

AMINOHETEROARYL KINASE INHIBITORS

1. CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to International Patent Application Nos. PCT/CN2024/074116, filed on January 25, 2024, and PCT/CN2024/118474, filed on September 12, 2024, the entirety of each of which is incorporated herein by reference.

2. FIELD

[0002] In some embodiments, provided herein are certain aminoheteroaryl compounds with tricyclic structure moiety, compositions comprising the same, methods of preparing and methods of using the same, *e.g.*, for inhibiting cyclin-dependent kinases and/or for treating or preventing various diseases or disorders provided herein.

3. BACKGROUND

[0003] Unrestrained cell growth is the hall mark of cancer and disrupted cell-cycle regulation is a common feature in malignant cells. Cyclin-dependent kinases (CDKs) are a family of serine/threonine protein kinases that regulate mammalian cell division and proliferation. At least 20 CDKs and 29 cyclins have been identified in human cells (Cao *et. al.*, *BMC Evol. Biol.* 2014; 14:10). In addition to regulate cell cycle progression, these CDKs and cyclins also play important roles in regulating transcription, DNA repair, differentiation and apoptosis (Palmer and Kaldis, *Semin Cell Dev Biol.* 2020; 107:54-62).

[0004] CDK4 and CDK6 are key regulators for G1-S transition. D type cyclins form complexes with CDK4/6 and phosphorylates the retinoblastoma (Rb) protein. This relieves the Rb-mediated inhibition of the transcription factor E2F and leads to S phase entrance. CDK4/6-CyclinD-Rb pathway is frequently perturbed in human cancers. Amplification of CDK4/6 and Cyclin D1, over-expression of D type cyclins, mutation, genetic deletion, or transcriptional silencing of endogenous CDK4/6 inhibitor p16 (CDKN2A) have all been reported as mechanisms which leads to pathway activation (Dickson, *Mol Cancer Res.* 2014; 20: 3379-3383). In breast cancer, dysregulation of CDK4/6 pathway is associated with resistance to endocrine therapy (Ding *et. al.*, *Int J Mol Sci.* 2020; 21:1960).

[0005] In recent years, targeted inhibition of CDKs has shown considerable therapeutic benefit in a variety of tumor types. The use of CDK4/6 inhibitors together with endocrine therapies were shown to be effective in treating human epidermal growth factor 2 (HER2)

negative, estrogen receptor (ER) positive breast cancer. As a result, there different CDK4/6 inhibitors, palbociclib, ribociclib and abemaciclib were approved in combination with endocrine therapies in both first or second line setting (Cogliati, *et. al.*, *Life*, 2022; 12:378). Most recently abemaciclib is also approved for adjuvant treatment of early breast cancer.

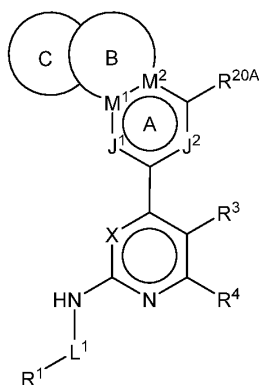
[0006] Despite the success of CDK4/6 inhibitors in clinic, treatment related adverse effects, especially hematologic toxicity such as neutropenia, prevented continued dosing of CDK4/6 inhibitors. Currently, both Palbociclib and Ribociclib are administrated on a three week on/one week off schedule. Mouse genetic and other emerging data suggest that the observed hematologic toxicity is likely linked to CDK6-cyclin D3 inhibition (Sicinska *et. al.*, *Mol Cell Biol*, 2006; 26: 8052-8060; Cooper *et. al.*, *Nat Immunol*, 2006; 5:489-497). On the other hand, CDK6-cyclin D3 is expressed at very low level in HR+/ HER2- breast cancer and CDK4 was identified as the oncogenic driver in this tumor type (Zhang *et. al.*, *Cancer Res*, 2022; epub).

4. SUMMARY

[0007] Inhibitors specific to a particular CDK such as CDK4 may have the advantage of improved safety profile and may enable improved dosing schedule and higher dosing, and may lead to deeper target inhibition, better efficacy and potentially overcome drug resistance. There remains a need for CDK inhibitors, such as selective CDK4 inhibitors, such as those with improved efficacy and reduced side effects in clinic.

[0008] In some embodiments, provided herein are certain aminoheteroaryl compounds with tricyclic structure moiety, which can inhibit CDKs, such as selectively inhibit CDK4. The compounds and compositions provided herein are useful for treating various diseases or disorders associated with abnormal CDK4 activity, such as Hormonal receptor positive, HER2-negative breast cancer.

[0009] In some embodiments, provided herein is a compound of Formula (I):



(I),

or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein L^1 , R^1 , X , R^3 , R^4 , J^1 , J^2 , R^{20A} , M^1 , M^2 , Ring B, and Ring C are as defined herein or elsewhere.

[0010] Also provided herein are pharmaceutical compositions comprising a compound provided herein, and one or more pharmaceutically acceptable excipients. The pharmaceutical composition can be typically formulated for oral administration.

[0011] Also provided herein are methods of inhibiting CDK activity such as CDK4 activity in a subject or biological sample. In some embodiments, the method comprises contacting the subject or biological sample with an effective amount of a compound provided herein or a pharmaceutical composition provided herein.

[0012] Also provided herein are methods of treating or preventing a CDK-mediated disease or disorder in a subject in need thereof. In some embodiments, the method comprises administering to the subject an effective amount of a compound provided herein or a pharmaceutical composition provided herein.

[0013] Also provided herein are methods of treating cancer in a subject in need thereof, which comprises administering to the subject an effective amount of a compound provided herein or a pharmaceutical composition provided herein. Also provided herein are method of preventing cancer in a subject in need thereof, which comprises administering to the subject an effective amount of a compound provided herein or a pharmaceutical composition provided herein. In some embodiments, the cancer is selected from breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer (including NSCLC, SCLC, squamous cell carcinoma or adenocarcinoma), esophageal cancer, head and neck cancer, colorectal cancer, kidney cancer (including RCC), liver cancer (including HCC), pancreatic cancer, stomach (i.e., gastric) cancer, thyroid cancer, and combinations thereof. In some embodiments, the cancer is breast cancer selected from ER-positive/HR-positive, HER2-negative breast cancer; ER-positive/HR-positive, HER2- positive breast cancer; triple negative breast cancer (TNBC); and inflammatory breast cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is breast cancer selected from endocrine resistant breast cancer, trastuzumab resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/CDK6 inhibition. In some embodiments, the cancer is advanced or metastatic breast cancer. In some embodiments, the cancer is ovarian cancer.

[0014] Also provided are uses of the compounds provided herein in the manufacture of a medicament for treating cancer, such as the cancers described herein. Also provided are uses of the compounds provided herein for treating cancer, such as the cancers described herein. Also provided are compounds provided herein for use in the treatment of cancer, such as the cancers described herein. Also provided are compounds provided herein for use in a method of treating cancer, such as the cancers described herein, wherein the method comprises administering to a subject in need thereof an effective amount of a compound provided herein.

5. DETAILED DESCRIPTION

5.1 Definitions

[0015] It is meant to be understood that proper valences are maintained for all moieties and combinations thereof.

[0016] It is also meant to be understood that a specific embodiment of a variable moiety herein can be the same or different as another specific embodiment having the same identifier.

[0017] Suitable groups for the variables in compounds of Formula (I), or a sub-formula thereof, as applicable, are independently selected. Non-limiting useful groups for the variables in compounds of Formula (I), or a sub-formula thereof, as applicable, include any of the respective groups, individually or in any combination, as shown in the Examples or in the specific compounds described in Table 1 or Table 1A herein. Using variable R^1 as an example, in some embodiments, compounds of Formula (I) can include a R^1 group according to any of the R^1 groups shown in the Examples or in the specific compounds described in Table 1 or Table 1A herein, without regard to the other variables shown in the specific compounds. In some embodiments, compounds of Formula (I) can include a R^1 group according to any of the R^1 groups shown in the Examples or in the specific compounds described in Table 1 or Table 1A herein in combination at least one other variable (*e.g.*, L^1) according to the Examples or the specific compounds described in Table 1 or Table 1A herein, wherein the R^1 and at least one other variable can derive from the same compound or a different compound. Any of such combinations are contemplated and within the scope of the present disclosure. Unless otherwise specified, a description of a variable in connection with a formula also applies to any other overlapping formulas (*e.g.*, sub-formulas) where said variable is present.

[0018] The described embodiments provided herein can be combined, as applicable. Such combination is contemplated and within the scope of the present disclosure. For example, it is contemplated that the definition(s) of any one or more of L^1 , R^1 , X, R^3 , R^4 , J^1 , J^2 , R^{20A} , M^1 ,

M², Ring B, and Ring C of Formula (I) (or a sub-formula thereof) can be combined with the definition of any one or more of the other(s) of L¹, R¹, X, R³, R⁴, J¹, J², R^{20A}, M¹, M², Ring B, and Ring C, as applicable.

[0019] Headings and subheadings are used for convenience and/or formal compliance only, do not limit the subject technology, and are not referred to in connection with the interpretation of the description of the subject technology. Features described under one heading or one subheading may be combined, in some embodiments, with features described under other headings or subheadings. Further it is not necessarily the case that all features under a single heading or a single subheading are used together in embodiments.

[0020] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0021] As used herein, the singular form “a”, “an”, and “the”, includes plural references unless it is expressly stated or is unambiguously clear from the context that such is not intended.

[0022] As used herein, the terms “comprising” and “including” can be used interchangeably. The terms “comprising” and “including” are to be interpreted as specifying the presence of the stated features or components as referred to, but does not preclude the presence or addition of one or more features, or components, or groups thereof. Additionally, the terms “comprising” and “including” are intended to include examples encompassed by the term “consisting of”. Consequently, the term “consisting of” can be used in place of the terms “comprising” and “including” to provide for more specific embodiments.

[0023] As used herein, the term “or” is to be interpreted as an inclusive “or” meaning any one or any combination. Therefore, “A, B or C” means any of the following: “A; B; C; A and B; A and C; B and C; A, B and C”. An exception to this definition will occur only when a combination of elements, functions, steps or acts are in some way inherently mutually exclusive.

[0024] The term “and/or” as used in a phrase such as “A and/or B” herein is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0025] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example “C₁₋₆” is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆.

[0026] It should be noted that if there is a discrepancy between a depicted structure and a name for that structure, the depicted structure is to be accorded more weight.

[0027] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987. The disclosure is not intended to be limited in any manner by the exemplary listing of substituents provided herein.

[0028] As used herein, and unless otherwise specified, the term “alkyl” as used by itself or as part of another group refers to a straight- or branched-chain aliphatic saturated hydrocarbon. In some embodiments, the alkyl can include one to twelve carbon atoms (i.e., C₁₋₁₂ alkyl) or the number of carbon atoms designated. In some embodiments, the alkyl group is a straight chain C₁₋₁₀ alkyl group. In another embodiment, the alkyl group is a branched chain C₃₋₁₀ alkyl group. In another embodiment, the alkyl group is a straight chain C₁₋₆ alkyl group. In another embodiment, the alkyl group is a branched chain C₃₋₆ alkyl group. In another embodiment, the alkyl group is a straight chain C₁₋₄ alkyl group. For example, a C₁₋₄ alkyl group includes methyl, ethyl, propyl (n-propyl), isopropyl, butyl (n-butyl), sec-butyl, tert-butyl, and iso-butyl. As used herein, and unless otherwise specified, the term “alkylene” as used by itself or as part of another group refers to a multivalent (e.g., divalent) radical derived from an alkyl group. For example, non-limiting straight chain alkylene groups include -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-, and the like. Unless otherwise specified, an alkyl group is optionally substituted. In some embodiments, an alkyl group is unsubstituted. In some embodiments, an alkyl groups is substituted.

[0029] As used herein, and unless otherwise specified, the term “alkenyl” as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one or more (*e.g.*, 1, 2, or 3) carbon-to-carbon double bonds. In some embodiments, the alkenyl group is a C₂₋₆ alkenyl group. In another embodiment, the alkenyl group is a C₂₋₄ alkenyl group. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, sec-butenyl, pentenyl, and hexenyl. Unless otherwise specified, an alkenyl group is optionally substituted. In some embodiments, an alkenyl group is unsubstituted. In some embodiments, an alkenyl group is substituted.

