step 1: 5-Bromo-2-chloro-3-(2-methoxyethoxy)pyridine (64-1): A mixture of 5-bromo-2-chloropyridin-3-ol (2.10 g, 10.0 mmol), 1-bromo-2-methoxyethane (1.50 g, 10.8 mmol) and Cs_2CO_3 (6.6 g, 20.2 mmol) in DMF was stirred at 80 °C for 2 h, quenched with water and extracted with EtOAc (2x). The combined extracts were washed with aq saturated NaCl, dried over anhyd Na_2SO_4 and concentrated to give crude Compound **64-1** (2.68 g, 100% yield). MS for $C_8H_9BrClNO_2$, found 268 (MH+).

[01208] Step 2: 5-Bromo-2-methoxy-3-(2-methoxyethoxy)pyridine (64-2): Compound **64-1** (2.68 g, 10.0 mmol) was mixed with NaOMe (3.0 g, 55.5 mmol) in MeOH (40 mL) and heated at 80 °C

overnight. The reaction mixture was concentrated to remove MeOH. The residue was partitioned between water and EtOAc. The EtOAc solution was washed with aq saturated NaCl, dried over anhyd Na_2SO_4 and concentrated to give crude Compound **64-2** (3.0 g) contaminated with residual solvent. MS for $C_9H_{12}BrNO_3$, found 262/264 (MH+).

[01209] Step 3: 6-Methoxy-5-(2-methoxyethoxy)pyridin-3-amine (64-3): Compound **64-2** (3.0 g, crude) was mixed with diphenylmethanimine (3.6 g, 20 mmol), Pd(OAc)2 (360 mg, 1.61 mmol), BINAP (1.3 g, 2.08 mmol) and NaO^{t}Bu (1.6 g, 16.7 mmol) in toluene (60 mL). The resulting mixture was degassed with nitrogen and stirred at 85 °C overnight. The resulting reaction mixture was partitioned between water and EtOAc. The organic phase was separated and evaporated to dryness. To the resulting residue was added THF (40 mL) and HCl (aq, 2M, 40 mL) and resulting mixture was stirred at room temperature overnight. The pH of the resulting reaction mixture was adjusted to pH 10 with $NaHCO_3$ and extracted with EtOAc. The extract was concentrated, and the resulting residue purified by silica gel chromatography (0-90% EtOAc in hexanes) to give Compound **64-3** (1.4 g). MS for $C_9H_{14}N_2O_3$, found 199 (MH+).

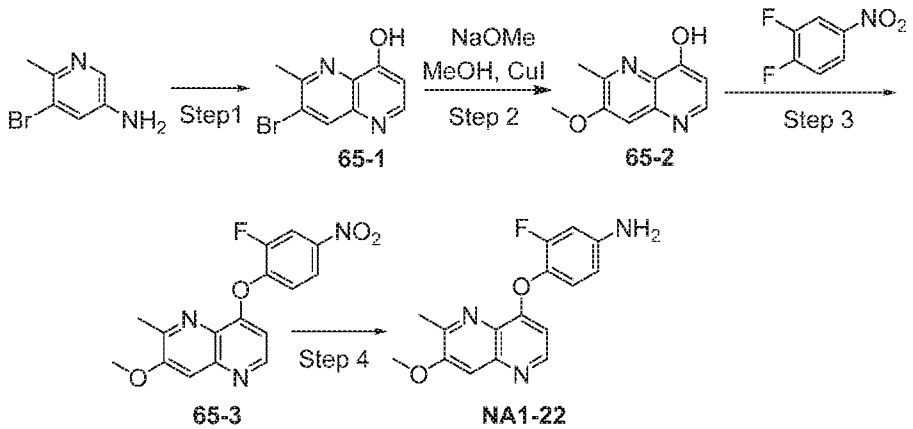
[01210] Step 4: 6-Methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-ol (64-4): Compound **64-4** was made from Compound **64-3** using step 1 of **General Procedure G**. MS for $C_{12}H_{14}N_2O_4$, found 251 (MH+).

[01211] Step 5: 8-Chloro-2-methoxy-3-(2-methoxyethoxy)-1,5-naphthyridine (64-5): Compound **64-5** was made from Compound **64-4** in the same manner that Compound **61-2** was made from Compound **61-1** in **Example 61**. MS for $C_{12}H_{13}ClN_2O_3$, 269 (MH+).

[01212] Step 6: 8-(2-Fluoro-4-nitrophenoxy)-2-methoxy-3-(2-methoxyethoxy)-1,5-naphthyridine (64-6): Compound **64-6** was made from Compound **64-5** using step 1 of **General Procedure H**.

Step 7: 3-Fluoro-4-((6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-19): Compound **NA1-19** was made from Compound **64-6** using step 3 of **General Procedure G**. MS for $C_{18}H_{18}FN_3O_4$, 360 (MH+).

Example 65: 3-Fluoro-4-((7-methoxy-6-methyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-22)



[01213] Step 1: 7-Bromo-6-methyl-1,5-naphthyridin-4-ol (65-1): Compound **65-1** was made from 5-bromo-6-methylpyridin-3-amine using step 1 of **General Procedure G**.

[01214] Step 2: 7-Methoxy-6-methyl-1,5-naphthyridin-4-ol (65-2): To a mixture of Compound **65-1** (100 mg, 0.418 mmol) and CuI (38 mg, 0.20 mmol) in DMF (2 mL) was added freshly prepared sodium methoxide in MeOH (1.2 mL, 3.5 M). The resulting mixture was stirred at 120 °C for 1 h. The mixture was concentrated, and the residue was washed with 5% MeOH in DCM. The organic phase was concentrated to give crude Compound **65-2** (40 mg, 50% yield) which was used in the next step without further purification. MS for $C_{10}H_{10}N_2O_2$, found: 191 (MH+).

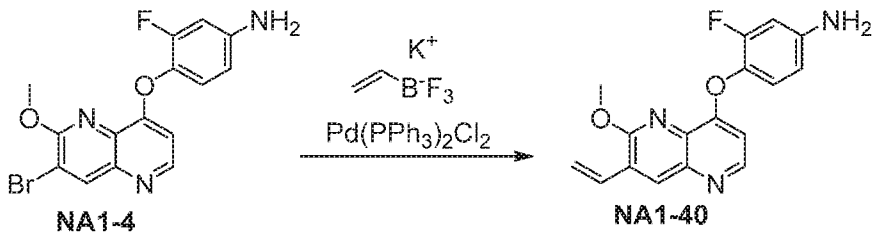
[01215] Step 3: 8-(2-Fluoro-4-nitrophenoxy)-3-methoxy-2-methyl-1,5-naphthyridine (65-3): Compound **65-3** was made from Compound **65-2** using step 2 of **General Procedure G**.

[01216] Step 4: 3-Fluoro-4-((7-methoxy-6-methyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-22): Compound **NA1-22** was made from Compound **65-3** using step 3 of **General Procedure G**. MS for $C_{16}H_{14}FN_3O_2$, found 300 (MH+).

[01217] The following compounds were made in a similar fashion to that of Compound **NA1-22** in **Example 65**.

[01218] 2,5-Difluoro-4-((7-methoxy-6-methyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-42): MS for $C_{16}H_{13}F_2N_3O_2$, found 318 (MH+).

Example 66: 3-Fluoro-4-((6-methoxy-7-vinyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-40)



[01219] 3-Fluoro-4-((6-methoxy-7-vinyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-40): A mixture of Compound **NA1-4** (330 mg, 0.91 mmol), $Pd(PPh_3)_2Cl_2$ (72 mg, 0.10 mmol), potassium vinyltriflouroborate (230 mg, 1.72 mmol), and CsF (500 mg, 3.3 mmol) in dioxane/water (2/1 mL) was stirred at 85 °C for 2 h and then cooled to room temperature. The resulting mixture was diluted with aq Na_2CO_3 (2M, 2 mL) and extracted twice with EtOAc. The combined organic extracts were dried over anhyd Na_2SO_4 and concentrated to give crude Compound **NA1-40** which was used without further purification. MS for $C_{17}H_{14}FN_3O_2$: *m/z* 312 (MH+).

[01220] The following compounds were made in a similar fashion to that used to make Compound **NA1-40** in **Example 66**.

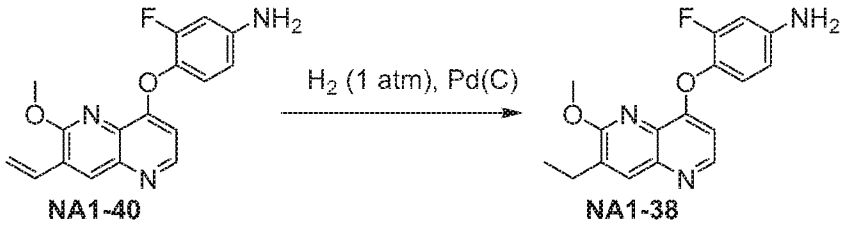
[01221] 3-Fluoro-4-((7-vinyl-1,5-naphthyridin-4-yl)oxy)aniline (NA1-32B): Compound **NA1-4** was replaced with Compound **NA1-5**. MS for $C_{16}H_{12}FN_3O$: *m/z* 282 (MH+).

[01222] 3-Fluoro-4-((6-methoxy-7-(prop-1-en-2-yl)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-23): The potassium vinyltriflouroborate was replaced with potassium isopropenyltrifluoroborate. MS for $C_{18}H_{16}FN_3O_2$: *m/z* 326 (MH+).

[01223] 3-Fluoro-4-((7-(prop-1-en-2-yl)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-24): The potassium vinyltriflouroborate was replaced with potassium isopropenyltrifluoroborate and Compound **NA1-4** was replaced with Compound **NA1-5**. MS for $C_{17}H_{14}FN_3O$: *m/z* 296 (MH+).

[01224] 4-((7-(Prop-1-en-2-yl)-1,5-naphthyridin-4-yl)oxy)aniline (NA1-25): The potassium vinyltriflouroborate was replaced with potassium isopropenyltrifluoroborate and Compound **NA1-4** was replaced with Compound **NA1-11**. MS for $C_{17}H_{15}N_3O$: *m/z* 278 (MH+).

Example 67: 4-((7-Ethyl-6-methoxy-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-38)

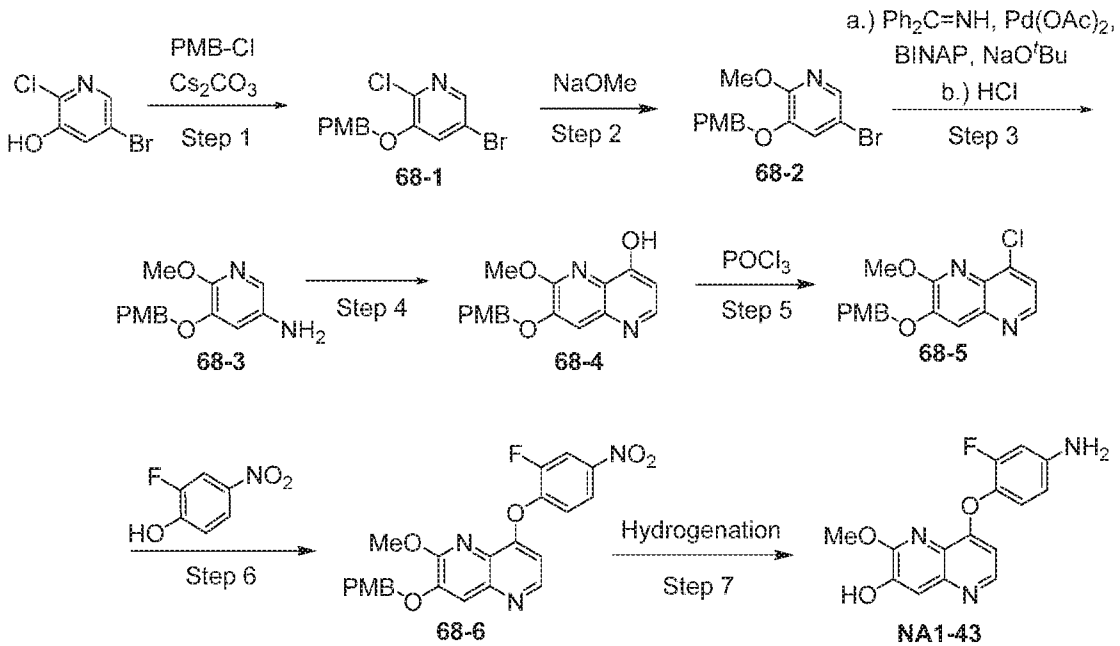


[01225] 4-((7-Ethyl-6-methoxy-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-38): Crude Compound **NA1-40** was mixed with Pd (10% on C, 53% wet, 107 mg) in EtOAc (15 mL) and the resulting suspension was degassed under vacuum for 2 min then stirred under an atmosphere of hydrogen at room temperature overnight. The reaction mixture was filtered, and the filtrate was concentrated. The resulting residue was purified by silica gel chromatography to give Compound **NA1-38** (155 mg, 54% yield over 2 steps from Compound **NA1-4**). MS for $C_{17}H_{16}FN_3O_2$: *m/z* 314 (MH+).

[01226] The following compound was made in a manner very similar to that used to make Compound **NA1-38** in **Example 67**.

[01227] 4-((7-Ethyl-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-32): Compound **NA1-40** was replaced with Compound **NA1-32B**. MS for $C_{16}H_{14}FN_3O$: *m/z* 284 (MH+).

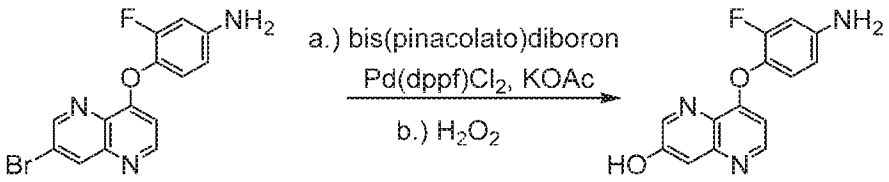
Example 68: 8-(4-Amino-2-fluorophenoxy)-2-methoxy-1,5-naphthyridin-3-ol (NA1-43)



[01228] Steps 1-6: 8-(2-Fluoro-4-nitrophenoxy)-2-methoxy-3-((4-methoxybenzyl)oxy)-1,5-naphthyridine (68-6): Compound **68-6** was made in 6 steps from 5-bromo-2-chloropyridin-3-ol following the same 6-step procedure used to make Compound **64-6** from 5-bromo-2-chloropyridin-3-ol in **Example 64**. The 1-bromo-2-methoxyethane was replaced with 4-methoxybenzyl chloride.

Step 7: 8-(4-Amino-2-fluorophenoxy)-2-methoxy-1,5-naphthyridin-3-ol (NA1-43): The nitro group if Compound **68-6** was reduced and the PMB protecting group was removed to give Compound **NA1-43** in a single step using standard hydrogenation conditions such as those used in Step 6 of **Example 71**. MS for $C_{15}H_{12}FN_3O_3$, found 302 (MH+).

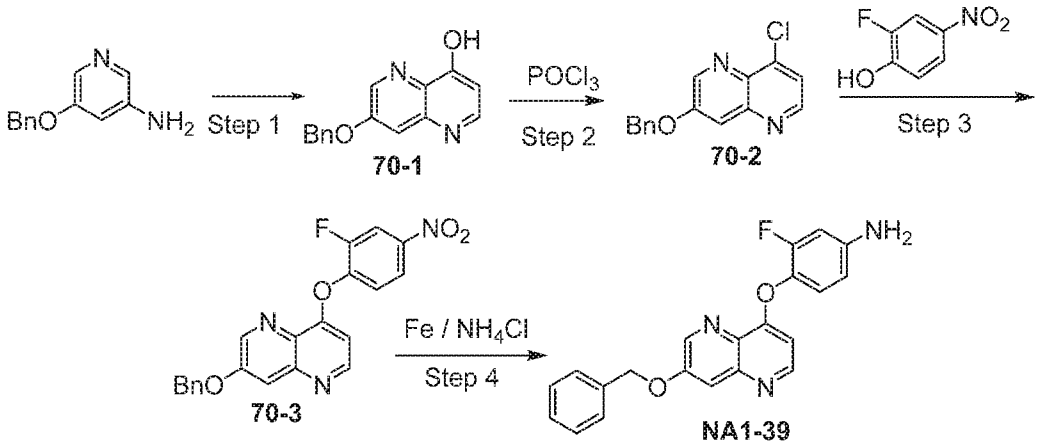
Example 69: 8-(4-Amino-2-fluorophenoxy)-1,5-naphthyridin-3-ol (NA1-51)



NA1-5 **NA1-51**

[01229] 8-(4-Amino-2-fluorophenoxy)-1,5-naphthyridin-3-ol (NA1-51): A mixture of Compound **NA1-5** (375 mg, 1.12 mmol), bis(pinacolato)diboron (700 mg, 2.75 mmol), $Pd(dppf)Cl_2$ (78 mg, 0.11 mmol) and KOAc (250 mg, 2.55 mmol) in 1,4- dioxane (6.0 mL) was stirred at 85 °C for 2 h under an atmosphere of nitrogen. The reaction mixture was cooled to room temperature and 30% aq hydrogen peroxide (0.25 mL) and aq saturated $NaHCO_3$ (5.0 mL) were added. The mixture was stirred at room temperature for 5 h and then partitioned between aq saturated NaCl and EtOAc. The EtOAc layer was collected, dried over anhyd Na_2SO_4 and evaporated to remove the solvent. The resulting residue was purified by silica gel column chromatography (EtOAc-hexane) to give Compound **NA1-51** (122 mg, 40% yield). MS for $C_{14}H_{10}FN_3O_2$, *m/z* 272 (MH+).

Example 70: 4-((7-(Benzyloxy)-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-39)



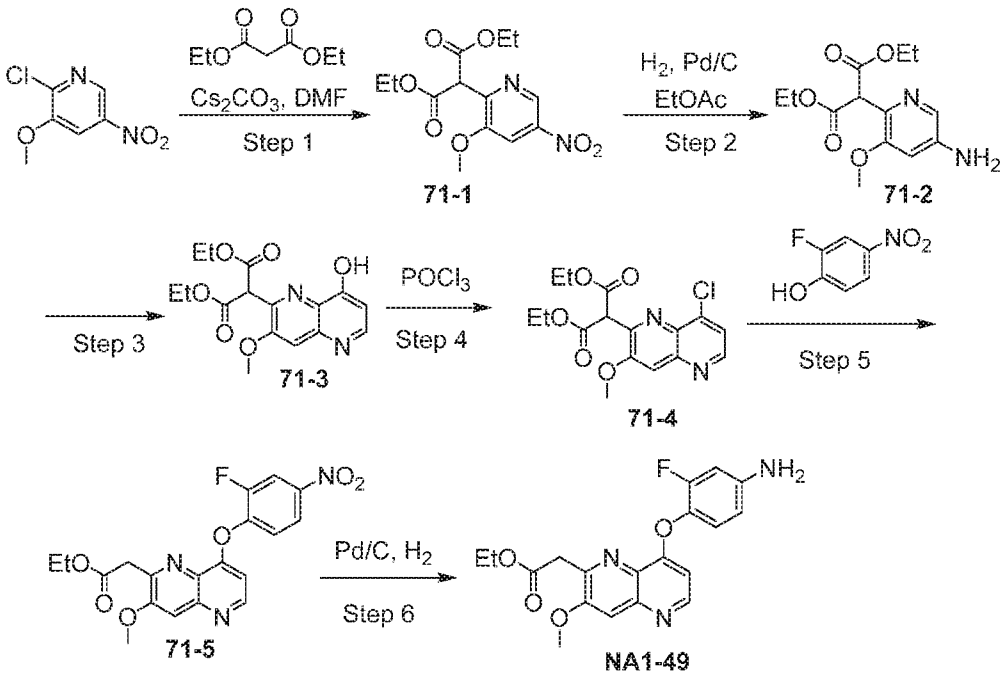
[01230] Step 1: 7-(Benzyloxy)-1,5-naphthyridin-4-ol (70-1): Compound **70-1** was made from 5-(benzyloxy)pyridin-3-amine using step 1 of **General Procedure G**. MS for $C_{15}H_{12}N_2O_2$: 252.8 (MH+).

[01231] Step 2: 3-(Benzyloxy)-8-chloro-1,5-naphthyridine (70-2): Compound **70-2** was made from Compound **70-1** in the same manner that Compound **61-2** was made from Compound **61-1** in **Example 61**. MS for $C_{15}H_{11}ClN_2O$, *m/z* 271 (MH+).

[01232] Step 3: 3-(Benzyloxy)-8-(2-fluoro-4-nitrophenoxy)-1,5-naphthyridine (70-3): Compound **70-3** was made from Compound **70-2** using step 1 of **General Procedure H**. MS for $C_{21}H_{14}FN_3O_4$, *m/z* for 392 (MH+).

[01233] Step 4: 4-((7-(Benzyloxy)-1,5-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA1-39): Compound **NA1-39** was made from Compound **70-3** using step 3 of **General Procedure G**. MS for $C_{21}H_{16}FN_3O_2$, *m/z* 362 (MH+).

Example 71: Ethyl 2-(8-(4-amino-2-fluorophenoxy)-3-methoxy-1,5-naphthyridin-2-yl)acetate (NA1-49)



[01234] Step 1: Diethyl 2-(3-methoxy-5-nitropyridin-2-yl)malonate (71-1): To a mixture of diethyl malonate (4.1 g, 25 mmol, 3.85 mL, 1.2 eq) in DMF (50 mL) was added Cs_2CO_3 (15.2 g, 47 mmol, 2.2 eq). The resulting mixture was stirred at 70 °C under an atmosphere of nitrogen for 30 min. 2-Chloro-3-methoxy-5-nitro-pyridine (4 g, 21 mmol, 1 eq) was added and the resulting mixture was stirred for 8.5 h. The solution was poured into water (200 mL) and the resulting mixture was stirred vigorously for 1 h. The resulting solids were filtered, washed with water (100 mL) and dried in the air to give crude Compound **71-1** (7.81 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, 1H), 7.94 (d, 1H), 5.15 (s, 1H), 4.29 (q, 4H), 3.97 (s, 3H), 1.28 (t, 6H).

[01235] Step 2: Diethyl 2-(5-amino-3-methoxypyridin-2-yl)malonate (71-2): To a mixture of Compound **71-1** (4.4 g, 14.2 mmol, 1 eq) in EtOAc (5 mL) was added 10% Pd/C (400 mg) in one portion at 25 °C under an atmosphere of hydrogen (15 psi). The mixture was stirred at 25 °C for 3 h. The reaction was filtered and washed with MeOH (70 mL). The filtrate was concentrated to give Compound

71-2 (3.9 g, 97% yield) which was used in subsequent reactions without further purification. MS for $C_{13}H_{18}N_2O_5$, *m/z* 283.1 (MH+).

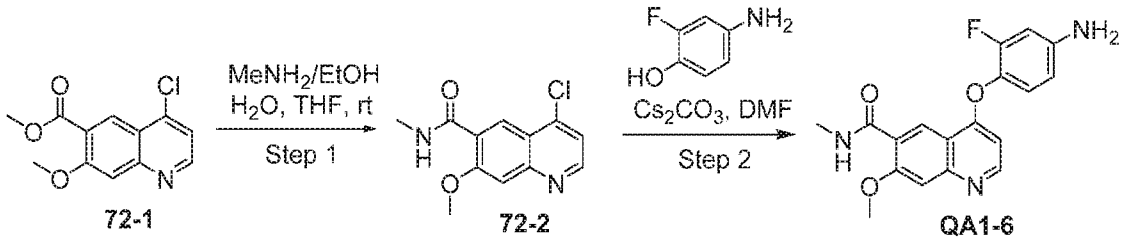
[01236] Step 3: Diethyl 2-(8-hydroxy-3-methoxy-1,5-naphthyridin-2-yl)malonate (71-3): Compound **71-3** was made from Compound **71-2** using step 1 of **General Procedure G**.

[01237] Step 4: Diethyl 2-(8-chloro-3-methoxy-1,5-naphthyridin-2-yl)malonate (71-4): Compound **71-4** was made from Compound **71-3** in the same manner that Compound **61-2** was made from Compound **61-1** in **Example 61**. MS for $C_{16}H_{17}ClN_2O_5$ *m/z* 353.0 (MH+).

[01238] Step 5: Ethyl 2-(8-(2-fluoro-4-nitrophenoxy)-3-methoxy-1,5-naphthyridin-2-yl)acetate (71-5): Compound **71-5** was made from Compound **71-4** using step 1 of **General Procedure H**. MS for $C_{19}H_{16}FN_3O_6$, *m/z* for 402.0 (MH+).

[01239] Step 6: Ethyl 2-(8-(4-amino-2-fluorophenoxy)-3-methoxy-1,5-naphthyridin-2-yl)acetate (NA1-49): To a mixture of Compound **71-5** (100 mg, 0.25 mmol, 1 eq) in EtOAc (20 mL) was added 10% Pd/C (100 mg) in one portion at 25 °C under an atmosphere of hydrogen (15 Psi). The mixture was stirred at 25 °C for 60 min. The reaction mixture was filtered and washed with EtOAc (20 mL). The filtrate was concentrated under reduced pressure to give Compound **NA1-49** (90 mg, 97% yield) which was used in subsequent steps without further purification. MS for $C_{19}H_{18}FN_3O_4$, *m/z* 372.0 (MH+).

Example 72: 4-(4-Amino-2-fluorophenoxy)-7-methoxy-N-methylquinoline-6-carboxamide (QA1-6)



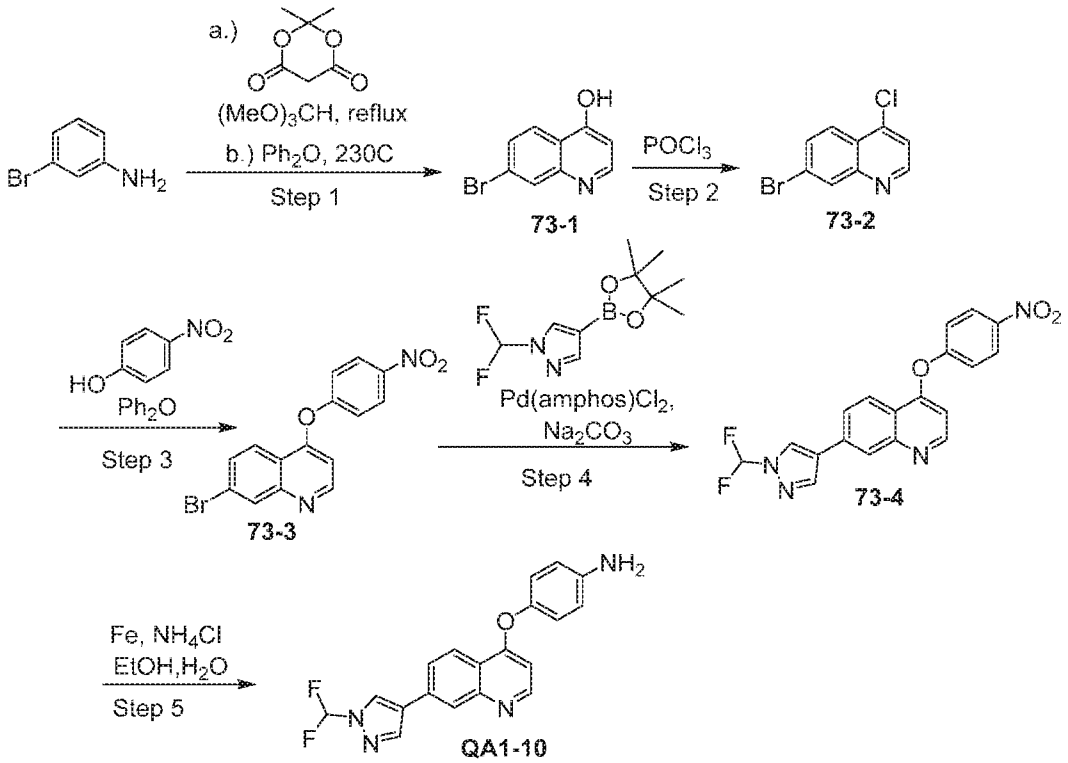
[01240] Step 1: 4-Chloro-7-methoxy-N-methylquinoline-6-carboxamide (72-2): Methylamine (8 M, 50 mL, 10 eq) in EtOH was added to a solution of Compound **72-1** (10 g, 40 mmol, 1 eq) in THF (150 mL) at 30 °C. The reaction mixture was stirred at 30 °C for 25 h. The mixture was concentrated under vacuum. The residue was slurried with warm water (100 mL) and filtered. The filtered cake was dried under vacuum to give Compound **72-2** (9 g, 90% yield). MS for $C_{12}H_{11}ClN_2O_2$, *m/z* 251.0 (MH+).

[01241] Step 2: 4-(4-Amino-2-fluorophenoxy)-7-methoxy-N-methylquinoline-6-carboxamide (QA1-6): To a mixture of Compound **72-2** (2 g, 8 mmol, 1 eq) and 4-amino-2-fluoro-phenol (1.5 g, 12 mmol, 1.5 eq) in DMF (20 mL) was added Cs_2CO_3 (5.2 g, 16 mmol, 2 eq) in one portion at 25 °C. The mixture was stirred at 85 °C for 20 hr. The mixture was cooled to 25 °C, diluted with water, and filtered. The crude residue was purified by flash silica gel chromatography (0~5% MeOH/DCM) to give Compound **QA1-6** (276 mg, 10% yield). MS for $C_{18}H_{16}FN_3O_3$, *m/z* 342.1 (MH+).

[01242] The following compound was made in the same fashion as Compound **QA1-6** in **Example 72**:

[01243] 4-(4-Aminophenoxy)-7-methoxy-N-methylquinoline-6-carboxamide (QA1-5): The 4-amino-2-fluoro-phenol in step 2 was replaced with 4-aminophenol. MS for $C_{18}H_{17}N_3O_3$, *m/z* 324 (MH+).

Example 73: 4-((7-(1-(Difluoromethyl)-1H-pyrazol-4-yl)quinolin-4-yl)oxy)aniline (QA1-10)



[01244] Step 1: 7-Bromoquinolin-4-ol (73-1): A mixture of 2,2-dimethyl-1,3-dioxane-4,6-dione (10 g, 70 mmol, 1.2 eq) in trimethyl orthoformate (97 g, 912 mmol, 100 mL, 16 eq) was stirred at 105 °C for 1.5 h. 3-Bromoaniline (10 g, 58 mmol, 6.3 mL, 1 eq) was then added and the resulting mixture stirred for 1 h. The resulting suspension was filtered and the solid was washed with methanol and dried under vacuum. The recovered solid was added to Ph_2O (90 mL) at 230 °C and the mixture was stirred for 0.5 h. The reaction mixture was poured into petroleum ether after being cooled to room temperature. The resulting precipitate was filtered and washed with petroleum ether to give Compound **73-1** (6.1 g) which was used in subsequent reactions without further purification.

[01245] Step 2: 7-Bromo-4-chloroquinoline (73-2): Compound **73-2** was made from Compound **73-1** in the same manner that Compound **61-2** was made from Compound **61-1** in **Example 61**. MS for C_9H_5BrClN, found 243.9 (MH+).

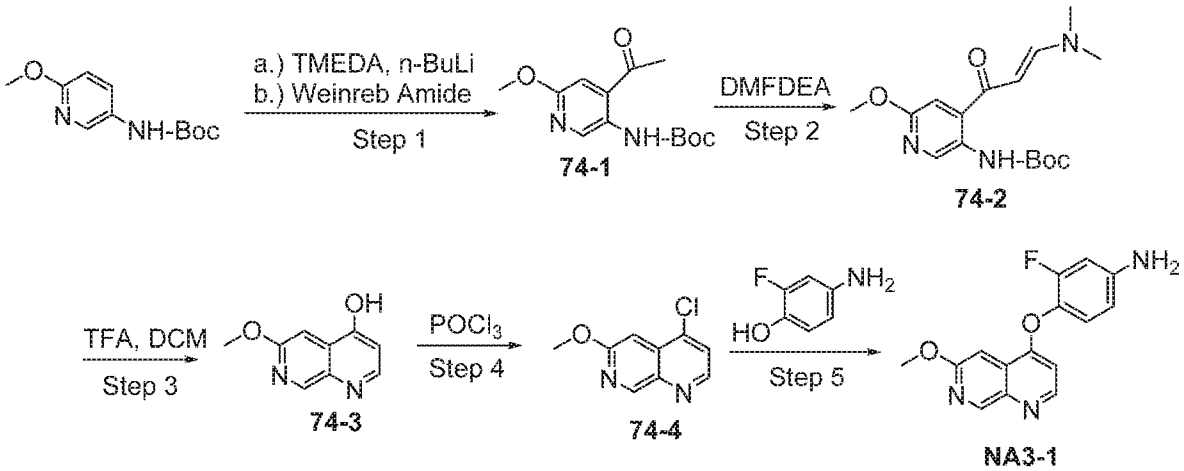
[01246] Step 3: 7-Bromo-4-(4-nitrophenoxy)quinoline (73-3): A mixture of Compound **73-2** (1 g, 4 mmol, 1 eq) and 4-nitrophenol (574 mg, 4.1 mmol, 1 eq) in Ph_2O (10 mL) was heated and stirred at 140 °C for 16 h, followed by stirring at 150 °C for another 4 h. The mixture was added to petroleum ether (10ml), then filtered and concentrated to give Compound **73-3** (1.23 g, 86% yield). MS for $C_{15}H_9BrN_2O_3$, found 346.9 (MH+).

[01247] Step 4: 7-(1-(Difluoromethyl)-1H-pyrazol-4-yl)-4-(4-nitrophenoxy)quinoline (73-4): Na_2CO_3 (460 mg, 4.3 mmol, 3 eq) and Pd(amphos)Cl_2 (105 mg, 0.15 mmol, 0.1 eq) were added to a mixture of Compound **73-3** (500 mg, 1.4 mmol, 1 eq) and 1-(difluoromethyl)-4-(4, 4, 5, 5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazole (435 mg, 1.8 mmol, 1.2 eq) in dioxane (10 mL) and water (2 mL) which was purged with nitrogen. The mixture was stirred at 90 °C under an atmosphere of nitrogen for 16

h. After cooling to room temperature, the mixture was diluted with EtOAc (20 mL) and filtered through a pad of Celite. The filtrate was quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were dried over anhyd Na_2SO_4 and concentrated. The resulting residue was purified by flash silica gel chromatography (30~50% petroleum ether: EtOAc) to give Compound **73-4** (374 mg, 65% yield). MS for $C_{19}H_{12}F_2N_4O_3$, found 383.0 (MH+).

[01248] Step 5: 4-((7-(1-(Difluoromethyl)-1H-pyrazol-4-yl)quinolin-4-yl)oxy)aniline (QA1-10): Compound **QA1-10** was made from Compound **73-4** using step 3 of **General Procedure G**. MS for $C_{19}H_{14}F_2N_4O$, *m/z* 352.9 (MH+).

Example 74: 3-Fluoro-4-((6-methoxy-1,7-naphthyridin-4-yl)oxy)aniline (NA3-1)



[01249] Step 1: tert-Butyl (4-acetyl-6-methoxypyridin-3-yl)carbamate (74-1): tert-Butyl (6-methoxypyridin-3-yl)carbamate (2.5g, 11 mmol) was added to an oven dried round bottom flask equipped with a magnetic stir bar under nitrogen. Anhyd Et_2O (50 mL) was added to the flask under nitrogen, followed by tetramethylethylenediamine (TMEDA) (5.0 mL, 3 eq). The homogenous mixture was cooled to -78 °C and stirred for 15 min under nitrogen. *N*-Butyl lithium (10 mL, 2.5 M in hexanes) was added to the mixture dropwise. After addition was complete, the mixture was warmed to -20 °C and stirred at that temperature for 2 h, after which the reaction mixture was cooled back down to -78 °C and Weinreb amide was added to the mixture. The resulting mixture was allowed to warm up to -20 °C and stirred under nitrogen for 2 h. The mixture was quenched at low temperature with water. EtOAc was used to extract the aqueous layer. The organic extracts were dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The resulting residue was absorbed into silica gel and purified by flash chromatography (EtOAc/hexanes) to give Compound **74-1** (745 mg, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (bs, 1H), 9.20 (s, 1H), 7.10 (s, 1H), 3.97 (s, 3H), 2.64 (s, 3H), 1.54 (s, 9H).