[0030] As used herein, and unless otherwise specified, the term “alkynyl” as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one or more (*e.g.*, 1, 2, or 3) carbon-to-carbon triple bonds. In some embodiments, the alkynyl has one carbon-carbon triple bond. In some embodiments, the alkynyl group is a C₂₋₆ alkynyl group. In another embodiment, the alkynyl group is a C₂₋₄ alkynyl group. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups. Unless otherwise specified, an alkynyl group is optionally substituted. In some embodiments, an alkynyl group is unsubstituted. In some embodiments, an alkynyl group is substituted.

[0031] As used herein, and unless otherwise specified, the term “alkoxy” as used by itself or as part of another group refers to -O-(alkyl), wherein alkyl is as described herein. As used herein, and unless otherwise specified, the term “cycloalkoxy” as used by itself or as part of another group refers to -O-(cycloalkyl), wherein cycloalkyl is as described herein.

[0032] As used herein, and unless otherwise specified, the term “haloalkyl” as used by itself or as part of another group refers to an alkyl substituted with one or more fluorine, chlorine, bromine and/or iodine atoms. In some embodiments, the haloalkyl is an alkyl group substituted with one, two, or three fluorine atoms. In some embodiments, the haloalkyl group is a C₁₋₁₀ haloalkyl group. In some embodiments, the haloalkyl group is a C₁₋₆ haloalkyl group. In some embodiments, the haloalkyl group is a C₁₋₄ haloalkyl group.

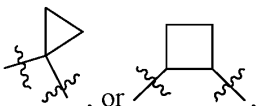
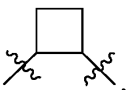
[0033] As used herein, and unless otherwise specified, the term “heteroalkyl” as used by itself or in combination with another term refers to a stable straight or branched-chain alkyl group, *e.g.*, having from 2 to 14 carbons, such as 2 to 10 carbons in the chain, wherein one or more of the carbon(s) has been replaced by a heteroatom selected from S, O, P and N, and wherein the N, P, and S atoms can optionally be oxidized and the nitrogen heteroatom can

optionally be quaternized. The heteroatom(s) S, O, P and N may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. When the heteroalkyl is said to be substituted, the substituent(s) can replace one or more hydrogen atoms attached to the carbon atom(s) and/or the heteroatom(s) of the heteroalkyl. In some embodiments, the heteroalkyl is a C₁₋₄ heteroalkyl, which refers to the heteroalkyl defined herein having 1-4 carbon atoms. Examples of C₁₋₄ heteroalkyl include, but are not limited to, C₄ heteroalkyl such as -CH₂-CH₂-N(CH₃)-CH₃, C₃ heteroalkyl such as -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, and -CH₂-CH₂-S(O)₂-CH₃, C₂ heteroalkyl such as -CH₂-CH₂-OH, -CH₂-CH₂-NH₂, -CH₂-NH(CH₃), and -O-CH₂-CH₃, and C₁ heteroalkyl such as, -CH₂-OH, -CH₂-NH₂, and -O-CH₃. In some embodiments, the C₁₋₄ heteroalkyl has 1 or 2 heteroatoms, such as those having one oxygen, one oxygen and one nitrogen, two oxygen atoms, or two nitrogen atoms. Similarly, the term “heteroalkylene” as used by itself or as part of another substituent means a multivalent (*e.g.*, divalent) radical derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-O-CH₂-CH₂- and -O-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkyleneedioxy, alkyleneamino, alkylene-diamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like. Unless otherwise specified, a heteroalkyl group is optionally substituted. In some embodiments, a heteroalkyl group is unsubstituted. In some embodiments, a heteroalkyl groups is substituted.

[0034] As used herein, and unless otherwise specified, the term “carbocyclyl” or “carbocyclic” as used by itself or as part of another group refers to a radical of a non-aromatic cyclic hydrocarbon group having at least 3 carbon atoms, *e.g.*, from 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”), and zero heteroatoms in the non-aromatic ring system. The carbocyclyl group can be either monocyclic (“monocyclic carbocyclyl”) or contain a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic carbocyclyl”) and can be saturated or can be partially unsaturated. Non-limiting exemplary carbocyclyl groups include cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclopentenyl, and cyclohexenyl. As used herein, the term “carbocyclylene” as used by itself or as part of another group refers to a multivalent (*e.g.*, divalent) radical derived from the carbocyclyl group defined herein. Unless otherwise specified, a carbocyclyl group is optionally substituted. In some embodiments, a carbocyclyl group is unsubstituted. In some embodiments, a carbocyclyl groups is substituted.

[0035] In some embodiments, “carbocyclyl” is fully saturated, which is also referred to as “cycloalkyl”. In some embodiments, the cycloalkyl can have from 3 to 10 ring carbon atoms (“C₃₋₁₀ cycloalkyl”). In some embodiments, the cycloalkyl is a monocyclic ring. As used herein, the term “cycloalkylene” as used by itself or as part of another group refers to a multivalent (*e.g.*,

divalent) radical derived from a cycloalkyl group, for example, , or , etc.

[0036] As used herein, and unless otherwise specified, the term “heterocyclyl” or “heterocyclic” as used by itself or as part of another group refers to a radical of a 3-membered or larger, such as 3– to 14–membered, non–aromatic ring system having ring carbon atoms and at least one ring heteroatom (*e.g.*, 1, 2, 3, or 4) ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon, wherein the N, P, and S atoms can optionally be oxidized and the nitrogen heteroatom can optionally be quaternized. In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or a fused, bridged, or spiro ring system, such as a bicyclic system (“bicyclic heterocyclyl”), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings, and the point of attachment can be on any ring. As used herein, and unless otherwise specified, the term “heterocyclylene” as used by itself or as part of another group refers to a multivalent (*e.g.*, divalent) radical derived from the heterocyclyl group defined herein. The heterocyclyl or heterocyclylene can be optionally linked to the rest of the molecule through a carbon or nitrogen atom. Unless otherwise specified, a heterocyclyl group is optionally substituted. In some embodiments, a heterocyclyl group is unsubstituted. In some embodiments, a heterocyclyl groups is substituted.

[0037] Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, aziridiny, oxiranyl, thiiranyl. Exemplary 4–membered heterocyclyl groups

containing one heteroatom include, without limitation, azetidiny, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridiny, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indoliny, isoindoliny, dihydrobenzofuranyl, dihydrobenzothiényl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinoliny, tetrahydroisoquinoliny, and the like.

[0038] As used herein, and unless otherwise specified, the term “aryl” as used by itself or as part of another group refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic hydrocarbon ring system (*e.g.*, having 6, 10, or 14 pi electrons shared in a cyclic array). In some embodiments, an aryl group has 6–14 ring carbon atoms (“C_{6–14} aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). As used herein, and unless otherwise specified, the term “arylene” as used by itself or as part of another group refers to a multivalent (*e.g.*, divalent) radical derived from the aryl group defined herein. Unless otherwise specified, an aryl group is optionally substituted. In some embodiments, an aryl group is unsubstituted. In some embodiments, an aryl groups is substituted.

[0039] As used herein, and unless otherwise specified, the term “aralkyl” as used by itself or as part of another group refers to an alkyl substituted with one or more aryl groups, *e.g.*, substituted with one aryl group. Examples of aralkyl include benzyl, phenethyl, etc. Unless otherwise specified, an aralkyl group is optionally substituted. When an aralkyl is said to be optionally substituted, either the alkyl portion or the aryl portion of the aralkyl can be optionally substituted.

[0040] As used herein, and unless otherwise specified, the term “heteroaryl” as used by itself or as part of another group refers to a radical of a monocyclic, bicyclic, or tricyclic $4n+2$ aromatic ring system (*e.g.*, having 6 or 10 pi electrons shared in a cyclic array) having ring carbon atoms and at least one (*e.g.*, 1, 2, 3, or 4) ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur. In some embodiments, a heteroaryl group has 5–14 membered ring atoms (“5–14 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. In bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, and the like), the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl). As used herein, and unless otherwise specified, the term “heteroarylene” as used by itself or as part of another group refers to a multivalent (*e.g.*, divalent) radical derived from the heteroaryl group defined herein. Unless specified or otherwise contrary from context, when a heteroaryl group is fused to a non-aromatic ring, the resulted fused ring systems is referred to as a heterocyclyl group. Unless otherwise specified, a heteroaryl group is optionally substituted. In some embodiments, a heteroaryl group is unsubstituted. In some embodiments, a heteroaryl groups is substituted.

[0041] Exemplary 5-membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two

heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0042] As used herein, and unless otherwise specified, the term “heteroaralkyl” as used by itself or as part of another group refers to an alkyl substituted with one or more heteroaryl groups, *e.g.*, substituted with one heteroaryl group. Unless otherwise specified, a heteroaralkyl group is optionally substituted. When a heteroaralkyl is said to be optionally substituted, either the alkyl portion or the heteroaryl portion of the heteroaralkyl can be optionally substituted.

[0043] As used herein, and unless otherwise specified, the term “amino” refers to $-N(R^{\#})(R^{\#})$, wherein each $R^{\#}$ independently can be, but is not limited to, hydrogen, alkyl, heteroaralkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, each of which is defined herein. When a $-N(R^{\#})(R^{\#})$ group has two $R^{\#}$ other than hydrogen, they can be combined with the nitrogen atom to form a ring. In some embodiments, the ring is a 3-, 4-, 5-, 6-, 7-, or 8-membered ring. In some embodiments, one or more ring atoms are heteroatoms independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon. The term “amino” also includes N-oxide ($-N^+(R^{\#})(R^{\#})O^-$). In certain embodiments, each $R^{\#}$ or the ring formed by $-N(R^{\#})(R^{\#})$ independently may be unsubstituted or substituted with one or more substituents.

[0044] As used herein, and unless otherwise specified, an “optionally substituted” group, such as an optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl groups, refers to the respective group that is unsubstituted or substituted. In general, the term “substituted”, whether preceded by the term “optionally” or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously

undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent can be the same or different at each position. In some embodiments, when substituted, the optionally substituted groups provided herein can be substituted with 1-5 substituents. Substituents can be a carbon atom substituent, a nitrogen atom substituent, an oxygen atom substituent or a sulfur atom substituent, as applicable, each of which can be optionally isotopically labeled, such as deuterated. Two of the optional substituents can join to form a ring structure, such as an optionally substituted cycloalkyl, heterocyclyl, aryl, or heteroaryl ring. Substitution can occur on any available carbon, oxygen, or nitrogen atom, and can form a spirocycle.

[0045] As used herein, and unless otherwise specified, the permissible substituents provided herein include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. The heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a cycloalkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, an aryl, or a heteroaryl, each of which can be substituted, if appropriate

[0046] Exemplary substituents include, but not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, -alkylene-aryl, -arylene-alkyl, -alkylene-heteroaryl, -alkenylene-heteroaryl, -alkynylene-heteroaryl, —OH, hydroxyalkyl, haloalkyl, —O-alkyl, —O-haloalkyl, -alkylene-O-alkyl, —O-aryl, —O-alkylene-aryl, acyl, —C(O)-aryl, halo, —NO₂, —CN, —SF₅, —C(O)OH, —C(O)O-alkyl, —C(O)O-aryl, —C(O)O—alkylene-aryl, —S(O)-alkyl, —S(O)₂-alkyl, —S(O)-aryl, —S(O)₂-aryl, —S(O)-heteroaryl, —S(O)₂-heteroaryl, —S-alkyl, —S-aryl, —S-heteroaryl, —S-alkylene-aryl, —S-alkylene-heteroaryl, —S(O)₂-alkylene-aryl, —S(O)₂-alkylene-heteroaryl, cycloalkyl, heterocycloalkyl, —O—C(O)-alkyl, —O—C(O)-aryl, —O—C(O)-cycloalkyl, —

$C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(alkyl)$, $-N(Y_1)(Y_2)$, -alkylene- $N(Y_1)(Y_2)$, $-C(O)N(Y_1)(Y_2)$ and $-S(O)_2N(Y_1)(Y_2)$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and -alkylene-aryl.