[01250] Step 2: tert-Butyl (E)-(4-(3-(dimethylamino)acryloyl)-6-methoxypyridin-3-yl)carbamate (74-2): To a solution of Compound **74-1** (745 mg, 2.8 mmol) in toluene was added N,N-dimethylformamide diethyl acetal (DMF-DEA) (1.5 mL, 2.0 eq) and the reaction mixture was heated at 80 °C. Upon completion of reaction, the solution was concentrated under reduced pressure to remove toluene. EtOAc was added to the residue and the mixture was absorbed into silica gel and purified by flash chromatography (EtOAc/hexanes) to give Compound **74-2** (800 mg, 89% yield). ^{1}H NMR (400

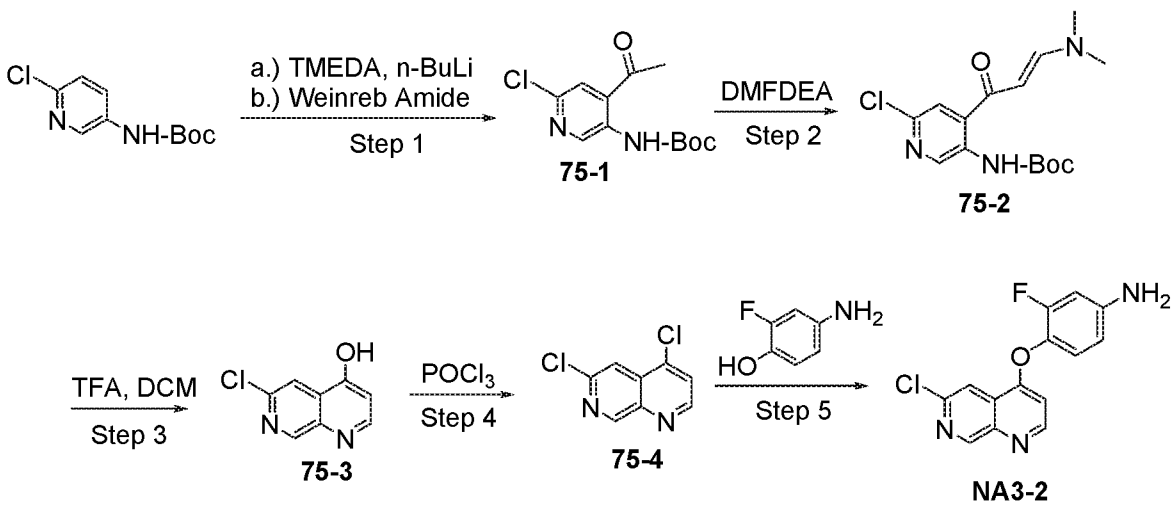
MHz, $CDCl_3$) δ 9.50 (bs, 1H), 9.03 (s, 1H), 7.79 (d, 1H), 6.95 (s, 1H), 5.56 (d, 1H), 3.97 (s, 3H), 3.21 (s, 3H), 2.96 (s, 3H), 1.51 (s, 9H); MS for $C_{16}H_{23}N_3O_4$, found 322 (MH+).

[01251] Step 3: 6-Methoxy-1,7-naphthyridin-4-ol (74-3): Compound **74-2** (800 mg, 2.5 mmol) was dissolved in DCM (12.5 mL) and trifluoroacetic acid (TFA) (3.8 mL, 20 eq) was added dropwise. The resulting mixture was stirred at room temperature for 1 h. Upon completion of reaction, the reaction mixture was concentrated under reduced pressure to remove TFA. The residual solid was suspended in EtOAc and aq saturated $NaHCO_3$ solution was added dropwise until solid dissolved into the organic layer. The phases were separated, solid NaCl was added to the aqueous phase and the resulting mixture was extracted with DCM. The EtOAc and DCM layers were combined, dried over anhyd Na_2SO_4 and concentrated under reduced pressure to give crude Compound **74-3** (435 mg, 99% yield) which was used for the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 7.97 (d, 1H), 7.24 (s, 1H), 6.02 (d, 1H), 3.91 (s, 3H); MS for $C_9H_8N_2O_2$, found 177 (MH+).

[01252] Step 4: 4-Chloro-6-methoxy-1,7-naphthyridine (74-4): Compound **74-4** was made from Compound **74-3** in the same manner that Compound **61-2** was made from Compound **61-1** in **Example 61**. MS for $C_9H_7ClN_2O$, found 195 (MH+).

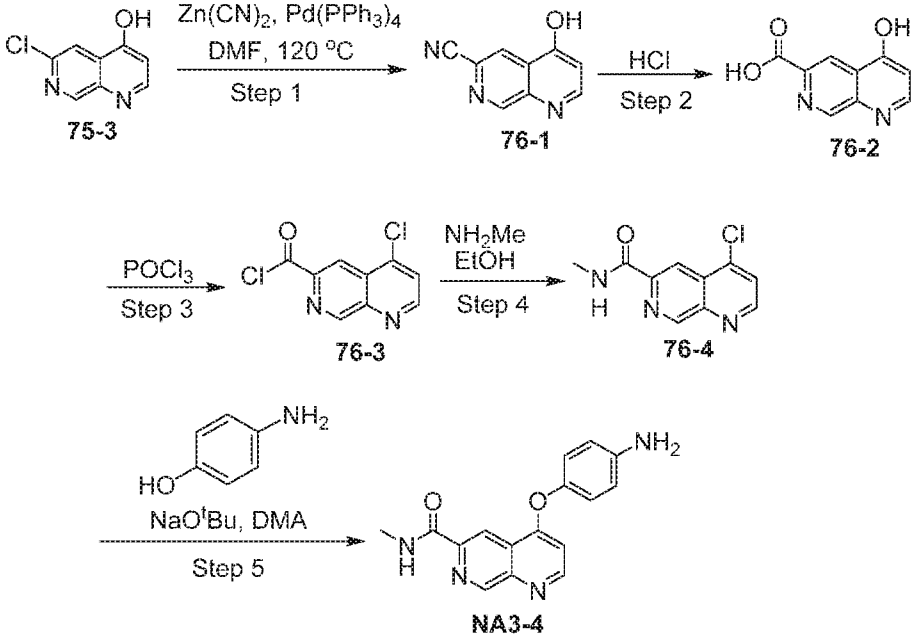
[01253] Step 5: 3-Fluoro-4-((6-methoxy-1,7-naphthyridin-4-yl)oxy)aniline (NA3-1): Compound **74-4** (353 mg, 1.8 mmol) was dissolved in anhyd DMF (9 mL) in a 20 mL microwave tube. Cs_2CO_3 (1.77 g, 3 eq) was added to the mixture followed by 4-amino-2-fluoro-phenol (461 mg, 2 eq). The mixture was degassed with nitrogen for 5 min, capped heated to 85 °C under microwave irradiation for 15 min. The resulting mixture was diluted with DCM and filtered. The mother liquor was washed with water and concentrated under reduced pressure. The resulting residue was diluted with DCM, washed with water, dried over anhyd Na_2SO_4, absorbed onto silica gel and purified by flash column chromatography (0-5% MeOH in DCM) to give Compound **NA3-1** (402 mg, 78% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.62 (d, 1H), 7.39 (s, 1H), 7.10 (t, 1H), 6.66 (d, 1H), 6.56 (d, 1H), 6.48 (d, 1H), 5.54 (s, 2H), 4.01 (s, 3H). MS for $C_{15}H_{12}FN_3O_2$, found 286 (MH+).

Example 75: 4-((6-Chloro-1,7-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA3-2)



[01254] Steps 1-5: 4-((6-Chloro-1,7-naphthyridin-4-yl)oxy)-3-fluoroaniline (NA3-2): Starting with tert-butyl (6-chloropyridin-3-yl)carbamate instead of tert-butyl (6-methoxypyridin-3-yl)carbamate, Compound **NA3-2** was made using the same 5 step sequence used to synthesize Compound **NA3-1** in **Example 74**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.85 (d, 1H), 8.25 (s, 1H), 7.13 (t, 1H), 6.85 (d, 1H), 6.57 (d, 1H), 6.48 (d, 1H), 5.71 (s, 2H).

Example 76: 4-(4-Aminophenoxy)-N-methyl-1,7-naphthyridine-6-carboxamide (NA3-4)



[01255] Step 1: 4-Hydroxy-1,7-naphthyridine-6-carbonitrile (76-1): To a solution of Compound **75-3** (1 g, 5.5 mmol, 1 eq) and zinc cyanide (390 mg, 3.3 mmol, 0.6 eq) in DMF (15 mL) was added Pd $(PPh_3)_4$ (1.3 g, 1.1 mmol, 0.2 eq). The mixture was stirred at 120 °C under nitrogen for 10 h. The mixture was diluted with water (50 mL) and filtered. The filtrate was concentrated, and the resulting residue was purified by silica gel column chromatography (0 - 10% MeOH in DCM) to give Compound **76-1** (800 mg, 85% yield). MS for $C_9H_5N_3O$, found 171.9 (MH+).

[01256] Step 2: 4-Hydroxy-1,7-naphthyridine-6-carboxylic acid (76-2): A solution of Compound **76-1** (1 g, 5.8 mmol, 1 eq) in aq HCl (15 mL) was stirred at 100 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give crude Compound **76-2** (1.1 g, quantitative yield). MS for $C_9H_6N_2O_3$, found 190.8 (MH+).

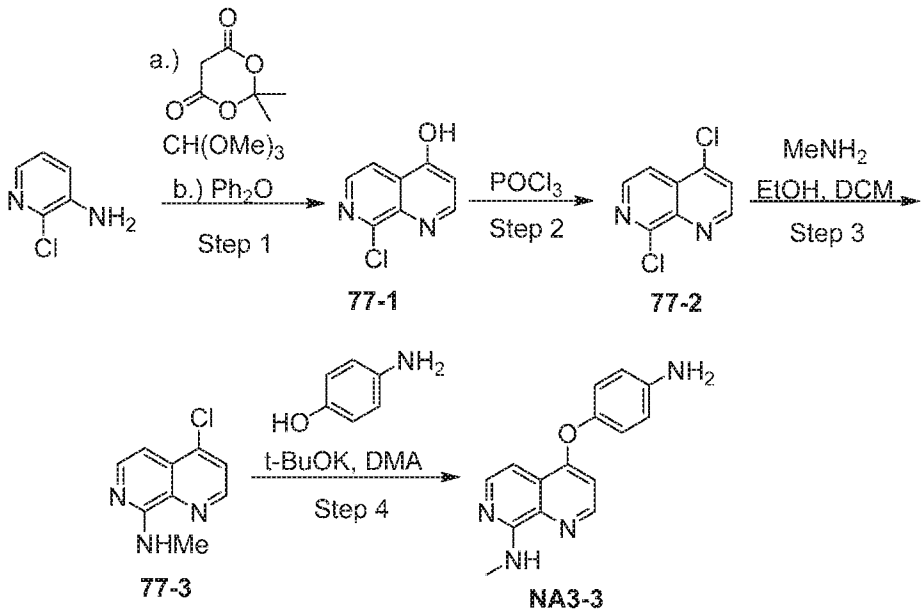
[01257] Step 3: 4-Chloro-1,7-naphthyridine-6-carbonyl chloride (76-3): A solution of Compound **76-2** (300 mg, 1.6 mmol, 1 eq) in $POCl_3$ (6 mL) was stirred at 100 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give crude Compound **76-3** (350 mg, quantitative yield).

[01258] Step 4: 4-Chloro-N-methyl-1,7-naphthyridine-6-carboxamide (76-4): A solution of Compound **76-3** (350 mg, 1.5 mmol, 1 eq) in THF (6 mL) was stirred at 0 °C for 0.5 h. To the mixture was added methylamine (47.9 mg, 1.5 mmol, 1 eq) and the resulting mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified

by flash silica gel chromatography (0~70% EtOAc/Petroleum ether) to give Compound **76-4** (46 mg, 13% yield). MS for $C_{10}H_8ClN_3O$, found 221.9 (MH+).

[01259] Step 5: 4-(4-Aminophenoxy)-N-methyl-1,7-naphthyridine-6-carboxamide (NA3-4): To a solution of Compound **76-4** (140 mg, 0.64 mmol, 1 eq) and 4-aminophenol (75.8 mg, 0.69 mmol, 1.1 eq) in DMA (2 mL) was added NaO^tBu (91 mg, 0.95 mmol, 1.5 eq). The mixture was stirred at 100 °C for 12 h. The mixture was adjusted to pH 5 with aq 1 M HCl, diluted with water (50 mL) and extracted with EtOAc (150 mL). The organic extracts were washed with aq saturated NaCl (50 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (0~5% MeOH/DCM) to give Compound **NA3-4** (180 mg, 97% yield). MS for $C_{16}H_{14}N_4O_2$, found 295.1 (MH+).

Example 77: 4-(4-Aminophenoxy)-N-methyl-1,7-naphthyridin-8-amine (NA3-3)



[01260] Step 1: 8-Chloro-1,7-naphthyridin-4-ol (77-1): A mixture of 2,2-dimethyl-1,3-dioxane-4,6-dione (6.7 g, 46.7 mmol, 1 eq) in triethoxymethane (60 mL, 361 mmol, 7.7 eq) was stirred at 105 °C for 1 h. 2-Chloropyridin-3-amine (6 g, 46.7 mmol, 1 eq) was added and the resulting mixture was stirred at 105 °C for 0.5 h. The mixture was concentrated, diluted with petroleum ether (100 mL), filtered, washed with petroleum ether (50 mL) and concentrated. A portion of the resulting solid (4 g) was mixed with Ph_2O (40 mL) and then stirred at 170 °C for 1 h. After cooling to 30 °C, the mixture was diluted with petroleum ether (200 mL) and filtered. The filtered cake was washed with petroleum ether (80 mL) and dried to give Compound **77-1** (2.4 g, 94% yield) which was used in subsequent reactions without further purification.

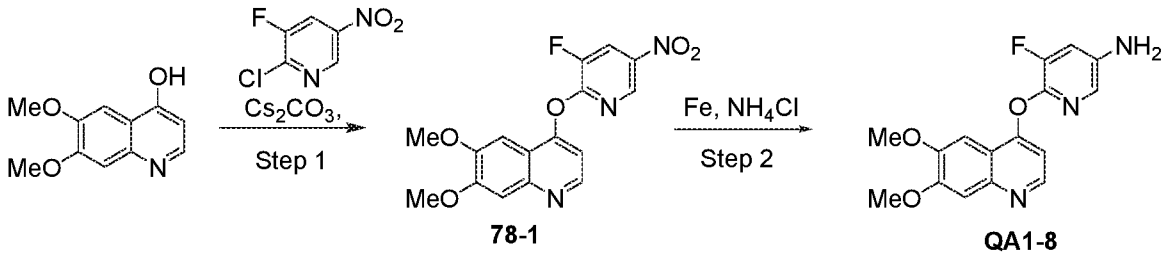
[01261] Step 2: 4,8-Dichloro-1,7-naphthyridine (77-2): Compound **77-2** was made from Compound **77-1** in the same manner that Compound **61-2** was made from Compound **61-1** in Step 2 of **Example 61**. MS for $C_8H_4Cl_2N_2$, found 198.9 (MH+).

[01262] Step 3: 4-Chloro-N-methyl-1,7-naphthyridin-8-amine (77-3): To a mixture of Compound **77-2** (82 mg, 0.41 mmol, 1 eq) in EtOH (1 mL) and DCM (3 mL) was added 33% $MeNH_2$ in EtOH (465

mg, 4.9 mmol, 12 eq). The mixture was stirred at 25 °C for 72 h. The mixture was concentrated and purified by flash silica gel chromatography (0~100% EtOAc/Petroleum ether) to give Compound **77-3** (63 mg, 79% yield). MS for $C_9H_8ClN_3$, found 193.8 (MH+).

[01263] Step 4: 4-(4-Aminophenoxy)-N-methyl-1,7-naphthyridin-8-amine (NA3-3): To a mixture of Compound **77-3** (63 mg, 0.32 mmol, 1 eq) and 4-aminophenol (107 mg, 0.98 mmol, 3 eq) in DMA (2 mL) was added t-BuOK (128 mg, 1.1 mmol, 3.5 eq) at 25 °C. The mixture was stirred at 100 °C for 12 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with aq saturated NaCl (10 mL), dried over anhyd Na_2SO_4 and concentrated. The resulting residue was purified by flash silica gel chromatography (0~30% EtOAc/petroleum ether gradient) to give Compound **NA3-3** (84 mg, 97% yield). MS for $C_{15}H_{14}N_4O$, found 266.9 (MH+).

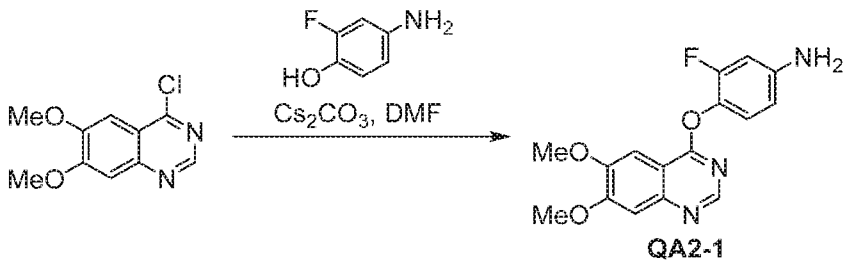
Example 78: 6-((6,7-Dimethoxyquinolin-4-yl)oxy)-5-fluoropyridin-3-amine (QA1-8)



[01264] Step 1: 4-((3-Fluoro-5-nitropyridin-2-yl)oxy)-6,7-dimethoxyquinoline (78-1): A mixture of 6,7-dimethoxy-1,5-naphthyridin-4-ol (1.05 g, 5 mmol), 2-chloro-3-fluoro-5-nitropyridine (0.91 g, 5.1 mmol) and Cs_2CO_3 (3.0, 9.1 mmol) in ACN (20 mL) was stirred at room temperature overnight. The resulting reaction mixture was diluted with EtOAc (100 mL) and filtered. The filtrate was concentrated, and the resulting residue purified by silica gel chromatography (0-100% EtOAc in hexane) to give Compound **78-1** (1.02 g, 59% yield). MS for $C_{16}H_{12}FN_3O5$: *m/z* 346 (MH+).

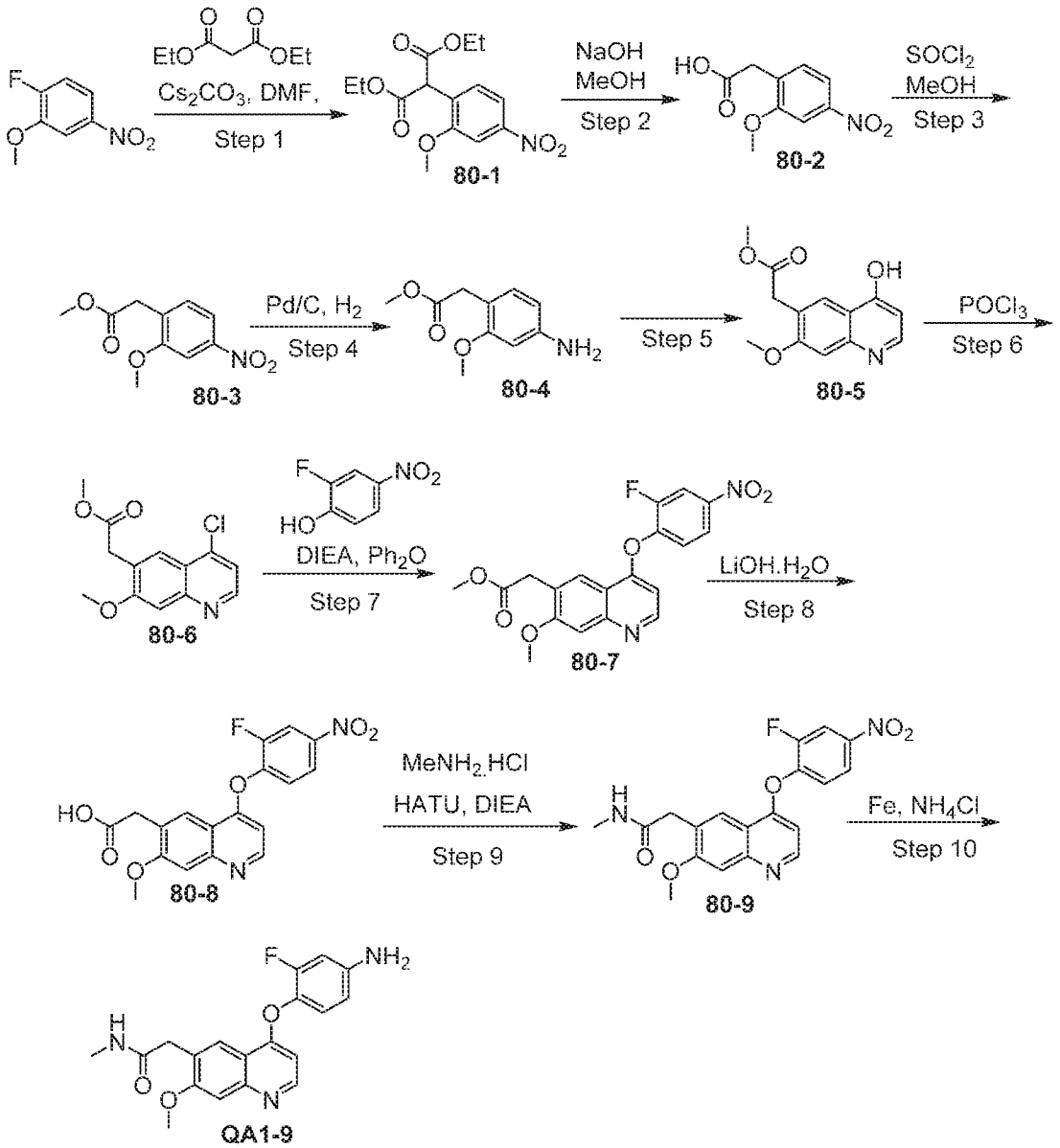
[01265] Step 2: 6-((6,7-Dimethoxyquinolin-4-yl)oxy)-5-fluoropyridin-3-amine (QA1-8): Compound **78-1** (702 mg, 2.03 mmol) was mixed with Fe (600 mg, 10.7 mmol), NH_4Cl (1.1 g, 20.6 mmol), water (20 mL), and MeOH (100 mL). The mixture was stirred at 85 °C for 60 min, cooled to room temperature and filtered through Celite. The filtrate was concentrated, and the residue partitioned between water and EtOAc. The phases were separated, and the aqueous phase was extracted with EtOAc (2x). The combined organic extracts were dried over anhyd Na_2SO_4 and evaporated to give Compound **QA1-8** (620 mg, 97% yield). MS for $C_{16}H_{14}FN_3O_3$: *m/z* 316 (MH+).

Example 79: 4-((6,7-Dimethoxyquinazolin-4-yl)oxy)-3-fluoroaniline (QA2-1)



[01266] 4-((6,7-Dimethoxyquinazolin-4-yl)oxy)-3-fluoroaniline (QA2-1): A mixture of 4-chloro-6,7-dimethoxyquinazoline (225 mg, 1 mmol), 4-amino-2-fluorophenol (150 mg, 1.09 mmol) and Cs_2CO_3 (500 mg, 1.52 mmol) in DMF (2 mL) was stirred at 80 °C for 20 min and then cooled to room temperature. Water was added and the resulting suspension was filtered. The collected solid was washed with water and dried to give crude Compound **QA2-1** (336 mg). MS for $C_{16}H_{14}FN_3O_3$: *m/z* 316 (MH+).

Example 80: 2-(4-(4-Amino-2-fluorophenoxy)-7-methoxyquinolin-6-yl)-N-methylacetamide (QA1-9)



[01267] Step 1: Diethyl 2-(2-methoxy-4-nitrophenyl)malonate (80-1): Compound **80-1** was made from 1-fluoro-2-methoxy-4-nitrobenzene using the same method that Compound **71-1** was made from 2-chloro-3-methoxy-5-nitropyridine in Step 1 of **Example 71**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, 1H), 7.75 (d, 1H), 7.55 (d, 1H), 5.16 (s, 1H), 4.35-4.15 (m, 4H), 3.95 (s, 3H), 1.29 (t, 6H).

[01268] Step 2: 2-(2-Methoxy-4-nitrophenyl)acetic acid (80-2): NaOH (1.93 g, 48 mmol, 3 eq) was added to a solution of Compound **80-1** (5 g, 16 mmol, 1 eq) in MeOH (40 mL). The reaction mixture

was stirred at 50 °C for 16 h. The mixture was concentrated under vacuum. To the resulting residue was added water (10 mL) and aq saturated citric acid (30 mL). The resulting solid was filtered, washed with water (20 mL) and dried in the air to give Compound **80-2** (2.67 g, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, 1H), 7.73 (d, 1H), 7.35 (d, 1H), 3.93 (s, 3H), 3.75 (s, 2H).

[01269] Step 3: Methyl 2-(2-methoxy-4-nitrophenyl)acetate (80-3): Compound **80-2** (2.6 g, 12.3 mmol, 1 eq) was dissolved in MeOH (30 mL). Thionyl chloride (5.86 g, 49.2 mmol, 4 eq) was added dropwise at 0 °C. After addition was complete, the reaction mixture was stirred at 25 °C for 1 h. The solvent was concentrated in vacuum and the mixture was extracted with EtOAc (3 x 20 mL). The combined EtOAc extracts were dried over anhyd Na_2SO_4 and concentrated under vacuum to give Compound **80-3** (2.49 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (br d, 1H), 7.70 (s, 1H), 7.33 (d, 1H), 3.91 (s, 3H), 3.70 (s, 2H), 3.695 (s, 3H).

[01270] Step 4: Methyl 2-(4-amino-2-methoxyphenyl)acetate (80-4): 10% Pd/C (700 mg, 4.2 mmol, 0.1 eq) was added to a mixture of Compound **80-3** (9.57 g, 42.5 mmol, 1 eq) in EtOAc (150 mL) under an atmosphere of hydrogen (15 psi). The mixture was stirred at 25 °C for 4 h. The solution was filtered through Celite and washed with EtOAc (20 mL). The filtrate was concentrated in vacuo to give Compound **80-4** (8.27 g, 100 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 - 6.81 (m, 1H), 6.18 - 6.11 (m, 2H), 3.68 - 3.62 (m, 3H), 3.58 (s, 3H), 3.43 (s, 2H).

[01271] Step 5: Methyl 2-(4-hydroxy-7-methoxyquinolin-6-yl)acetate (80-5): Compound **80-5** was made from Compound **80-4** using the same method that Compound **77-1** was made from 2-chloropyridin-3-amine in Step 1 of **Example 77**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.82 (br d, 1H), 6.93 (s, 1H), 5.96 (d, 1H), 3.85 (s, 3H), 3.71 (s, 2H), 3.60 (s, 3H).

[01272] Step 6: Methyl 2-(4-chloro-7-methoxyquinolin-6-yl)acetate (80-6): Compound **80-6** was made from Compound **80-5** in the same manner that Compound **61-2** was made from Compound **61-1** in Step 2 of **Example 61**. MS for $C_{13}H_{12}ClNO_3$: *m/z* 265.9 (MH+).

[01273] Step 7: Methyl 2-(4-(2-fluoro-4-nitrophenoxy)-7-methoxyquinolin-6-yl)acetate (80-7): To a solution of Compound **80-6** (1 g, 3.8 mmol, 1 eq) and 2-fluoro-4-nitro-phenol (769 mg, 4. 9 mmol, 1.3 eq) in Ph_2O (10 mL) was added DIEA (730 mg, 5.6 mmol, 1.5 eq) at 180 °C for 2 h. The reaction mixture was cooled to 25 °C, filtered and washed with EtOAc (40 mL). The combined organic layers were concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0-50% EtOAc in petroleum) to give Compound **80-7** (800 mg, 55% yield). MS for $C_{19}H_{15}FN_2O_6$: *m/z* 387.0 (MH+).

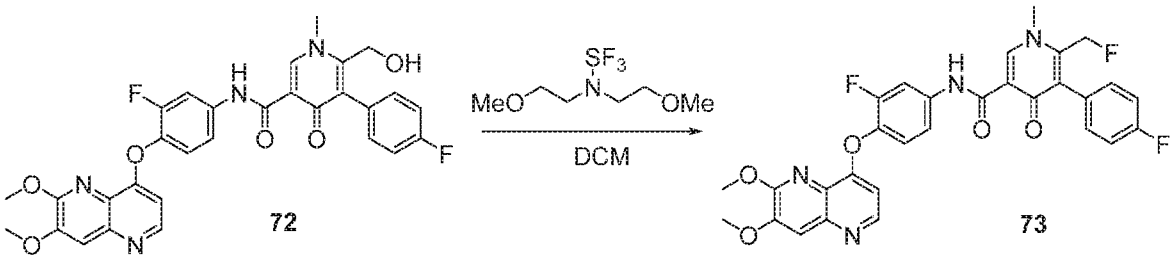
[01274] Step 8: 2-(4-(2-Fluoro-4-nitrophenoxy)-7-methoxyquinolin-6-yl)acetic acid (80-8): To a mixture of Compound **80-7** (750 mg, 1.9 mmol, 1 eq) in THF (10 mL) and water (3 mL) was added $LiOH·H_2O$ (326 mg, 7.8 mmol, 4 eq) slowly. The mixture was stirred at 25 °C for 2 h. The mixture was concentrated under vacuum to remove the organic solvent. The aqueous layer was acidified with aq 2 M HCl to pH 4-5. The resulting precipitate was filtered, and the filtered cake was washed with water (2 x 30 mL). The collected solid was dissolved in EtOAc (10 mL), dried over anhyd Na_2SO_4 and

concentrated under vacuum to give Compound **80-8** (600 mg, 83% yield). MS for $C_{18}H_{13}FN_2O_6$: *m/z* 373.0 (MH+).

[01275] Step 9: 2-(4-(2-Fluoro-4-nitrophenoxy)-7-methoxyquinolin-6-yl)-N-methylacetamide (80-9): To a mixture of Compound **80-8** (570 mg, 1.5 mmol, 1 eq) and methylamine hydrochloride (207 mg, 3.0 mmol, 2 eq) in DMF (5 mL) was added HATU (699 mg, 1.8 mmol, 1.2 eq) and DIEA (594. mg, 4.6 mmol, 3 eq). The resulting solution was stirred at 25 °C for 15 h. The reaction mixture was diluted with EtOAc (50 mL), washed with a 1:1 mixture of water and aq saturated NaCl (4 x 100 mL). The organic layer was dried over anhyd Na_2SO_4 and concentrated under reduced pressure to give crude Compound **80-9** (680 mg). MS for $C_{19}H_{16}FN_3O_5$: *m/z* 386.0 (MH+).

[01276] Step 10: 2-(4-(4-Amino-2-fluorophenoxy)-7-methoxyquinolin-6-yl)-N-methylacetamide (QA1-9): Compound **QA1-9** was made Compound **80-9** using the same method that Compound **QA1-8** was made from Compound **78-1** in Step 2 of **Example 78**. MS for $C_{19}H_{18}FN_3O_3$: *m/z* 356.2 (MH+).

Example 81: N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (73)



[01277] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (73): To a stirring mixture of Compound **72** (39.7 mg, 0.069 mmol, 1 eq) and DCM (1.0 mL) was added deoxo-fluor (50 mg, 0.2 mmol, 3 eq) at ambient temperature. After 1 h, the reaction was quenched by the addition of water (3 mL) and a few drops of aq $NaHCO_3$. The mixture was extracted with DCM (4 x Veq). The combined extracts were dried over anhyd Na_2SO_4, adsorbed onto Celite and purified by silica gel chromatography (0% to 10% MeOH in DCM) to give Compound **73** (33 mg, 83% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.89 (s, 1H), 8.56 (d, 1H), 8.05 – 7.98 (m, 1H), 7.66 (s, 1H), 7.45 (d, 1H), 7.38 – 7.26 (m, 5H), 6.83 (d, 1H), 5.31 (d, 2H), 4.03 (s, 3H), 3.98 (s, 3H), 3.95 (s, 3H); MS for $C_{30}H_{23}F_3N_4O_5$: *m/z* 577.2 (MH+).

[01278] The following compounds were made using the same method used to convert Compound **72** to Compound **73** in **Example 81**:

[01279] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(fluoromethyl)-5-(4-fluoro-2-methylphenyl)-1-methyl-4-oxopyridine-3-carboxamide (556): Made in one step from Compound **282**. MS for $C_{31}H_{25}F_3N_4O_5$: *m/z* 591.2 (MH+).

[01280] N-[3-Fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (557): Made in one step from Compound **228**. MS for $C_{32}H_{27}F_3N_4O_6$: *m/z* 621.2 (MH+).

[01281] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-ethyl-6-(fluoromethyl)-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (558): Made in one step from Compound **272**. MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573.2 (MH+).

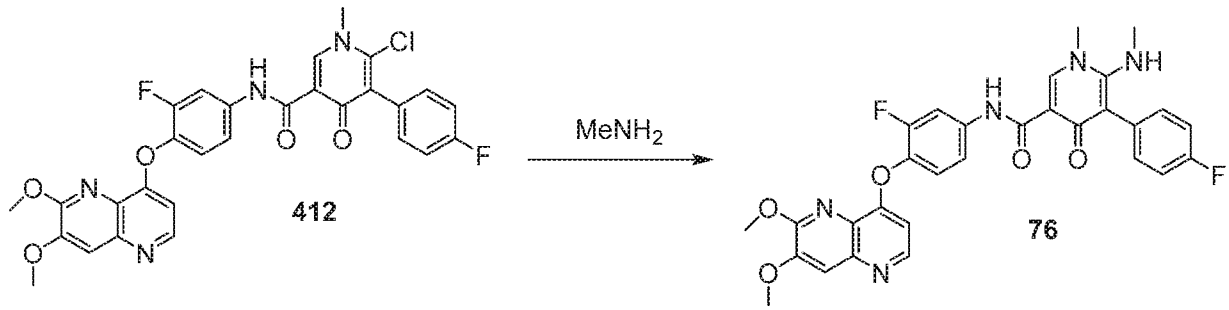
[01282] 1-Ethyl-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (559): Made in one step from Compound **273**. MS for $C_{30}H_{23}F_3N_4O_4$: *m/z* 561.2 (MH+).

[01283] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (560): Made in one step from Compound **221**. MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[01284] N-[3-Fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (561): Made in one step from Compound **224**. MS for $C_{29}H_{21}F_3N_4O_4$: *m/z* 547.2 (MH+).

[01285] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-6-(fluoromethyl)-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (562): Made in one step from Compound **271**. MS for $C_{31}H_{25}F_3N_4O_5$: *m/z* 591.2 (MH+).

Example 82: N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-6-(methylamino)-4-oxopyridine-3-carboxamide (76)

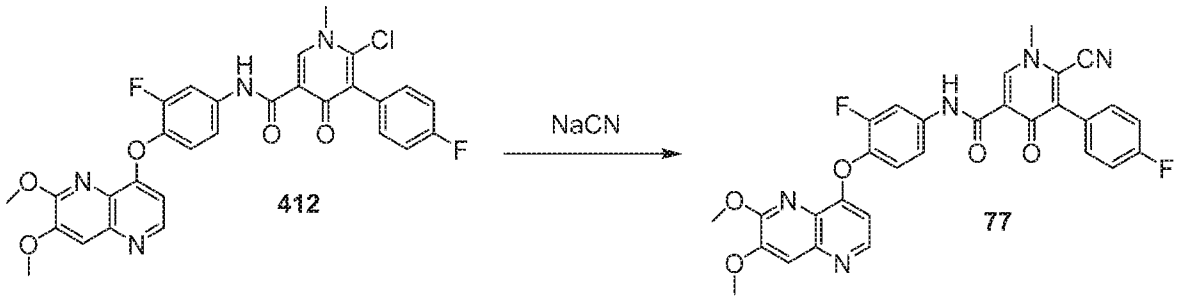


[01286] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-6-(methylamino)-4-oxopyridine-3-carboxamide (76): A mixture of Compound **412** (10 mg, 0.018 mmol) and 8 M $MeNH_2$ in MeOH (0.3 mL) in DMF (0.5 mL) was heated at 70 °C. Upon completion of the reaction as monitored by LC-MS, the reaction mixture was purified by prep HPLC to give Compound **76** (4 mg, 40% yield). MS for $C_{30}H_{25}F_2N_5O_5$: *m/z* 574 (MH+).

[01287] The following compound was made using the same method used to convert Compound **412** to Compound **76** in **Example 82**:

[01288] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methyl-6-(methylamino)-4-oxopyridine-3-carboxamide (585): Made in one step from Compound **411**. MS for $C_{29}H_{23}F_2N_5O_4$: *m/z* 544 (MH+).

Example 83: 6-Cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (77)

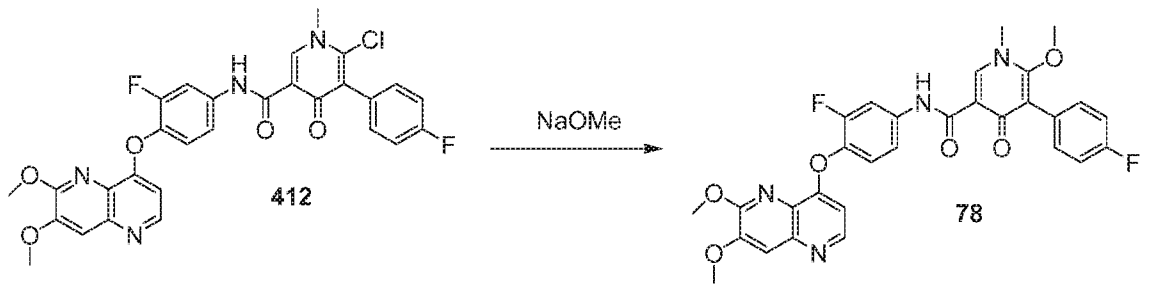


[01289] 6-Cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (77): A mixture of Compound **412** (10 mg, 0.018 mmol), TEA (72 mg, 0.72 mmol), and NaCN (50 mg, 1 mmol) in DMF (0.5 mL) was stirred at 70 °C for 2 h and quenched with water. The precipitate was collected by filtration and purified by prep HPLC to give Compound **77** (7 mg, 70% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.5 (s, 1H), 8.99 (s, 1H), 8.56 (d, 1H), 8.01 (dd, 1H), 7.66 (s, 1H), 7.62 – 7.54 (m, 1H), 7.48 (dd, 1H), 7.44 – 7.30 (m, 4H), 6.85 (d, 1H), 4.09 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H). MS for $C_{30}H_{21}F_2N_5O_5$: *m/z* 570 (MH+).

[01290] The following compound was made using the same method used to convert Compound **412** to Compound **77** in **Example 83**:

[01291] 6-Cyano-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide (586): Made in one step from Compound **411**. MS for $C_{29}H_{19}F_2N_5O_4$: *m/z* 540 (MH+).

Example 84: N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methoxy-1-methyl-4-oxopyridine-3-carboxamide (78)

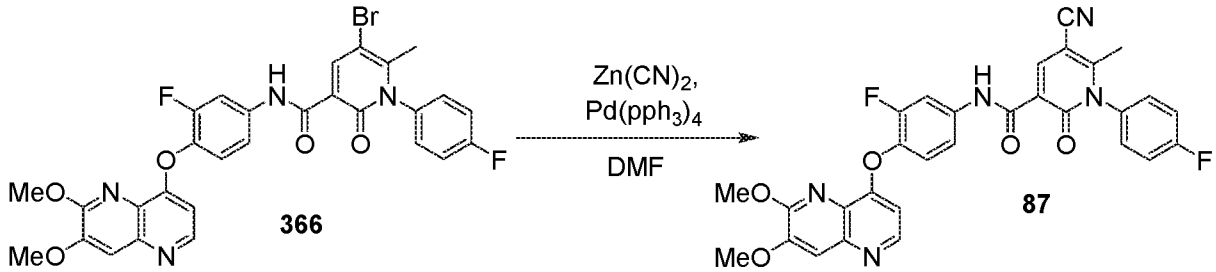


[01292] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methoxy-1-methyl-4-oxopyridine-3-carboxamide (78): A mixture of Compound **412** (25 mg, 0.043 mmol) and NaOMe (15 mg, 0.28 mmol) in DMF (1.0 mL) was stirred at room temperature until the reaction was complete. The resulting mixture was quenched with aq saturated $NaHCO_3$. The resulting solid was filtered, washed with water and dried under vacuum to give Compound **78** (18 mg, 72% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.1 (s, 1H), 8.71 (s, 1H), 8.56 (d, 1H), 8.02 (d, 1H), 7.66 (s, 1H), 7.50 – 7.38 (m, 3H), 7.38 – 7.25 (m, 3H), 6.83 (d, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.80 (s, 3H), 3.50 (s, 3H). MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 575 (MH+).

[01293] The following compound was made using the same method used to convert Compound **412** to Compound **78** in **Example 84**:

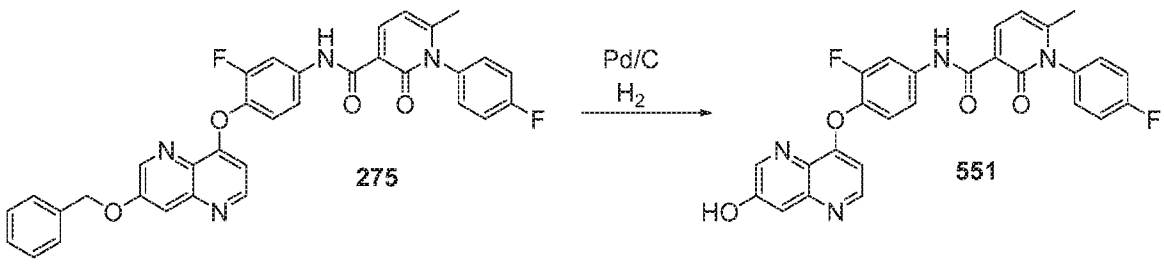
[01294] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methoxy-1-methyl-4-oxopyridine-3-carboxamide (587): Made in one step from Compound **411**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.1 (s, 1H), 8.76 (d, 1H), 8.72 (s, 1H), 8.71 (d, 1H), 8.06 (dd, 1H), 7.81 (d, 1H), 7.52 – 7.37 (m, 4H), 7.30 (t, 2H), 6.76 (d, 1H), 4.01 (s, 3H), 3.81 (s, 3H), 3.50 (s, 3H); MS for $C_{29}H_{22}F_2N_4O_5$: *m/z* 545 (MH).

Example 85: 5-Cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (87)



[01295] 5-Cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (87): A mixture of Compound **366** (80 mg, 0.13 mmol, 1 eq), $Pd(PPh_3)_4$ (15 mg, 0.013 mmol, 0.1 eq) and $Zn(CN)_2$ (48 mg, 0.41 mmol, 3.2 eq) in DMF (2 mL) was stirred at 140 °C under microwave irradiation and under an atmosphere of nitrogen for 0.5 h. The reaction was allowed to cool to room temperature. Aq saturated $FeSO_4$ solution was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water, aq saturated NaCl, dried over anhyd Na_2SO_4 and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 50~100%) and triturated with MTBE (2 x 10 mL) to give Compound **87** (34.1 mg, 45% yield). MS for $C_{30}H_{21}F_2N_5O_5$: *m/z* 570.1 (MH+).

Example 86: N-[3-Fluoro-4-[(7-hydroxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (551)



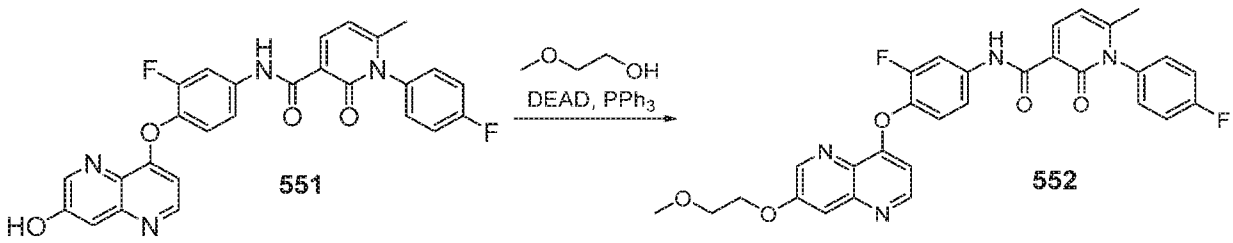
[01296] N-[3-Fluoro-4-[(7-hydroxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (551): A stirring mixture Compound **275** (25 mg, 0.042 mmol, 1 eq), THF (2.1 mL), DCM (0.3 mL) and 10% Pd/C (16 mg, 0.015 mmol, 0.36 eq) was placed under an atmosphere of hydrogen(1 atm). After 16 h the reaction was filtered through Celite and purified by silica gel chromatography (0% to 5% MeOH in EtOAc) followed by further purification by prep HPLC (10%

to 100% ACN in water (+FA)) to give Compound **551** (13 mg, 62% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (s, 1H), 11.2 – 10.6 (bs, 1H) 8.65 (d, 1H), 8.63 (d, 1H), 8.52 (d, 1H), 8.05 (d, 1H), 7.59 – 7.34 (m, 7H), 6.73 (d, 1H), 6.64 (d, 1H), 2.10 (s, 3H); MS for $C_{27}H_{18}F_2N_4O_4$: *m/z* 501 (MH+).

[01297] The following compound was made using the same method used to convert Compound **275** to Compound **551** in **Example 86**:

[01298] N-[3-Fluoro-4-[(7-hydroxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (554): Made in one step from Compound **277**. MS for $C_{28}H_{20}F_2N_4O_4$: *m/z* 515.2 (MH+).

Example 87: N-[3-Fluoro-4-[[7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (552)

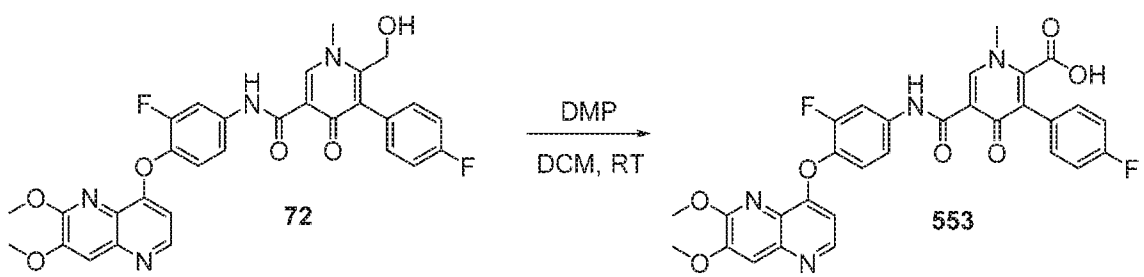


[01299] N-[3-Fluoro-4-[[7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide (552): To a stirring mixture of Compound **551** (6 mg, 0.012 mmol, 1 eq), 2-methoxyethanol (12 mg, 0.16 mmol, 13 eq), triphenylphosphine (16 mg, 0.061 mmol, 5 eq) and DCM (0.40 mL) was added diisopropyl azodicarboxylate (20 mg, 0.10 mmol, 8 eq). The mixture was stirred for 1 h at ambient temperature and then purified by silica gel chromatography (0% to 5% MeOH in DCM) followed by further purification by prep HPLC (10% to 100% ACN in water (+FA)) to give Compound **552** (2.1 mg, 31% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 12.12 (s, 1H), 8.84-8.62 (m, 2H), 8.55 (d, 1H), 7.97 (d, 1H), 7.75 (s, 1H), 7.45 – 7.25 (m, 6H), 6.73 (d, 1H), 6.66 (d, 1H), 4.37 (t, 2H), 3.87 (t, 2H), 3.47 (s, 3H), 2.14 (s, 3H); MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[01300] The following compound was made using the same method used to convert Compound **551** to Compound **552** in **Example 87**:

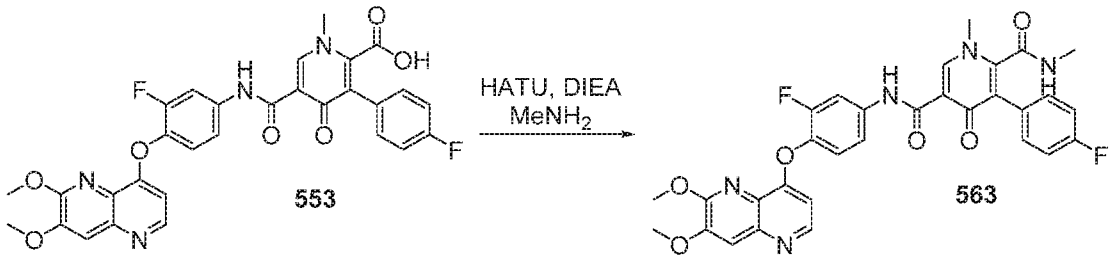
[01301] N-[3-Fluoro-4-[[7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (555): Made in two steps from Compound **277**. MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573.2 (MH+).

Example 88: 5-[[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]carbamoyl]-3-(4-fluorophenyl)-1-methyl-4-oxopyridine-2-carboxylic acid (553)



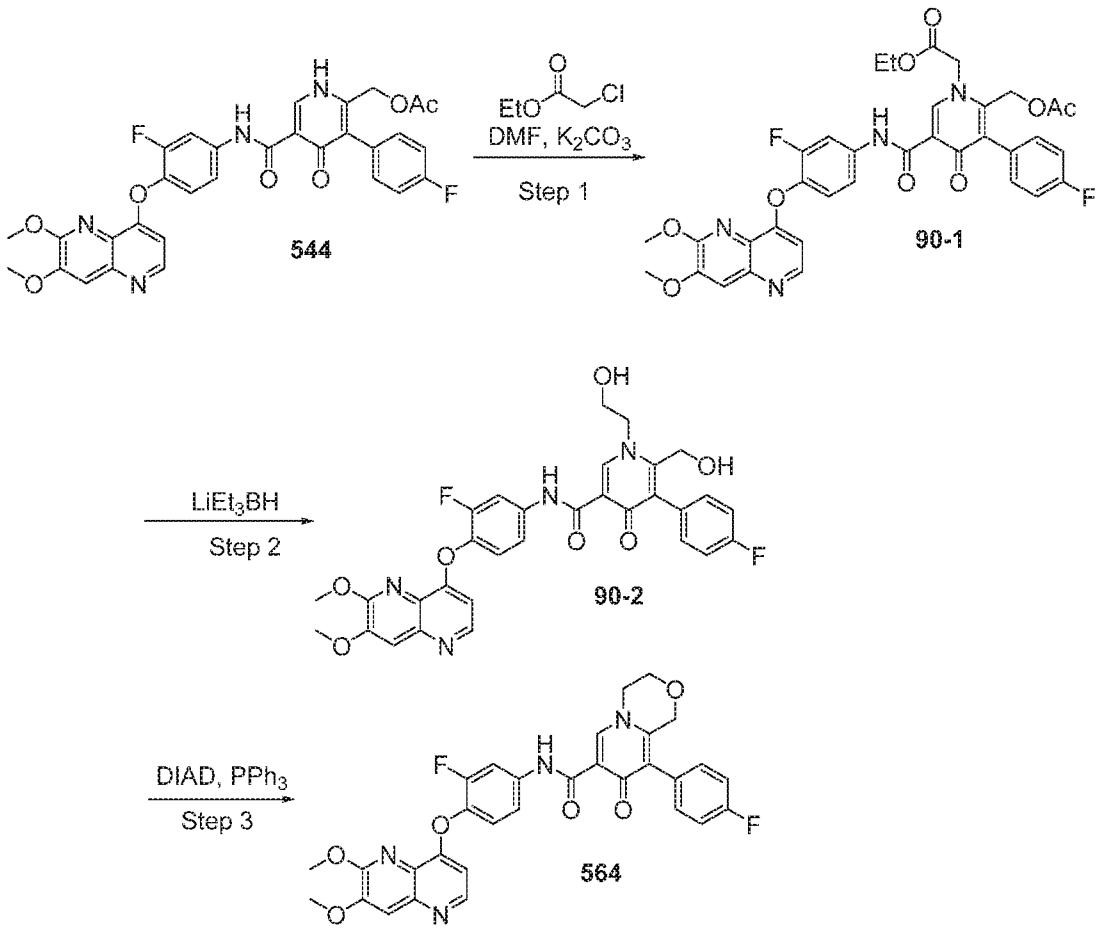
[01302] 5-[[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]carbamoyl]-3-(4-fluorophenyl)-1-methyl-4-oxopyridine-2-carboxylic acid (553): A mixture of Compound **72** (43 mg, 0.075 mmol, 1 eq), DCM (1.0 mL), DMF (0.60 mL) and Dess-Martin periodinane (90 mg, 0.21 mmol, 2.8 eq) was stirred at ambient temperature. After 3 days the DCM was removed and the reaction was purified by prep HPLC (10% to 100% ACN in water (+FA)) to give Compound **553** (15 mg, 35% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.19 (s, 1H), 12.75 (s, 1H), 8.68 (s, 1H), 8.55 (d, 1H), 8.14 (s, 1H), 8.02 (d, 1H), 7.66 (s, 1H), 7.47 – 7.29 (m, 3H), 7.19 (t, 2H), 6.83 (d, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.84 (s, 3H); MS for $C_{30}H_{22}F_2N_4O_7$: *m/z* 589.2 (MH+).

Example 89: 5-N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-2-N,1-dimethyl-4-oxopyridine-2,5-dicarboxamide (563)



[01303] 5-N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-2-N,1-dimethyl-4-oxopyridine-2,5-dicarboxamide (563): Compound **563** was made from Compound **553** and methylamine using standard HATU coupling techniques such as that exemplified in **Step 1** of **Example 1** for coupling Compound **NA1-1** to Compound **PA2-2**. MS for $C_{31}H_{25}F_2N_5O_6$: *m/z* 602.2 (MH+).

Example 90: N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-9-(4-fluorophenyl)-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-7-carboxamide (564)



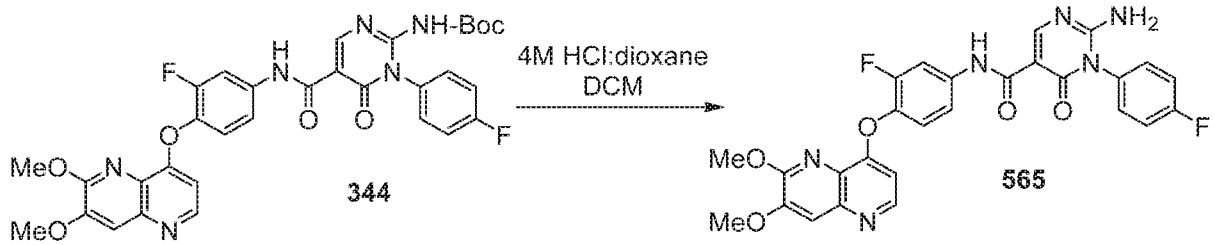
[01304] Step 1: Ethyl 2-(2-(acetoxymethyl)-5-((4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)carbamoyl)-3-(4-fluorophenyl)-4-oxopyridin-1(4H)-yl)acetate (90-1): A mixture of Compound **544** (139 mg, 0.23 mmol, 1 eq), DMF (0.5 mL), ethyl 2-chloroacetate (150 mg, 1.2 mmol, 5.3 eq) and potassium carbonate (0.11 g, 1.1 mmol, 4.8 eq) was stirred at ambient temperature overnight. The reaction mixture was then heated to 65 °C for 18 h. The crude reaction mixture was purified by silica gel chromatography (0 to 1% MeOH in DCM) to give Compound **90-1** (110 mg, 0.14 mmol, 62% yield). MS for $C_{35}H_{30}F_2N_4O_9$: *m/z* 689 (MH+).

[01305] Step 2: N-(4-((6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-(2-hydroxyethyl)-6-(hydroxymethyl)-4-oxo-1,4-dihydropyridine-3-carboxamide (90-2): To a stirring mixture of Compound **90-1** (59 mg, 0.086 mmol,1 eq) in THF (1.1 mL) was added a 1 M solution of lithium triethylborohydride (0.446 g, 0.505 mmol, 5.9 eq) and the resulting mixture was stirred for 2 h. The reaction mixture was then poured onto ice and acidified with dilute aq HCl to pH 3. The resulting aqueous mixture was extracted with DCM (4 x Veq). The combined organic extracts were concentrated to give crude Compound **90-2** (52 mg) which was used in the subsequent step without further purification.

[01306] Step 3: N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-9-(4-fluorophenyl)-8-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazine-7-carboxamide (564): To a solution

of Compound **90-2** (52 mg, 0.086 mmol, 1 eq), DCM (4.0 mL) and triphenylphosphine (50 mg, 0.19 mmol, 2.2 eq) was added DIAD (60 mg, 0.30 mmol, 3.5 eq). After 1 h the mixture was purified by silica gel chromatography (0% to 2% MeOH in DCM) followed by further purification by prep HPLC (10% to 60% ACN in water + FAC) to give Compound **564** (5 mg, 0.0085 mmol, 10% yield over 2 steps from Compound **90-1**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H), 8.63 (s, 1H), 8.47 (d, 1H), 7.93 (dd, 1H), 7.58 (s, 1H), 7.40 – 7.33 (m, 1H), 7.24 (dd, 5H), 6.75 (d, 1H), 4.42 (s, 2H), 4.26 (t, 2H), 3.99 (t, 2H), 3.90 (s, 3H), 3.87 (s, 3H); MS for $C_{31}H_{24}F_2N_4O_6$: *m/z* 587 (MH+).

Example 91: 2-Amino-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-oxopyrimidine-5-carboxamide (565)

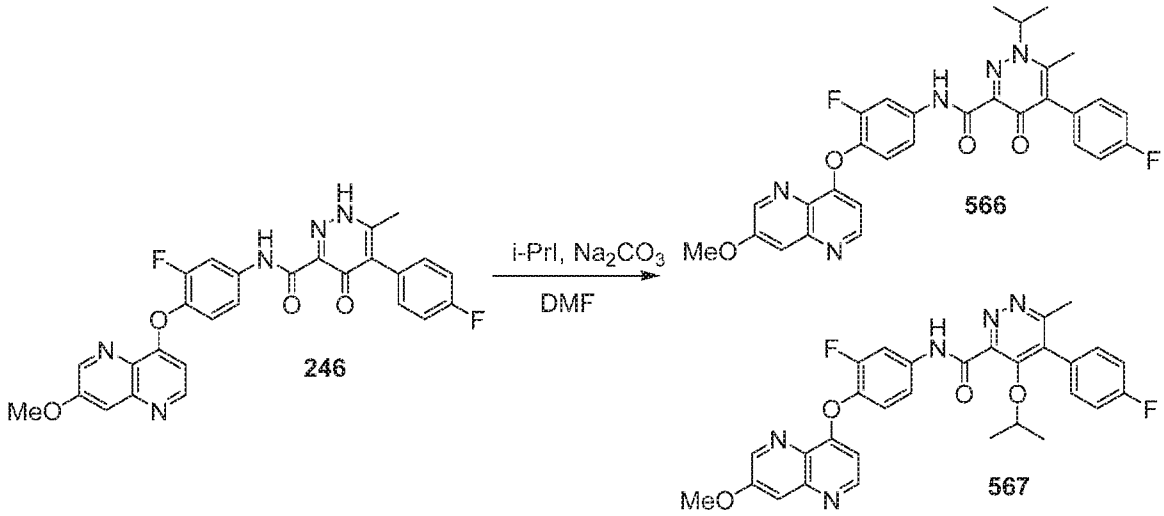


[01307] 2-Amino-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-oxopyrimidine-5-carboxamide (565): A 20-mL scintillation vial bearing Compound **344** (11 mg, 0.017 mmol) was charged with a Teflon stir bar and fitted with a rubber septa. An atmosphere of nitrogen was established, and the material was dissolved in dry DCM and cooled to 0 °C. A 4 M solution of HCl in dioxane (1 mL, 4 mmol, 235 eq) was slowly added to the vial and the reaction was allowed to warm to room temperature and stirred for 6 h. The reaction was then diluted with toluene and reduced to dryness. The resulting solid purified by prep HPLC to give Compound **565** (3.4 mg, 37% yield). ^{1}H NMR (DMSO-d_6) δ: 11.11 (s, 1H), 8.58 (s, 1H), 8.47 (d, 2H), 8.36 (s, 1H), 7.90 (dd, 1H), 7.57 (s, 1H), 7.43 (dd, 2H), 7.40 – 7.28 (m, 3H), 7.22 (t, 1H), 6.73 (d, 1H), 3.88 (d, 6H); MS for $C_{27}H_{20}F_2N_6O_5$, found 547 (MH+).

[01308] The following compound was made using standard techniques for the removal of Boc protecting groups from amines such as that exemplified by the conversion of Compound **344** to Compound **565** in **Example 91**:

[01309] 1-(Azetidin-3-yl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide (576): Made in one step from Compound **114**. MS for $C_{31}H_{25}F_2N_5O_5$: *m/z* 586 (MH+).

Example 92: N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridazine-3-carboxamide (566) and N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-propan-2-yloxypyridazine-3-carboxamide (567)



[01310] N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridazine-3-carboxamide (566) and N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-propan-2-yloxypyridazine-3-carboxamide (567): To a mixture of Compound **246** (0.2 g, 0.39 mmol, 1 eq) and $NaHCO_3$ (97.79 mg, 1.2 mmol, 0.045 mL, 3 eq) in DMF (3 mL) was added 2-iodopropane (132 mg, 0.78 mmol, 2 eq) and the resulting mixture was stirred at 20 °C for 15 h. Na_2CO_3 (123 mg, 1.2 mmol, 3 eq) was added and stirring continued at room temperature for an additional 15 h, followed by stirring at 60 °C for 15 h. The reaction mixture was added to water (80 mL) and stirred for 15 min. The resulting solid was filtered and washed with water (2 x 5 mL) and dissolved in DCM (50 mL). The resulting DCM solution was dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (DCM:MeOH = 1:0-20:1) twice followed by further purification by prep TLC (DCM:EtOAc:MeOH = 10:10:1, then EtOAc three times) to give Compound **566** (52.3 mg, 0.09 mmol, 24% yield) and Compound **567** (57.2 mg, 26% yield). Compound **566**: ^{1}H NMR ($CDCl_3$) δ: 12.90 (s, 1H), 8.79 (d, 1H), 8.67 (d, 1H), 8.07 (dd, 1H), 7.66 (d, 1H), 7.44 (br d, 1H), 7.27 - 7.19 (m, 5H), 6.63 (d, 1H), 4.83 (quin, 1H), 4.01 (s, 3H), 2.43 (s, 3H), 1.67 (d, 6H); MS for $C_{30}H_{25}F_2N_5O_4$: *m/z* 558.2 (MH+). Compound **567**: ^{1}H NMR ($CDCl_3$) δ: 13.69 (br s, 1H), 8.79 (d, 1H), 8.66 (d, 1H), 7.97 (dd, 1H), 7.66 (d, 1H), 7.44 (br d, 1H), 7.37 - 7.27 (m, 3H), 7.24 - 7.17 (m, 2H), 6.60 (d, 1H), 6.31 (br s, 1H), 4.01 (s, 3H), 2.39 (s, 3H), 1.66 (d, 6H); MS for $C_{30}H_{25}F_2N_5O_4$: *m/z* 558.1 (MH+).

[01311] The following compounds were made using the same method used to make Compounds **566** and **567** from Compound **246** in **Example 92**:

[01312] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-6-methyl-4-oxopyridazine-3-carboxamide (568) and **N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-ethoxy-5-(4-fluorophenyl)-6-methylpyridazine-3-**

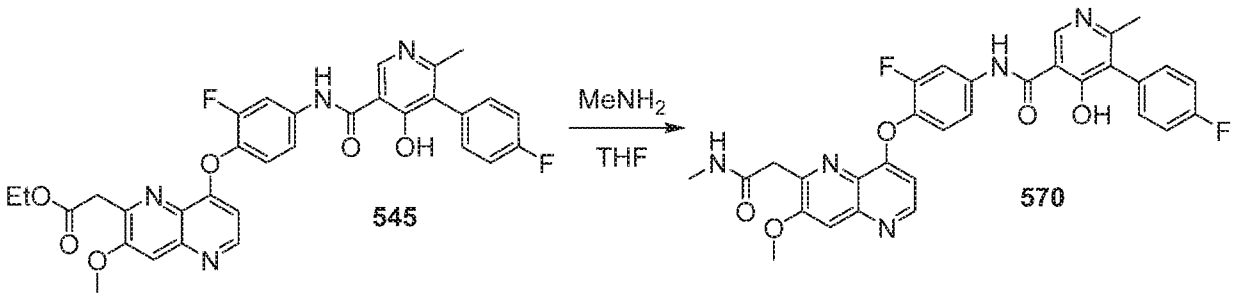
carboxamide (569): Made in one step from Compound **88**. Compound **568**: ^{1}H NMR ($CDCl_3$) δ: 12.77 (s, 1H), 8.46 (d, 1H), 7.93 (dd, 1H), 7.45 (s, 1H), 7.31 (br d, 1H), 7.18 - 7.13 (m, 4H), 7.12 - 7.06 (m, 1H), 6.70 (d, 1H), 4.42 (q, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 2.34 (s, 3H), 1.54 (t, 3H); MS for $C_{30}H_{25}F_2N_5O_5$, *m/z* 574.2 (MH+). Compound **569:** ^{1}H NMR ($CDCl_3$) δ: 14.00 (s, 1H), 8.46 (d, 1H), 7.86 (dd, 1H), 7.45 (s, 1H), 7.32 - 7.23 (m, 3H), 7.18 - 7.08 (m, 3H), 6.69 (d, 1H), 5.17 (q, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 2.29 (s, 3H), 1.66 (t, 3H); MS for $C_{30}H_{25}F_2N_5O_5$, *m/z* 574.1 (MH+).

[01313] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-4-methoxy-6-methylpyridazine-3-carboxamide (571): Made in one step from Compound **546**. ^{1}H NMR ($CDCl_3$) δ: 14.09 (s, 1H), 8.51 (d, 1H), 7.97 (dd, 1H), 7.59 (s, 1H), 7.47 - 7.40 (m, 2H), 7.37 - 7.33 (m, 2H), 7.26 - 7.20 (m, 3H), 6.45 (d, 1H), 4.82 (s, 3H), 4.07 (d, 6H), 2.37 (s, 3H); MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[01314] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-4-ethoxy-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxamide (572) and **N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-6-methyl-4-oxopyridazine-3-carboxamide (573):** Made in one step from Compound **546**. Compound **572**: ^{1}H NMR ($CDCl_3$) δ: 14.15 (s, 1H), 8.50 (d, 1H), 7.98 (dd, 1H), 7.59 (s, 1H), 7.48 - 7.41 (m, 2H), 7.35 (dd, 2H), 7.25 - 7.20 (m, 3H), 6.45 (d, 1H), 5.25 (q, 2H), 4.07 (d, 6H), 2.38 (s, 3H), 1.75 (t, 3H); MS for $C_{31}H_{26}F_2N_4O_5$, *m/z* 573.1 (MH+). Compound **573**: ^{1}H NMR ($CDCl_3$) δ: 12.71 (s, 1H), 8.48 (d, 1H), 8.03 (dd, 1H), 7.55 - 7.29 (m, 8H), 6.49 (d, 1H), 4.40 (q, 2H), 3.95 (s, 6H), 2.37 (s, 3H), 1.46 (t, 3H); MS for $C_{31}H_{26}F_2N_4O_5$, *m/z* 573.1 (MH+).

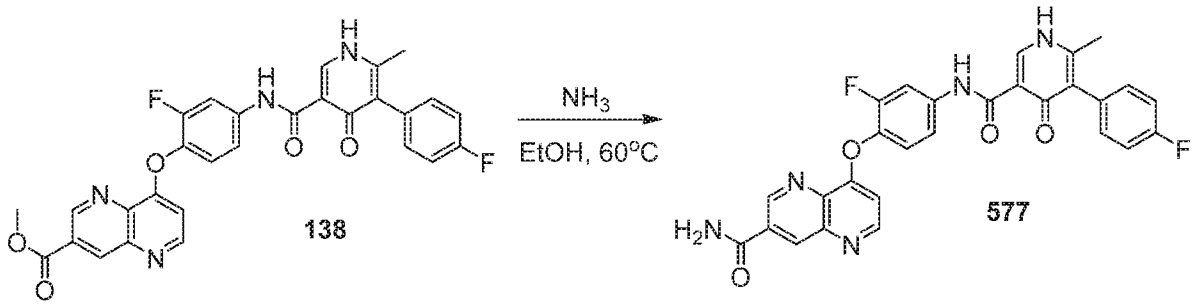
[01315] N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-propan-2-yloxypyridazine-3-carboxamide (574) and **N-[4-(6,7-Dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridazine-3-carboxamide (575):** Made in one step from Compound **546**. Compound **574**: ^{1}H NMR ($CDCl_3$) δ: 13.64 (br s, 1H), 8.50 (d, 1H), 7.97 (dd, 1H), 7.57 (s, 1H), 7.48 - 7.38 (m, 2H), 7.32 - 7.27 (m, 2H), 7.25-7.15 (m, 3H), 6.41 (d, 1H), 6.30 - 6.20 (m, 1H), 4.07 - 4.04 (m, 3H), 4.03 (s, 3H), 2.39 (s, 3H), 1.65 (d, 6H).; MS for $C_{32}H_{28}F_2N_4O_5$: *m/z* 587.1 (MH+). Compound **575:** ^{1}H NMR ($CDCl_3$) δ: 12.72 (s, 1H), 8.49 (d, 1H), 8.06 (dd, 1H), 7.55 - 7.30 (m, 8H), 6.50 (d, 1H), 5.01 - 4.92 (m, 1H), 3.99 - 3.93 (m, 6H), 2.40 (s, 3H), 1.49 (d, 6H); MS for $C_{32}H_{28}F_2N_4O_5$: *m/z* 587.1 (MH+).

Example 93: N-[3-Fluoro-4-[[7-methoxy-6-[2-(methylamino)-2-oxoethyl]-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (570)



[01316] N-[3-Fluoro-4-[[7-methoxy-6-[2-(methylamino)-2-oxoethyl]-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (570): To a mixture of Compound **545** (200 mg, 0.33 mmol, 1 eq) in THF (0.5 mL) was added 30% methylamine in EtOH (690 mg, 6.7 mmol, 20 eq). The mixture was stirred at 66 °C for 15 h. The reaction mixture was concentrated under reduced pressure. 1 N HCl (100 mL) was added to the resulting residue and the mixture was stirred for 5 min. The pH was then adjusted to 7 with aq saturated $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over anhyd Na_2SO_4 and concentrated. The resulting residue was purified by prep HPLC (water (0.05% HCl)-ACN) to give Compound **570** (19 mg, 19% yield). MS for $C_{31}H_{25}F_2N_5O_5$: *m/z* 586.0 (MH+).

Example 94: 8-[2-Fluoro-4-[[5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carbonyl]amino]phenoxy]-1,5-naphthyridine-3-carboxamide (577)

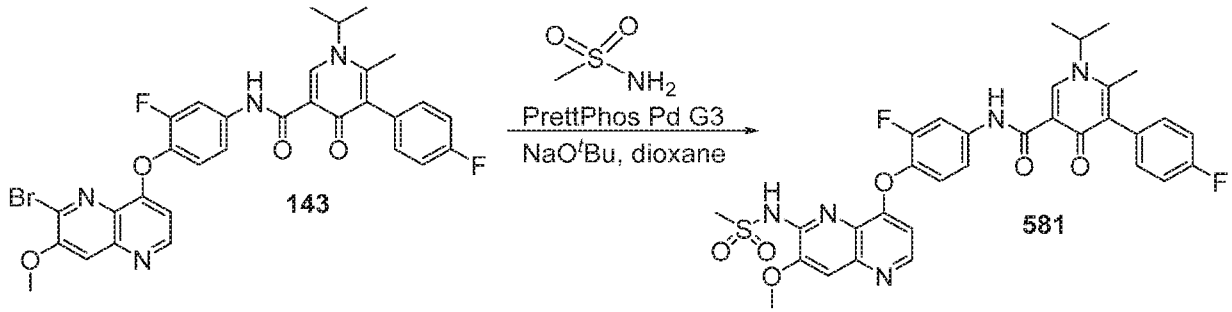


[01317] 8-[2-Fluoro-4-[[5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carbonyl]amino]phenoxy]-1,5-naphthyridine-3-carboxamide (577): Compound **138** (20 mg, 0.037 mmol) was mixed with 7M NH_3 in MeOH (1 mL) and EtOH (3 mL). The resulting mixture was stirred at 60 °C for 2 days. All volatiles were removed and resulting residue was purified by silica gel column chromatography (5% MeOH in EtOAc) to give Compound **577** (12 mg, 62% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33 (s, 1H), 12.61 (s, 1H), 9.37 (d, 1H), 8.87 (d, 1H), 8.84 (d, 1H), 8.54 (s, 1H), 8.47 (s, 1H), 8.05 (dd, 1H), 7.83 (s, 1H), 7.50 – 7.35 (m, 2H), 7.35 – 7.12 (m, 4H), 6.96 (d, 1H), 2.15 (s, 3H). MS for $C_{28}H_{19}F_2N_5O_4$: *m/z* 528 (MH+).

[01318] The following compound was made in the same way that Compound **138** was converted to Compound **577** in **Example 94**:

[01319] 8-[2-Fluoro-4-[[5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carbonyl]amino]phenoxy]-N-methyl-1,5-naphthyridine-3-carboxamide (578): Made in one step from Compound **138**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.42 (s, 1H), 12.68 (br. s, 1H), 9.38 (d, 1H), 8.99 (d, 1H), 8.87 (d, 1H), 8.83 (d, 1H), 8.57 (s, 1H), 8.17 – 7.99 (m, 1H), 7.57 – 7.35 (m, 2H), 7.35 – 7.16 (m, 4H), 6.98 (d, 1H), 2.90 (d, 3H), 2.18 (s, 3H); MS for $C_{29}H_{21}F_2N_5O_4$: *m/z* 542 (MH+).

Example 95: N-[3-Fluoro-4-[[6-(methanesulfonamido)-7-methoxy-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (581)



[01320] N-[3-Fluoro-4-[[6-(methanesulfonamido)-7-methoxy-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (581): A mixture of Compound **143** (26 mg, 0.041 mmol), methanesulfonamide (10 eq), NaO^{t}Bu (50 mg, 0.52 mmol) and BrettPhos Pd G3 catalyst (25 mg, 0.027 mmol) in dioxane (1.5 mL) was stirred at 90 °C overnight. The resulting mixture purified by silica gel chromatography to give Compound **581**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (s, 1H), 10.81 (br. s, 1H), 8.72 (s, 1H), 8.54 (d, 1H), 8.03 (dd, 1H), 7.67 (s, 1H), 7.42 (dd, 1H), 7.35 – 7.15 (m, 5H), 6.79 (d, 1H), 4.79 (p, 1H), 4.00 (s, 3H), 3.40 (s, 3H), 2.30 (s, 3H), 1.52 (d, 6H). MS for $C_{32}H_{29}F_2N_5O_6S$: *m/z* 650 (MH+).

[01321] The following compounds were made in the same way that Compound **143** was converted to Compound **581** in **Example 95**:

[01322] N-[4-[(6-Amino-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (579): Made in one step from Compound **143** and ammonia. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (s, 1H), 8.71 (s, 1H), 8.28 (d, 1H), 8.02 (dd, 1H), 7.49 – 7.35 (m, 2H), 7.35 – 7.17 (m, 4H), 6.80 (s, 2H), 6.65 (s, 1H), 6.55 (d, 1H), 4.79 (p, 1H), 3.98 (s, 3H), 2.30 (s, 3H), 1.52 (d, 6H); MS for $C_{31}H_{27}F_2N_5O_4$: *m/z* 572 (MH+).