[0047] Some examples of suitable substituents include, but not limited to, $(C_1-C_8)alkyl$ groups, $(C_2-C_8)alkenyl$ groups, $(C_2-C_8)alkynyl$ groups, $(C_3-C_{10})cycloalkyl$ groups, halogen (F, Cl, Br or I), halogenated $(C_1-C_8)alkyl$ groups (for example but not limited to $-CF_3$), $-O-(C_1-C_8)alkyl$ groups, $-OH$, $-S-(C_1-C_8)alkyl$ groups, $-SH$, $-NH(C_1-C_8)alkyl$ groups, $-N((C_1-C_8)alkyl)_2$ groups, $-NH_2$, $-C(O)NH_2$, $-C(O)NH(C_1-C_8)alkyl$ groups, $-C(O)N((C_1-C_8)alkyl)_2$, $-NHC(O)H$, $-NHC(O)(C_1-C_8)alkyl$ groups, $-NHC(O)(C_3-C_8)cycloalkyl$ groups, $-N((C_1-C_8)alkyl)C(O)H$, $-N((C_1-C_8)alkyl)C(O)(C_1-C_8)alkyl$ groups, $-NHC(O)NH_2$, $-NHC(O)NH(C_1-C_8)alkyl$ groups, $-N((C_1-C_8)alkyl)C(O)NH_2$ groups, $-NHC(O)N((C_1-C_8)alkyl)_2$ groups, $-N((C_1-C_8)alkyl)C(O)N((C_1-C_8)alkyl)_2$ groups, $-N((C_1-C_8)alkyl)C(O)NH((C_1-C_8)alkyl)$, $-C(O)H$, $-C(O)(C_1-C_8)alkyl$ groups, $-CN$, $-NO_2$, $-S(O)(C_1-C_8)alkyl$ groups, $-S(O)_2(C_1-C_8)alkyl$ groups, $-S(O)_2N((C_1-C_8)alkyl)_2$ groups, $-S(O)_2NH(C_1-C_8)alkyl$ groups, $-S(O)_2NH(C_3-C_8)cycloalkyl$ groups, $-S(O)_2NH_2$ groups, $-NHS(O)_2(C_1-C_8)alkyl$ groups, $-N((C_1-C_8)alkyl)S(O)_2(C_1-C_8)alkyl$ groups, $-(C_1-C_8)alkyl-O-(C_1-C_8)alkyl$ groups, $-O-(C_1-C_8)alkyl-O-(C_1-C_8)alkyl$ groups, $-C(O)OH$, $-C(O)O(C_1-C_8)alkyl$ groups, $NHOH$, $NHO(C_1-C_8)alkyl$ groups, $-O$ -halogenated $(C_1-C_8)alkyl$ groups (for example but not limited to $-OCF_3$), $-S(O)_2$ -halogenated $(C_1-C_8)alkyl$ groups (for example but not limited to $-S(O)_2CF_3$), $-S$ -halogenated $(C_1-C_8)alkyl$ groups (for example but not limited to $-SCF_3$), $-(C_1-C_6)$ heterocycle (for example but not limited to pyrrolidine, tetrahydrofuran, pyran or morpholine), $-(C_1-C_6)$ heteroaryl (for example but not limited to tetrazole, imidazole, furan, pyrazine or pyrazole), -phenyl, $-NHC(O)O-(C_1-C_6)alkyl$ groups, $-N((C_1-C_6)alkyl)C(O)O-(C_1-C_6)alkyl$ groups, $-C(=NH)-(C_1-C_6)alkyl$ groups, $-C(=NOH)-(C_1-C_6)alkyl$ groups, or $-C(=N-O-(C_1-C_6)alkyl)-(C_1-C_6)alkyl$ groups.

[0048] Exemplary carbon atom substituents include, but are not limited to, deuterium, halogen, $-CN$, $-NO_2$, $-N_3$, hydroxyl, alkoxy, cycloalkoxy, aryloxy, amino, monoalkyl amino, dialkyl amino, amide, sulfonamide, thiol, acyl, carboxylic acid, ester, sulfone, sulfoxide, alkyl, haloalkyl, alkenyl, alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl, etc. For example, exemplary carbon atom substituents can include F, Cl, $-CN$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}alkyl$, $-NH_2$, $-N(C_{1-6}alkyl)_2$, $-NH(C_{1-6}alkyl)$, $-SH$, $-SC_{1-6}$

alkyl, $-\text{C}(=\text{O})(\text{C}_{1-6} \text{ alkyl})$, $-\text{CO}_2\text{H}$, $-\text{CO}_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{OC}(=\text{O})(\text{C}_{1-6} \text{ alkyl})$, $-\text{OCO}_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{OC}(=\text{O})\text{NH}(\text{C}_{1-6} \text{ alkyl})$, $-\text{NHC}(=\text{O})(\text{C}_{1-6} \text{ alkyl})$, $-\text{N}(\text{C}_{1-6} \text{ alkyl})\text{C}(=\text{O})(\text{C}_{1-6} \text{ alkyl})$, $-\text{NHCO}_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{NHC}(=\text{O})\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{NHC}(=\text{O})\text{NH}(\text{C}_{1-6} \text{ alkyl})$, $-\text{NHC}(=\text{O})\text{NH}_2$, $-\text{NHSO}_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{SO}_2\text{NH}(\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{C}_{1-6} \text{ alkyl}$, $-\text{SO}_2\text{OC}_{1-6} \text{ alkyl}$, $-\text{OSO}_2\text{C}_{1-6} \text{ alkyl}$, $-\text{SOC}_{1-6} \text{ alkyl}$, $\text{C}_{1-6} \text{ alkyl}$, $\text{C}_{1-6} \text{ haloalkyl}$, $\text{C}_{2-6} \text{ alkenyl}$, $\text{C}_{2-6} \text{ alkynyl}$, $\text{C}_{3-10} \text{ carbocyclyl}$, $\text{C}_{6-10} \text{ aryl}$, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal substituents can be joined to form $=\text{O}$.

[0049] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, acyl groups, esters, sulfone, sulfoxide, $\text{C}_{1-10} \text{ alkyl}$, $\text{C}_{1-10} \text{ haloalkyl}$, $\text{C}_{2-10} \text{ alkenyl}$, $\text{C}_{2-10} \text{ alkynyl}$, $\text{C}_{3-10} \text{ carbocyclyl}$, 3–14 membered heterocyclyl, $\text{C}_{6-14} \text{ aryl}$, and 5–14 membered heteroaryl, or two substituent groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl can be further substituted as defined herein. In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups are well known in the art and include those described in detail in *Protective Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated by reference herein. Exemplary nitrogen protecting groups include, but not limited to, those forming carbamates, such as Carbobenzyloxy (Cbz) group, p-Methoxybenzyl carbonyl (Moz or MeOZ) group, tert-Butyloxycarbonyl (BOC) group, Troc, 9-Fluorenylmethyloxycarbonyl (Fmoc) group, etc., those forming an amide, such as acetyl, benzoyl, etc., those forming a benzylic amine, such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, etc., those forming a sulfonamide, such as tosyl, Nosyl, etc., and others such as p-methoxyphenyl.

[0050] Exemplary oxygen atom substituents include, but are not limited to, acyl groups, esters, sulfonates, $\text{C}_{1-10} \text{ alkyl}$, $\text{C}_{1-10} \text{ haloalkyl}$, $\text{C}_{2-10} \text{ alkenyl}$, $\text{C}_{2-10} \text{ alkynyl}$, $\text{C}_{3-10} \text{ carbocyclyl}$, 3–14 membered heterocyclyl, $\text{C}_{6-14} \text{ aryl}$, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl can be further substituted as defined herein. In certain embodiments, the oxygen atom substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups are well known in the art and include those described in detail in *Protective*

Groups in Organic Synthesis, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference. Exemplary oxygen protecting groups include, but are not limited to, those forming alkyl ethers or substituted alkyl ethers, such as methyl, allyl, benzyl, substituted benzyis such as 4-methoxybenzyl, methoxymethyl (MOM), benzyloxymethyl (BOM), 2-methoxyethoxymethyl (MEM), etc., those forming silyl ethers, such as trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), t-butyl dimethylsilyl (TBDMS), etc., those forming acetals or ketals, such as tetrahydropyranyl (THP), those forming esters such as formate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, etc., those forming carbonates or sulfonates such as methanesulfonate (mesylate), benzyisulfonate, and tosylate (Ts), etc.

[0051] Unless expressly stated to the contrary, combinations of substituents and/or variables are allowable only if such combinations are chemically allowed and result in a stable compound. A “stable” compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (*e.g.*, therapeutic administration to a subject).

[0052] In some embodiments, the “optionally substituted” alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkynyl, carbocyclic, carbocyclene, cycloalkyl, cycloalkylene, alkoxy, cycloalkoxy, heterocyclyl, or heterocyclene herein can each be independently unsubstituted or substituted with 1, 2, 3, or 4 substituents independently selected from deuterium, F, Cl, -OH, oxo (as applicable), NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)((C₁₋₄ alkyl), C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkoxy, phenyl, 5 or 6 membered heteroaryl containing 1, 2, or 3 ring heteroatoms independently selected from O, S, and N, 3-7 membered heterocyclyl containing 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein each of the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkoxy phenyl, heteroaryl, and heterocyclyl, is optionally substituted with 1, 2, or 3 substituents independently selected from deuterium, F, -OH, oxo (as applicable), C₁₋₄ alkyl, fluoro-substituted C₁₋₄ alkyl (*e.g.*, CF₃), C₁₋₄ alkoxy and fluoro-substituted C₁₋₄ alkoxy. In some embodiments, the “optionally substituted” aryl, arylene, heteroaryl or heteroarylene group herein can each be independently unsubstituted or substituted with 1, 2, 3, or 4 substituents independently selected from deuterium, F, Cl, -OH, -CN, NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)((C₁₋₄ alkyl), -S(=O)(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl), C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkoxy, phenyl, 5 or 6

membered heteroaryl containing 1, 2 or 3 ring heteroatoms independently selected from O, S, and N, 3-7 membered heterocyclyl containing 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein each of the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkoxy, phenyl, heteroaryl, and heterocyclyl, is optionally substituted with 1, 2, or 3 substituents independently selected from deuterium, F, -OH, oxo (as applicable), C₁₋₄ alkyl, fluoro-substituted C₁₋₄ alkyl, C₁₋₄ alkoxy and fluoro-substituted C₁₋₄ alkoxy.

[0053] As used herein, and unless otherwise specified, the term “halo” or “halogen” refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), or iodine (iodo, -I).

[0054] As used herein, and unless otherwise specified, the term “isomer” refers to different compounds that have the same molecular formula. “Stereoisomers” are isomers that differ only in the way the atoms are arranged in space. “Atropisomers” are stereoisomers from hindered rotation about single bonds. “Enantiomers” are a pair of stereoisomers that are non-superimposable mirror images of each other. A mixture of a pair of enantiomers in any proportion can be known as a “racemic” mixture. “Diastereoisomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry can be specified according to the Cahn-Ingold-Prelog *R-S* system. When a compound is an enantiomer, the stereochemistry at each chiral carbon can be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. However, the sign of optical rotation, (+) and (-), is not related to the absolute configuration of the molecule, *R* and *S*. Certain compounds provided herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry at each asymmetric atom, as (*R*)- or (*S*)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically substantially pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers can be prepared, for example, using chiral synthons or chiral reagents, or resolved using conventional techniques.

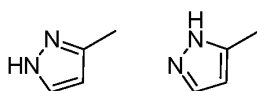
[0055] As used herein, and unless otherwise specified, the term “enantiomeric purity” or “enantiomer purity” refers to a qualitative or quantitative measure of a purified enantiomer. The enantiomeric purity of compounds provided herein may be described in terms of enantiomeric excess (ee), which indicates the degree to which a sample contains one enantiomer in greater

amounts than the other. A racemic mixture has an ee of 0%, while a single completely pure enantiomer has an ee of 100%. Examples of the enantiomeric purity include an ee of at least about 10%, at least about 12%, at least about 14%, at least about 16%, at least about 18%, at least about 20%, at least about 22%, at least about 24%, at least about 26%, at least about 28%, at least about 30%, at least about 32%, at least about 34%, at least about 36%, at least about 38%, at least about 40%, at least about 42%, at least about 44%, at least about 46%, at least about 48%, at least about 50%, at least about 52%, at least about 54%, at least about 56%, at least about 58%, at least about 60%, at least about 62%, at least about 64%, at least about 66%, at least about 68%, at least about 70%, at least about 72%, at least about 74%, at least about 76%, at least about 78%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about or at least about 99%. Similarly, “diastereomeric purity” may be described in terms of diastereomeric excess (de), which indicates the degree to which a sample contains one diastereoisomers in greater amounts than the other(s).