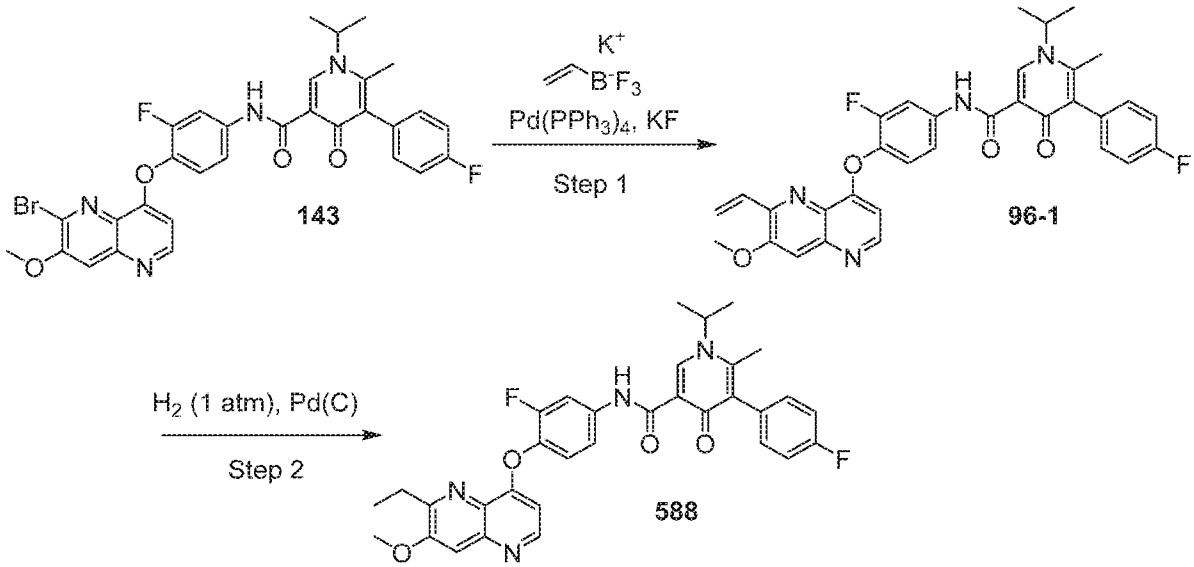
[01323] N-[3-Fluoro-4-[(6-hydroxy-7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (580): Compound **580** was recovered as a by-product from the reaction that produced Compound **579**. MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[01324] N-[3-Fluoro-4-[[7-methoxy-6-(methylamino)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (582): Made in one step from Compound **143** and methylamine. MS for $C_{32}H_{29}F_2N_5O_4$: *m/z* 586 (MH+).

[01325] N-[4-[[6-(Dimethylamino)-7-methoxy-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (583): Made in one step from Compound **143** and dimethylamine. MS for $C_{33}H_{31}F_2N_5O_4$: *m/z* 600 (MH+).

[01326] N-[3-Fluoro-4-[[6-(methanesulfonamido)-7-methoxy-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (584): Made in one step from Compound **142** and methanesulfonamide. MS for $C_{29}H_{23}F_2N_5O_6S$: *m/z* 608 (MH+).

Example 96: N-[4-[(6-Ethyl-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (588)



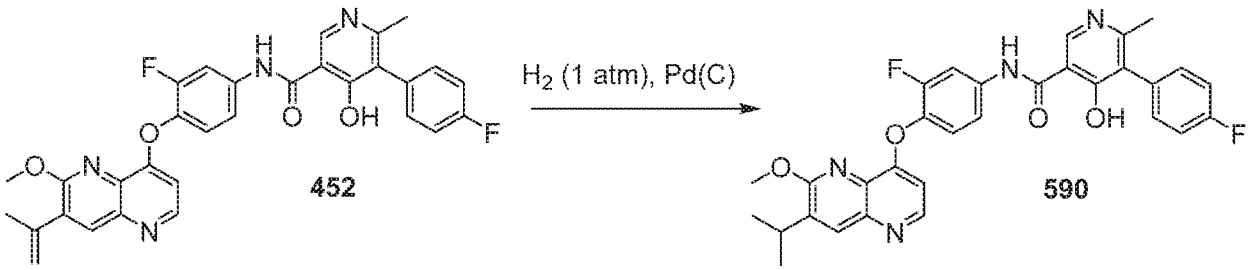
[01327] Step 1: N-(3-Fluoro-4-((7-methoxy-6-vinyl-1,5-naphthyridin-4-yl)oxy)phenyl)-5-(4-fluorophenyl)-1-isopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (96-1): A mixture of Compound **143** (45 mg, 0.071 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg, 0.028 mmol), potassium vinyltriflouroborate (30 mg, 0.22 mmol) and KF (50 mg, 0.86 mmol) in dioxane/water (2/1 mL) was stirred at 80 °C for 1h, after which the reaction mixture was allowed to cool to room temperature. The mixture was partitioned between EtOAc and water, the phases were separated, and the aqueous phase was further extracted with EtOAc (2x). The combined organic phases were dried over anhyd Na_2SO_4 and evaporated to dryness to give crude Compound **96-1** which was used without further purification. MS for $C_{33}H_{28}F_2N_4O_4$: *m/z* 583 (MH+).

[01328] Step 2: N-[4-[(6-Ethyl-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (588): Crude Compound **96-1** was mixed with 10% Pd/C (53% wet, 15 mg) in EtOAc (4 mL) and the resulting suspension was degassed under vacuum for 2 min, purged with hydrogen gas and then stirred under an atmosphere of hydrogen at room temperature overnight. The reaction mixture was filtered, the filtrate concentrated, and the resulting residue purified by prep HPLC to give Compound **588** (16 mg, 39% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.64 (s, 1H), 8.57 (d, 1H), 7.97 (dd, 1H), 7.63 (s, 1H), 7.38 (d, 1H), 7.36 – 7.30 (m, 1H), 7.30 – 7.18 (m, 4H), 6.68 (d, 1H), 4.72 (m, 1H), 3.94 (s, 3H), 2.88 (q, 2H), 2.22 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.17 (t, 3H). MS for $C_{33}H_{30}F_2N_4O_4$: *m/z* 585 (MH+).

[01329] The following compound was made using the same two step process to convert Compound **143** to Compound **588** in two steps **Example 96**:

[01330] N-[4-[(6-Ethyl-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (589): Made in 2 steps from Compound **142**. MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

Example 97: N-[3-Fluoro-4-[(6-methoxy-7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (590)



[01331] N-[3-Fluoro-4-[(6-methoxy-7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (590): Compound **590** was made from Compound **452** using standard hydrogenation conditions (10% Pd/C under 1 atmosphere of hydrogen) very similar to those employed in Step 2 of **Example 96** to convert Compound **96-1** to Compound **588**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.3 (s, 1H), 12.6 (s, 1H), 8.58 (d, 1H), 8.56 (s, 1H), 8.09 (s, 1H), 8.02 (d, 1H), 7.42 (d, 1H), 7.30 (m, 5H), 6.93 (d, 1H), 3.96 (s, 3H), 3.18 (m, 1H), 2.18 (s, 3H), 1.30 (d, 6H). MS for $C_{31}H_{26}F_2N_4O_4$: *m/z* 557 (MH+).

[01332] The following compounds were made using the hydrogenation conditions used to convert Compound **452** to Compound **590** in **Example 97**:

[01333] N-[3-Fluoro-4-[(6-methoxy-7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (591): Made in one step from Compound **449**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.3 (s, 1H), 12.5 (s, 1H), 8.57 (m, 2H), 8.08 (s, 1H), 8.02 (d, 1H), 7.40 (d, 1H), 7.32 (m, 1H), 7.16 (d, 1H), 7.07 (m, 2H), 6.92 (d, 1H), 3.96 (s, 3H), 3.18 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 1.30 (d, 6H); MS for $C_{32}H_{28}F_2N_4O_4$: *m/z* 571 (MH+).

[01334] N-[3-Fluoro-4-[(6-methoxy-7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (592): Made in one step from Compound **453**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.5 (s, 1H), 11.9 (s, 1H), 8.59 (d, 1H), 8.08 (s, 1H), 8.00 (d, 1H), 7.36 (m, 1H), 7.27 (m, 5H), 6.90 (d, 1H), 3.97 (s, 3H), 3.18 (m, 1H), 2.75 (s, 3H), 2.14 (s, 3H), 1.30 (d, 6H); MS for $C_{32}H_{28}F_2N_4O_4$: *m/z* 571 (MH+).

[01335] 5-(4-Fluoro-2-methylphenyl)-N-[3-fluoro-4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide (593): Made in one step from Compound **450**. MS for $C_{31}H_{26}F_2N_4O_3$: *m/z* 541 (MH+).

[01336] 5-(4-Fluorophenyl)-4-hydroxy-6-methyl-N-[4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide (594): Made in one step from Compound **454**. MS for $C_{30}H_{25}FN_4O_3$: *m/z* 509 (MH+).

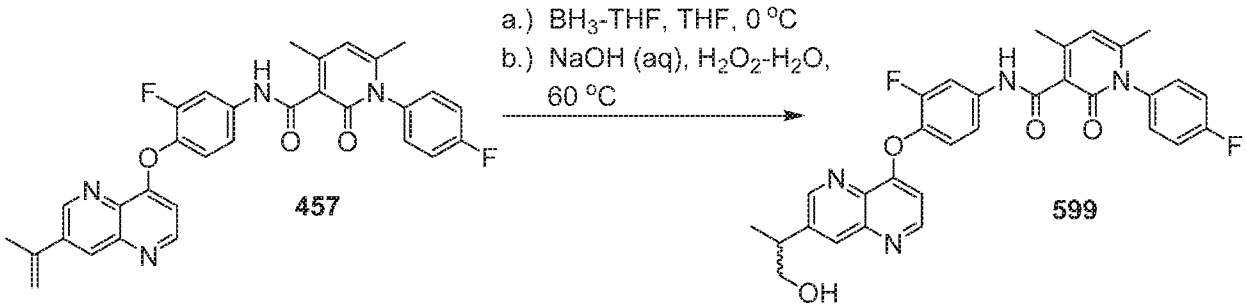
[01337] 5-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (595): Made in one step from Compound **451**. MS for $C_{31}H_{26}F_2N_4O_3$: *m/z* 541 (MH+).

[01338] 5-(4-Fluorophenyl)-N-[3-fluoro-4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-hydroxy-6-methylpyridine-3-carboxamide (596): Made in one step from Compound **456**. MS for $C_{30}H_{24}F_2N_4O_3$: *m/z* 527 (MH+).

[01339] 5-(4-Fluoro-2-methylphenyl)-4-hydroxy-6-methyl-N-[4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide (597): Made in one step from Compound **448**. MS for $C_{31}H_{27}FN_4O_3$: *m/z* 523 (MH+).

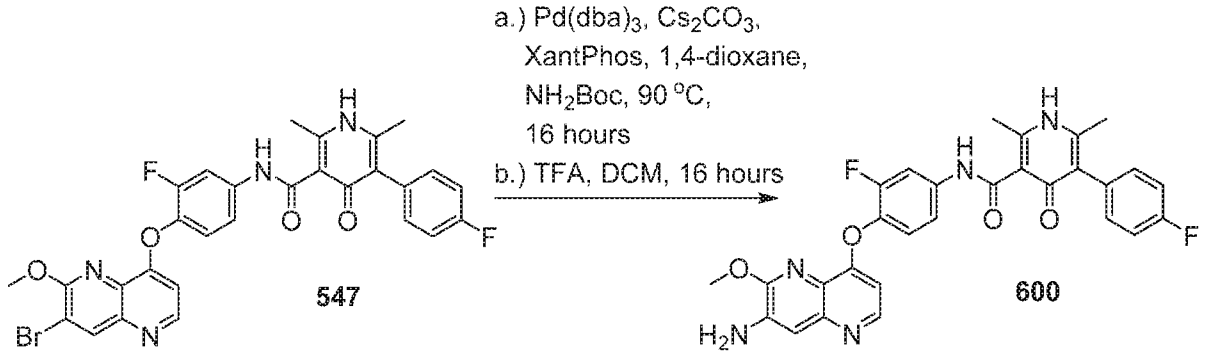
[01340] 5-(4-Fluorophenyl)-4-hydroxy-2,6-dimethyl-N-[4-[(7-propan-2-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide (598): Made in one step from Compound **455**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.2 (s, 1H), 11.9 (s, 1H), 8.96 (s, 1H), 8.74 (d, 1H), 8.21 (s, 1H), 7.79 (d, 2H), 7.25 (m, 6H), 6.81 (d, 1H), 3.18 (m, 1H), 2.76 (s, 3H), 2.15 (s, 3H), 1.38 (d, 6H); MS for $C_{31}H_{27}FN_4O_3$: *m/z* 523 (MH+).

Example 98: N-[3-Fluoro-4-[[7-(1-hydroxypropan-2-yl)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (599)



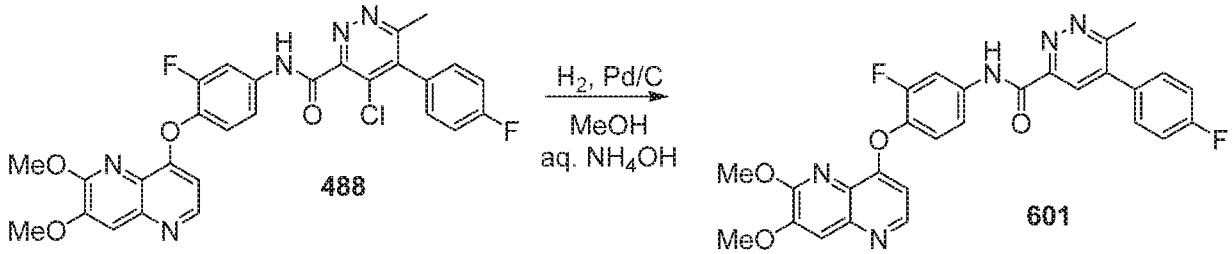
[01341] N-[3-Fluoro-4-[[7-(1-hydroxypropan-2-yl)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxopyridine-3-carboxamide (599): Borane-THF complex (BH_3-THF, 2M, 0.30 mL, 0.60 mmol) was added to a stirring solution of Compound **457** (50 mg, 0.09 mmol) in THF (2 mL) at 0 °C under a nitrogen atmosphere and the resulting mixture was allowed to warm to room temperature and stirred for 24 h. The resulting mixture was then cooled to 0 °C and aq 1 M NaOH (0.6 mL, 0.60 mmol,) and aq 30% hydrogen peroxide (1.8 mL, 0.60 mmol) were sequentially added and the resulting solution was stirred at 60 °C for 1 h. The reaction mixture was diluted in water (10 mL) and extracted with EtOAc (3 x 6 mL). The combined organic extracts were dried over anhyd $MgSO_4$, concentrated, redissolved in DMF, filtered and purified by prep HPLC (0-100% ACN in water (0.1% formic acid) to give Compound **599** (10 mg, 19% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.2 (s, 1H), 8.92 (d, 1H), 8.74 (d, 1H), 8.22 (s, 1H), 7.98 (dd, 1H), 7.49 (dd, 1H), 7.40 (m, 1H), m, 4H), 6.84 (dd, 1H), 6.39 (s, 1H), 4.10 (q, 1H), 3.65 (q, 1H), 3.16 (d, 3H), 2.38 (s, 3H), 1.98 (s, 3H), 1.34 (d, 2H). MS for $C_{31}H_{26}F_2N_4O_4$: *m/z* 557 (MH+).

Example 99: N-[4-[(7-Amino-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (600)



[01342] N-[4-[(7-Amino-6-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide (600): Cesium carbonate (70 mg, 0.21 mmol) was added to a mixture of Compound **547** (50 mg, 0.08 mmol), tert-butyl carbamate (15 mg, 0.13 mmol), XantPhos (10 mg, 0.02 mmol) and $Pd(dba)_3$ (16 mg, 0.02 mmol) in 1,4-dioxane (2 mL) and the reaction mixture was stirred at 90 °C for 16 h. The reaction mixture was cooled to room temperature, water (10 mL) was added and the resulting slurry was filtered. The filter cake was redissolved in DMF, filtered and the filtrate was purified by prep HPLC (0-100% ACN in water (0.1% formic acid) to give the Boc protected precursor to Compound **600**. This Boc protected intermediate was dissolved in DCM (6 mL) and TFA (0.1 mL, 1.3 mmol, 16 eq) and the resulting mixture was stirred at room temperature vigorously for 20 h, concentrated, redissolved in DMF and purified by prep HPLC (0-100% ACN in water (0.1% formic acid) to give Compound **600** (2 mg, 4.5% yield). MS for $C_{29}H_{23}F_2N_5O_4$: *m/z* 544 (MH+).

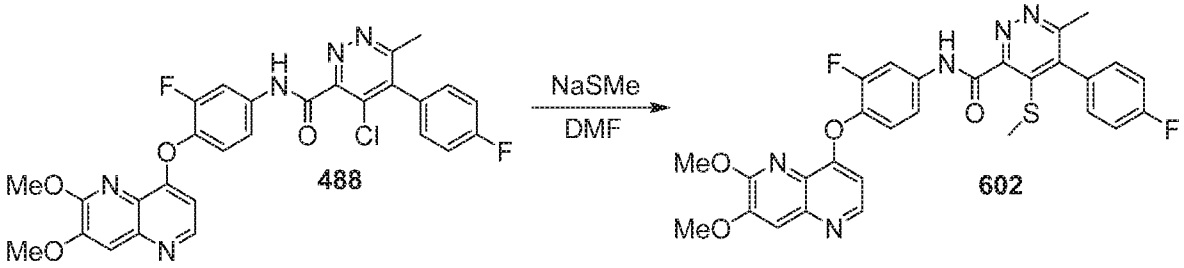
Example 100: N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxamide (601)



[01343] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methylpyridazine-3-carboxamide (601): To a 25 mL round bottom flask equipped with a magnetic stir bar and a rubber septum was added 10% Pd/C (67% water w/w) (20 mg) and the reaction was purged with nitrogen gas. A solution of **Compound 488** (25 mg, 0.04 mmol) in MeOH (2 mL) and was then added and the atmosphere was purged with hydrogen gas. The reaction was allowed to proceed at room temperature under 1 atm of hydrogen for 16 h. Ammonium hydroxide (0.2 mL) (30% aqueous solution) was added and a fresh hydrogen balloon attached, purging the solvent with hydrogen gas and stirring at room temperature for an additional 6 h. The reaction was filtered through Celite, concentrated and

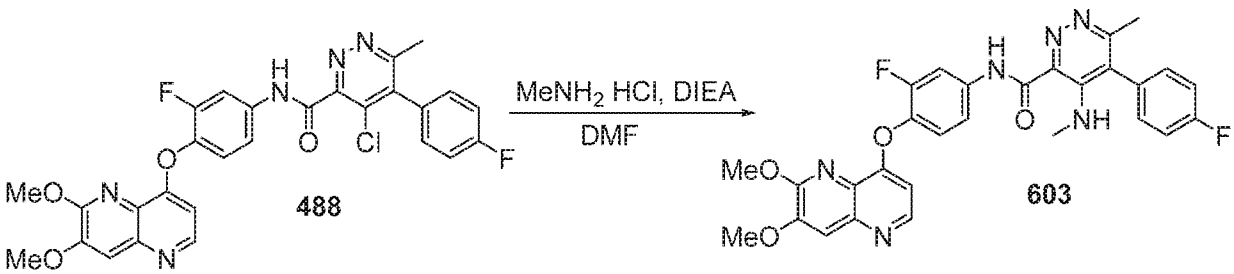
purified by prep HPLC to give Compound **601** (7.6 mg, 32% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 1H), 8.49 (d, 1H), 8.09 (dd, 1H), 8.01 (s, 1H), 7.91 – 7.80 (m, 1H), 7.69 – 7.56 (m, 3H), 7.34 (td, 3H), 6.77 (d, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.68 (s, 3H); MS for $C_{28}H_{21}F_2N_5O_4$: *m/z* 530.2 (MH+).

Example 101: N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-methylsulfanylpyridazine-3-carboxamide (602)



[01344] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-methylsulfanylpyridazine-3-carboxamide (602): To a 4 mL vial equipped with a magnetic stir bar and a pressure relief septum was added Compound **488** (25 mg, 0.044 mmol) in DMF (0.5 mL). Sodium thiomethoxide (11 mg, 0.16 mmol, 3.5 eq) was added in a single portion and the reaction was allowed to proceed at room temperature for 2 h. The reaction was diluted with water (3 mL), and a fine white precipitate was formed. The suspension was transferred to a separatory funnel and extracted with DCM. The organic extracts were concentrated to dryness under reduced pressure, dissolved in hot ACN (3 mL), filtered and purified by prep HPLC to give Compound **602**(9.1 mg, 36% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.49 (d, 1H), 7.91 (dd, 1H), 7.59 (s, 1H), 7.53 (d, 1H), 7.37 (dtd, 6H), 6.79 (d, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.35 (s, 3H), 2.01 (s, 2H); MS for $C_{29}H_{23}N_5O_4S$: *m/z* 576.2 (MH+).

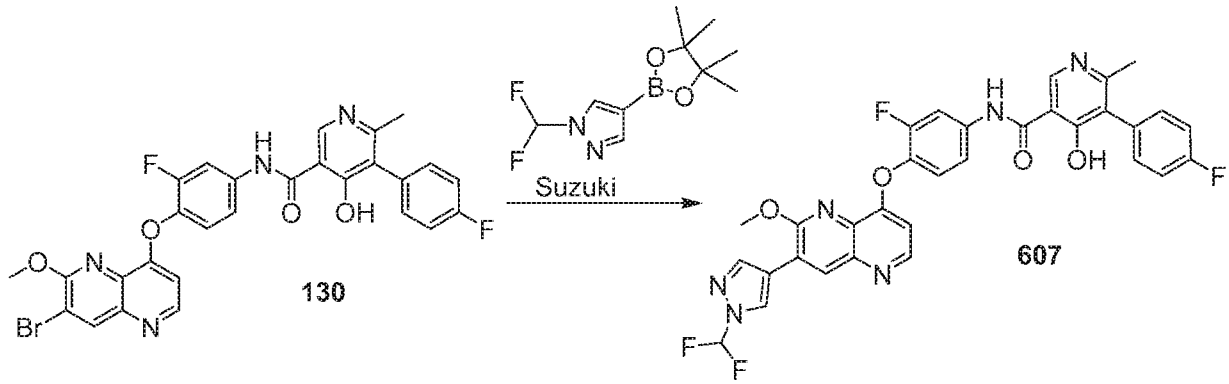
Example 102: N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-(methylamino)pyridazine-3-carboxamide (603)



[01345] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-(methylamino)pyridazine-3-carboxamide (603): To a 4 mL vial equipped with a magnetic stir bar and a pressure relief septum was added Compound **488** (25 mg, 0.044 mmol) and methylamine hydrochloride (50 mg, 0.74 mmol, 17 eq) in DMF (1 mL). DIEA (0.2 mL, 1 mmol, 30 eq) was added in a single portion and the reaction was heated to 60 °C overnight. The reaction mixture was diluted with water (3 mL) and stirred vigorously. The resulting white precipitate was filtered to yield a white powder which was subsequently purified by prep HPLC to give Compound **603**(2.5 mg, 10% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.49 (d, 1H), 8.41 (s, 1H), 8.04 – 7.96 (m, 1H), 7.73 (d, 1H), 7.59

(s, 1H), 7.41 – 7.21 (m, 5H), 6.77 (d, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.21 (d, 3H), 2.14 (s, 3H); MS for $C_{29}H_{24}F_2N_6O_4$: *m/z* 559.2 (MH+).

Example 103: N-[4-[[7-[1-(Difluoromethyl)pyrazol-4-yl]-6-methoxy-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (607)



[01346] N-[4-[[7-[1-(Difluoromethyl)pyrazol-4-yl]-6-methoxy-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (607): Compound **607** was made from Compound **130** using standard Suzuki conditions very similar to those employed in Step 4 of **Example 73** to convert Compound **73-3** to Compound **73-4**. MS for $C_{32}H_{22}F_4N_6O_4$: *m/z* 631.2 (MH+).

[01347] The following compounds were made using the standard Suzuki conditions used to convert Compound **130** to Compound **607** in **Example 103**:

[01348] N-[3-Fluoro-4-[(6-methoxy-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide hydrochloride (604): Made in one step from Compound **130**. MS for $C_{33}H_{23}F_2N_5O_4$: *m/z* 592.2 (MH+).

[01349] N-[3-Fluoro-4-[(6-methoxy-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide hydrochloride (605): Made in one step from Compound **131**. MS for $C_{35}H_{27}F_2N_5O_4$: *m/z* 620.2 (MH+).

[01350] N-[3-Fluoro-4-[(6-methoxy-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide hydrochloride (606): Made in one step from Compound **132**. MS for $C_{36}H_{29}F_2N_5O_4$: *m/z* 634.2 (MH+).

[01351] N-[4-[[7-[1-(Difluoromethyl)pyrazol-4-yl]-6-methoxy-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide (608): Made in one step from Compound **131**. MS for $C_{34}H_{26}F_4N_6O_4$: *m/z* 659.2 (MH+).

[01352] N-[4-[[7-[1-(Difluoromethyl)pyrazol-4-yl]-6-methoxy-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (609): Made in one step from Compound **132** MS for $C_{35}H_{28}F_4N_6O_4$: *m/z* 673.2 (MH+).

[01353] N-[4-[[7-[1-(Difluoromethyl)pyrazol-4-yl]-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide hydrochloride (610): Made in one step from Compound **133**. MS for $C_{31}H_{20}F_4N_6O_3$: *m/z* 601.2 (MH+).

[01354] N-[4-[[7-[1-(Difluoromethyl)pyrazol-4-yl]-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide (611): Made in one step from Compound **149**. MS for $C_{31}H_{21}F_3N_6O_3$: *m/z* 583.2 (MH+).

[01355] N-[4-[[7-[1-(Difluoromethyl)pyrazol-4-yl]-6-methyl-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide hydrochloride (612): Made in one step from Compound **548**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.89 (s, 1H), 8.83 (d, 1H), 8.63 (s, 1H), 8.43 (s, 1H), 8.21 (s, 1H), 7.93 (d, 2H), 7.65 (t, 1H), 7.38 (d, 2H), 7.33 – 7.19 (m, 4H), 7.08 (d, 1H), 4.97 – 4.90 (m, 1H), 2.96 (d, 3H), 2.38 (s, 3H), 1.63 (d, 6H); MS for $C_{35}H_{29}F_3N_6O_3$: *m/z* 639.2 (MH+).

[01356] 5-(4-Fluorophenyl)-6-methyl-N-[4-[(6-methyl-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-4-oxo-1-propan-2-ylpyridine-3-carboxamide hydrochloride (613): Made in one step from Compound **548**. MS for $C_{36}H_{30}FN_5O_3$: *m/z* 600.2 (MH+).

[01357] N-[4-[[7-[1-(Difluoromethyl)pyrazol-4-yl]-6-methyl-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide hydrochloride (614): Made in one step from Compound **153**. MS for $C_{35}H_{28}F_4N_6O_3$: *m/z* 657.2 (MH+).

[01358] N-[4-[[7-[1-(Difluoromethyl)pyrazol-4-yl]-6-methyl-1,5-naphthyridin-4-yl]oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide hydrochloride (615): Made in one step from Compound **549**. MS for $C_{32}H_{22}F_4N_6O_3$: *m/z* 615.2 (MH+).

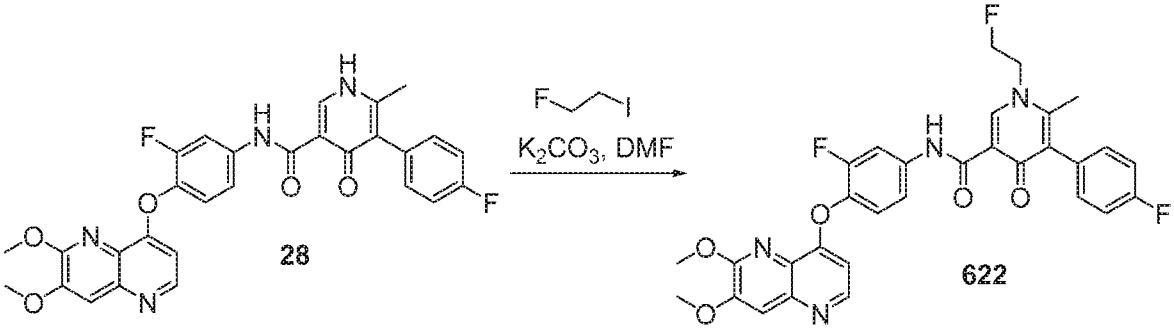
[01359] 5-(4-Fluorophenyl)-4-hydroxy-6-methyl-N-[4-[(6-methyl-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]pyridine-3-carboxamide hydrochloride (616): Made in one step from Compound **550**. MS for $C_{33}H_{24}FN_5O_3$: *m/z* 558.2 (MH+).

[01360] N-[4-[[7-[1-(Difluoromethyl)pyrazol-4-yl]-6-methyl-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide hydrochloride (617): Made in one step from Compound **550**. MS for $C_{32}H_{23}F_3N_6O_3$: *m/z* 597.2 (MH+).

[01361] N-[3-Fluoro-4-[(6-methyl-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide hydrochloride (618): Made in one step from Compound **549**. MS for $C_{33}H_{23}F_2N_5O_3$: *m/z* 576.2 (MH+).

[01362] N-[3-Fluoro-4-[(6-methyl-7-pyridin-3-yl-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide (620): Made in one step from Compound **153**. MS for $C_{36}H_{29}F_2N_5O_3$: *m/z* 618.2 (MH+).

Example 104: N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (622)



[01363] **N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (622)**: To a solution of Compound **28** (50 mg, 0.092 mmol) in DMF (0.5 mL) was added 1-fluoro-2-iodo-ethane (0.92 mmol, 10 eq) and K_2CO_3 (0.55 mmol, 6 eq). The reaction mixture was heated to 85 °C overnight. Water was added and the resulting mixture was extracted with DCM (3x). The combined organic extracts were concentrated, and the resulting residue was purified using flash silica gel chromatography (0-100% EtOAc/Hexanes and 0-20% MeOH/EtOAc) to give Compound **622** (34.4 mg, 57% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.75 (s, 1H), 8.55 (d, 1H), 8.01 (dd, 1H), 7.65 (s, 1H), 7.47 – 7.39 (m, 1H), 7.39 – 7.27 (m, 4H), 7.27 (s, 1H), 6.82 (dd, 1H), 4.96 – 4.56 (m, 4H), 3.96 (d, 6H), 2.24 (s, 3H). MS for $C_{31}H_{25}F_3N_4O_5$: *m/z* 591 (MH+).

[01364] The following compounds were made using the method used to convert Compound **28** to Compound **622** in **Example 103**:

[01365] **N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(2-hydroxyethyl)-6-methyl-4-oxopyridine-3-carboxamide (619):** Made in two steps from Compound **28**. MS for $C_{31}H_{26}F_2N_4O_6$: *m/z* 589.2 (MH+).

[01366] **N-[3-Fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-(2-hydroxyethyl)-6-methyl-4-oxopyridine-3-carboxamide (621):** Made in two steps from Compound **64**. ^{1}H NMR (400 MHz, CD_3OD) δ 13.05 (s, 1H), 8.80 (s, 1H), 8.77 – 8.63 (m, 2H), 8.20 – 7.92 (m, 1H), 7.77 (d, 1H), 7.42 (dt, 2H), 7.35 – 7.17 (m, 4H), 6.79 (d, 1H), 4.38 (d, 2H), 4.08 (s, 3H), 3.96 (t, 2H), 2.35 (s, 3H); MS for $C_{30}H_{24}F_2N_4O_5$: *m/z* 559.2 (MH+).

[01367] **1-(2,2-Difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (623):** Made in one step from Compound **28**. MS for $C_{31}H_{24}F_4N_4O_5$: *m/z* 609 (MH+).

[01368] 1-**(2-Fluoroethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (624):** Made in one step from Compound **64**. MS for $C_{30}H_{23}F_3N_4O_4$: *m/z* 561 (MH+).

[01369] **1-(2,2-Difluoroethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (625):** Made in one step from Compound **64**. MS for $C_{30}H_{22}F_4N_4O_4$: *m/z* 579 (MH+).

[01370] **1-(Difluoromethyl)-N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (626):** Made in one step from Compound **64**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 8.95 (s, 1H), 8.78 – 8.68 (m, 2H), 8.29 – 7.87 (m, 2H), 7.80 (d, 1H), 7.53 (d, 1H), 7.43 (t, 1H), 7.32 (d, 4H), 6.76 (dd, 1H), 4.01 (s, 3H), 2.35 – 2.31 (m, 3H); MS for $C_{29}H_{20}F_4N_4O_4$: *m/z* 565 (MH+).

[01371] **5-(4-Fluorophenyl)-1-(2-hydroxyethyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide (627):** Made in two steps from Compound **147.** MS for $C_{30}H_{25}FN_4O_5$: *m/z* 541 (MH+).

[01372] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1-(2-hydroxyethyl)-6-methyl-4-oxopyridine-3-carboxamide (628): Made in two steps from Compound **119**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.68 (s, 1H), 8.54 (d, 1H), 7.77 (d, 2H), 7.64 (s, 1H), 7.33 – 7.15 (m, 6H), 6.80 (d, 1H), 4.30 (s, 2H), 3.95 (d, 7H), 3.76 (t, 2H), 2.25 (s, 3H); MS for $C_{31}H_{27}FN_4O_6$: *m/z* 571 (MH+).

[01373] 1-(2,2-Difluoroethyl)-5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide (629): Made in one step from Compound **147**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 8.77 (s, 1H), 8.75 – 8.67 (m, 2H), 7.86 – 7.76 (m, 3H), 7.34 – 7.21 (m, 6H), 6.74 (d, 1H), 6.55 (t, 1H), 4.93 – 4.82 (m, 2H), 4.00 (s, 3H), 2.25 (s, 3H); MS for $C_{30}H_{23}F_3N_4O_4$: *m/z* 561 (MH+).

[01374] 1-(2,2-Difluoroethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (630): Made in one step from Compound **119**. MS for $C_{31}H_{25}F_3N_4O_5$: *m/z* 591 (MH+).

[01375] N-[4-[(6,7-Dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (631): Made in one step from Compound **119**. MS for $C_{31}H_{26}F_2N_4O_5$: *m/z* 573 (MH+).

[01376] 1-(2-Fluoroethyl)-5-(4-fluorophenyl)-N-[4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-6-methyl-4-oxopyridine-3-carboxamide (632): Made in one step from Compound **147**. MS for $C_{30}H_{24}F_2N_4O_4$: *m/z* 543 (MH+).

[01377] 1-(Difluoromethyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide (633): Made in one step from Compound **119**. ^{1}H NMR (400 MHz, CD_3OD) δ 12.14 (s, 1H), 8.85 (s, 1H), 8.40 (d, 1H), 7.90 (s, 1H), 7.81 – 7.71 (m, 2H), 7.15 – 7.05 (m, 6H), 6.97 (m, 1H), 6.77 (d, 1H), 4.09 (s, 3H), 4.02 (s, 3H), 2.32 (s, 3H); MS for $C_{30}H_{23}F_3N_4O_5$: *m/z* 577 (MH+).

[01378] The following compounds in **Table 4** were also made, using the same or similar techniques to those described in the preceding examples or using procedures reported in the literature or otherwise typically familiar to those skilled in the art.