[0056] As used herein, and unless otherwise specified, the term “substantially purified enantiomer” refers to a compound wherein one enantiomer has been enriched over the other, such as the other enantiomer represents less than about 20%, less than about 10%, less than about 5%, or less than about 2% of the enantiomer. In some embodiments, a substantially purified enantiomer has an enantiomeric excess of *S* enantiomer of at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5% or at least about 99.9%. In some embodiments, a substantially purified enantiomer has an enantiomeric excess of *R* enantiomer of at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5% or at least about 99.9%.

[0057] “Stereoisomers” can also include E and Z isomers, or a mixture thereof, and cis and trans isomers or a mixture thereof. In certain embodiments, a compound provided herein is isolated as either the E or Z isomer. In other embodiments, a compound provided herein is a mixture of the E and Z isomers.

[0058] “Tautomers” refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. For example, in aqueous solution, pyrazoles may exhibit the following isomeric forms, which are referred to as tautomers of each other:



[0059] As used herein, and unless otherwise specified, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. As used herein, and unless otherwise specified, the term “pharmaceutically acceptable salt” includes both acid and base addition salts.

[0060] Examples of pharmaceutically acceptable acid addition salts include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic

acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

[0061] Examples of pharmaceutically acceptable base addition salt include, but are not limited to, salts prepared from addition of an inorganic base or an organic base to a free acid compound. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. In some embodiments, the inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. In some embodiments, the organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

[0062] Compounds provided herein can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , and ^{125}I . In some embodiments, compounds contain other isotopes of these and/or other atoms.

[0063] As used herein, and unless otherwise specified, the term “administration” of a compound, “administering” a compound, or other variants thereof means providing the compound to a subject in need of treatment.

[0064] As used herein, and unless otherwise specified, the term “subject” (alternatively referred to herein as “patient”) refers to an animal, *e.g.*, a mammal, *e.g.*, a human, who has been the object of treatment, observation or experiment.

[0065] As used herein, and unless otherwise specified, the terms “treat,” “treating,” “treatment,” and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition

does not require that the disease, condition, or symptoms associated therewith be completely eliminated. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a compound provided herein to a subject in need of such treatment.

[0066] As used herein, and unless otherwise specified, the terms "prevent," "preventing," "prevention," and the like refer to reducing the probability of the onset of a disease or condition, of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, developing or redeveloping a disease or condition or a recurrence of the disease or condition.

[0067] As used herein, and unless otherwise specified, the term "effective amount" refers to that amount of a compound or combination of compounds provided herein that is sufficient to effect the intended application including, but not limited to, prophylaxis or treatment of diseases. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.*, the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, etc. which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells and/or tissues. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

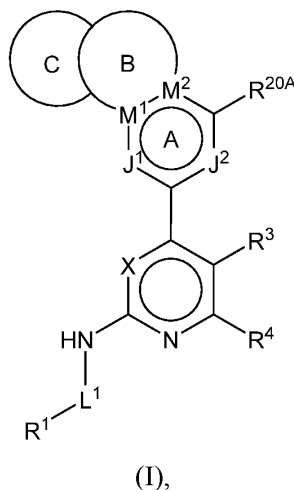
[0068] As used herein, and unless otherwise specified, the term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term "about" or "approximately" means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

5.2 Compounds

[0069] In some embodiments, provided herein are compounds and compositions that are useful for inhibiting CDKs such as CDK4 and/or treating or preventing various diseases or disorders provided herein, *e.g.*, cancer. In some embodiments, the compounds are aminoheteroaryl (*e.g.*, aminopyridine or aminopyrimidine) compounds with additional a tricyclic

structure moiety. The compounds provided herein can typically inhibit CDKs, such as CDK4. In some embodiments, the compounds provided herein can selectively inhibit CDK4 over other CDKs.

[0070] In some embodiments, provided herein is a compound of Formula (I):



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

L^1 is an optionally substituted phenylene, optionally substituted 5- or 6-membered heteroarylene, optionally substituted 4- to 8-membered heterocyclylene, or optionally substituted C_{3-8} carbocyclylene;

R^1 is hydrogen, OH, NH_2 , $NHCH_3$, or $N(CH_3)_2$;

X is N or CR^{10} ;

R^3 is hydrogen, deuterium, halogen, CN, OR^{11} , $NR^{12}R^{13}$, $C(O)NR^{12}R^{13}$, $COOR^A$, COR^B , optionally substituted C_{1-6} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{1-4} heteroalkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted 5-10 membered heteroaryl;

R^4 is hydrogen, deuterium, halogen, optionally substituted C_{1-6} alkyl, or $NR^{12}R^{13}$;

R^{10} is hydrogen, halogen, CN, -OH, an optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} heteroalkyl, optionally substituted C_{3-8} carbocyclyl, or optionally substituted 4-10 membered heterocyclyl;

R^{11} is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted 4-10 membered heterocyclyl;

each of R^{12} and R^{13} , at each occurrence, is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted 4-10 membered heterocyclyl; or R^{12} and R^{13} together with the nitrogen they are attached to form an optionally substituted 4-10 membered heterocyclyl or an optionally substituted 5- or 6-membered heteroaryl;

R^A is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted 4-10 membered heterocyclyl;

R^B is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted 5- or 6-membered heteroaryl;

J^1 and J^2 are independently N or CR^{30} , wherein R^{30} at each occurrence is independently hydrogen, halogen, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F;

R^{20A} is hydrogen, deuterium, halogen, CN, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, C_{1-4} heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or an optionally substituted 3-6 membered ring structure;

M^1 is C or N;

M^2 is C or N;

Ring B is an optionally substituted 5-7 membered ring that is fused to Ring A at the bond formed by M^1 and M^2 ;

Ring C is an optionally substituted 5-7 membered ring that is fused to Ring B.

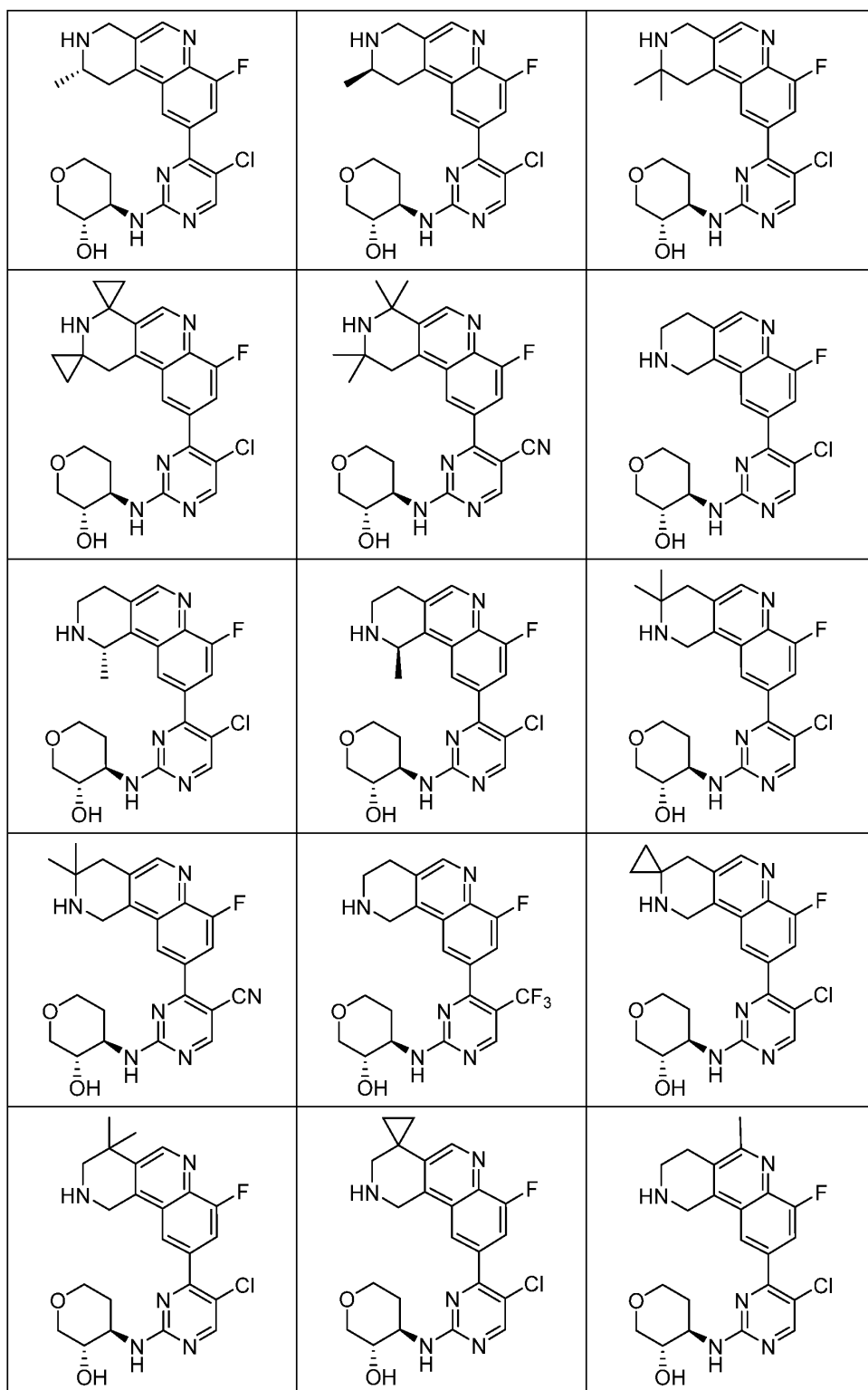
[0071] In some embodiments, the compound is not a compound described in WO 2024/022487 (*e.g.*, the compounds described in Table 1 and examples of WO 2024/022487), the entirety of which is incorporated herein by reference.

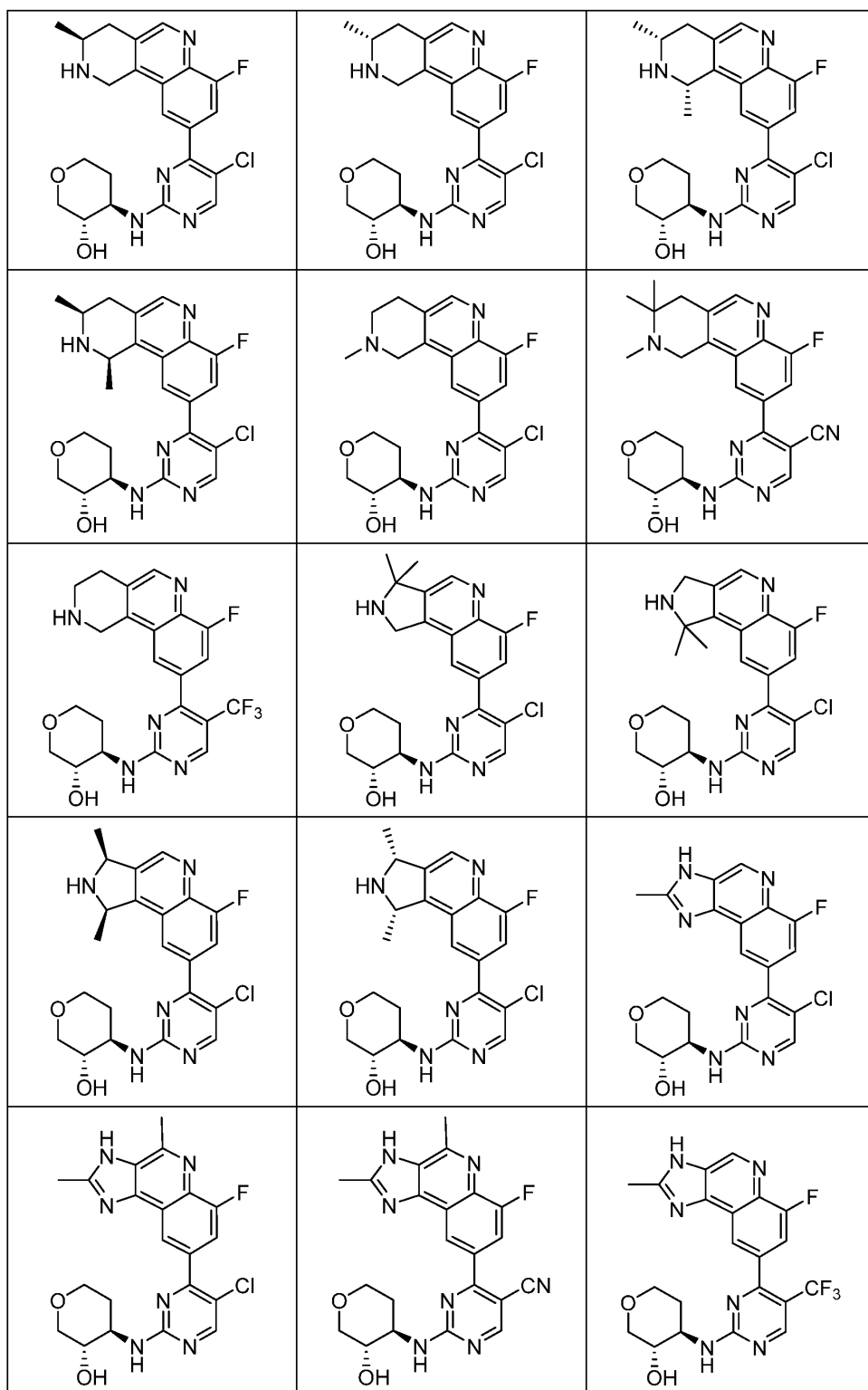
[0072] In some embodiments, the compound is not a compound described in WO 2019/207463 (*e.g.*, the compounds described in Preparation of Examples of WO 2019/207463), the entirety of which is incorporated herein by reference.

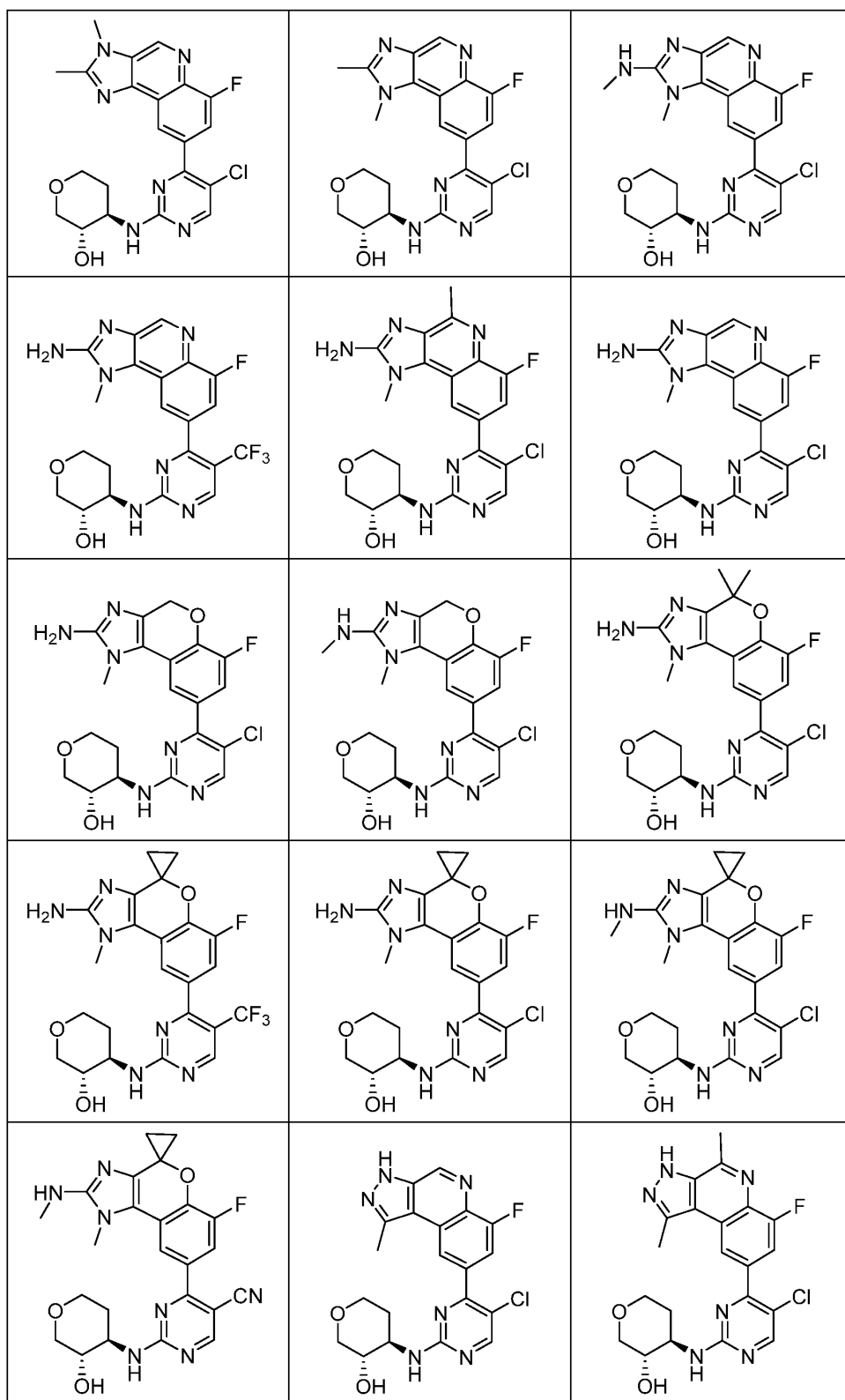
[0073] In some embodiments, the compound is not a compound of Table X, or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof. For example, in some embodiments of Formula (I-A), (I-I), (I-J), (I-K), (I-V), or (I-W),

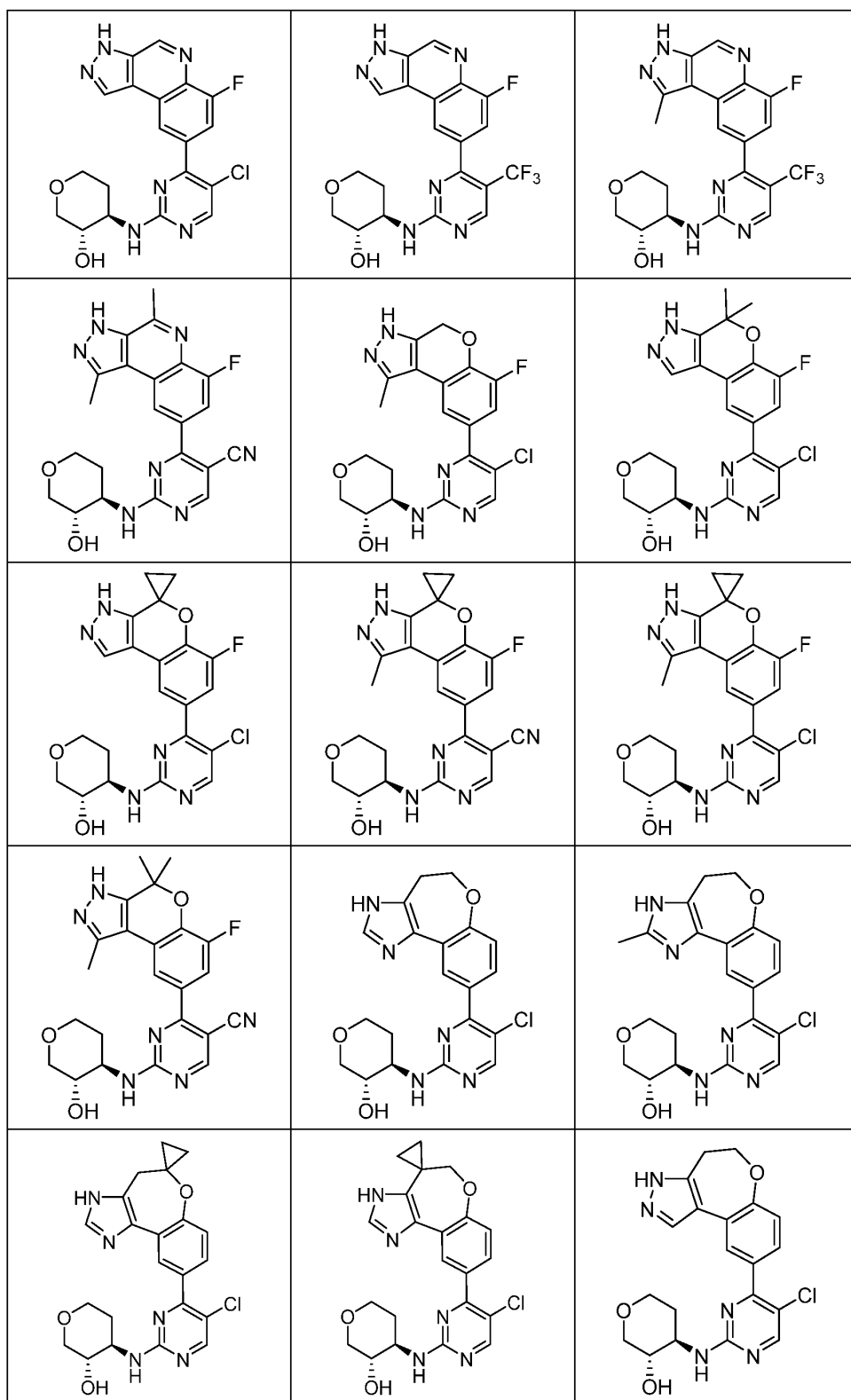
or a sub-formula thereof, the compound is not a compound of Table X, or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof.