Table 4

Cpd #	Molecular Formula	Observed MS (MH+)
647	C30 H23 Cl F2 N4 O5	593
648	C31 H26 F2 N4 O6	589.1
649	C31 H27 F2 N5 O5	588.2
650	C30 H25 F2 N5 O6	590.2

Cpd #	Molecular Formula	Observed MS (MH+)
651	C29 H22 F2 N4 O5	545.2
652	C30 H24 F2 N4 O6	575.2
653	C28 H21 F2 N5 O5	546.1
654	C31 H24 F2 N4 O6	587.1

Cpd #	Molecular Formula	Observed MS (MH+)
655	C29 H23 F2 N5 O5	559.9
656	C30 H22 F2 N4 O5	557.1
657	C29 H23 F2 N5 O5	559.9
658	C30 H22 F2 N4 O4	541.1
659	C31 H25 F N4 O6	569.1
660	C31 H25 F N4 O6	569.1
661	C30 H22 F2 N4 O5	557
662	C31 H24 F2 N4 O5	571.4
663	C32 H28 F2 N4 O6	603.2
664	C29 H21 F3 N4 O5	563
665	C29 H22 F2 N4 O5	545
666	C31 H25 F3 N4 O5	591.1
667	C32 H28 F2 N4 O5	587
668	C30 H22 F4 N4 O5	595
669	C29 H21 F3 N4 O4	547
670	C29 H22 F2 N4 O5	545
671	C30 H25 F N4 O5	541
672	C32 H29 F N4 O6	585
673	C31 H27 F N4 O5	555
674	C32 H29 F N4 O5	569
675	C30 H24 F2 N4 O5	559
676	C32 H28 F2 N4 O6	603
677	C31 H26 F2 N4 O5	573
678	C32 H28 F2 N4 O5	587
679	C30 H24 F2 N4 O5	559.1
680	C30 H25 F N4 O5	541.1
681	C31 H27 F N4 O5	555.2
682	C30 H25 F N4 O4	525.1
683	C32 H28 F2 N4 O5	587.2
684	C28 H21 F2 N5 O5	546.1
685	C31 H24 F2 N4 O4	555.2
686	C30 H24 F2 N4 O5	559
687	C29 H21 F3 N4 O4	547
688	C30 H24 F2 N4 O5	559
689	C30 H24 F2 N4 O4	543
690	C32 H29 F N4 O4	553
691	C30 H24 F2 N4 O5	559
692	C31 H27 F N4 O5	555
693	C30 H24 F2 N4 O5	559
694	C30 H25 F N4 O6 S	589
695	C31 H27 F N4 O6	571
696	C30 H25 F N4 O6	557
697	C29 H23 F N4 O6 S	575
698	C29 H22 F2 N4 O5	545
699	C30 H25 F N4 O5	541
700	C29 H22 F2 N4 O5	545
701	C29 H22 F2 N4 O4	529
702	C31 H24 F4 N4 O5	609.1

Cpd #	Molecular Formula	Observed MS (MH+)
703	C31 H26 F2 N4 O6	589.1
704	C31 H27 F N4 O6	571.1
705	C31 H27 F N4 O4	539
706	C28 H19 F3 N4 O4	533
707	C29 H22 F2 N4 O5	545
708	C30 H23 F3 N4 O5	577
709	C31 H26 F2 N4 O6	589
710	C31 H26 F2 N4 O5	573
711	C33 H31 F N4 O5	583
712	C32 H29 F N4 O6	585
713	C32 H29 F N4 O7	601
714	C28 H21 F2 N5 O4	530.1
715	C30 H24 F2 N4 O6	575
716	C29 H22 F2 N4 O5	545
717	C29 H23 F N4 O5	527
718	C30 H25 F N4 O6	557
719	C29 H22 F2 N4 O4	529.1
720	C32 H26 F2 N4 O6	601.2
721	C29 H21 F4 N5 O5	596.1
722	C32 H27 F3 N4 O5	605
723	C31 H24 F4 N4 O4	593
724	C32 H29 F N4 O5	569.2
725	C33 H31 F N4 O6	599.2
726	C31 H23 F3 N4 O4	573.1
727	C31 H23 F5 N4 O5	627.1
728	C32 H26 F2 N4 O5	585.1
729	C30 H22 F4 N4 O5	595.1
730	C32 H26 F4 N4 O5	623
731	C31 H25 F3 N4 O4	575
732	C29 H24 F N5 O5	542
733	C28 H22 F N5 O4	512
734	C28 H21 F2 N5 O4	530
735	C30 H24 Cl F N4 O4	559
736	C30 H23 Cl F2 N4 O4	577
737	C30 H22 Cl F3 N4 O4	595
738	C29 H23 F2 N5 O5	560.1
739	C32 H26 F2 N4 O6	601.2
740	C34 H30 F2 N4 O6	629.2
741	C34 H31 F N4 O6	611.2
742	C33 H28 F2 N4 O5	599.2
743	C31 H26 F2 N4 O6	589
744	C31 H26 F2 N4 O5	573
745	C31 H26 F2 N4 O6	589
746	C31 H26 F2 N4 O5	573
747	C30 H24 Br F N4 O5	621
748	C28 H20 F2 N4 O4	515.1
749	C29 H22 F2 N4 O4	529.1

Cpd #	Molecular Formula	Observed MS (MH+)
750	C30 H25 F2 N5 O5	574.2
751	C30 H23 F3 N4 O4	561.1
752	C33 H27 F3 N4 O4	601.2
753	C31 H25 F N4 O7	585.1
754	C31 H24 F2 N4 O7	603.1
755	C31 H27 F N4 O5	555.2
756	C32 H27 F3 N4 O5	605.1
757	C33 H29 F N4 O7	613.2
758	C32 H26 F2 N4 O6	601.2
759	C31 H24 F2 N4 O6	587.1
760	C32 H28 F2 N4 O6	603
761	C32 H28 F2 N4 O7	619
762	C31 H27 F N4 O6	571
763	C31 H27 F N4 O5	555
764	C28 H21 F2 N5 O4	530.2
765	C32 H28 F2 N4 O7	619.2
766	C32 H26 F2 N4 O6	601.1
767	C30 H23 F3 N4 O4	561.1
768	C30 H22 F4 N4 O4	579.1
769	C31 H25 F3 N4 O5	591
770	C30 H23 Cl F2 N4 O4	577.1
771	C31 H26 F2 N4 O4	557
772	C32 H27 F3 N4 O5	605
773	C30 H25 F2 N5 O5	574
774	C32 H28 F2 N4 O5	587
775	C32 H26 F2 N4 O6	601.1
776	C30 H24 F3 N5 O5	592
777	C30 H22 F4 N4 O5	595
778	C31 H24 F4 N4 O6	625
779	C29 H20 F4 N4 O4	565
780	C33 H31 F N4 O6	599
781	C32 H29 F N4 O5	569
782	C33 H28 F2 N4 O6	615.1
783	C31 H24 F2 N4 O5	571.1
784	C32 H26 F2 N4 O5	585.1
785	C32 H28 F2 N4 O6	603.1
786	C32 H26 F4 N4 O5	623.2
787	C31 H26 F2 N4 O6	589.1
788	C31 H25 F3 N4 O5	591.1
789	C31 H24 F4 N4 O5	609.1
790	C30 H21 F5 N4 O4	597.1
791	C32 H29 F N4 O5	569
792	C30 H24 F2 N4 O6	575
793	C29 H22 F2 N4 O5	545
794	C30 H24 F2 N4 O5	559
795	C29 H22 F2 N4 O4	529
796	C29 H21 F3 N4 O5	563

Cpd #	Molecular Formula	Observed MS (MH+)
797	C28 H19 F3 N4 O4	533
798	C31 H26 F2 N4 O4	557
799	C31 H25 F3 N4 O4	575
800	C32 H28 F2 N4 O5	587
801	C32 H27 F3 N4 O5	605
802	C32 H25 F5 N4 O5	641.1
803	C29 H23 F2 N5 O4	544
804	C30 H25 F2 N5 O4	558
805	C32 H27 F3 N4 O6	621
806	C32 H27 F3 N4 O5	605
807	C30 H22 F4 N4 O4	579
808	C31 H24 F2 N4 O6	587.1
809	C30 H22 F2 N4 O5	557.1
810	C32 H26 F4 N4 O6	639

Cpd #	Molecular Formula	Observed MS (MH+)
811	C31 H24 F4 N4 O5	609
812	C32 H26 F4 N4 O5	623
813	C31 H25 F3 N4 O4	575
814	C31 H24 F4 N4 O4	593
815	C31 H24 F4 N4 O5	609
816	C31 H23 F5 N4 O5	627
817	C30 H21 F5 N4 O4	597
818	C31 H26 F2 N4 O5	573
819	C31 H26 F2 N4 O4	557
820	C30 H23 F3 N4 O4	561
821	C32 H28 F2 N4 O5	587
822	C31 H25 F3 N4 O5	591
823	C31 H25 F3 N4 O5	591
824	C30 H23 F3 N4 O4	561

[01379] The following compounds from **Table 1** were made following the method detailed in **Example 1**, with appropriately substituted boronic acids or esters being used in Step 2: Compounds **670**, **686-701**, **705-713**, and **792-797**.

[01380] The following compounds were made following the method detailed in **Example 2** and using different combinations of the intermediate anilines and carboxylic acids described within: Compounds **656**, **659**, **667**, **671-678**, **681-683**, **703-704**, **719**, **724-725**, **732-734**, **741-742**, **748-749**, **757-758** and **780-781**.

[01381] The following compounds were made by N and/or O-alkylation methods similar to either **Example 92** or **Example 13** followed by amide coupling as in **Example 2**: Compounds **663**, **685**, and **728**.

[01382] The following compounds were made by installing an acetyl group in a manner similar to **Example 28** followed by amide coupling as in **Example 2**: Compounds **654**, **720** and **739**.

[01383] The following compounds from were made in a manner similar to **Example 29** followed by amide coupling as in **Example 2**: Compounds **679** and **680**.

[01384] The following compounds from were made in a manner similar to **Example 29:** Compounds **660-661** and **765-766**. Alternatively, a similar sequence of reactions can be performed on an intermediate such as Compound **5-3** to form the corresponding bicyclic carboxylic acid intermediate which can then be coupled to aniline intermediates as in **Example 2**.

[01385] The following compounds were made by N and/or O-alkylation methods similar to **Example 92**: Compounds **655**, **657**, **721**, **750**, **773** and **776**.

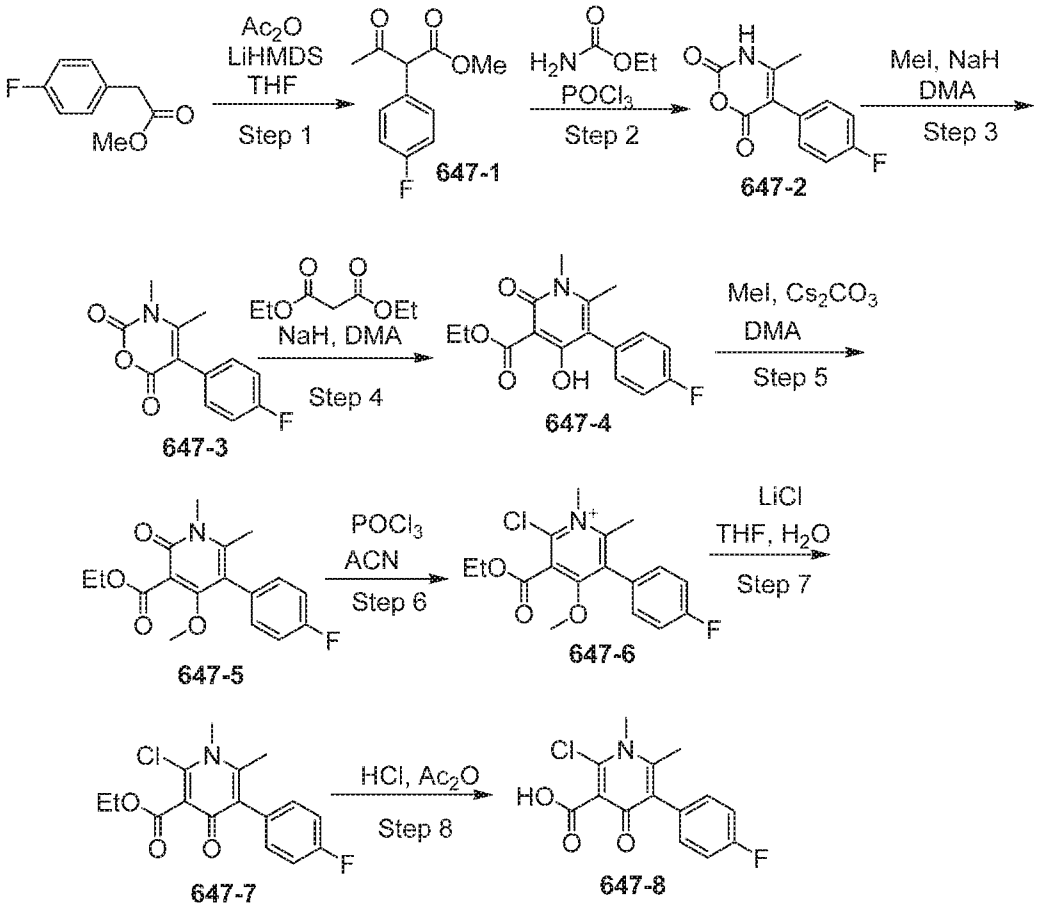
[01386] The following compounds were made by N-alkylation methods similar to **Example 104:** Compounds **666**, **668-669**, **702**, **722-723**, **727**, **729-731**, **756**, **786**, **788-790**, **798-802**, **805-807** and **810-817**.

[01387] The following compounds were made by N-alkylation methods similar to **General Procedure F1** followed by amide coupling as in **Example 2:** Compounds **771-772**, **774** and **791**.

[01388] The following compounds were made by a modification of **General Procedure C2** where an intermediate such as Compound **C3-B** is N-alkylated (such as by **General Procedure F1**) prior to the bromination and Suzuki steps. The resulting intermediates were then coupled to anilines via **Example 2:** Compounds **818-824**.

[01389] The following compounds were by the method of **Example 2** where the corresponding anilines were made by **General Procedure G** using the appropriately substituted fluoronitrophenols (Compound **15**) in Step 2: Compounds **743-746**, **751**, **762-763**, **767-770** and **777-779**.

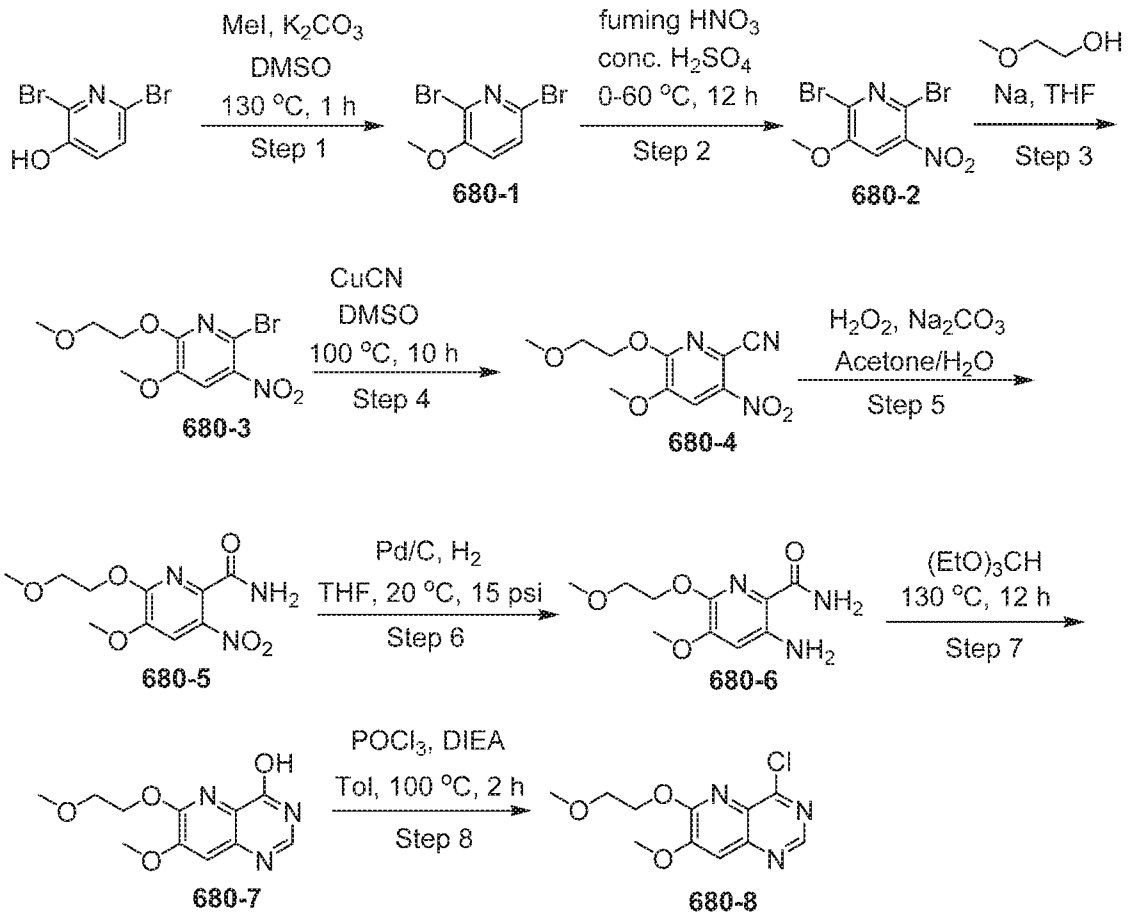
[01390] Compound **647** was made by the method of **Example 2**. The carboxylic acid intermediate used in the amide coupling was made by the following scheme.



[01391] Compound **648** was made from Compound **647** using the same method employed in **Example 84**.

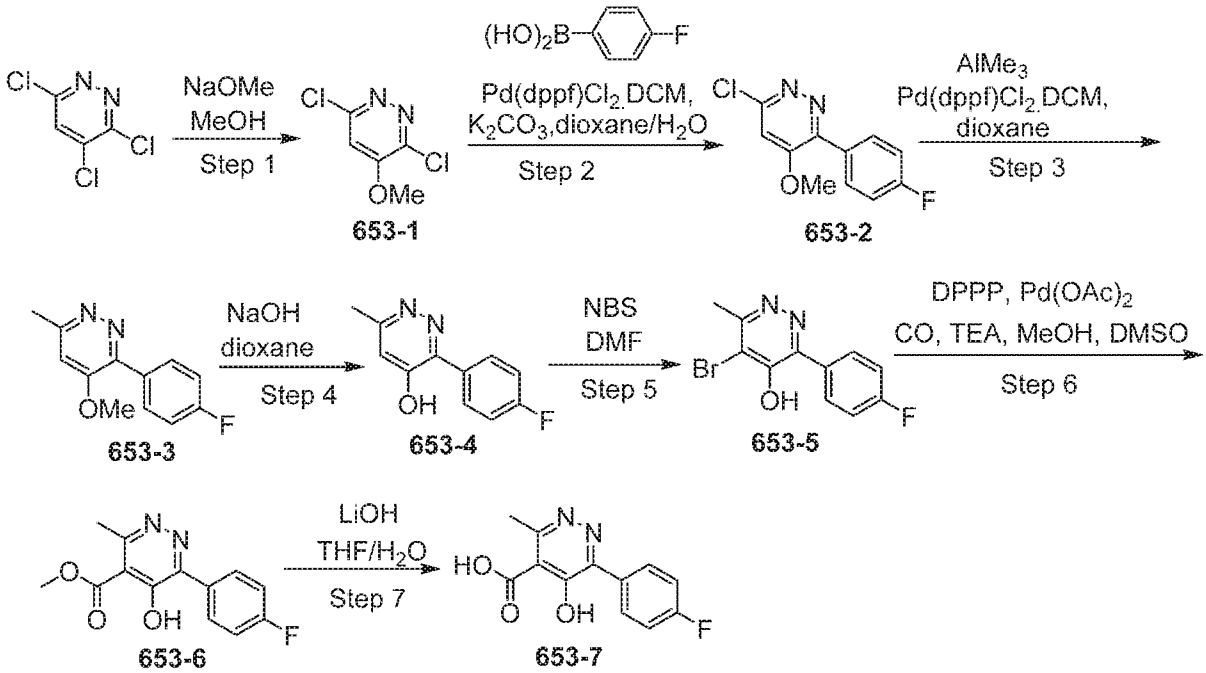
[01392] Compound **649** was made from Compound **647** using the same method employed in **Example 82**.

[01393] Compound **650** was made by the method of **General Procedure J** using Compound **I3-2** and Intermediate **650-8**. Intermediate **650-8** made by the following scheme.

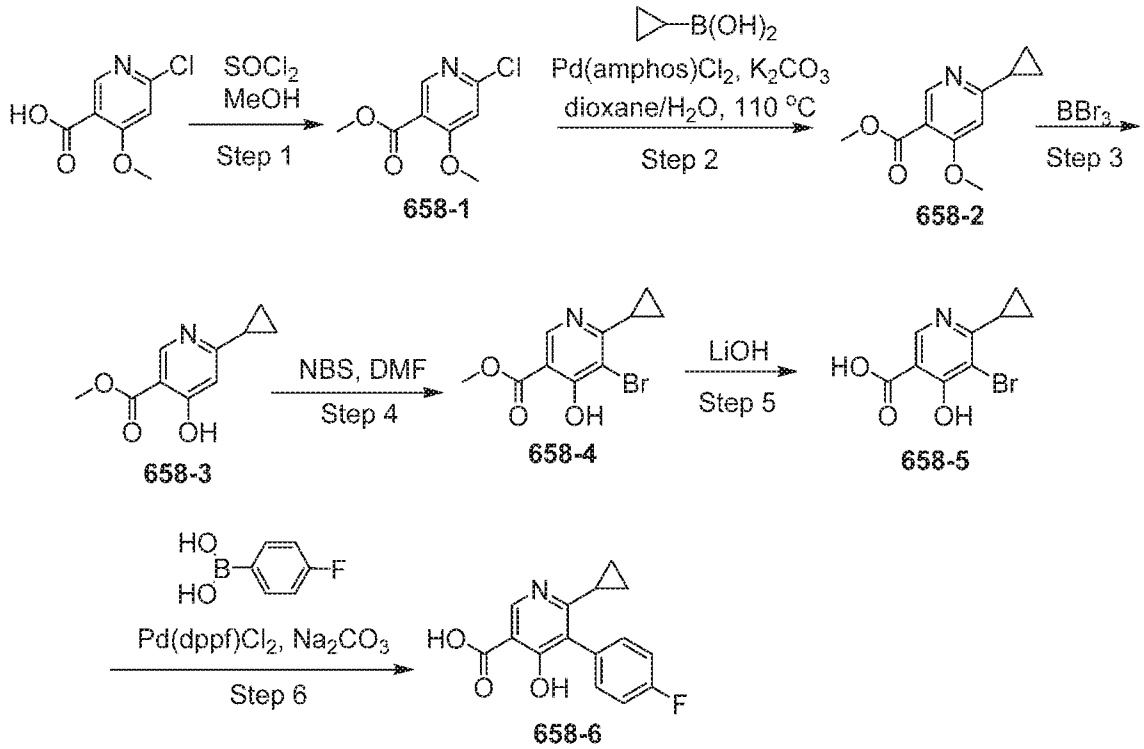


[01394] Compounds **651** and **652** were made by De-methylation using BBr_3 of Compound **PA5-11**, followed by protection of the resulting alcohol with TBS-Cl, coupling to the desired aniline by the method of **Example 2** and subsequent deprotection of the TBS group.

[01395] Compound **653** was made by the method of **Example 2**. The carboxylic acid intermediate used in the amide coupling was made by the following scheme. Compound **738** was made in a similar fashion.



[01396] Compound **658** was made by the method of **Example 2**. The carboxylic acid intermediate used in the amide coupling was made by the following scheme. Compound **662** was made in a similar fashion.



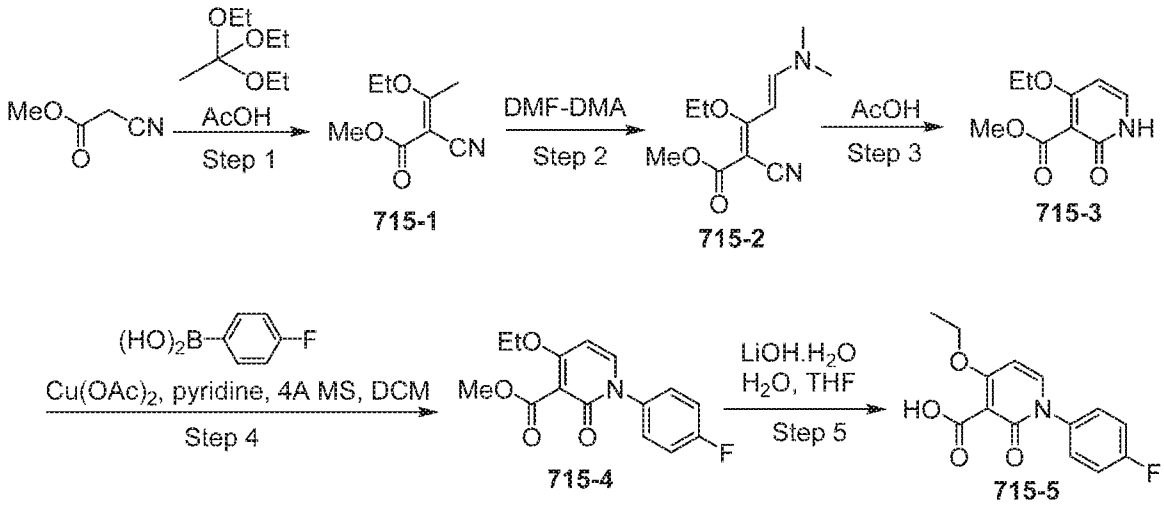
[01397] Compounds **664-665** were made in a manner similar to **Example 40** followed by amide coupling as in **Example 2**.

[01398] Compound **684** was made by the method of **Example 2**. The carboxylic acid intermediate used in the amide coupling was made by a modification of the method used in **Example 53**. Starting with commercially available methyl 6-bromo-3-oxo-3,4-dihydropyrazine-2-carboxylate, the fluorophenyl group was installed by a Chan-Lam reaction and the resulting bromide intermediate was converted to the

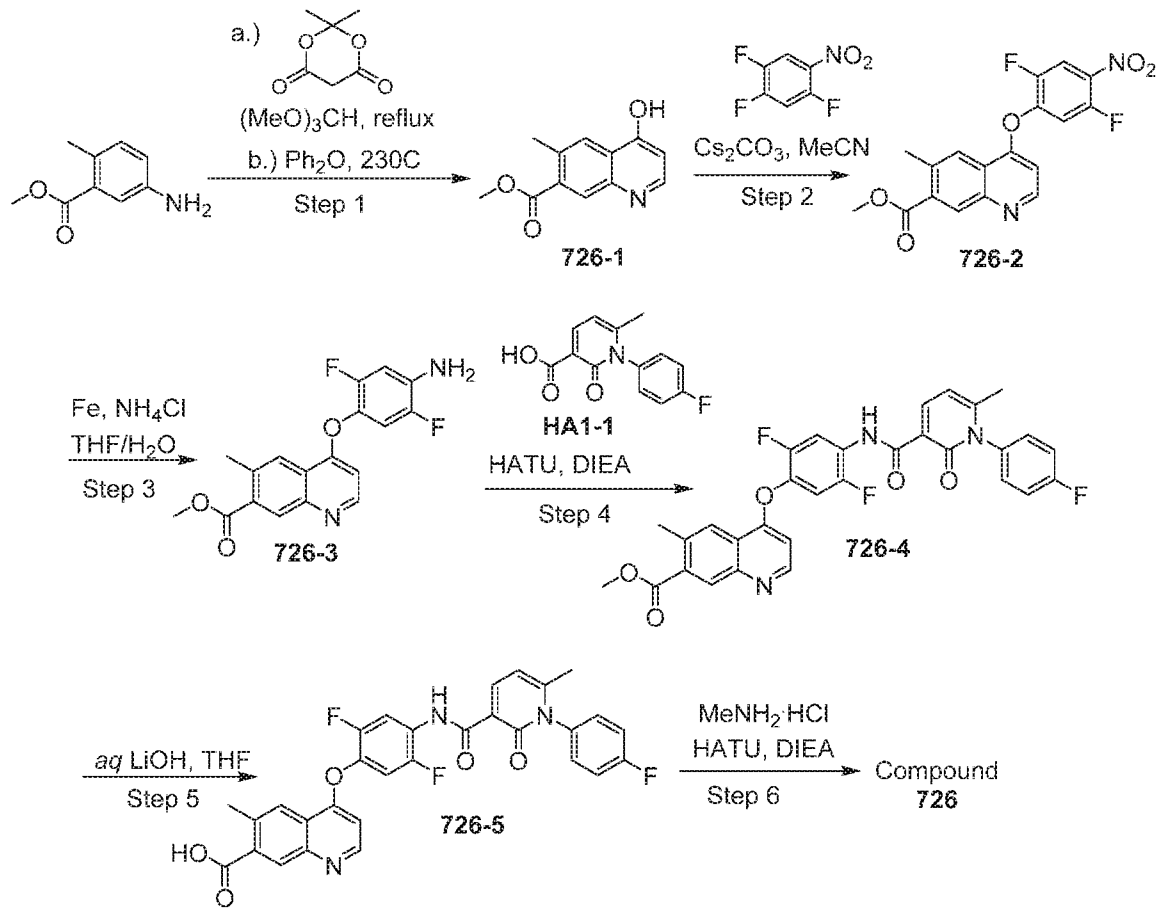
corresponding methyl intermediate as in Step 2 of **Example 53** followed by ester hydrolysis to give the desired carboxylic acid intermediate.

[01399] Compound **714** was made by **General Procedure I** followed by **General Procedure J**.

[01400] Compound **715** was made by the method of **Example 2**. The carboxylic acid intermediate used in the amide coupling was made by the following scheme. Compounds **716-718** were made in a similar fashion.



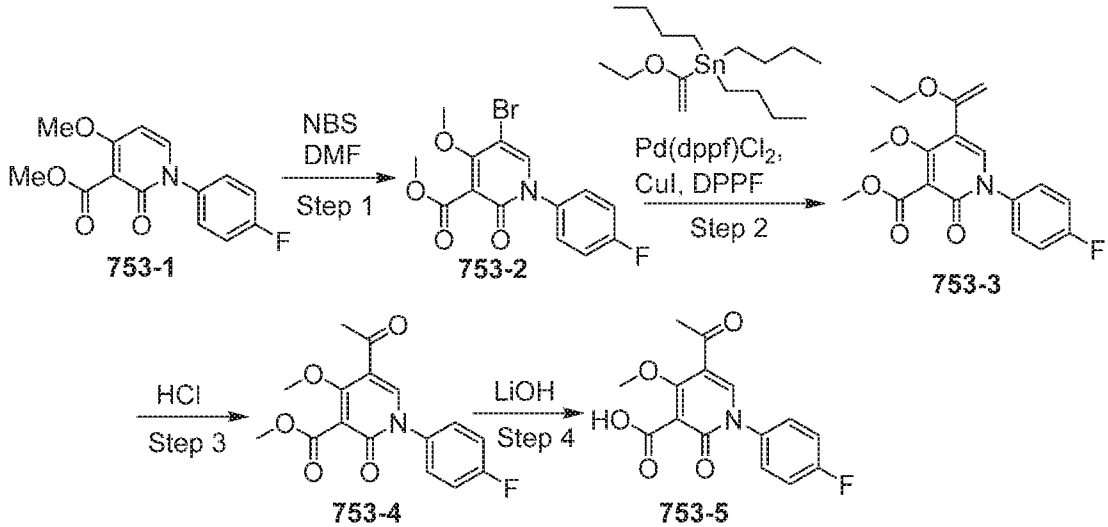
[01401] Compound **726** was made by the following scheme. Compound **752** was made in a similar fashion.



[01402] Compounds **735-737** were made by the method of **Example 2**. The aniline used for these compounds was made by the method of **General Procedure G** starting from commercially available 6-chloro-5-methoxypyridin-3-amine.

[01403] Compound **747** was made in a manner similar to **Example 31** followed by amide coupling as in **Example 2**.

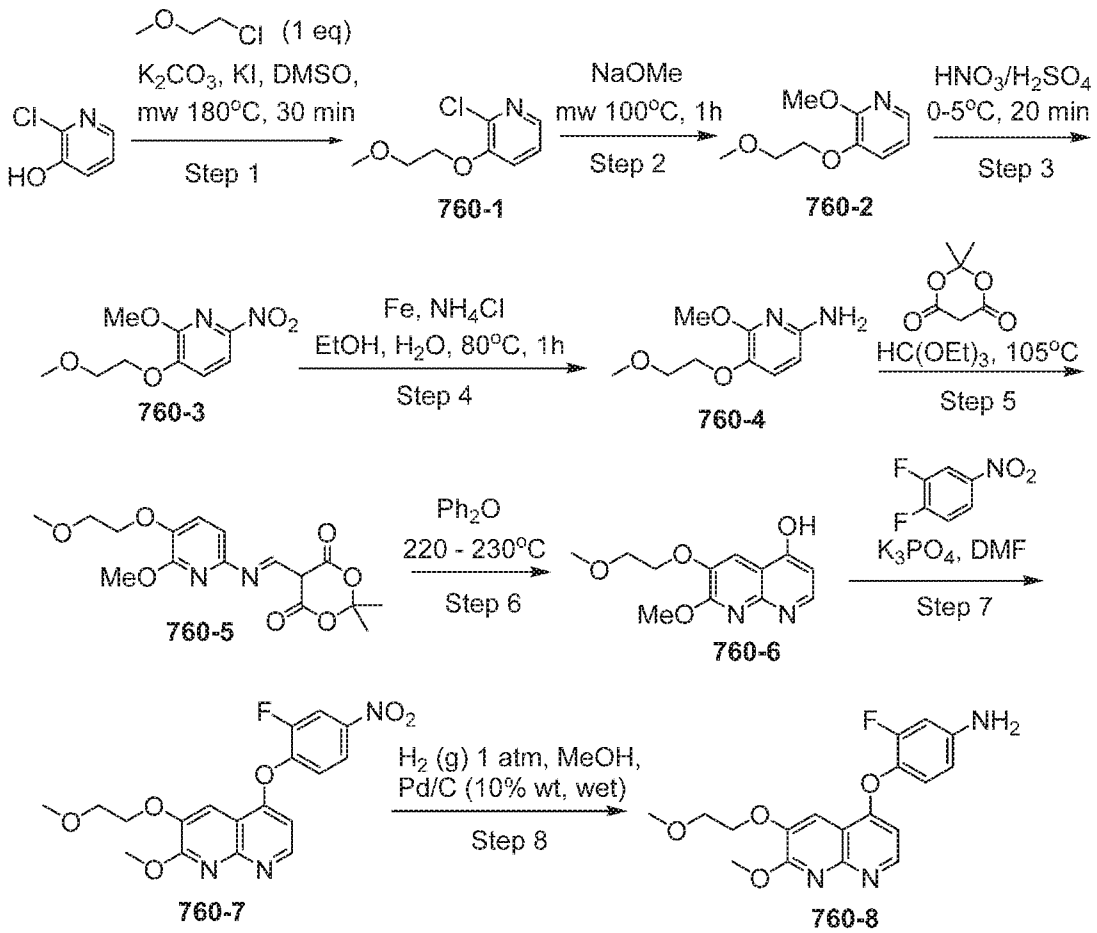
[01404] Compound **753** was made by the method of **Example 2**. The carboxylic acid intermediate used in the amide coupling was made by the following scheme. Intermediate **753-1** was made in the same fashion as intermediate **715-4**. The rest of the scheme is very similar to the synthesis of Compound **HA1-3** in **Example 28**. Compound **754** was made in a similar fashion.



[01405] Compound **755** was made in a manner similar to **Example 32** followed by amide coupling as in **Example 2**.

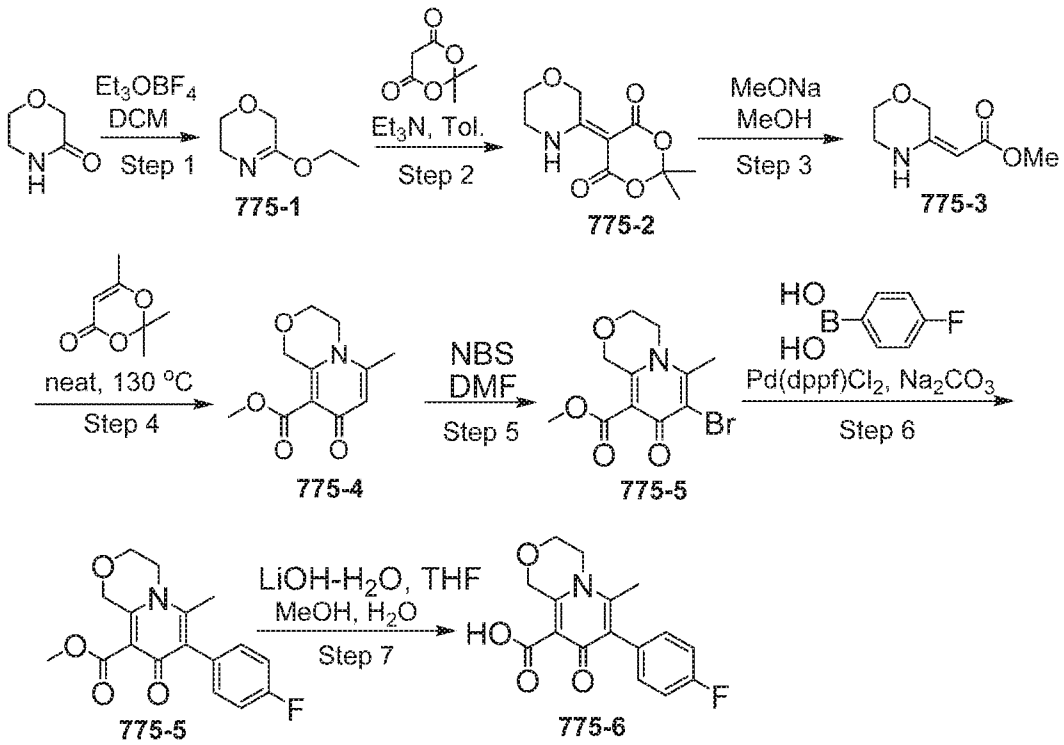
[01406] Compound **759** was made from the double bond reduction of Compound **491**.

[01407] Compound **760** was made by the method of **Example 2**. The aniline intermediate used in the amide coupling was made by the following scheme. Compound **761** was made in a similar fashion.

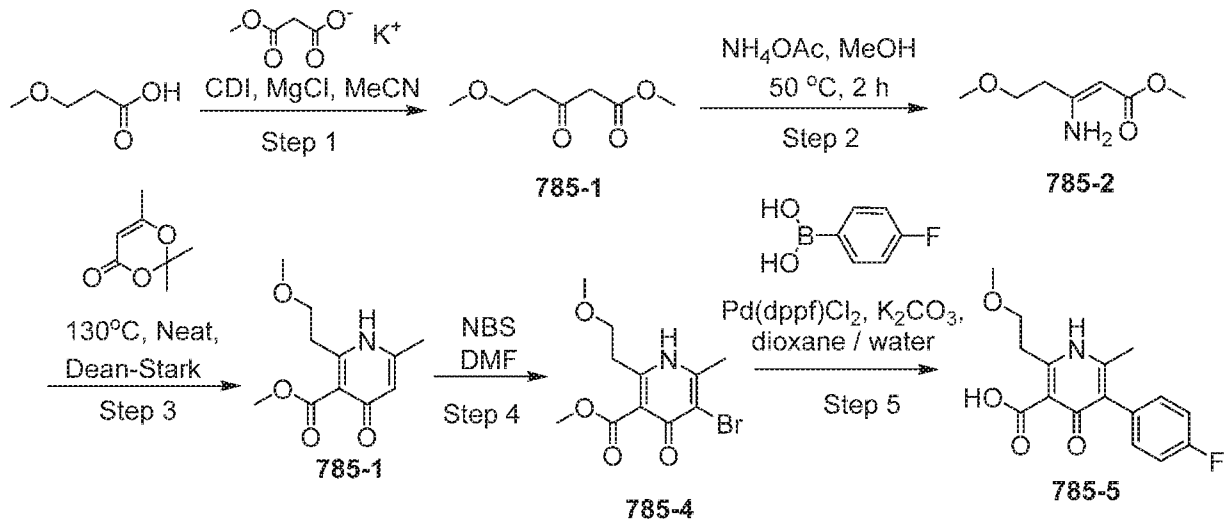


[01408] Compound **764** was made by a modification of the method of **Example 1** in which Compound **NA1-1** was coupled to commercially available 5-methylpyrazine-2-carboxylic acid followed by bromination and then Suzuki reaction.