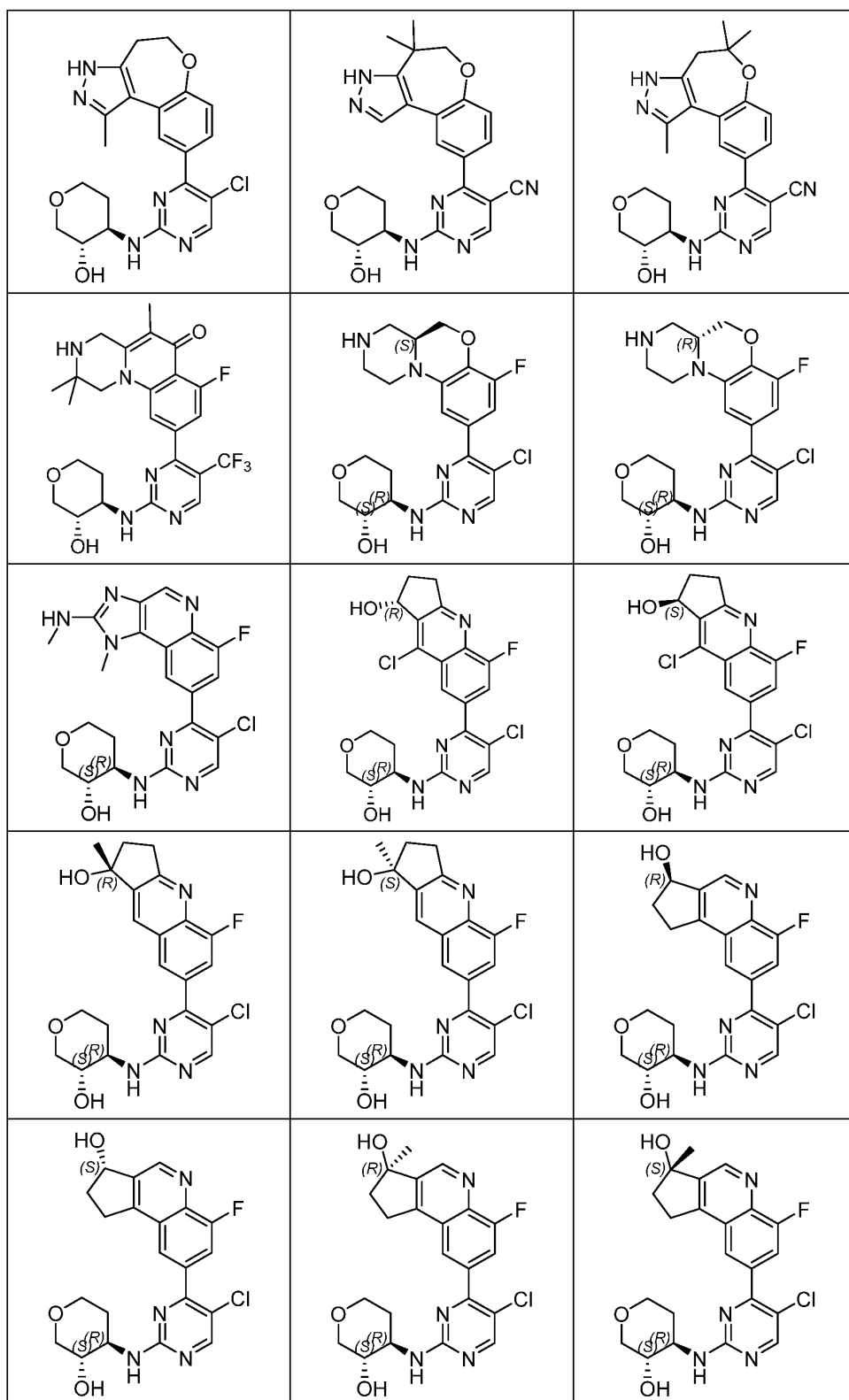
Table X. List of Compounds

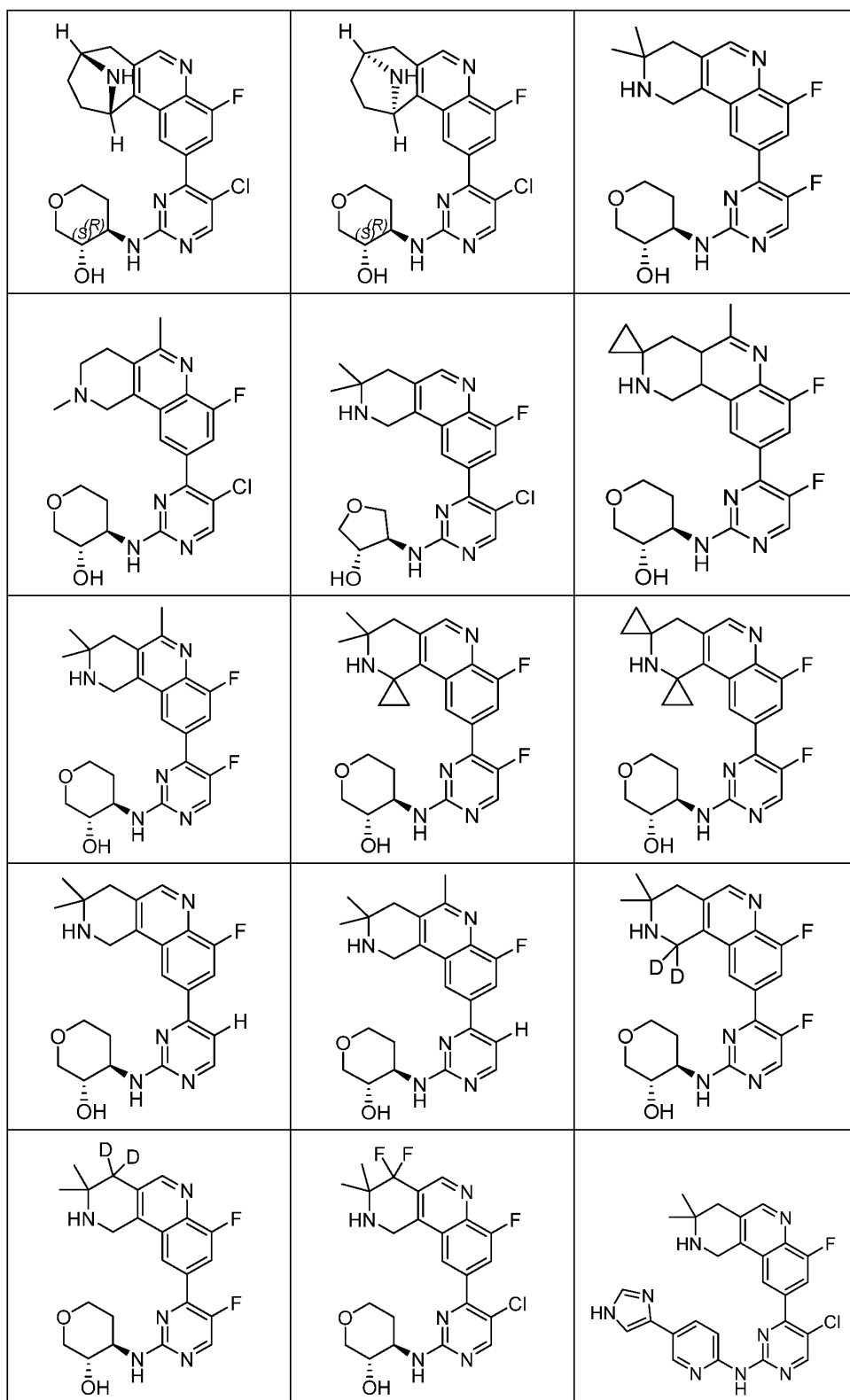


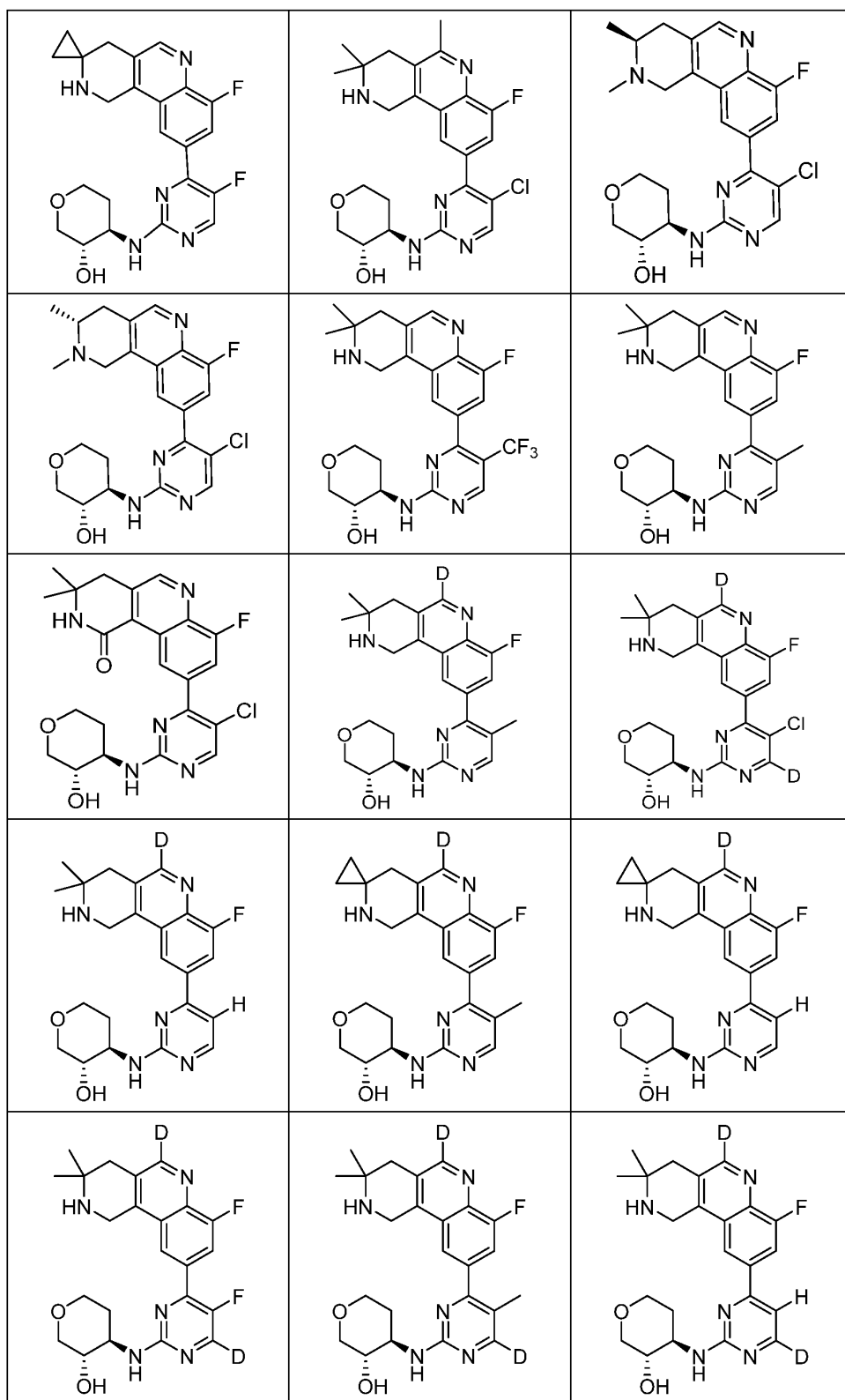


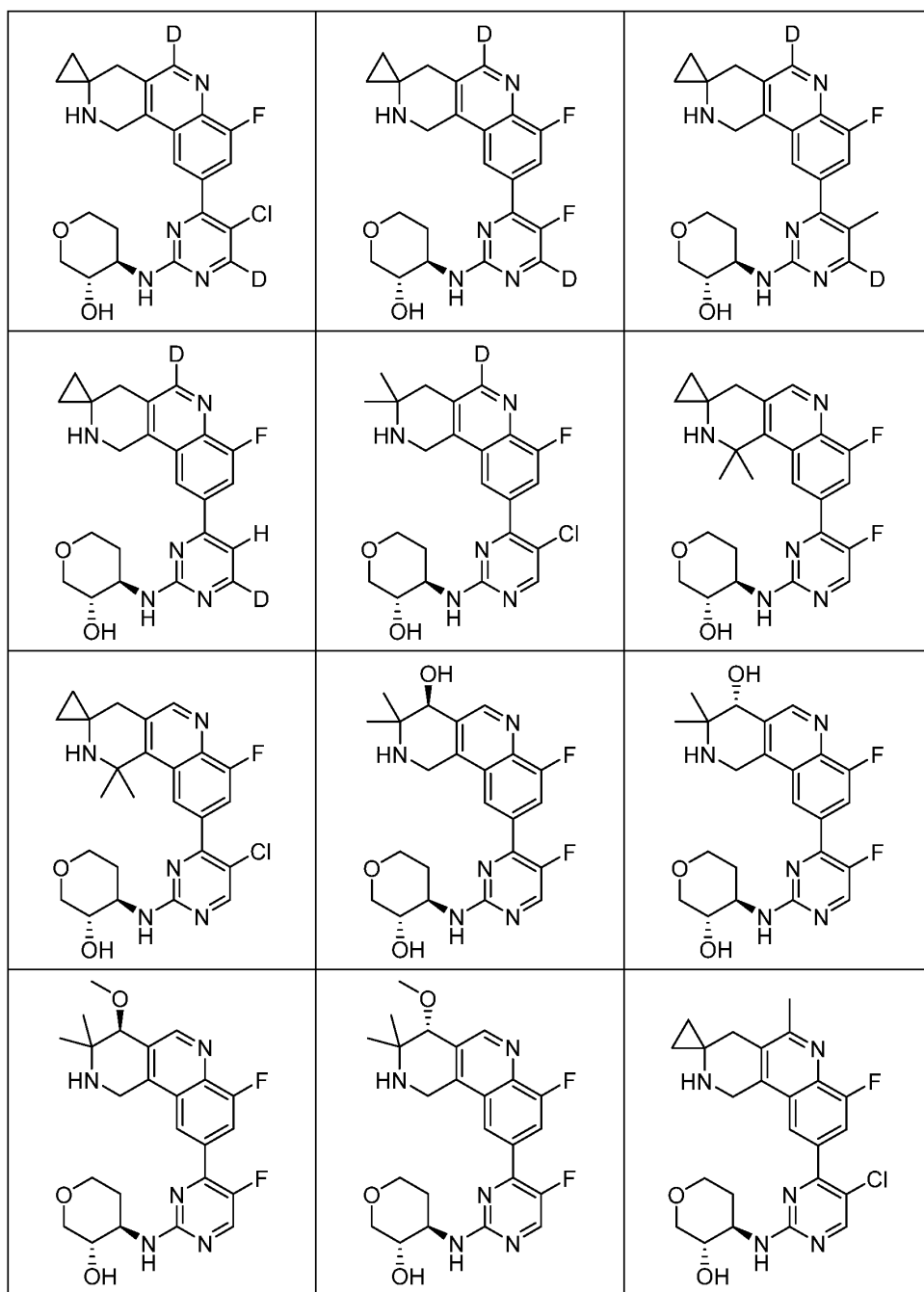


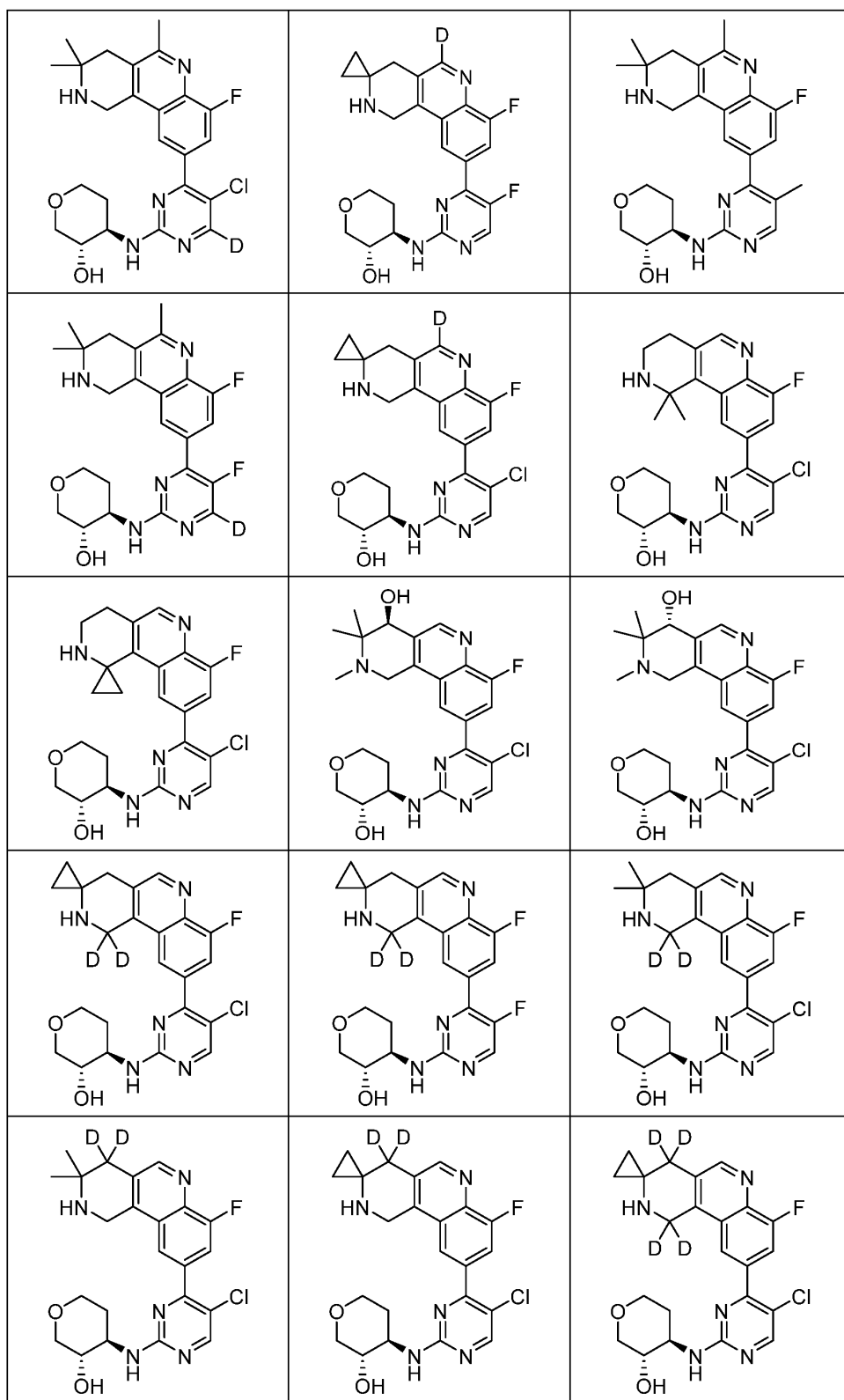


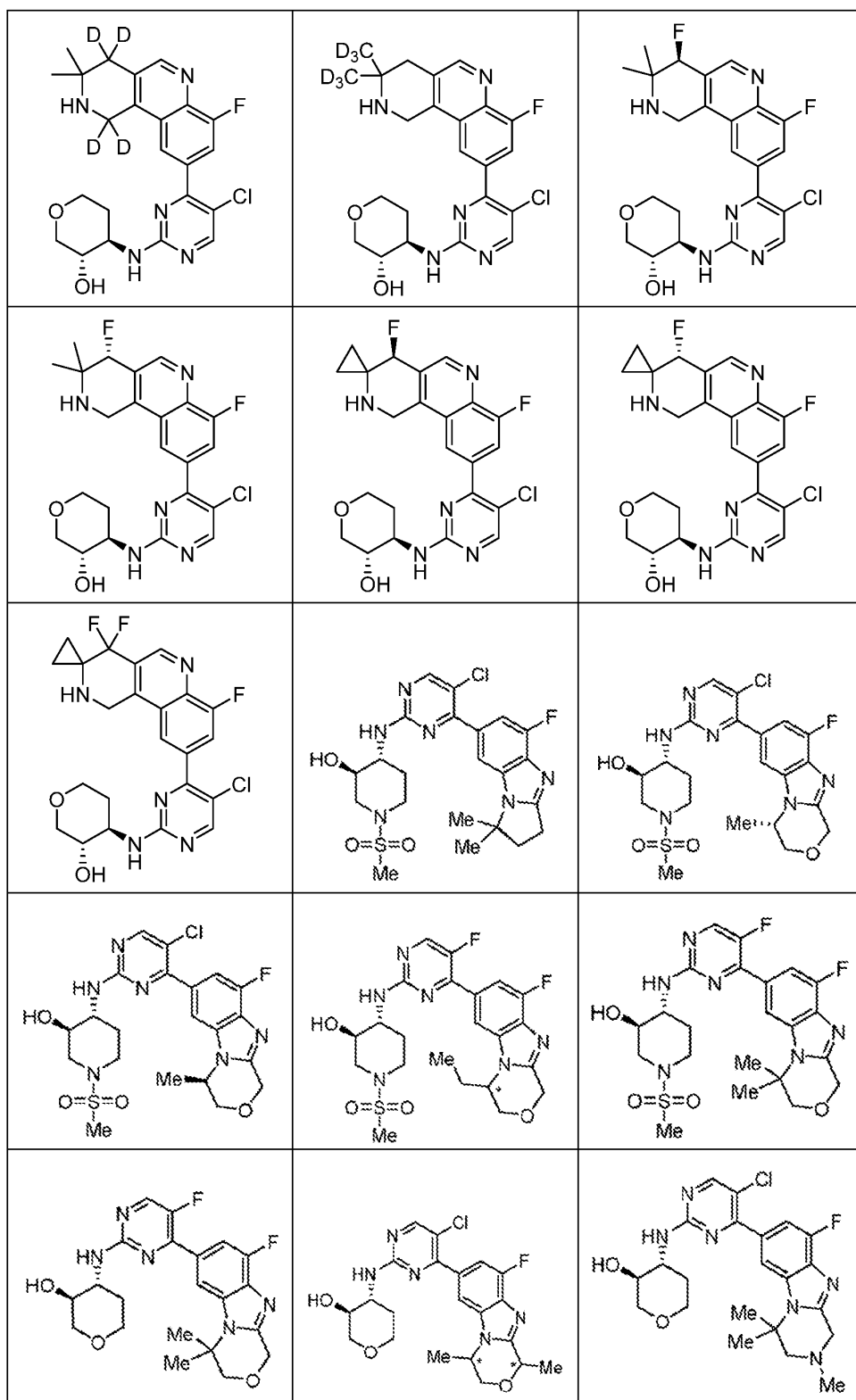


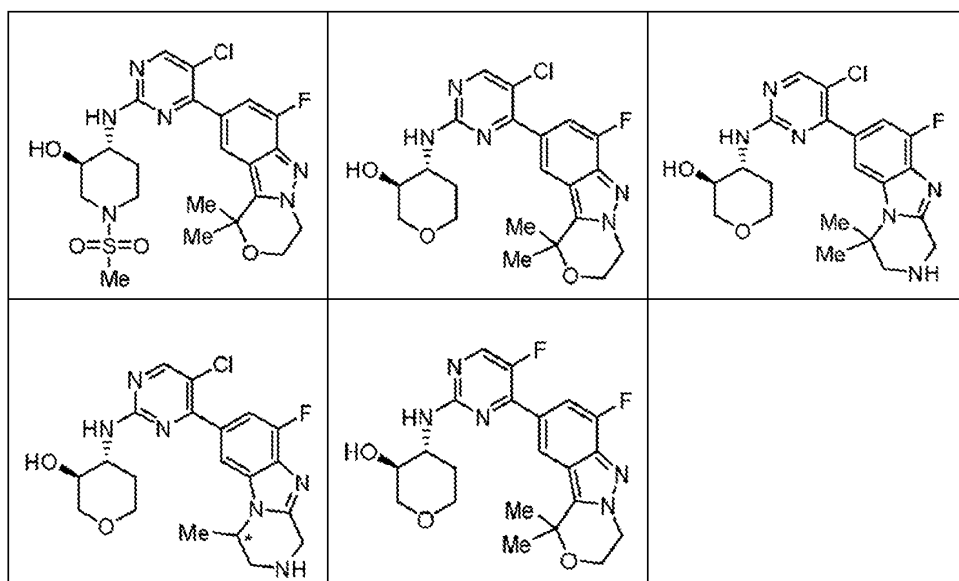












[0074] In some embodiments, the compound of Formula (I) (including any of the applicable sub-formulae as described herein) can comprise one or more asymmetric centers and/or axial chirality, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. In some embodiments, the compound can exist in the form of an individual enantiomer and/or diastereomer, as applicable, or a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomers. In some embodiments, when applicable, the compound can have an enantiomeric excess (“ee”) of greater than 60%, such as having greater than 80% ee, greater than 90% ee, greater than 95% ee, greater than 98% ee, greater than 99% ee, or with a non-detectable amount of the other enantiomer. In some embodiments, when applicable, the compound can also exist as a mixture of stereoisomers in any ratio, such as a racemic mixture.

[0075] In some embodiments, the compound of Formula (I) (including any of the applicable sub-formulae as described herein) can exist as an isotopically labeled compound, *e.g.*, a deuterated analog, wherein one or more of the hydrogen atoms of the compound is/are substituted with a deuterium atom with an abundance above its natural abundance, *e.g.