[01409] Compound **775** was made by the method of **Example 2**. The carboxylic acid intermediate used in the amide coupling was made by the following scheme. Compounds **782-784** and **808-809** were made in a similar fashion.



[01410] Compound **785** was made by the method of **Example 2**. The carboxylic acid intermediate used in the amide coupling was made by the following scheme.



[01411] Compound **787** was made by reduction of the carbonyl of the acetyl group of Compound **86** to the corresponding alcohol.

[01412] Compounds **803-804** were made in a manner similar to **Example 99**.

Kinase Assays

[01413] Kinase activity and compound inhibition were investigated using the ^{33}P-Phosphoryl transfer radiometric kinase assay, performed using the KinaseProfiler™ service of Eurofins Pharma Discovery Services UK Limited. Dose-response experiments were performed using nine compound concentrations in a 96-well microtiter plate. For each assay, all compounds were prepared to a 50x final assay concentration (50 μM) in 100% DMSO, then diluted in a half-log series, with the final top concentration at 1 μM. This working stock of the compound was added to the assay well as the first component in the

reaction, followed by the remaining components as detailed in the following assay protocols below. The positive control wells (100% kinase activity) contain all components of the reaction including 2% DMSO (control for solvent effects), except the compound of interest. Blank wells contain all components of the reaction, with the reference inhibitor, staurosporine. This reference compound was used to abolish kinase activity and generated the 0% kinase activity base-line. IC_{50} values were calculated by nonlinear regression analysis using the sigmoidal dose-response (variable slope) curve fit on XLFit version 5.3 (ID Business Solutions).

[01414] Kinase activity and compound inhibition were also investigated using the HTRF ® KinEase assay (Cisbio Cat # 62TK0PEB) per manufacturer's instructions. In short, compounds were delivered in 300 nL volumes at 10 different concentrations in DMSO (3% final) to empty 384-well assay plates (Corning cat # 3824). A mixture of enzyme, 1 μM biotynlated peptide substrate, and buffer in 10 μLvolume was added. The assay was started upon the addition of ATP (at Km). The 10 μL reaction was incubated at room temperature. The reaction was stopped upon the addition of detection buffer containing streptavidin-XL665 (5 μL) and TK antibody-Eu3+ (5 μL). After a 60 min incubation at room temperature, the fluorescence at 665 nm and 620 nm was read on an Envision microplate reader (Perkin Elmer).

[01415] Kinase activity normalized to DMSO (100% activity) and reference compound at 1 μM and (0% activity) was calculated using the fluorescence ratio 620/665 x 10,000. IC_{50} values were calculated by nonlinear regression analysis using a 4-parameter logistic curve fit in ActivityBase XE (IDBS).

Example A: Human AXL Kinase Assay

[01416] **Example A-1:** Human Axl (residues H473-A894 with Q764R, 161 nM) was incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 μM KKSRGDYMTMQIG (SEQ ID NO:1), 10 mM magnesium acetate and 10 μM [γ-^{33}P-ATP]. The reaction was initiated by the addition of the Mg/ATP mix. After incubation for 40 minutes at room temperature, the reaction was stopped by the addition of phosphoric acid to a concentration of 0.5%. A reaction aliquot of 10 μL was then spotted onto a P30 filtermat and washed four times for 4 minutes in 0.425% phosphoric acid and once in methanol prior to drying and scintillation counting. Incorporated ^{33}P was measured using the Wallac Microbeta scintillation counter (Perkin Elmer).

[01417] **Example A-2:** Human AXL (residues 464-885; CarnaBio, 1 ng/ well) was also incubated with enzymatic buffer (Cisbio) supplemented with 5 mM $MgCl_2$, 1 mM DTT, and Supplemental Enzymatic Buffer (SEB; Cisbio). The mixture was added to the pre-plated compounds. The reaction was initiated upon addition of ATP at Km (1.0 μM). The reaction was incubated at room temperature for 50 min and stopped upon the addition of SA-XL665 and TK-antibody both diluted in EDTA-containing kinase detection buffer (Cisbio). The kinase activity was calculated as stated above and the IC_{50} values were reported.

Example B: Human KDR Kinase Assay

[01418] Example B-1: Human KDR (residues K790-V1356, 55nM) was incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.33 mg/mL myelin basic protein, 10 mM magnesium acetate, and 10 μM [γ-^{33}P-ATP]. The reaction was initiated by the addition of the Mg/ATP mix. After incubation for 40 minutes at room temperature, the reaction was stopped by the addition of phosphoric acid to a concentration of 0.5%. A reaction aliquot of 10 μL was then spotted onto a P30 filtermat and washed four times for 4 minutes in 0.425% phosphoric acid and once in methanol prior to drying and scintillation counting. Incorporated ^{33}P was measured using the Wallac Microbeta scintillation counter (Perkin Elmer).

[01419] Example B-2: Human KDR (residues 790-1356; CarnaBio, 0.1 ng/ well) was also incubated with enzymatic buffer (Cisbio) supplemented with 5 mM $MgCl_2$, 1 mM $MnCl_2$, and 1 mM DTT. The mixture was added to the pre-plated compounds. The reaction was initiated upon addition of ATP at Km (4.0 μM). The reaction was incubated at room temperature for 40 min and stopped upon the addition of SA-XL665 and TK-antibody both diluted in EDTA-containing kinase detection buffer (Cisbio). The kinase activity was calculated as stated above and the IC_{50} values were reported.

Example C: Human Mer Kinase Assay

[01420] Example C-1: Human Mer (residues R557-E882 with H628Q and R794A, 0.7nM) was incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 30 mM NaCl, 250 μM GGMEDIYFEFMGGKKK (SEQ ID NO:2), 10 mM magnesium acetate, and 10 μM [γ-^{33}P-ATP]. The reaction was initiated by the addition of the Mg/ATP mix. After incubation for 40 minutes at room temperature, the reaction was stopped by the addition of phosphoric acid to a concentration of 0.5%. A reaction aliquot of 10 μL was then spotted onto a P30 filtermat and washed four times for 4 minutes in 0.425% phosphoric acid and once in methanol prior to drying and scintillation counting. Incorporated ^{33}P was measured using the Wallac Microbeta scintillation counter (Perkin Elmer).

[01421] Example C-2: Human MER (residues 528-999; CarnaBio, 1 ng/ well) was also incubated with enzymatic buffer (Cisbio) supplemented with 5 mM $MgCl_2$ and 1 mM DTT. The mixture was added to the pre-plated compounds. The reaction was initiated upon addition of ATP at Km (40 μM). The reaction was incubated at room temperature for 60 min and stopped upon the addition of SA-XL665 and TK-antibody both diluted in EDTA-containing kinase detection buffer (Cisbio). The kinase activity was calculated as stated above and the IC_{50} values were reported.

Example D: Human Met Kinase Assay

[01422] Example D-1: Human Met (residues R974-S1390 with A1209G and V1290L, 3.4nM) was incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 μM KKKGQEEEYVFIE (SEQ ID NO:3), 1 mM sodium orthovanadate, 5 mM sodium-6-glycerophosphate, 10 mM magnesium acetate, and 10 μM [γ-^{33}P-ATP]. The reaction was initiated by the addition of the Mg/ATP mix. After incubation for 40 minutes at room temperature, the reaction was stopped by the addition of phosphoric acid to a concentration of 0.5%. A reaction aliquot of 10 μL was then spotted onto a P30 filtermat and washed four times for 4 minutes in 0.425% phosphoric acid and once in methanol prior to drying and scintillation

counting. Incorporated ^{33}P was measured using the Wallac Microbeta scintillation counter (Perkin Elmer).

[01423] Example D-2: Human MET (residues 956-1390; CarnaBio, 0.1 ng/ well) was also incubated with enzymatic buffer (Cisbio) supplemented with 5 mM $MgCl_2$, 1 mM DTT and 1 mM $MnCl_2$. The mixture was added to the pre-plated compounds. The reaction was initiated upon addition of ATP at Km (3.0 μM). The reaction was incubated at room temperature for 40 min and stopped upon the addition of SA-XL665 and TK-antibody both diluted in EDTA-containing kinase detection buffer (Cisbio). The kinase activity was calculated as stated above and the IC_{50} values were reported.

Example E: AXL Autophosphorylation ELISA in A-172 Cells

[01424] A-172 glioblastoma cells (ATCC #CRL-1620) were seeded at 2.5 x 10^5 cells/well onto 24-well plates (Greiner #662165), in DMEM (Thermo Fisher #11995-040) containing 10% FBS (Thermo Fisher #26140-079), 1% MEM NEAA (Thermo Fisher #11140-050), 1% GlutaMax (Thermo Fisher #35050-061), and 1% Penicillin Streptomycin (Thermo Fisher #15140-122). A-172 cells were incubated at 37°C, 5% CO_2 for 24 h and then starved for 24 h in serum-free medium. Test compounds were serially diluted to produce an 8-point dose curve in fresh serum-free medium to a final concentration of 0.3% DMSO (vehicle) and added to the cells and incubated for 1 h. Cells were then stimulated with 1 μg/mL recombinant human Gas6 (R&D Systems #885-GSB-500) for 15 min, washed with cold PBS, and immediately lysed with 150 μL of cold 1X lysis buffer [20 mM Tris, 137 mM sodium chloride, 2 mM EDTA, 10% glycerol, 1% NP-40 alternative, 1 mM activated sodium orthovanadate, 1 mM PefaBloc SC (Sigma-Aldrich #11429868001), protease/phosphatase inhibitor tablet (Thermo Fisher #A32959)]. Lysates were collected and 100 μL/well added into the human phospho-AXL DuoSet IC ELISA (R&D Systems #DYC2228-2). Assay was performed according to manufacturer's instructions and sample phospho-AXL concentrations were extrapolated using human phospho-AXL control (R&D Systems #841645) as a standard. Positive control wells (100% activity) contained Gas6-stimulated, DMSO-treated cell lysates. Negative control wells (0% activity) contained Gas6-stimulated, reference inhibitor-treated cell lysates. IC_{50} values were calculated by nonlinear regression analysis using a 4-parameter logistic curve fit in ActivityBase XE (IDBS).

Example F: Met Autophosphorylation ELISA in PC-3 Cells

[01425] PC-3 prostate cancer cells (ATCC #CRL-1435) were seeded at 4 x 10^4 cells/well onto 24-well plates (Greiner #662165), in DMEM (Thermo Fisher #11995-040) containing 10% FBS (Thermo Fisher #26140-079), 1% MEM NEAA (Thermo Fisher #11140-050), 1% GlutaMax (Thermo Fisher #35050-061), and 1% Penicillin Streptomycin (Thermo Fisher #15140-122). PC-3 cells were incubated at 37°C, 5% CO_2 for 24 h and then starved for 3 h in serum-free medium. Test compounds were serially diluted to produce an 8-point dose curve in fresh serum-free medium to a final concentration of 0.3% DMSO (vehicle) and added to the cells and incubated for 1 h. Cells were then stimulated with 100 ng/mL recombinant human HGF (R&D Systems #294-HG-250) for 10 min, washed with cold PBS, and immediately lysed with 130 μL of cold 1X lysis buffer [20 mM Tris, 137 mM sodium chloride, 2 mM

EDTA, 10% glycerol, 1% NP-40 alternative, 1 mM activated sodium orthovanadate, 1 mM PefaBloc SC (Sigma-Aldrich #11429868001), protease/phosphatase inhibitor tablet (Thermo Fisher #A32959)]. Lysates were clarified by centrifugation and 100 µL/well added into the PathScan phospho-Met (panTyr) Sandwich ELISA (Cell Signaling Technology #7333). Assay was performed according to manufacturer's instructions. Positive control wells (100% activity) contained HGF-stimulated, DMSO-treated cell lysates. Negative control wells (0% activity) contained HGF-stimulated, reference inhibitor-treated cell lysates. IC_{50} values were calculated by nonlinear regression analysis using a 4-parameter logistic curve fit in ActivityBase XE (IDBS).

Example G: KDR Autophosphorylation ELISA in HUVEC Cells

[01426] Human umbilical vein endothelial cells or HUVEC (Lonza #C2519A) were seeded at 2 x 10^4 cells/well onto 96-well plates (Corning #3904), in EGM-2 growth medium (Lonza #CC-3162) containing 1% Penicillin Streptomycin (Thermo Fisher #15140-122). HUVEC cells were incubated at 37°C, 5% CO_2 for 24 h and then starved for 24 h in serum-free EBM-2 basal medium (Lonza #CC-3156) containing 1% Penicillin Streptomycin. Test compounds were serially diluted to produce an 8-point dose curve in fresh serum-free medium to a final concentration of 0.3% DMSO (vehicle) and added to the cells and incubated for 1 h. Cells were then stimulated with 100 ng/mL recombinant human VEGF165 (R&D Systems #293-VE-500) for 5 min, washed with cold PBS, and immediately lysed with 130 µL of cold 1X lysis buffer [20 mM Tris, 137 mM sodium chloride, 2 mM EDTA, 10% glycerol, 1% NP-40 alternative, 1 mM activated sodium orthovanadate, 1 mM PefaBloc SC (Sigma-Aldrich #11429868001), protease/phosphatase inhibitor tablet (Thermo Fisher #A32959)]. Lysates were collected and 100 µL/well added into the human phospho-KDR DuoSet IC ELISA (R&D Systems #DYC1766-2). Assay was performed according to manufacturer's instructions and sample phospho-KDR concentrations were extrapolated using human phospho-KDR control (R&D Systems #841421) as a standard. Positive control wells (100% activity) contained VEGF165-stimulated, DMSO-treated cell lysates. Negative control wells (0% activity) contained non-stimulated cell lysates. IC_{50} values were calculated by nonlinear regression analysis using a 4-parameter logistic curve fit in ActivityBase XE (IDBS).

Example H: Mer Autophosphorylation ELISA in Transient Transfected 293A Cells

[01427] 293A cells (Thermo Fisher #R70507) were seeded at 1.5 x 10^6 cells/well onto 100 mm dish (Greiner #664169), in DMEM (Thermo Fisher #11995-040) containing 10% FBS (Thermo Fisher #26140-079), 1% MEM NEAA (Thermo Fisher #11140-050), 1% GlutaMax (Thermo Fisher #35050-061), and 1% Penicillin Streptomycin (Thermo Fisher #15140-122). 293A cells were incubated at 37°C, 5% CO_2 for 24 h and then transfected with 6 µg MERTK DNA (Genecopoeia #EX-Z8208-M02) using TransIT LT1 transfection reagent (Mirus-Bio #MIR2305). After 24 h incubation, the transfected 293A cells were seeded at 1 x 10^5 cells/well onto 96-well plates (Corning #3904) in DMEM growth medium overnight. Test compounds were serially diluted to produce an 8-point dose curve in fresh serum-free medium to a final concentration of 0.3% DMSO (vehicle) and added to the cells and incubated for 1 h. Cells were then immediately lysed with 150 µL of cold 1X lysis buffer [20 mM Tris, 137 mM sodium

chloride, 2 mM EDTA, 10% glycerol, 1% NP-40 alternative, 1 mM activated sodium orthovanadate, 1 mM PefaBloc SC (Sigma-Aldrich #11429868001), protease/phosphatase inhibitor tablet (Thermo Fisher #A32959)]. Lysates were clarified by centrifugation and 50 µL/well added into the human phospho-Mer DuoSet IC ELISA (R&D Systems #DYC2579-2). Assay was performed according to manufacturer's instructions and sample phospho-Mer concentrations were extrapolated using human phospho-Mer control (R&D Systems #841793) as a standard. Positive control wells (100% activity) contained DMSO-treated cell lysates. Negative control wells (0% activity) contained reference inhibitor-treated cell lysates. IC_{50} values were calculated by nonlinear regression analysis using a 4-parameter logistic curve fit in ActivityBase XE (IDBS).

[01428] Results of Examples A-H are summarized in Table 5 and Table 6. A, B, and C of Tables 5 and 6 have the following meanings: A = $IC_{50} \leq 100$ nM; B = $100 < IC_{50} \leq 300$ nM; C = $IC_{50} > 300$ nM. "NT" refers to "Not Tested." The data for compounds 21-27, 41-47, 99, and 104 in Table 5 were obtained using the protocols set forth in Examples A-1, B-1, C-1 and D-1. The data for other compounds in Table 5 were obtained using the protocols set forth in Examples A-2, B-2, C-2, and D-2.

Table 5. Biological Activities of Selected Compounds

Compound No.	Axl IC_{50} (nM)	Mer IC_{50} (nM)	c-Met IC_{50} (nM)	KDR IC_{50} (nM)
21	A	A	A	A
22	A	A	A	A
23	A	B	A	A
24	A	A	A	A
25	A	A	A	A
26	A	A	A	A
27	A	A	A	A
28	A	A	A	A
29	A	A	A	A
30	A	A	A	A
31	A	A	A	A
32	A	A	A	B
33	A	A	A	A
34	A	A	B	A
35	A	A	A	A
36	A	A	A	A
37	A	A	A	B
38	A	A	A	B
39	A	A	A	A
40	A	A	A	C
41	A	A	A	A
42	A	A	A	A
43	A	A	A	A
44	A	A	A	A
45	A	A	A	A
46	A	A	A	A
47	A	A	A	A
48	A	A	A	C
49	A	NT	A	NT
50	A	NT	A	NT

51	A	NT	A	NT
52	NT	NT	A	NT
53	A	A	A	C
58	A	A	A	A
59	A	A	A	B
60	A	A	A	C
61	A	A	A	C
62	A	A	A	C
63	A	A	A	A
64	A	A	A	A
65	A	A	A	A
66	A	A	A	A
67	A	A	A	A
68	A	A	A	A
69	A	A	A	A
70	A	A	A	B
71	A	A	A	A
72	A	A	A	B
73	A	A	A	B
74	A	A	A	A
75	A	A	A	B
76	A	A	A	A
77	A	A	A	C
78	A	A	A	A
79	A	A	B	C
80	A	A	A	A
81	A	A	A	A
82	A	A	A	B
83	A	A	A	A
84	A	A	A	B
85	A	A	B	C
86	A	A	A	C
87	A	A	A	C
88	A	A	A	A
89	A	A	A	A
90	A	A	A	A
91	A	A	A	B
92	A	A	A	B
93	A	A	A	A
94	A	A	A	C
95	A	A	A	B
96	A	A	A	A
97	A	A	A	A
98	A	A	A	A
99	A	A	A	A
100	A	A	A	A
101	A	A	A	A
102	A	A	A	A
103	A	A	A	C
104	C	C	C	C
105	A	A	A	B
106	A	A	A	C
107	A	A	A	C
108	A	A	A	A

109	A	A	A	A
110	A	A	A	NT
111	A	A	A	C
112	A	A	A	C
113	A	A	B	C
114	NT	NT	A	NT
115	A	A	A	A
116	A	A	A	A
117	A	A	A	A
118	A	A	A	A
119	A	A	A	A
120	A	A	A	A
121	A	A	A	C
122	A	A	A	A
123	A	A	A	C
124	A	A	A	C
125	A	A	A	C
126	A	A	A	A
127	A	A	A	A
128	A	A	A	B
129	A	A	A	A
130	A	A	A	A
131	A	A	A	C
132	A	A	A	B
133	A	NT	A	NT
134	A	NT	A	NT
135	A	A	A	NT
136	A	A	A	NT
137	A	NT	A	NT
138	A	B	A	C
139	A	A	A	C
140	A	A	A	C
141	A	A	A	C
142	A	A	A	A
143	A	A	A	C
144	A	A	A	A
145	A	NT	A	NT
146	A	A	A	A
147	A	A	A	NT
148	A	A	A	C
149	A	A	A	B
150	A	A	A	C
151	A	A	A	C
152	A	C	C	C
153	A	A	A	C
154	A	A	A	A
155	A	A	A	C
156	A	A	A	C
157	A	A	A	C
158	A	NT	A	NT
159	A	NT	A	NT
160	A	A	A	A
161	A	A	A	A
162	A	B	A	C

163	A	A	A	C
164	A	A	A	C
165	A	A	A	C
166	A	A	A	C
167	A	A	A	B
168	A	A	A	B
169	A	A	A	C
170	A	A	A	C
171	A	A	A	A
172	A	A	A	B
173	A	A	A	A
174	A	A	A	A
175	A	A	A	B
176	A	A	A	C
177	A	A	A	A
178	A	A	A	A
179	A	A	A	A
180	A	A	A	A
181	A	A	A	C
182	A	A	A	B
183	A	A	A	C
184	A	A	A	A
185	A	A	A	A
186	A	A	A	A
187	A	A	A	C
188	A	A	A	A
189	A	A	A	B
190	A	A	A	A
191	A	A	A	A
192	A	A	A	A
193	A	A	A	B
194	A	A	A	B
195	A	A	B	C
196	A	A	A	B
197	A	A	A	A
198	A	A	A	B
199	A	A	A	A
200	A	A	A	C
201	A	A	A	B
202	A	A	B	B
203	A	A	B	A
204	A	A	B	B
205	A	A	A	C
206	A	A	B	C
216	A	A	A	A
217	A	A	A	B
218	A	A	A	B
219	A	A	A	A
220	A	A	A	A
221	A	A	A	B
222	A	A	A	C
223	A	A	A	C
224	A	A	A	C
225	A	A	A	A

226	A	A	A	B
227	A	A	A	A
228	A	A	A	B
229	A	A	A	A
230	A	A	A	C
231	A	A	A	B
232	A	A	A	C
233	A	A	B	A
234	A	A	C	C
235	A	A	A	A
236	A	A	A	A
237	A	A	A	A
238	A	A	A	C
239	A	A	A	C
240	A	A	A	C
241	A	A	B	C
242	A	A	A	A
243	A	A	C	C
245	A	A	A	B
246	A	A	A	A
247	A	A	A	A
248	A	A	A	C
249A	A	A	A	C
249B	A	A	A	C
249C	A	A	A	C
250	A	A	A	C
251	A	A	A	C
252	A	A	A	B
254	A	A	A	A
255	A	A	B	C
256	A	A	A	B
257	A	A	A	A
258	A	A	A	A
259	A	A	B	B
260	A	A	A	C
261	A	A	A	C
262	A	A	A	A
263	A	A	A	C
264	A	A	A	C
265	A	A	A	C
266	A	A	A	C
267	C	C	NT	C
268	A	A	A	C
269	A	A	A	C
270	A	A	A	C
271	A	A	A	A
272	A	A	A	B
273	A	A	A	C
274	A	A	A	C
275	A	A	B	B
276	A	A	B	C
277	A	A	A	B
278	A	A	A	A
279	A	A	A	A

280	A	A	A	A
281	A	A	A	A
282	A	A	A	C
283	A	A	A	C
284	A	A	A	C
285	A	A	A	C
286	A	A	A	A
287	A	A	B	A
288	A	A	A	A
289	A	A	A	A
290	A	A	B	A
291	A	A	A	C
292	A	A	A	C
293	A	A	A	A
294	A	A	A	A
295	A	A	A	A
296	A	A	B	B
297	A	A	A	A
298	A	A	B	A
299	A	A	A	A
300	A	A	B	B
301	A	A	A	A
302	A	A	NT	C
303	A	B	NT	C
304	A	A	NT	C
305	A	A	NT	C
306	A	A	NT	C
307	A	A	NT	C
308	A	A	NT	C
309	A	A	NT	C
310	A	B	NT	C
339	A	B	B	C
340	A	A	A	A
341	A	A	A	C
342	A	A	A	B
343	A	A	A	B
344	A	A	B	B
345	A	A	A	B
346	A	A	A	B
347	A	A	A	B
348	A	A	A	B
349	A	A	A	A
350	A	A	A	B
351	A	A	A	C
352	A	A	A	B
353	A	A	A	C
354	A	A	A	B
355	A	A	A	A
356	A	A	B	C
357	A	A	NT	A
364	A	A	A	A
365	A	B	C	C
366	A	A	B	B
367	A	A	B	C

368	A	A	A	B
369	A	A	C	B
370	A	A	A	A
371	A	A	NT	A
372	A	A	NT	A
373	A	A	A	C
374	A	A	A	C
375	A	A	A	C
376	A	A	NT	A
377	A	A	B	A
378	A	A	A	C
379	A	A	A	A
380	A	A	A	C
381	A	A	A	C
382	A	A	A	C
383	A	A	A	C
384	A	A	A	B
385	A	A	NT	C
386	A	A	A	A
388	A	A	A	A
389	A	A	C	C
390	A	A	A	C
391	A	A	A	B
392	A	A	A	C
393	A	A	A	A
394	A	A	A	C
399	NT	A	A	C
400	A	A	A	C
401	A	A	A	C
402	A	A	A	C
403	A	A	B	C
404	A	A	A	NT
405	A	A	A	NT
406	A	A	A	C
407	A	A	A	B
408	A	A	A	A
409	A	A	A	A
410	A	A	A	C
411	A	A	A	C
412	A	A	A	A
413	A	A	A	A
414	A	A	A	C
415	A	A	A	B
416	A	A	A	C
417	A	B	A	C
418	A	A	A	B
419	A	A	A	C
420	A	A	B	B
421	A	A	B	C
422	A	A	A	A
423	A	A	B	C
424	A	A	A	A
425	A	A	A	A
426	A	A	A	B

427	A	A	B	C
428	A	A	A	B
429	A	A	A	C
430	A	A	A	C
431	A	A	A	A
432	A	A	A	A
433	A	A	A	C
434	A	A	A	C
435	A	A	A	C
436	A	A	A	B
437	A	A	A	A
438	A	A	A	A
439	A	A	B	C
440	A	A	A	C
441	A	A	B	C
442	A	A	A	A
443	A	A	A	A
444	A	C	C	C
448	A	A	A	B
449	A	A	C	C
450	A	A	A	B
451	A	A	A	A
452	A	A	C	B
453	A	A	C	B
454	A	A	A	A
455	A	A	A	A
456	A	A	A	A
457	A	A	A	A
458	A	A	B	B
459	A	A	B	B
460	A	A	B	C
479	A	A	A	A
480	A	B	B	B
481	A	A	A	B
482	A	A	A	A
483	A	B	C	C
494	A	A	A	B
503	A	A	A	A
504	A	A	A	A
505	A	B	A	C
506	A	A	A	C
507	A	B	A	C
508	A	A	A	C
509	A	A	A	A
510	A	A	A	B
511	A	A	A	B
512	A	A	A	A
513	A	A	A	A
514	A	A	A	A
515	A	A	A	A
516	A	A	A	C
517	A	A	A	A
518	A	A	A	A
519	A	A	B	C

520	A	A	A	C
521	A	A	A	C
522	A	B	B	C
523	A	A	A	C
524	A	A	B	B
525	A	A	B	C
526	A	A	B	C
527	A	A	NT	B
528	A	A	NT	B
529	A	B	NT	C
530	A	B	B	C
539	NT	A	B	B
540	A	NT	A	NT
541	A	A	A	A
542	A	A	A	B
543	A	A	B	C
544	A	A	A	A
551	A	A	A	B
552	A	A	A	A
553	A	A	A	C
554	A	A	A	A
555	A	A	A	A
556	A	A	B	C
557	A	A	A	B
558	A	A	B	C
559	A	A	A	C
560	A	A	A	C
561	A	A	B	C
562	A	A	B	C
563	A	A	NT	C
565	A	A	A	A
566	A	A	NT	C
567	A	A	NT	A
568	A	A	A	A
569	A	A	NT	A
576	NT	NT	A	NT
577	A	A	A	A
578	A	A	A	B
579	A	A	A	C
580	A	A	A	C
581	A	A	A	A
582	A	A	A	A
583	A	A	A	C
584	A	A	A	A
585	A	A	A	C
586	A	A	A	C
587	A	A	A	C
588	A	A	A	C
589	A	A	A	A
590	A	A	C	C
591	A	B	C	C
592	A	A	C	C
593	A	B	B	C
594	A	A	A	C

595	A	A	B	B
596	A	A	A	C
597	A	C	B	C
598	A	A	A	B
604	A	NT	A	NT
605	A	A	A	NT
606	A	A	A	NT
607	A	NT	A	NT
608	A	NT	A	NT
609	A	A	A	NT
610	A	A	A	B
611	A	A	A	A
612	A	A	A	C
613	A	A	A	C
614	A	A	A	C
615	A	A	A	A
616	A	A	A	C
617	A	A	A	B
618	A	A	A	B
619	A	A	A	C
620	A	A	A	C
621	A	A	A	C
636	A	A	A	A
637	A	A	A	C
639	A	A	A	C
640	A	A	A	C
641	A	A	B	C
642	NT	A	A	A
643	A	A	A	A
644	A	A	A	B
645	A	A	A	A

Table 6. Cellular Activities of Selected Compounds

Compound No.	Axl IC_{50} (nM)	Mer IC_{50} (nM)	c-Met IC_{50} (nM)	KDR IC_{50} (nM)
21	A	A	A	A
22	A	A	A	B
23	A	A	B	C
24	A	A	A	B
25	A	A	A	B
26	A	A	A	A
27	A	A	A	A
28	A	A	A	A
29	A	A	A	B
30	A	A	A	C
31	A	A	B	C
32	A	A	A	C
33	A	A	A	A
35	A	A	A	A
36	A	A	A	B
37	A	A	A	B
38	A	A	B	A
39	A	A	A	A

40	A	A	A	A
41	A	A	A	B
42	A	A	A	A
43	A	A	A	A
44	A	A	A	B
45	A	A	A	A
46	A	A	A	B
47	A	A	A	C
48	A	A	A	C
49	A	A	A	C
50	A	A	A	B
51	A	A	A	C
52	A	A	A	C
53	A	A	A	C
54	A	A	A	C
55	A	A	A	C
56	A	A	A	C
57	A	A	A	C
58	A	A	A	A
59	A	A	A	C
60	A	A	A	C
61	A	A	A	C
62	A	A	A	C
63	A	A	A	A
64	A	A	A	A
65	A	A	A	A
66	A	A	A	A
67	A	A	A	A
68	A	A	A	A
69	A	A	A	A
70	A	A	A	A
71	A	A	A	A
72	A	A	A	B
73	A	A	A	A
74	A	A	A	B
75	A	A	A	A
76	A	A	A	A
77	A	A	A	C
78	A	A	A	B
79	A	A	B	NT
80	A	A	A	A
81	A	A	A	A
82	A	A	A	B
83	A	A	A	A
84	A	A	A	A
85	A	A	A	A
86	A	A	A	B
87	A	A	A	C
88	A	A	A	A
89	A	A	A	A
90	A	A	A	A
91	A	A	A	B
92	A	A	A	A
93	A	A	A	A

94	A	A	A	C
95	A	A	A	C
96	A	A	A	A
97	A	A	A	A
98	A	A	A	A
99	A	A	A	A
100	A	A	A	A
101	A	A	A	A
102	A	A	A	A
104	A	A	A	A
105	A	A	A	A
106	A	A	A	B
107	A	A	B	B
108	A	A	B	A
109	A	A	A	A
110	A	A	A	C
111	A	A	B	C
112	A	A	A	C
113	A	A	A	C
115	A	A	A	C
116	A	A	A	A
117	A	A	A	A
118	A	A	A	A
119	A	A	A	A
120	A	A	A	A
121	A	A	A	C
122	A	A	A	B
123	A	A	A	C
124	A	A	A	NT
125	A	A	A	C
126	A	A	A	A
127	A	A	A	A
128	A	A	A	A
129	A	A	B	A
130	A	A	A	A
131	A	A	A	C
132	A	A	B	B
133	A	B	B	B
134	A	B	C	A
135	A	A	A	A
136	A	A	A	A
137	A	A	A	B
138	A	B	C	B
139	A	A	B	C
140	A	A	A	C
141	A	A	A	NT
142	A	A	A	A
143	A	A	A	B
144	A	A	A	A
145	A	A	A	NT
146	A	A	A	A
147	A	A	A	A
148	A	A	A	C
149	A	A	A	NT

151	A	A	A	A
153	A	A	A	C
154	A	A	A	A
155	A	A	B	C
156	A	A	A	C
157	A	A	A	B
158	A	A	A	A
159	A	A	B	C
160	A	NT	A	A
162	A	A	B	C
163	A	A	A	C
164	A	A	A	C
165	A	A	NT	NT
166	A	A	A	C
167	A	A	A	A
168	A	A	A	B
169	NT	A	A	C
170	A	A	A	C
171	A	A	A	A
172	A	A	A	A
173	A	A	A	A
174	A	A	A	A
175	A	A	A	A
176	A	A	A	A
177	A	A	A	A
178	A	A	A	A
179	A	A	A	A
180	A	A	A	A
181	A	A	A	C
182	A	A	A	A
183	A	A	B	C
184	A	A	A	A
185	A	A	A	A
186	A	A	A	A
187	A	A	A	C
188	A	A	A	A
189	A	A	A	A
190	A	A	A	A
191	A	A	A	A
192	A	A	A	A
193	A	A	A	A
194	A	A	A	A
195	A	A	A	A
196	A	A	A	A
197	NT	A	A	A
198	A	A	A	A
199	A	A	A	A
200	A	A	A	A
201	A	A	A	A
202	A	A	A	A
203	A	A	A	A
204	A	A	A	A
205	A	A	A	A
206	A	A	A	A

207	A	A	A	A
208	A	A	A	A
209	A	A	A	NT
210	A	A	A	NT
211	A	A	A	NT
212	A	A	A	NT
213	A	A	A	NT
214	A	A	A	NT
216	A	A	A	A
217	A	A	A	A
218	A	A	A	A
219	A	A	A	A
220	A	A	A	A
221	A	A	A	B
222	A	A	A	C
223	A	A	A	C
224	A	A	B	C
225	A	A	A	A
226	A	A	A	A
227	A	A	A	A
228	A	A	A	C
229	A	A	A	A
230	A	A	B	B
231	A	A	A	A
232	A	A	A	B
233	A	A	B	A
234	A	A	A	B
235	A	A	A	A
236	A	A	A	A
237	A	A	A	A
238	A	A	A	NT
239	A	A	B	C
240	A	A	A	C
241	A	A	A	C
242	A	A	A	A
243	A	A	A	C
244	A	A	A	C
245	A	A	A	A
246	A	A	A	A
247	A	A	A	A
248	A	A	A	C
249A	A	A	A	B
249B	A	A	A	A
249C	A	A	A	A
250	A	A	A	C
251	A	A	A	C
252	A	A	A	A
253	A	A	A	A
254	A	A	A	A
255	NT	A	B	NT
256	A	A	B	C
257	A	A	A	A
258	A	A	A	B
259	A	A	A	B

260	A	A	B	C
261	A	A	A	C
262	A	A	A	A
263	A	A	A	C
264	A	A	A	C
265	A	A	A	B
266	A	A	A	C
267	A	NT	A	C
268	A	A	A	C
269	A	A	A	C
270	A	A	B	C
271	A	A	A	B
272	A	A	A	C
273	A	A	A	C
274	A	A	A	C
275	A	A	A	A
276	A	A	B	A
277	A	A	A	A
278	A	A	A	A
279	A	A	A	A
280	A	A	A	A
281	A	A	A	A
282	A	A	A	A
283	A	A	A	B
284	A	A	A	C
285	A	A	A	C
286	A	A	A	A
287	A	A	A	A
288	A	A	A	A
289	A	A	A	A
290	A	A	A	A
291	A	A	A	A
292	A	A	A	A
293	A	A	A	A
294	A	A	A	A
295	A	A	A	A
296	A	A	A	A
297	A	A	A	A
298	A	A	A	A
299	A	A	A	A
300	A	A	A	A
301	A	A	A	A
302	A	A	A	B
303	C	A	A	C
304	B	A	A	B
305	A	A	A	B
306	A	A	A	B
307	A	A	A	C
308	A	A	A	A
309	A	A	A	C
310	A	A	A	C
311	A	A	A	A
312	A	A	A	B
313	A	A	A	A

314	A	A	A	A
315	A	A	A	A
316	A	A	A	A
317	A	A	A	A
318	A	A	A	C
319	A	A	A	C
320	A	A	A	C
321	A	A	A	B
322	A	A	A	B
323	A	A	A	B
324	A	A	A	A
325	A	A	A	A
326	A	A	A	B
327	A	A	A	A
328	A	A	A	C
329	A	A	A	B
330	A	A	A	C
331	A	A	A	C
332	A	A	A	A
333	A	A	A	B
334	B	A	A	A
335	A	A	A	C
336	A	A	A	NT
337	A	A	A	NT
338	A	A	A	NT
340	A	A	A	A
341	A	A	A	C
342	A	A	A	A
343	A	A	A	A
345	A	A	A	A
346	A	A	A	A
347	A	A	A	A
348	A	A	A	A
349	A	A	A	A
350	A	A	A	A
351	A	A	A	A
352	A	A	A	A
353	A	A	A	A
354	A	A	A	A
355	A	A	A	A
356	A	A	A	C
357	A	A	A	NT
358	A	A	A	A
359	A	A	A	C
360	A	A	B	C
361	A	A	A	A
362	A	A	A	A
363	A	A	A	A
364	A	A	A	A
366	A	A	A	NT
367	A	A	A	B
368	A	A	A	A
369	A	A	A	A
370	A	A	A	A