*, a CD₃ analog when the compound has a CH₃ group. Without being bound by a particular theory, it is believed that deuterium substitution at certain positions (*e.g.*, those explicitly specified herein) can lead to compounds with a better pharmacokinetic profile when compared with their hydrogen counterparts (*i.e.*, at natural abundance) and thus can have a better pharmacodynamic outcome *in vivo*. Compounds with specific deuterium substitutions can be prepared by methods using

commercially available deuterium enriched reagents, such as deuterium gas, deuterium oxide (D₂O), deuterated formic acid (DCOOD), deuterated methyl iodide (CD₃I), deuterated methanol (CD₃OD), sodium deuteroxide (NaOD), sodium borodeuteride (NaBD₄), lithium aluminum deuteride (LiAlD₄), etc.

[0076] It should be apparent to those skilled in the art that in certain cases, the compound of Formula (I) may exist as a mixture of tautomers. Unless otherwise specified, such compound is not limited to any specific tautomer. Rather, any and all of such tautomers are encompassed, whether or not explicitly drawn or referred to.

[0077] In some embodiments, Ring B is optionally substituted 5-membered ring (*e.g.*, 5-membered heteroarylene). In some embodiments, Ring B is optionally substituted 6-membered ring (*e.g.*, 6-membered heteroarylene). In some embodiments, Ring B is optionally substituted 7-membered ring (*e.g.*, 7-membered heterocyclylene).