371	A	A	A	A
372	A	A	A	A
373	A	A	A	C
374	A	A	A	C
375	A	A	A	C
376	A	A	A	A
377	A	A	A	A
378	A	A	A	C
379	A	A	A	A
380	A	A	A	C
381	A	A	A	C
382	A	A	A	C
383	A	A	A	C
384	A	A	A	A
385	A	A	A	C
386	A	A	A	A
387	A	A	A	A
388	A	A	A	A
389	A	A	A	C
390	A	A	A	A
391	A	A	A	C
392	A	A	A	C
393	A	A	A	A
394	A	A	A	C
395	A	A	A	A
396	A	A	A	A
398	A	A	A	NT
399	A	A	A	C
400	A	A	A	C
401	A	A	A	C
402	A	A	A	C
403	A	A	A	B
404	A	A	A	A
405	A	A	A	C
406	A	A	A	A
407	A	A	A	C
408	A	A	A	A
409	A	A	A	A
410	A	B	B	C
411	A	A	A	C
412	A	A	A	A
413	A	A	A	A
414	A	A	A	A
415	A	A	A	A
416	NT	A	A	A
417	A	B	A	B
418	A	A	A	A
419	A	A	A	A
420	A	A	A	A
421	A	A	A	A
422	A	A	A	A
423	A	A	A	A
424	A	A	A	A
425	A	A	A	A

426	A	A	A	A
427	A	A	A	A
428	A	A	A	A
429	B	A	A	C
430	A	A	A	C
431	A	A	A	A
432	A	A	A	A
433	A	A	A	C
434	A	A	A	C
435	A	A	A	C
436	A	A	A	A
437	A	A	A	A
438	A	A	A	A
439	A	A	A	C
440	A	A	A	C
441	A	A	A	C
442	A	A	A	A
443	C	A	B	C
445	A	A	A	A
446	A	A	A	A
448	A	A	A	A
450	A	A	A	A
451	A	A	A	A
454	A	A	A	A
455	A	A	A	A
456	A	A	A	A
457	A	A	A	A
458	A	A	A	A
459	A	A	A	A
460	A	A	A	A
461	A	A	A	A
462	A	A	A	A
463	A	A	A	A
464	A	A	A	A
465	A	A	A	B
466	A	A	A	A
467	A	A	A	A
468	A	A	A	A
469	A	A	A	A
470	A	A	A	A
471	A	A	A	A
472	A	A	A	A
473	A	A	C	C
474	A	A	A	A
475	A	A	A	A
476	A	A	A	A
477	A	A	A	C
478	A	A	A	A
479	A	A	A	A
480	A	A	A	A
481	A	A	A	A
482	A	A	A	A
483	A	A	A	C
484	A	A	A	A

485	A	A	A	A
486	A	A	A	A
487	A	A	A	A
488	B	A	C	C
489	A	A	A	A
490	B	A	A	A
491	A	A	A	C
492	B	A	A	NT
493	A	A	A	NT
494	A	A	A	A
496	A	A	A	A
497	A	A	A	C
498	A	A	A	C
499	A	A	A	B
500	A	A	A	B
501	A	A	A	A
502	A	A	A	A
503	A	A	A	A
504	A	A	A	A
505	A	B	A	A
506	A	A	A	A
507	A	B	NT	A
508	A	A	A	C
509	A	A	A	A
510	A	A	A	A
511	A	A	A	B
512	A	A	A	A
513	A	A	A	A
514	A	A	A	A
515	A	A	A	A
516	A	A	A	B
517	A	A	A	A
518	A	A	A	A
519	A	A	A	A
520	A	A	A	A
521	A	C	B	C
522	A	C	A	C
523	A	A	A	C
524	A	A	A	B
525	A	A	A	A
526	A	A	A	A
527	A	A	A	A
528	A	A	A	A
529	A	A	A	A
530	A	A	A	A
531	A	A	A	A
532	A	A	A	C
533	A	A	A	A
534	A	A	A	A
535	A	A	A	C
536	C	C	C	C
537	A	A	A	A
538	A	A	A	A
539	A	A	A	C

540	A	A	B	A
541	A	A	A	A
542	A	A	A	A
543	A	A	A	B
544	A	A	A	A
551	A	A	A	A
552	A	A	A	A
553	A	B	A	C
554	A	A	A	A
555	A	A	A	A
556	A	A	A	A
557	A	A	A	B
558	A	A	A	B
559	NT	A	A	C
560	A	A	A	B
561	A	A	A	C
562	A	A	A	B
563	A	A	A	C
564	A	A	A	B
565	A	A	A	A
566	A	A	A	C
567	A	A	A	A
568	A	A	A	A
569	A	A	A	A
570	A	A	A	A
571	A	A	A	A
572	A	A	A	A
573	A	A	A	A
574	A	A	A	A
575	A	A	A	A
576	A	A	A	C
577	A	B	A	A
578	B	C	C	C
579	A	A	A	C
580	A	A	A	C
581	A	A	B	C
582	A	A	A	B
584	A	B	A	A
585	A	A	A	C
586	A	A	B	C
587	A	A	A	C
588	A	A	A	C
589	A	A	A	A
593	A	A	A	A
594	A	A	A	A
595	A	A	A	A
596	A	A	A	A
597	B	NT	NT	B
598	A	A	A	A
599	A	A	A	NT
601	C	A	C	C
602	B	A	B	NT
604	A	A	A	A
605	A	A	A	B

606	A	A	A	B
607	A	A	A	A
608	A	A	A	A
609	A	A	A	A
610	A	A	A	A
611	A	A	A	A
612	A	A	B	C
613	A	A	A	C
614	A	A	B	C
615	NT	A	A	A
616	NT	B	C	A
617	NT	A	A	A
618	NT	A	B	A
619	A	A	A	A
620	A	A	B	C
621	A	B	NT	B
622	A	A	A	NT
623	A	A	A	NT
624	A	A	A	NT
625	A	A	A	NT
626	A	A	A	NT
635	A	A	A	A
636	A	A	A	C
637	A	A	A	C
638	A	A	A	A
639	A	A	A	A
640	A	A	A	C
641	A	A	A	A
642	A	A	A	A
643	A	A	A	A
644	A	A	A	A
645	A	A	A	A
646	A	A	A	A
647	A	A	A	C
648	A	A	A	B
649	B	A	A	C
650	A	A	A	A
651	A	A	A	A
652	A	A	A	A
653	A	A	A	A
654	A	A	A	A
655	A	A	A	A
656	A	A	A	C
657	A	A	A	A
658	A	A	A	C
659	A	A	A	C
660	A	A	A	B
661	A	A	A	C
662	A	A	A	B
663	A	A	A	C
664	A	A	A	A
665	A	A	A	B
666	A	A	A	B
667	A	A	A	C

668	A	A	A	A
669	A	A	A	C
670	A	A	A	A
671	A	A	A	A
672	A	A	A	A
673	A	A	A	A
674	A	A	A	A
675	A	A	A	A
676	A	A	A	A
677	A	A	A	A
678	A	A	A	A
679	A	A	A	A
680	A	A	A	A
681	A	A	A	A
682	A	A	A	A
683	A	A	A	A
684	A	A	A	C
685	A	A	A	C
686	A	A	A	A
687	A	A	A	A
688	A	A	A	A
689	A	A	A	A
690	C	B	C	C
691	B	A	A	A
692	B	A	A	A
693	C	A	B	A
694	C	A	B	C
695	C	A	A	A
696	C	A	B	A
697	C	A	B	C
698	C	A	C	A
699	C	A	B	A
700	C	A	A	A
701	A	A	A	A
702	A	A	A	B
703	A	A	A	A
704	A	A	A	A
705	NT	A	A	C
706	NT	A	A	A
707	NT	A	A	A
708	NT	A	A	A
709	NT	A	A	A
710	NT	A	A	A
711	NT	A	A	A
712	NT	A	A	A
713	NT	A	A	NT
714	NT	A	A	NT
715	NT	A	A	A
716	NT	A	A	C
717	NT	A	A	C
718	NT	A	A	B
719	NT	A	A	A
720	NT	A	A	C
721	A	A	A	B

722	A	A	A	C
723	A	A	A	C
724	A	A	A	A
725	A	A	A	A
726	A	A	A	A
727	NT	A	A	B
728	A	A	A	B
729	NT	A	A	A
730	A	A	A	B
731	A	A	A	C
732	A	A	A	C
733	C	A	A	C
734	B	A	A	C
735	A	A	A	A
736	A	A	A	A
737	A	A	A	A
738	A	A	A	A
739	A	A	A	C
740	A	A	A	A
741	A	A	A	B
742	A	A	A	C
743	A	A	A	C
744	A	A	A	C
745	A	A	A	C
746	A	A	A	C
747	A	A	A	B
748	A	A	A	C
749	A	A	A	C
750	A	A	A	B
751	A	A	A	A
752	A	A	A	A
753	A	A	A	C
754	A	A	A	C
755	NT	A	A	B
756	NT	A	A	A
757	A	A	A	C
758	A	A	A	C
759	A	A	A	A
760	A	A	A	C
761	NT	A	A	C
762	A	A	A	A
763	A	A	A	A
764	NT	A	A	C
765	A	A	A	C
766	A	A	A	C
767	A	A	A	A
768	NT	A	A	A
769	A	A	A	B
770	A	A	A	A
771	A	A	A	C
772	A	A	A	B
773	NT	A	A	A
774	A	A	A	B
775	NT	A	A	A

776	NT	A	A	C
777	NT	A	A	A
778	NT	A	A	A
779	NT	A	A	A
780	NT	A	A	B
781	NT	A	A	C
782	A	A	A	C
783	A	A	A	C
784	A	A	A	C
785	A	A	A	A
786	NT	A	A	A
787	NT	A	A	C
788	NT	A	A	B
789	NT	A	A	C
790	NT	A	A	C
791	NT	A	A	C
792	A	A	A	A
793	A	A	A	A
794	A	A	A	A
795	A	A	A	A
796	A	A	A	A
797	A	A	A	A
798	A	A	A	NT
799	A	A	A	NT
800	A	A	A	NT
801	A	A	A	NT
802	NT	A	A	NT
803	A	A	A	NT
804	A	A	A	NT
805	A	A	A	NT
806	A	A	A	NT
807	A	A	B	NT
808	A	A	A	C
809	A	A	A	C
810	A	A	A	A
811	A	A	A	A
812	A	A	A	C
813	A	A	A	B
814	A	A	A	C
815	A	A	A	B
816	A	A	A	C
817	NT	A	A	C
818	NT	A	A	C
819	NT	A	A	C
820	NT	A	A	C
821	A	A	A	B
822	NT	A	A	C
823	NT	A	A	C
824	NT	A	A	C

* * *

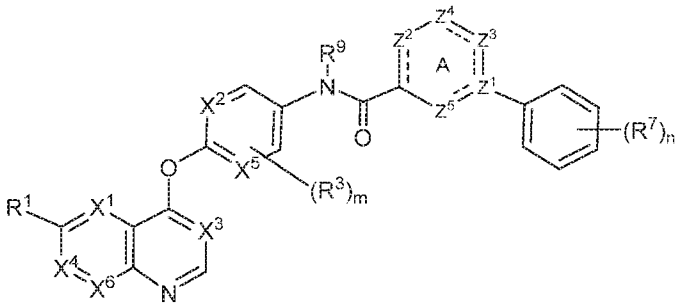
[01429] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[01430] The inventions illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including," "containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

[01431] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

CLAIMS:

1. A compound of formula (I'''):



(I''')

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

X^1 is N or CR^{11};

X^2 is N, CR^3, or CH;

X^3 is N or CH;

X^4 is N or CR^2;

X^5 is N, CR^3, or CH;

X^6 is N or CR^{10};

Z^1 is N, CH or C;

Z^2 is N, NR^{40}, -C(=O)-, or CR^{45};

Z^3 is N, NR^{41}, CR^{42}, -C(=O)-, -C(=S)-;

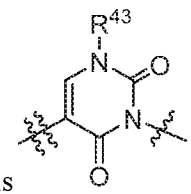
Z^4 is N, NR^{43}, CR^{44}, -C(=O)- or a bond;

Z^5 is N, COR^{46}, -C(=O)- or CR^{18};

⋯ is a single bond or a double bond;

one or two of Z^1, Z^2, Z^3, Z^4, and Z^5 are independently selected from N, NR^{40}, NR^{41}, and NR^{43};

no more than two of Z^2, Z^3, Z^4 and Z^5 are –C(=O)-;

when ring A is  then X^1 is N, wherein the single wavy line indicates the point of attachment to the phenyl ring and the double wavy line indicates the point of attachment to the carbonyl of the amide linkage;

R^1 and R^2 and R^{10} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$,

$NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^1, R^2 and R^{10} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

each R^3 is independently selected from halo, OH, CN, -COOH, -CONH(C_{1-6} alkyl), -SO_2(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, C_1-C_6 alkoxy, -NH(C_1-C_6alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl of R^3 are each optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{40}, R^{41} and R^{43} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $N{=}C(NR^aR^a)_2$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^{40}, R^{41} and R^{43} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

R^{45}, R^{42} and R^{44} are each independently H, halo, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, C_{2-6} alkenyl, C_{3-14} cycloalkyl, C_{1-6} alkoxy, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -S-C_{1-6} alkyl, -COOH, -COC_{1-4}alkyl, -$COOC_{1-4}$alkyl, -$CONH_2$, -CONHC_{1-4} alkyl, -NHC(O)OC_{1-4}alkyl, NH_2, -NHC_{1-4}alkyl, or –N(C_{1-4} alkyl)$_2$;

each R^7 is independently selected from halo, OH, $COOR^a$, $CONR^aR^a$, CN, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $CONR^aR^a$, NR^aCOR^a, $NR^aCONR^aR^a$, SO_2R^a, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4 alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4 alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene- of R^7 are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{46} is H, C_{1-6} alkyl or a hydroxy protecting group;

R^9 is H or C_{1-6} alkyl optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{11} is selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)- C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)- C_1-C_4 alkylene-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^{11} are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{18} is H, halo, CN, C_{1-6} alkyl, NH_2, -NHC_{1-4}alkyl, -$N(C_{1-4}$ alkyl$)_2$, or -S-C_{1-6} alkyl;

or R^{40} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{43} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{44} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or when Z^4 is a bond, R^{40} and R^{42} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{41} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{42} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or R^{41} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{43} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{44} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl, fused phenyl, or fused heteroaryl, wherein the fused C_{3-7} cycloalkyl, fused phenyl, and fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

each R^a is independently selected from the group consisting of H, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14 membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14 membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^b is independently selected from the group consisting of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, OH, NH_2, NO_2, NHOR^c, OR^c, SR^c, C(O)R^c, C(O)NR^{c}R^c, C(O)OR^c, C(O)NR^{c}S(O)$_2$R^c, OC(O)R^c, OC(O)NR^{c}R^c, C(=NOH)R^c, C(=NOH)NR^c, C(=NCN)NR^{c}R^c, NR^{c}C(=NCN)NR^{c}R^c, C(=NR^c)NR^{c}R^c, NR^{c}C(=NR^c)NR^{c}R^c, NHR^c, NR^{c}R^c, NR^{c}C(O)R^c, NR^{c}C(=NR^c)R^c, NR^{c}C(O)OR^c, NR^{c}C(O)NR^{c}R^c, NR^{c}S(O)R^c, NR^{c}S(O)$_2$R^c, NR^{c}S(O)$_2$NR^{c}R^c, S(O)R^c, S(O)NR^{c}R^c, S(O)$_2$R^c, S(O)$_2$NR^{c}C(O)R^c, Si(R^c)$_3$, P(O)R^{c}R^c, P(O)(OR^c)(OR^c), B(OH)$_2$, B(OR^c)$_2$, and S(O)$_2$NR^{c}R^c; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered

heterocycloalkyl)-C_1-C_4 alkylene- of R^b are each further optionally substituted with 1, 2, or 3 independently selected R^d substituents;

each R^c is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^d is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^d are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^e is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, C_6-C_{10} aryl, C_6-C_{10} aryl-C_1-C_4 alkylene-, 5- or 6-membered heteroaryl, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, 4-7-membered heterocycloalkyl, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_4 alkenyl, and C_2-C_4 alkynyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, 5 or 6-membered heteroaryl, 4-7-membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_2-C_4 alkenyl, and C_2-C_4 alkynyl of R^e are each optionally substituted with 1, 2, or 3 R^f substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^f is independently selected from the group consisting of halo, OH, CN, COOH, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl, wherein the C_1-C_6

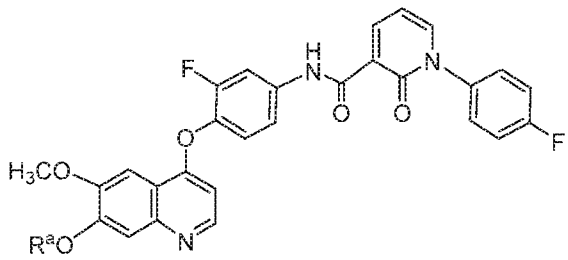
alkyl, phenyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^f are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, $-NH_2$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, C_3-C_{10} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^g is independently selected from the group consisting of halo, OH, CN, COOH, -COO-C_1-C_4 alkyl, -OC(O)C_1-C_4 alkyl, NH_2, NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl;

the ring nitrogen atom in Formula (I''') is optionally oxidized;

the subscript m is 0, 1, 2, or 3; and

the subscript n is 0, 1, 2, 3, 4 or 5;

with the proviso that the compound is not 

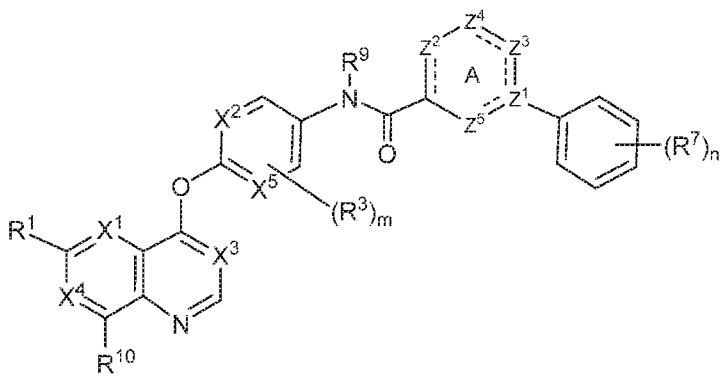
,

wherein R^a is H, methyl, benzyl, piperidin-4-yl, (piperidin-4-yl)methyl, (1-methylpiperidin-4-yl)methyl, or (1-t-butoxypiperidin-4-yl)methyl;

with the proviso that when X^1 is CH, X^2 is CF, X^3 is CH, X^4 is CR^2, X^5 is CH, m is 0, R^9 is H, R^{10} is H, n is 1, R^1 is OCH_3 or CN, R^2 is OCH_3, R^7 is fluoro and is para to ring A, and Z^3 is CR^{42}, then R^{42} cannot be CN, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2OCH_3$, or OH; and

with the proviso that when X^1 is CH, X^3 is CH, X^4 is CR^2, R^1 is OCH_3, R^2 is OCH_3, R^9 is H, n is 1, R^7 is fluoro and is para to ring A, one of X^2 and X^5 is N, or X^2 and X^5 are each N, then R^{43} is not cyclopropyl or isopropyl.

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



(I')

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

X^1 is N or CR^{11};

X^2 is N, CR^3, or CH;

X^3 is N or CH;

X^4 is N or CR^2;

X^5 is N, CR^3, or CH;

Z^1 is N, CH or C;

Z^2 is N, NR^{40}, -C(=O)-, or CR^{45};

Z^3 is N, NR^{41}, CR^{42}, -C(=O)-, -C(=S)-;

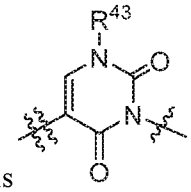
Z^4 is N, NR^{43}, CR^{44}, -C(=O)- or a bond;

Z^5 is COR^{46}, -C(=O)- or CR^{18};

⋯ is a single bond or a double bond;

one or two of Z^1, Z^2, Z^3 and Z^4 are independently selected from N, NR^{40}, NR^{41}, and NR^{43};

no more than two of Z^2, Z^3, Z^4 and Z^5 are –C(=O)-;

when ring A is  then X^1 is N, wherein the single wavy line indicates the point of attachment to the phenyl ring and the double wavy line indicates the point of attachment to the carbonyl of the amide linkage;

R^1 and R^2 and R^{10} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^1, R^2 and R^{10} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

each R^3 is independently selected from halo, OH, CN, -COOH, -CONH(C_{1-6} alkyl), -SO_2(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, C_1-C_6 alkoxy, -NH(C_1-C_6alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl of R^3 are each optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{40}, R^{41} and R^{43} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $N=C(NR^aR^a)_2$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^{40}, R^{41} and R^{43} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

R^{45}, R^{42} and R^{44} are each independently H, halo, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, C_{2-6} alkenyl, C_{1-6} alkoxy, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -S-C_{1-6} alkyl, -COOH, -COC_{1-4}alkyl, -$COOC_{1-4}$alkyl, -$CONH_2$, -$CONHC_{1-4}$ alkyl, -$NHC(O)OC_{1-4}$alkyl, NH_2, -NHC_{1-4}alkyl, or –$N(C_{1-4}$ alkyl$)_2$;

each R^7 is independently selected from halo, OH, $COOR^a$, $CONR^aR^a$, CN, NH_2, -$NH(C_1$-C_6 alkyl), -$N(C_1$-C_6 alkyl$)_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $CONR^aR^a$, NR^aCOR^a, $NR^aCONR^aR^a$, SO_2R^a, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4 alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4 alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene- of R^7 are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{46} is H, C_{1-6} alkyl or a hydroxy protecting group;

R^9 is H or C_{1-6} alkyl optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{11} is selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)- C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)- C_1-C_4 alkylene-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4

alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^{11} are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{18} is H, halo, CN, C_{1-6} alkyl, NH_2, -NHC_{1-4}alkyl, -$N(C_{1-4}$ alkyl$)_2$, or -S-C_{1-6} alkyl;

or R^{40} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{43} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{44} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or when Z^4 is a bond, R^{40} and R^{42} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{41} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{42} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or R^{41} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{43} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{44} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl, fused phenyl, or fused heteroaryl, wherein the fused C_{3-7} cycloalkyl, fused phenyl, and fused

heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

each R^a is independently selected from the group consisting of H, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14 membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14 membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^b is independently selected from the group consisting of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, OH, NH_2, NO_2, NHOR^c, OR^c, SR^c, C(O)R^c, C(O)NR^{c}R^c, C(O)OR^c, C(O)NR^{c}S(O)$_2$R^c, OC(O)R^c, OC(O)NR^{c}R^c, C(=NOH)R^c, C(=NOH)NR^{c}R^c, C(=NCN)NR^{c}R^c, NR^{c}C(=NCN)NR^{c}R^c, C(=NR^c)NR^{c}R^c, NR^{c}C(=NR^c)NR^{c}R^c, NHR^c, NR^{c}R^c, NR^{c}C(O)R^c, NR^{c}C(=NR^c)R^c, NR^{c}C(O)OR^c, NR^{c}C(O)NR^{c}R^c, NR^{c}S(O)R^c, NR^{c}S(O)$_2$R^c, NR^{c}S(O)$_2$NR^{c}R^c, S(O)R^c, S(O)NR^{c}R^c, S(O)$_2$R^c, S(O)$_2$NR^{c}C(O)R^c, Si(R^c)$_3$, P(O)R^{c}R^c, P(O)(OR^c)(OR^c), B(OH)$_2$, B(OR^c)$_2$, and S(O)$_2$NR^{c}R^c; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^b are each further optionally substituted with 1, 2, or 3 independently selected R^d substituents;

each R^c is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^d is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^d are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^e is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, C_6-C_{10} aryl, C_6-C_{10} aryl-C_1-C_4 alkylene-, 5- or 6-membered heteroaryl, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, 4-7-membered heterocycloalkyl, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_4 alkenyl, and C_2-C_4 alkynyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, 5 or 6-membered heteroaryl, 4-7-membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_2-C_4 alkenyl, and C_2-C_4 alkynyl of R^e are each optionally substituted with 1, 2, or 3 R^f substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

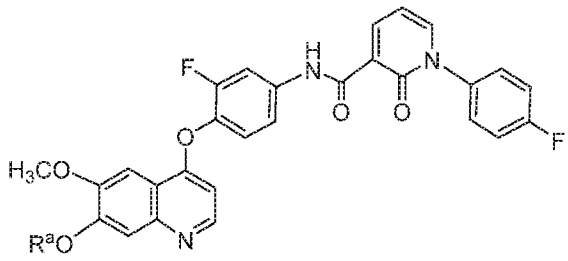
each R^f is independently selected from the group consisting of halo, OH, CN, COOH, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, phenyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^f are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, -NH_2, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, C_3-C_{10} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^g is independently selected from the group consisting of halo, OH, CN, COOH, -COO-C_1-C_4 alkyl, -OC(O)C_1-C_4 alkyl, NH_2, NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl;

the ring nitrogen atom in Formula (I') is optionally oxidized;

the subscript m is 0, 1, 2, or 3; and

the subscript n is 0, 1, 2, 3, 4 or 5;

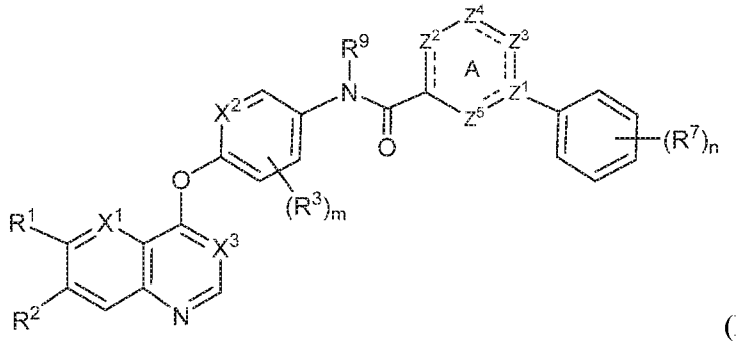
with the proviso that the compound is not  ,

wherein R^a is H, methyl, benzyl, piperidin-4-yl, (piperidin-4-yl)methyl, (1-methylpiperidin-4-yl)methyl, or (1-t-butoxypiperidin-4-yl)methyl;

with the proviso that when X^1 is CH, X^2 is CF, X^3 is CH, X^4 is CR^2, X^5 is CH, m is 0, R^9 is H, R^{10} is H, n is 1, R^1 is OCH_3 or CN, R^2 is OCH_3, R^7 is fluoro and is para to ring A, and Z^3 is CR^{42}, then R^{42} cannot be CN, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2OCH_3$, or OH; and

with the proviso that when X^1 is CH, X^3 is CH, X^4 is CR^2, R^1 is OCH_3, R^2 is OCH_3, R^9 is H, n is 1, R^7 is fluoro and is para to ring A, one of X^2 and X^5 is N, or X^2 and X^5 are each N, then R^{43} is not cyclopropyl or isopropyl.

3. The compound of claim 1 having Formula (I):



(I)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

X^1 is N or CR^{11};

X^2 is N, CR^3, or CH;

X^3 is N or CH;

Z^1 is N, CH or C;

Z^2 is N, NR^{40}, -C(=O)-, or CR^{45};

Z^3 is N, NR^{41}, CR^{42}, -C(=O)-, -C(=S)-;

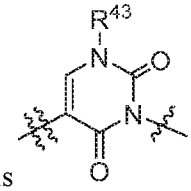
Z^4 is N, NR^{43}, CR^{44}, -C(=O)- or a bond;

Z^5 is COR^{46}, -C(=O)- or CR^{18};

===== is a single bond or a double bond;

one or two of Z^1, Z^2, Z^3 and Z^4 are independently selected from N, NR^{40}, NR^{41}, and NR^{43};

no more than two of Z^2, Z^3, Z^4 and Z^5 are –C(=O)-;

when ring A is  then X^1 is N, wherein the single wavy line indicates the point of attachment to the phenyl ring and the double wavy line indicates the point of attachment to the carbonyl of the amide linkage;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^1 and R^2 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

each R^3 is independently selected from halo, OH, CN, -COOH, -CONH(C_{1-6} alkyl), -SO_2(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, C_1-C_6 alkoxy, -NH(C_1-C_6alkyl), -N(C_1-C_6 alkyl)$_2$, and C_3-C_6 cycloalkyl of R^3 are each optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{40}, R^{41} and R^{43} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $N=C(NR^aR^a)_2$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^{40}, R^{41} and R^{43} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

R^{45}, R^{42} and R^{44} are each independently H, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, C_{1-6} alkoxy, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -COC_{1-4}alkyl, -$COOC_{1-4}$alkyl, -$CONHC_{1-4}$ alkyl, NH_2, -NHC_{1-4}alkyl, or –$N(C_{1-4}$ alkyl$)_2$;

each R^7 is independently selected from halo, OH, $COOR^a$, $CONR^aR^a$, CN, NH_2, -$NH(C_1$-C_6 alkyl), -$N(C_1$-C_6 alkyl$)_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $CONR^aR^a$, NR^aCOR^a, $NR^aCONR^aR^a$, SO_2R^a, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4 alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, (4- to 6-membered heterocycloalkyl)-C_1-C_4 alkylene-, phenyl-C_1-C_2 alkylene, and (5- or 6-membered heteroaryl)-C_1-C_4 alkylene- of R^7 are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{46} is H, C_{1-6} alkyl or a hydroxy protecting group;

R^9 is H or C_{1-6} alkyl optionally substituted with 1, 2, or 3 independently selected R^g substituents;

R^{11} is selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)- C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)- C_1-C_4 alkylene-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^{11} are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

R^{18} is H, halo, CN, or C_{1-6} alkyl;

or R^{40} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{43} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{44} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or when Z^4 is a bond, R^{40} and R^{42} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{41} and R^{45} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or when Z^4 is a bond, R^{42} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

or R^{41} and R^{44} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{43} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{44} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl, fused phenyl, or fused heteroaryl, wherein the fused C_{3-7} cycloalkyl, fused phenyl, and fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents and wherein one or two ring carbon atoms of the fused C_{3-7} cycloalkyl are optionally replaced by a carbonyl;

each R^a is independently selected from the group consisting of H, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14 membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-14 membered heteroaryl)-C_1-C_4 alkylene-, and (4-14 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

or any two R^a substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^b is independently selected from the group consisting of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, OH, NH_2, NO_2, NHOR^c, OR^c, SR^c, C(O)R^c, C(O)NR^{c}R^c, C(O)OR^c, C(O)NR^{c}S(O)$_2$R^c, OC(O)R^c, OC(O)NR^{c}R^c, C(=NOH)R^c, C(=NOH)NR^c, C(=NCN)NR^{c}R^c, NR^{c}C(=NCN)NR^{c}R^c, C(=NR^c)NR^{c}R^c, NR^{c}C(=NR^c)NR^{c}R^c, NHR^c, NR^{c}R^c, NR^{c}C(O)R^c, NR^{c}C(=NR^c)R^c, NR^{c}C(O)OR^c, NR^{c}C(O)NR^{c}R^c, NR^{c}S(O)R^c, NR^{c}S(O)$_2$R^c, NR^{c}S(O)$_2$NR^{c}R^c, S(O)R^c, S(O)NR^{c}R^c, S(O)$_2$R^c, S(O)$_2$NR^{c}C(O)R^c, Si(R^c)$_3$, P(O)R^{c}R^c, P(O)(OR^c)(OR^c), B(OH)$_2$, B(OR^c)$_2$, and S(O)$_2$NR^{c}R^c; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^b are each further optionally substituted with 1, 2, or 3 independently selected R^d substituents;

each R^c is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

or any two R^c substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^d is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene-, CN, NH_2, NHOR^e, OR^e, SR^e, C(O)R^e, C(O)NR^{e}R^e, C(O)OR^e, OC(O)R^e, OC(O)NR^{e}R^e, NHR^e, NR^{e}R^e, NR^{e}C(O)R^e, NR^{e}C(O)NR^{e}R^e, NR^{e}C(O)OR^e, C(=NR^e)NR^{e}R^e, NR^{e}C(=NR^e)NR^{e}R^e, NR^{e}C(=NOH)NR^{e}R^e, NR^{e}C(=NCN)NR^{e}R^e, S(O)R^e, S(O)NR^{e}R^e, S(O)$_2$R^e, NR^{e}S(O)$_2$R^e, NR^{e}S(O)$_2$NR^{e}R^e, and S(O)$_2$NR^{e}R^e; wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, C_3-C_{10} cycloalkyl-C_1-C_4 alkylene-, (5-10 membered heteroaryl)-C_1-C_4 alkylene-, and (4-10 membered heterocycloalkyl)-C_1-C_4 alkylene- of R^d are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^e is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl-C_1-C_4 alkylene-, C_6-C_{10} aryl, C_6-C_{10} aryl-C_1-C_4 alkylene-, 5- or 6-membered heteroaryl, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, 4-7-membered heterocycloalkyl, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_4 alkenyl, and C_2-C_4 alkynyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, 5 or 6-membered heteroaryl, 4-7-membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkylene-, (5- or 6-membered heteroaryl)-C_1-C_4 alkylene-, (4-7-membered heterocycloalkyl)-C_1-C_4 alkylene-, C_2-C_4 alkenyl, and C_2-C_4 alkynyl of R^e are each optionally substituted with 1, 2, or 3 R^f substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

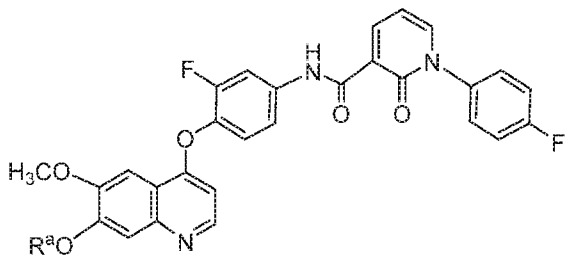
each R^f is independently selected from the group consisting of halo, OH, CN, COOH, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, phenyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^f are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, -NH_2, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, C_3-C_{10} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^g is independently selected from the group consisting of halo, OH, CN, COOH, -COO-C_1-C_4 alkyl, NH_2, NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and C_3-C_6 cycloalkyl;

the ring nitrogen atom in Formula (I) is optionally oxidized;

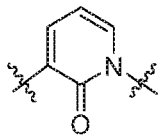
the subscript m is 0, 1, 2, or 3; and

the subscript n is 0, 1, 2, 3, 4 or 5;

with the proviso that the compound is not 

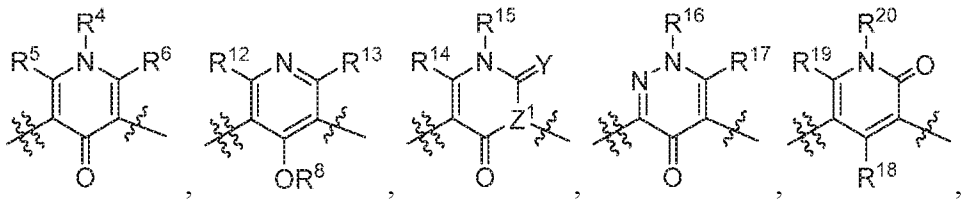
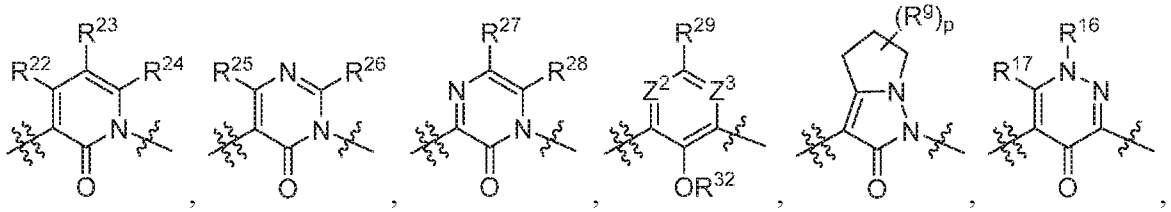
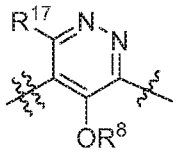
,

wherein R^a is H, methyl, benzyl, piperidin-4-yl, (piperidin-4-yl)methyl, (1-methylpiperidin-4-yl)methyl, or (1-t-butoxypiperidin-4-yl)methyl.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein when ring A is 

, then X^1 is N.

5. The compound of any of one of claims 1-4, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

ring A is  ,  , or  , wherein the single wavy line indicates the point of attachment to the phenyl ring and the double wavy line indicates the point of attachment to the carbonyl of the amide linkage;

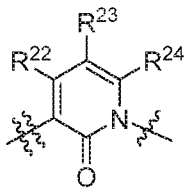
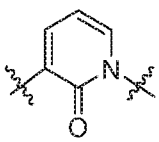
Y is O or S;

Z^1 is N or CH;

Z^2 is N or CR^{45};

Z^3 is N or CR^{42};

when Y is O and Z^1 is N, then X^1 is N;

alternatively, when  is  , then X^1 is N;

R^4, R^{15}, R^{16} and R^{20} are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene-, (4-14 membered heterocycloalkyl)-C_{1-4} alkylene-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $C(O)NR^aS(O)_2R^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $N{=}C(NR^aR^a)_2$, $NR^aC(=NR^a)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NOH)R^a$, $C(=NOH)NR^a$, $C(=NCN)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $S(O)_2NR^aC(O)R^a$, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$ and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-14} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene-, C_{3-14} cycloalkyl-C_{1-4} alkylene-, (5-14 membered heteroaryl)-C_{1-4} alkylene- and (4-14 membered heterocycloalkyl)-C_{1-4} alkylene- of R^4, R^{15}, R^{16} and R^{20} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

R^5, R^{12}, R^{14}, R^{19}, R^{22}, R^{25}, R^{27}, R^{28}, and R^{45} are each independently H, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -$COOC_{1-4}$alkyl, -$CONC_{1-4}$alkyl, NH_2, -NHC_{1-4}alkyl, or –$N(C_{1-4}$ alkyl$)_2$;

R^6, R^{13}, R^{17}, R^{23}, R^{24}, R^{26}, R^{29} and R^{42} are each independently H, C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents, CN, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, -$COOC_{1-4}$alkyl, -$CONC_{1-4}$alkyl, NH_2, -NHC_{1-4}alkyl, or –$N(C_{1-4}$ alkyl$)_2$;

or R^4 and R^5 taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^4 and R^6 taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{14} and R^{15} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{16} and R^{17} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{19} and R^{20} taken together with the atoms to which they are attached form 4- to 7-membered fused heterocycloalkyl or 5- to 6-membered fused heteroaryl, wherein the 4- to 7-membered fused heterocycloalkyl and 5- to 6-membered fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{22} and R^{23} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{23} and R^{24} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl, fused phenyl, or fused heteroaryl, wherein the fused C_{3-7} cycloalkyl, fused phenyl, and fused heteroaryl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{27} and R^{28} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{29} and R^{45} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

or R^{42} and R^{29} taken together with the atoms to which they are attached form fused C_{3-7} cycloalkyl or fused phenyl, wherein the fused C_{3-7} cycloalkyl and fused phenyl are each optionally substituted with 1 or 2 independently selected R^g substituents;

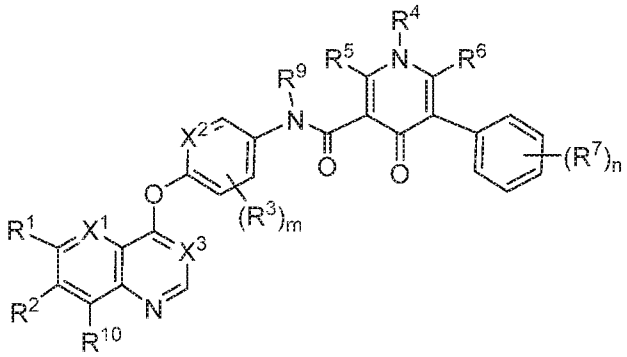
R^8 and R^{32} are each independently H, C_{1-6} alkyl or a hydroxy protecting group;

R^{12} is H or C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents;

R^{13} is H or C_{1-6} alkyl optionally substituted with 1 or 2 independently selected R^g substituents; and

the subscript p is 0, 1, or 2.

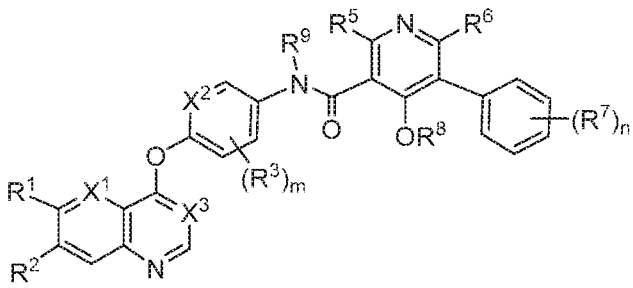
6. The compound of claim 5, having formula (Ia):



(Ia)

or pharmaceutically acceptable salt or stereoisomer thereof.

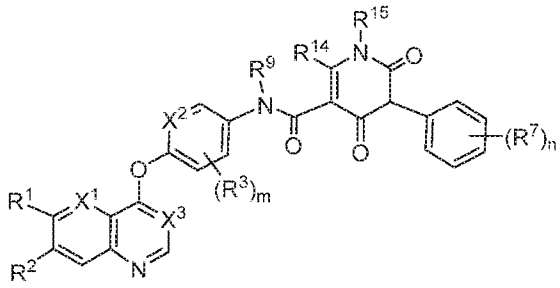
7. The compound of claim 5, having formula (Ib):



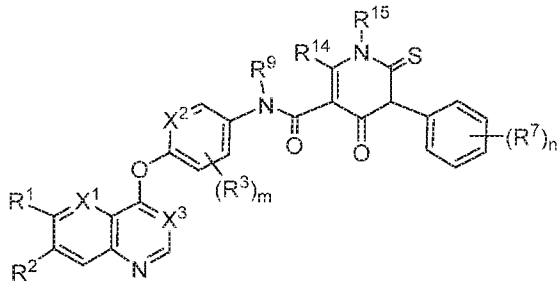
(Ib)

or pharmaceutically acceptable salt or stereoisomer thereof.

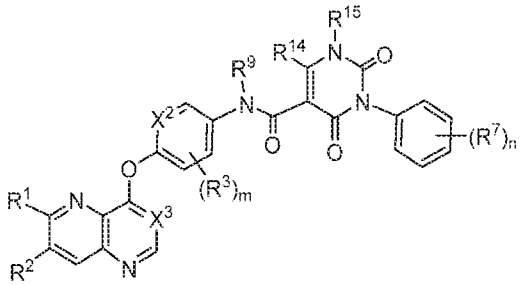
8. The compound of any one of claims 1-5, having formula (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), (It), (Iu), (Iv), (Ix), (Iy), (Iz), (Iaa), or (Ibb):



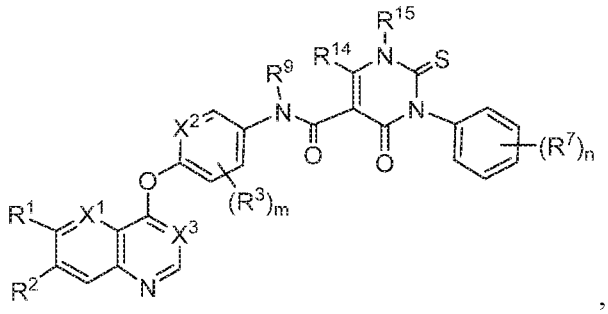
(Ic)



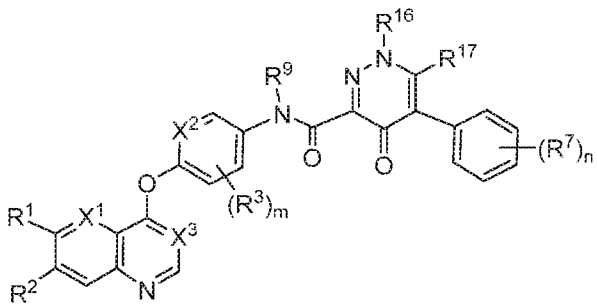
(Id)



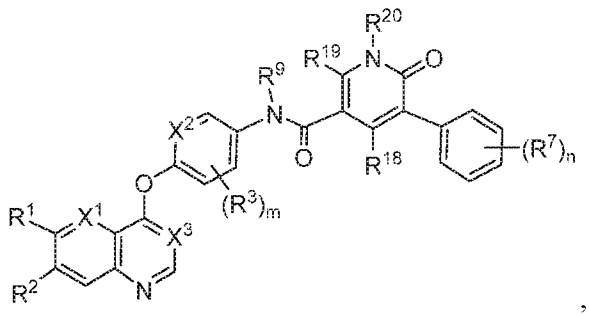
(Ie)



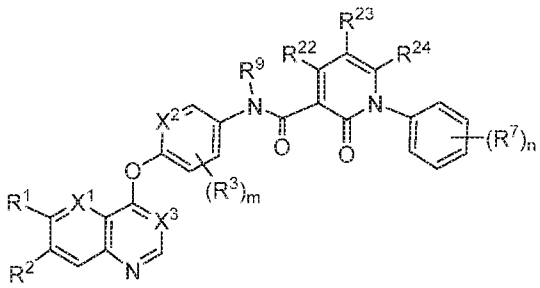
(If)



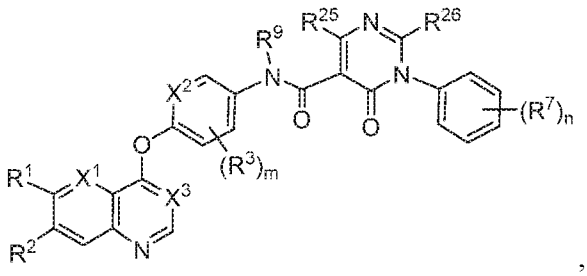
(Ig)



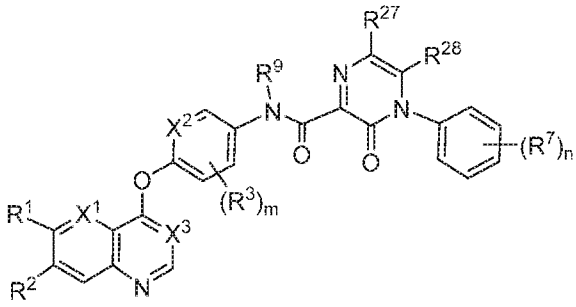
(Ih)



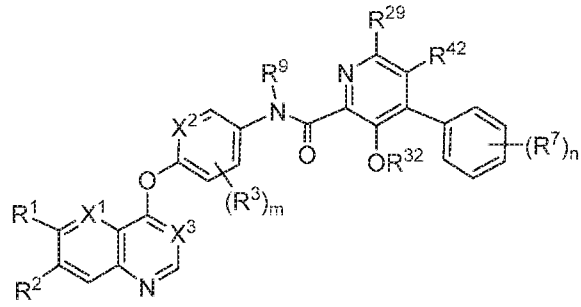
(Ij)



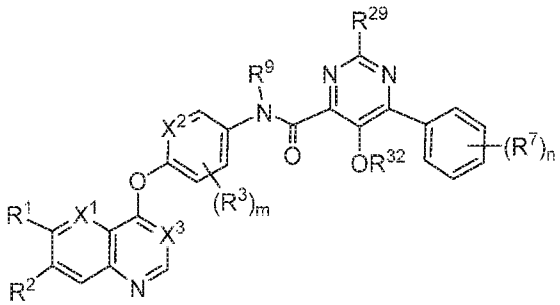
(Ik)



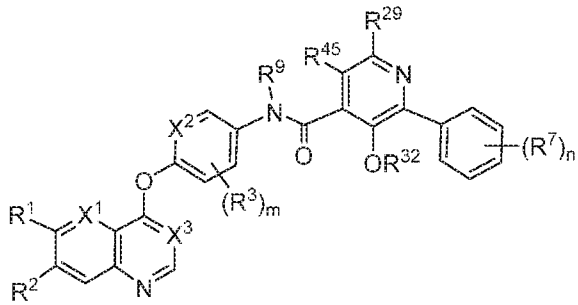
(Im)



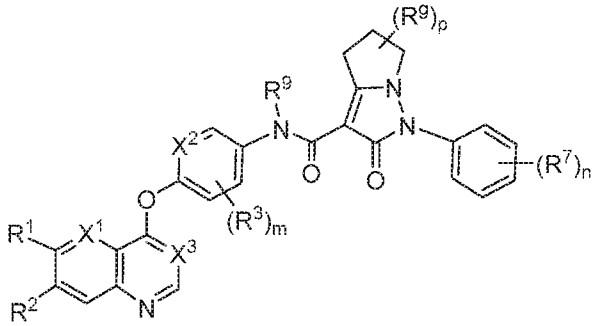
(In)



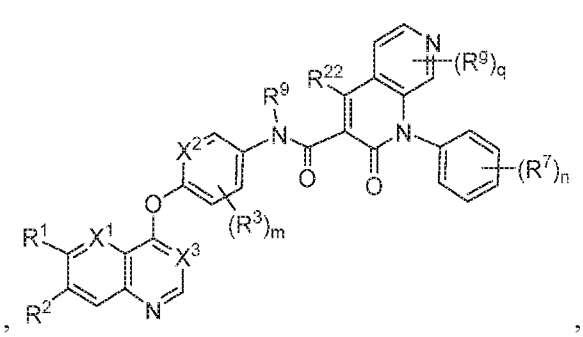
(Io)



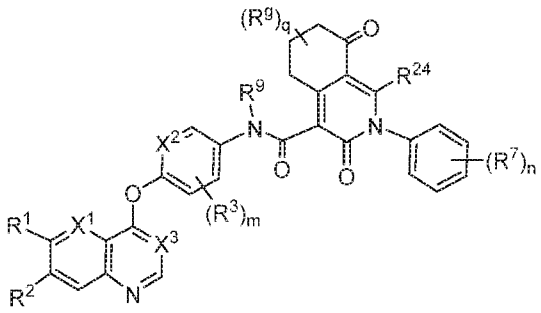
(Ip)



(Iq)

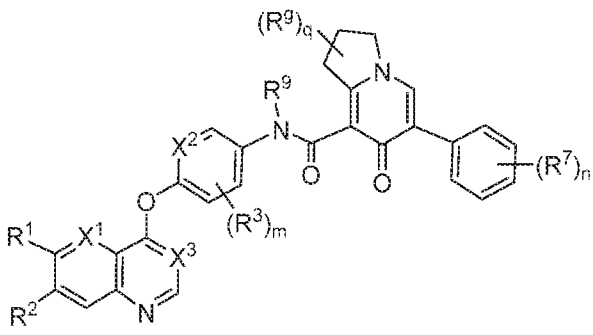


(Ir)

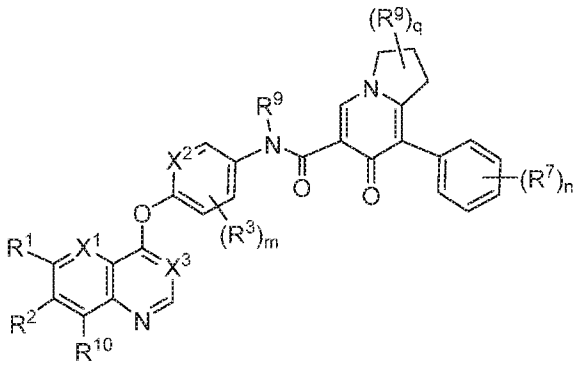


(Is)

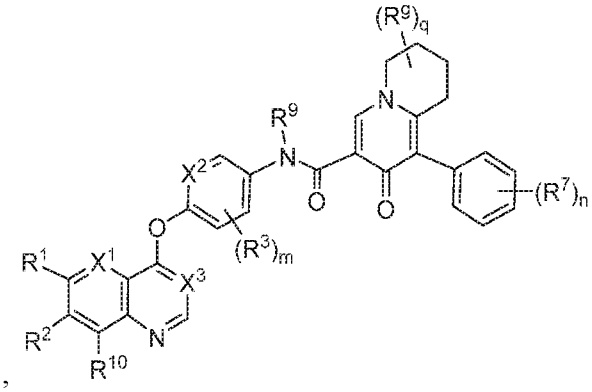
, or



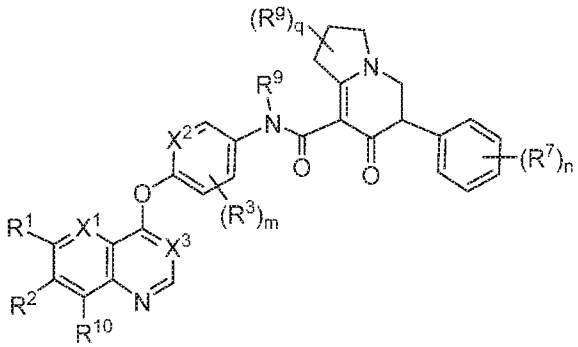
(It)



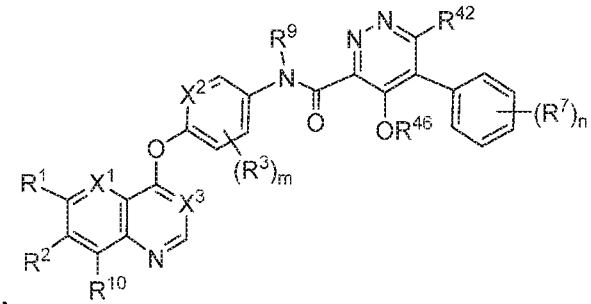
(Iu)



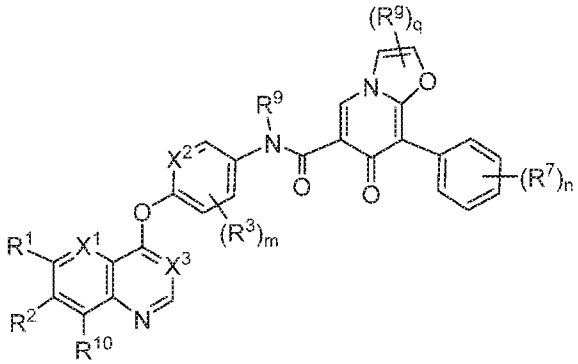
(Iv)



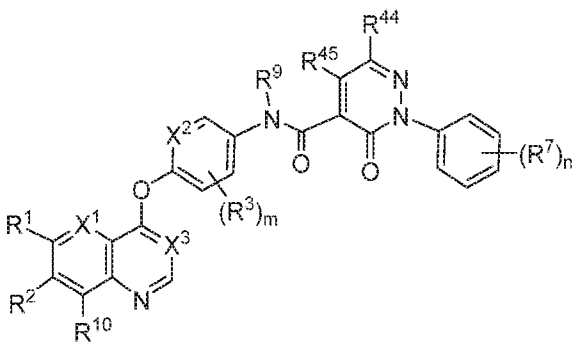
(Iw)



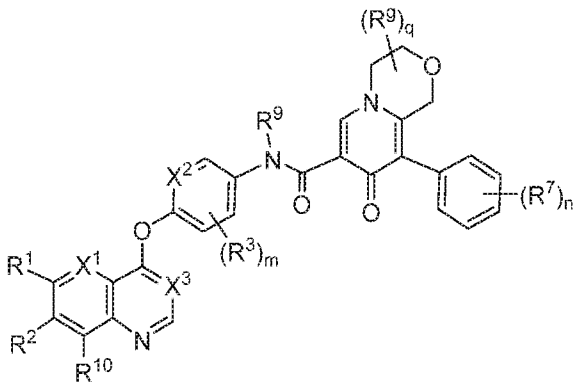
(Ix)

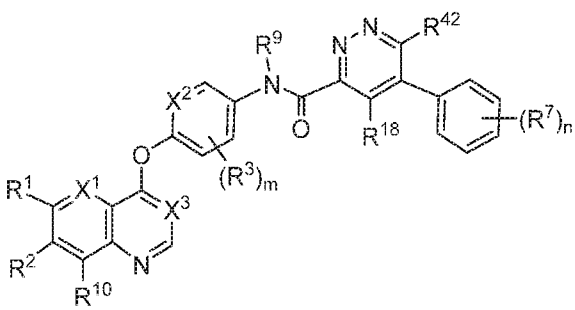


(Iy)



(Iz)

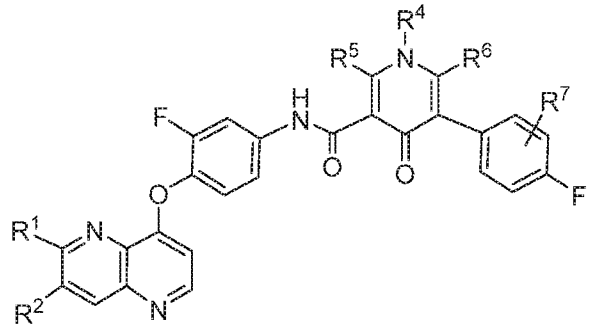




(Iaa) (Ibb)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each subscript q is independently 0, 1, or 2.

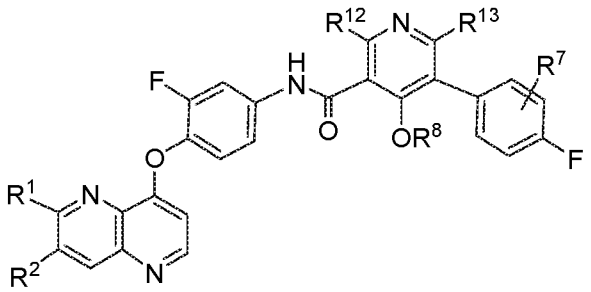
9. The compound of any one of claims 5 or 6, having formula (Ia-1):



(Ia-1)

or a pharmaceutically acceptable salt or stereoisomer thereof.

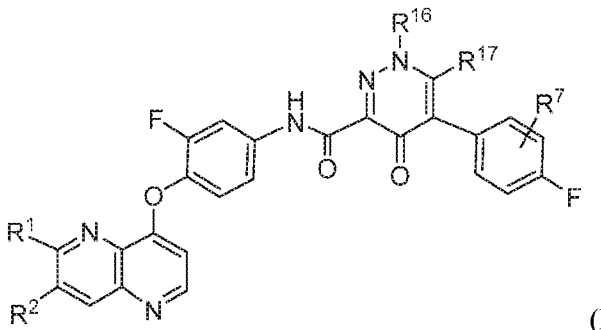
10. The compound of claim 5, having formula (III-1):



(III-1)

or a pharmaceutically acceptable salt or stereoisomer thereof.

11. The compound of any one of claims 5 or 8, having formula (IV-1):



(IV-1)

or a pharmaceutically acceptable salt or stereoisomer thereof.

12. The compound of claim 11, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{16} is H, C_{1-6} alkyl, or C_{1-6} haloalkyl; and R^{17} is H or C_{1-6} alkyl.

13. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^1 is H, C_{1-6} alkyl, C_{1-6} alkoxy, halo, NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, C_{1-6} alkylNHC(O)-, or C_{1-6}alkylSO_2NH-.

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^2 is H, C_{1-6} alkyl, C_{1-6} alkoxy, halo, OH, NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -C_{1-6} alkylNHC(O)-, CF_3, C_{1-6} alkylOC(O)-, pyridyl, C_{1-6}alkylSO_2NH- or 1H-pyrazol-4-yl optionally substituted with R^g.

15. The compound of any one of claims 1-8, or a pharmaceutically salt or stereoisomer thereof, wherein R^3 is H or halo.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^7 is H, halo, C_{1-6} alkyl or C_{1-6} alkoxy.

17. The compound of any one of claims 1-7 and 13-16, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^9 is H.

18. The compound of any one of claims 1-6, 8, 9, 11, and 13-17-, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{43}, R^4, R^{15}, R^{16}, R^{20}, R^{23}, R^{27} and R^{29} are each independently selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, OH, NH_2, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkylene-, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-4} alkylene-, 5-6 membered heteroaryl, (5-6 membered heteroaryl)-C_{1-4} alkylene-, and N=C[N(C_{1-6} alkyl)(C_{1-6} alkyl)]$_2$, wherein the C_{1-6} alkyl, C_{1-6} alkoxy, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkylene-, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-4} alkylene-, 5-6 membered heteroaryl, (5-6 membered heteroaryl)-C_{1-4} alkylene-, and N=C[N(C_{1-6} alkyl)(C_{1-6} alkyl)]$_2$ of R^{43}, R^4, R^{15}, R^{16}, R^{20}, R^{23}, R^{27} and R^{29} are each optionally substituted with 1 or 2 independently selected R^b or R^g substituents.

19. The compound of claim 14, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{43}, R^4, R^{15}, R^{16}, R^{20}, R^{23}, R^{27} and R^{29} are each independently selected from H, methyl, isopropyl, t-butyl, ethyl, OH, methoxy, NH_2, methylamino, dimethylamino, -N=C(N(CH_3)$_2$)$_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopropyl, 1-(trifluoromethyl)cyclopropyl, oxetan-3-yl, 3-methyloxetan-3-yl, 2,2,2-trifluoroethyl, azetidin-3-yl, 1-methylazetidin-3-yl, 1-t-butoxycarbonylazetidin-3-yl, morpholino, 2-morpholinoethyl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1-methylpyrazol-4-yl, 1-(difluoromethyl)pyrazol-4-yl, 2-hydroxyethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-(imidazol-1-yl)ethyl, 2-

(benzotriazol-1-yloxy)ethyl, and 2-hydroxy-1,1-dimethyl-ethyl, each of which when applicable is optionally substituted with 1 or 2 independently selected R^g substituents.

20. The compound of any one of claims 1-9, 11, and 13-17, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{45}, R^{42}, R^{44}, R^5, R^{17} and R^6 are each independently selected from H, OH, halo, CN, C_{1-6} alkyl C_{2-6} alkenyl, C_{1-6} halo alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl-C(O)- and C_{1-6} alkylamino, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl-C(O)- and C_{1-6} alkylamino of R^{45}, R^{42}, R^{44}, R^5, R^{17} and R^6 are each optionally substituted with 1 or 2 independently selected R^g substituents.

21. The compound of any of claims 1-9, 11, 13-17 and 20, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{45}, R^{42}, R^{44}, R^5 and R^6 are each independently selected from H, CH_3, propen-2-yl, Br, Cl, CN, methoxy, 2-fluoroethyl, isopropyl, $CH_3C(O)$-, OH, t-butyl, ethyl, hydroxymethyl, isopropylthio, and methoxymethyl.

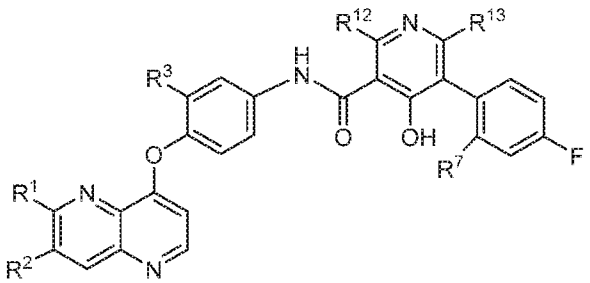
22. The compound of any one of claims 1-5, 7, 8 and 10, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{46}, R^8 and R^{32} are each independently H or C_{1-6} alkyl.

23. The compound of any one of claims 1, 5 and 8, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{18} is H or halo.

24. The compound of any one of claims 1-8 and 13-23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein X^1 is N.

25. The compound of any one of claims 1-8 and 13-23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein X^3 is CH.

26. The compound of any one of claims 1-5, having formula (III-3):



(III-3)

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

R^1 is H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH;

R^2 is C_{1-6} alkoxy;

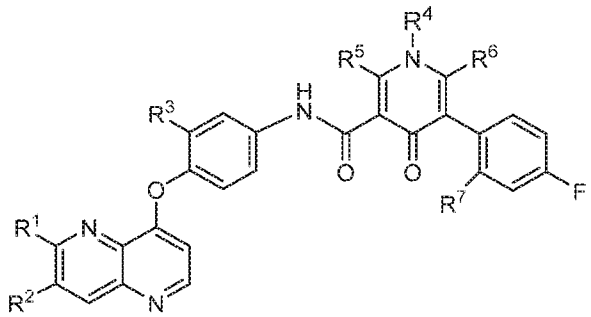
R^3 is H or halo;

R^{12} is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH;

R^{13} is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH; and

R^7 is H or C_{1-6} alkyl.

27. The compound of any one of claims 1-5, having formula (Ia-3):



(Ia-3)

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

R^1 is H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH;

R^2 is C_{1-6} alkoxy;

R^3 is H or halo;

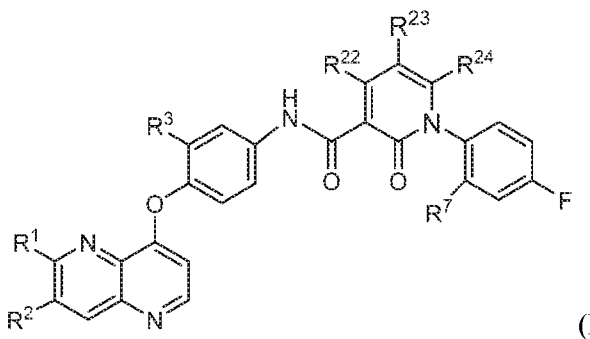
R^4 is H, C_{1-6} haloalkyl, or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH;

R^5 is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH;

R^6 is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH and

R^7 is H or C_{1-6} alkyl.

28. The compound of any one of claims 1-5, having formula (Ij-1):



(Ij-1)

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

R^1 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 is optionally substituted with C_{1-6} alkoxy or OH

R^2 is C_{1-6} alkoxy;

R^3 is H or halo;

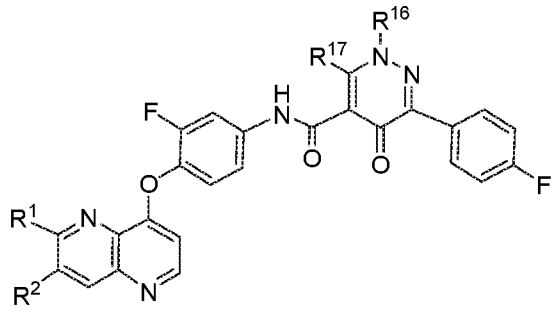
R^{22} is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH;

R^{23} is H, C_{1-6} alkyl or C_{1-6} alkyl-C(O)-, wherein the C_{1-6} alkyl and C_{1-6} alkyl-C(O)- of R^{23} are each optionally substituted with C_{1-6} alkoxy or OH;

R^{24} is H or C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or OH and

R^7 is H or C_{1-6} alkyl.

29. The compound of any one of claims 1-5, having formula (V):



(V)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

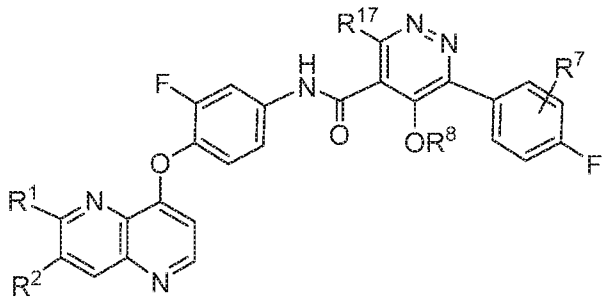
R^1 is H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH;

R^2 is C_{1-6} alkoxy;

R^{16} is H, C_{1-6} alkyl, or C_{1-6} haloalkyl; and

R^{17} is H or C_{1-6} alkyl.

30. The compound of any one of claims 1-5, having formula (VI):



(VI)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R^1 is H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH;

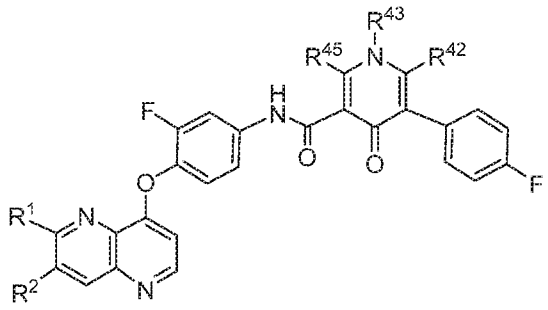
R^2 is C_{1-6} alkoxy;

R^7 is H or C_{1-6} alkyl.

R^8 is H or C_{1-6} alkyl; and

R^{17} is H or C_{1-6} alkyl.

31. The compound of any one of claims 1-4, having formula (VII):



(VII)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

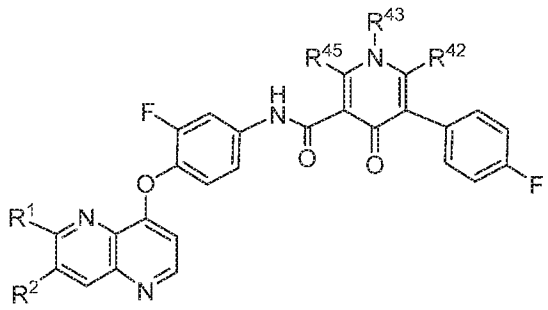
R^1 is H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH;

R^2 is C_{1-6} alkoxy;

R^{42} and R^{43} taken together with the atoms to which they are attached form 5- to 6-membered fused heterocycloalkyl having 0-1 additional ring heteroatoms selected from O and N; and

R^{45} is H or C_{1-6} alkyl.

32. The compound of any one of claims 1-4, having formula (VII):



(VII)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R^1 is H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-C(O)-, $NH_2C(O)$-, C_{1-6} alkyl-NHC(O)-, wherein the C_{1-6} alkyl, C_{1-6} alkyl-C(O)- and C_{1-6} alkyl-NHC(O)- of R^1 are each optionally substituted with C_{1-6} alkoxy or OH;

R^2 is C_{1-6} alkoxy;

R^{43} and R^{45} taken together with the atoms to which they are attached form 5- to 6-membered fused heterocycloalkyl having 0-1 additional ring heteroatoms selected from O and N; and

R^{42} is H or C_{1-6} alkyl.

33. The compound of any of claims 1-5 and 8, selected from:

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

5-(3,4-dichlorophenyl)-N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

5-(3-chloro-4-fluorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

5-(3,4-dichlorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

1-cyclopentyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide;

5-(3-chloro-4-fluorophenyl)-1-cyclopentyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-methyl-4-oxo-5-phenyl-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-methoxyphenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-methoxyphenyl)-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1,6-dimethyl-4-oxo-5-phenylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(3-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide;

5-(4-chlorophenyl)-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-methyl-4-oxo-5-phenylpyridine-3-carboxamide;

1-cyclopropyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxypyridine-3-carboxamide;

N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-propan-2-ylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide;

1-cyclopentyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(oxetan-3-yl)-4-oxopyridine-3-carboxamide;

1-tert-butyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide;

1-cyclobutyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-4-yl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylazetidin-3-yl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-methylpyrazol-3-yl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(3-methyloxetan-3-yl)-4-oxopyridine-3-carboxamide;

N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-1-(3-methyloxetan-3-yl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-hydroxy-2-methylpropan-2-yl)-4-oxopyridine-3-carboxamide;

N-[4-(6,7-dimethoxyquinolin-4-yl)oxy-3-fluorophenyl]-5-(4-fluorophenyl)-1-(1-hydroxy-2-methylpropan-2-yl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-[1-(trifluoromethyl)cyclopropyl]pyridine-3-carboxamide;

1-[1-(difluoromethyl)pyrazol-4-yl]-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(1H-pyrazol-3-yl)pyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(1H-pyrazol-4-yl)pyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-6-methyl-4-oxopyridine-3-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide;

N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide;

N-[3-fluoro-4-[[7-methoxy-6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-6-methylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-6-methylpyridine-3-carboxamide;

N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluoro-2-methylphenyl)-4-hydroxy-2,6-dimethylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(hydroxymethyl)pyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-(hydroxymethyl)-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(fluoromethyl)-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-1,6-dimethyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-6-(methylamino)-4-oxopyridine-3-carboxamide;

6-cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methoxy-1-methyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-4-hydroxy-6-(trifluoromethyl)pyridine-3-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-4-hydroxy-2-methylpyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,2-dimethyl-4-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-ethyl-5-(4-fluorophenyl)-2-methyl-4-oxopyridine-3-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide;

N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide;

N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxopyridine-3-carboxamide;

5-acetyl-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide;

5-cyano-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxopyridine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide;

N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluoro-2-methylphenyl)-6-methyl-4-oxo-1H-pyridazine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-5-(4-fluorophenyl)-1,6-dimethyl-4-oxopyridazine-3-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide;

N-[3-fluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-4-(4-fluorophenyl)-5-methyl-3-oxopyrazine-2-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-4-(4-fluorophenyl)-5,6-dimethyl-3-oxopyrazine-2-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-6-(4-fluorophenyl)-5-hydroxypyrimidine-4-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-methyl-6-oxopyrimidine-5-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-4-methyl-6-oxopyrimidine-5-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2-(methylamino)-6-oxopyrimidine-5-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-2-(dimethylamino)-1-(4-fluorophenyl)-6-oxopyrimidine-5-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-(4-fluorophenyl)-2,4-dimethyl-6-oxopyrimidine-5-carboxamide;

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-2,4-dioxo-1H-pyrimidine-5-carboxamide;

N-[3-fluoro-4-[(6-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-3-(4-fluorophenyl)-2,4-dioxo-1H-pyrimidine-5-carboxamide; and

N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-3-(4-fluorophenyl)-4-oxo-2-sulfanylidene-1H-pyrimidine-5-carboxamide;

or a pharmaceutically acceptable salt or stereoisomer thereof.

34. The compound of any one of claims 1-5 and 7, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from those in Table 1.

35. The compound of any one of claims 1-5 and 7, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from those in Table 2.

36. A compound, or a pharmaceutically acceptable salt thereof, selected from those in Table 3.

37. A pharmaceutical composition comprising a compound of any one of claims 1-36, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient.

38. A method of modulating in vivo activity of a protein kinase in a subject, the method comprising: administering to the subject a therapeutically effective amount of a compound of any one of claims 1-36, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of claim 37.

39. A method of treating a disease, disorder, or syndrome in a subject, the method comprising: administering to the subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-36, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of claim 37, wherein the disease, disorder, or syndrome is mediated at least in part by modulating in vivo activity of a protein kinase.

40. The method of claim 39, wherein the protein kinase is AXL, KDR, Mer, or Met.

41. The method of any one of claims 38-40, wherein the disease is cancer.

42. A method of treating a disease, disorder, or syndrome in a subject, the method comprising: administering to the subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-36, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of claim 31, in combination with a therapeutic agent or therapy.

43. The method of claim 42, wherein the therapeutic agent is an immunotherapeutic agent or a cancer vaccine.

44. The method of claim 43, wherein the immunotherapeutic agent is an anti-PD-1 antibody or anti-PD-L1 antibody.