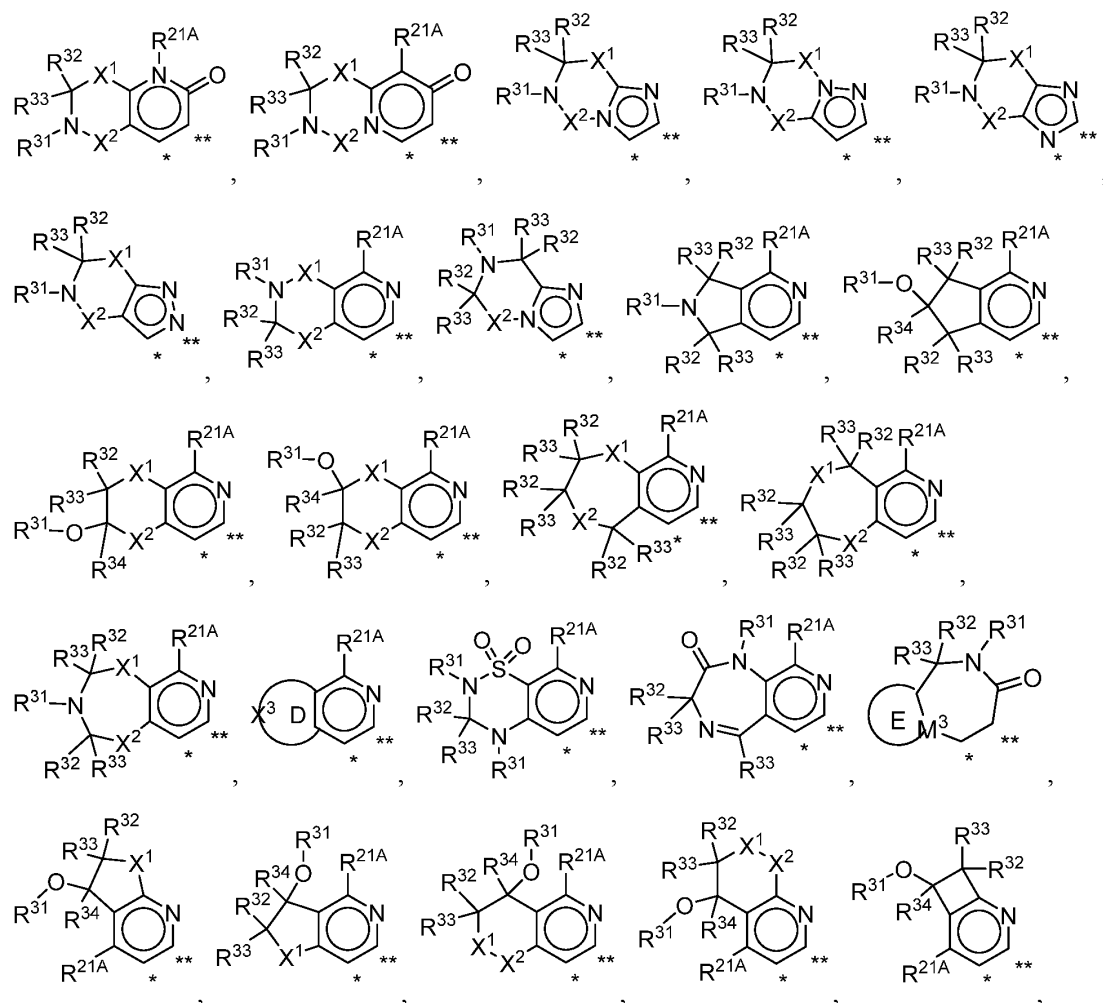
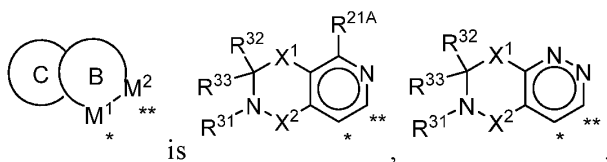
[0078] In some embodiments, Ring C is optionally substituted 5-membered ring (*e.g.*, 5-membered heteroarylene, or C₅ carbocyclylene). In some embodiments, Ring C is optionally substituted 6-membered ring (*e.g.*, 6-membered heterocyclylene, or C₆ carbocyclylene). In some embodiments, Ring C is optionally substituted 7-membered ring (*e.g.*, 7-membered heterocyclylene). In some embodiments, Ring B is optionally substituted N-containing heterocyclylene. In some embodiments, Ring B is optionally substituted O-containing heterocyclylene. In some embodiments, Ring B is optionally substituted S-containing heterocyclylene. In some embodiments, Ring B is optionally substituted P-containing heterocyclylene.

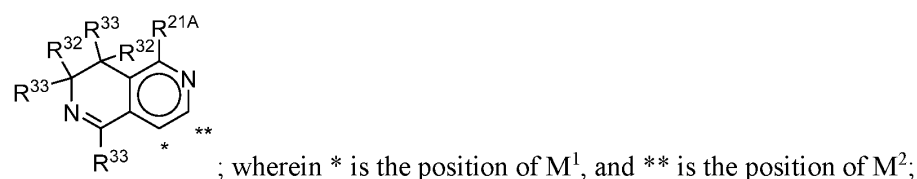
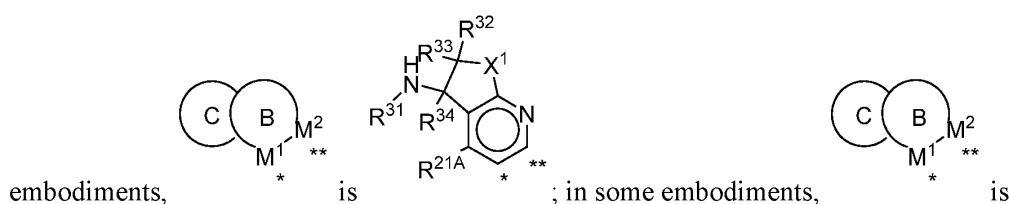
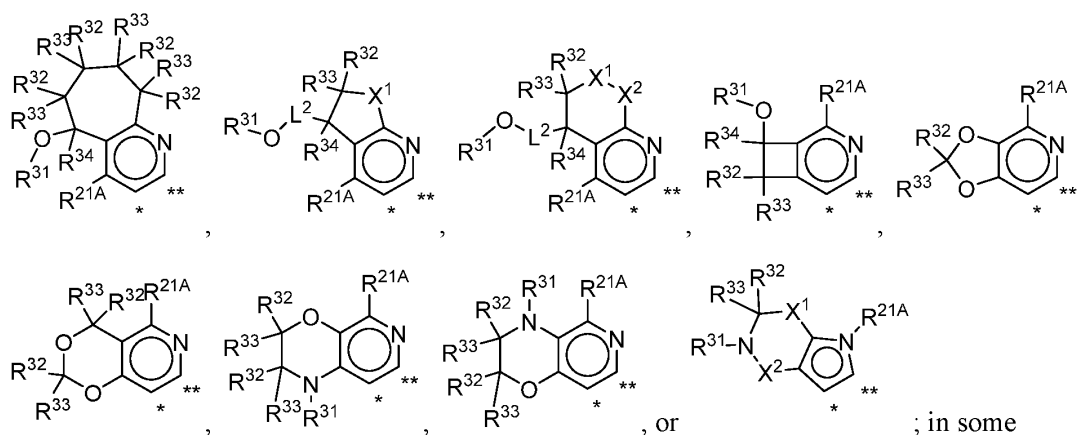
[0079] In some embodiments, Ring B is optionally substituted 5-membered heteroarylene, and Ring C is optionally substituted 6-membered heterocyclylene.

[0080] In some embodiments, Ring B is optionally substituted 6-membered heteroarylene, and Ring C is optionally substituted 5-membered heterocyclylene. In some embodiments, Ring B is optionally substituted 6-membered heteroarylene, and Ring C is optionally substituted 6-membered heterocyclylene. In some embodiments, Ring B is optionally substituted 6-membered heteroarylene, and Ring C is optionally substituted 7-membered heterocyclylene. In some embodiments, Ring B is optionally substituted 6-membered heteroarylene, and Ring C is optionally substituted C₅ carbocyclylene. In some embodiments, Ring B is optionally substituted 6-membered heteroarylene, and Ring C is optionally substituted C₆ carbocyclylene.

[0081] In some embodiments, Ring B is optionally substituted 7-membered heterocyclylene, and Ring C is optionally substituted 5-membered heteroarylene. In some embodiments, Ring B is optionally substituted 7-membered heterocyclylene, and Ring C is optionally substituted 6-membered heteroarylene.

[0082] In some embodiments,





R^{21A} is hydrogen, deuterium, halogen, CN, C_{1-4} alkyl optionally substituted with one or more (e.g., 1, 2, or 3) deuterium or F, C_{1-4} heteroalkyl optionally substituted with one or more (e.g., 1, 2, or 3) deuterium or F, or an optionally substituted 3-6 membered ring structure;

X^1 is O, NR^{31} , or $CR^{32}R^{33}$;

X^2 is O, NR^{31} , or $CR^{32}R^{33}$;

Ring D is an optionally substituted 5-7 membered ring, wherein all the ring atoms other than X^3 are carbon atoms, and X^3 is -O-, -S(O)-, -S(O)₂-, -S(O)₂- NR^{31} -, - NR^{31} -S(O)₂-, -S(O)(NH)-, -P(O)(R^{34})-, -P(O)(R^{34})- NR^{31} -, or - NR^{31} -P(O)(R^{34})-;

M^3 is C or N;

Ring E is an optionally substituted phenyl, or optionally substituted 5 or 6 membered heteroaryl;

R^{31} at each occurrence is independently hydrogen, C_{1-4} alkyl, O(C_{1-4} alkyl), C(O)H, C(O)(C_{1-4} alkyl), C(O)O(C_{1-4} alkyl), C(O)NH₂, C(O)NH(C_{1-4} alkyl), C(O)N(C_{1-4} alkyl)₂, C(O)(C_{3-6} carbocyclyl), C(O)(phenyl), C(O)(4-6 membered heterocyclyl), C(O)(5- or 6-membered heteroaryl), SO₂(C_{1-4} alkyl), SO₂NH₂, SO₂NH(C_{1-4} alkyl), SO₂N(C_{1-4} alkyl)₂, SO₂(C_{3-6}

carbocyclyl), SO₂(phenyl), SO₂(4-6 membered heterocyclyl), SO₂(5- or 6-membered heteroaryl), C₃₋₆ carbocyclyl, phenyl, 4-6 membered heterocyclyl, or 5- or 6-membered heteroaryl; wherein the alkyl moiety in R³¹ at each occurrence is independently optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each of which is independently deuterium, halo, OH, O(C₁₋₄ alkyl), SO₂(C₁₋₄ alkyl), NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)(C₁₋₄ alkyl), NH(C₃₋₆ cycloalkyl), N(C₁₋₄ alkyl)(C₃₋₆ cycloalkyl), or N(C₃₋₆ cycloalkyl)(C₃₋₆ cycloalkyl); and wherein the carbocyclyl, phenyl, heterocyclyl, and heteroaryl moieties in R³¹ at each occurrence is independently optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each of which is independently oxo, halo, OH, NH₂, C₁₋₄ alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C₁₋₄ heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F;

each of R³² and R³³ at each occurrence is independently:

- (1) hydrogen or deuterium;
- (2) halogen or cyano;
- (3) OH, NH₂, NH(C₁₋₄ alkyl), or N(C₁₋₄ alkyl)(C₁₋₄ alkyl);
- (4) C₁₋₄ alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each of which is independently deuterium, F, OH, NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)(C₁₋₄ alkyl), NH(C₃₋₆ cycloalkyl), N(C₁₋₄ alkyl)(C₃₋₆ cycloalkyl), or N(C₃₋₆ cycloalkyl)(C₃₋₆ cycloalkyl); (in some embodiments, the independent optional substituent options also include SO₂(C₁₋₄ alkyl).)
- (5) C₁₋₄ alkoxy optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C₁₋₄ heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F;
- (6) an optionally substituted C₃₋₆ carbocyclyl, optionally substituted phenyl, optionally substituted 4-6 membered heterocyclyl, or optionally substituted 5- or 6-membered heteroaryl;
- (7) R³² and R³³, together with the carbon atom they are attached to, form a carbonyl (CO);
- (8) R³² and R³³, together with the carbon atom they are attached to, form a C₃₋₆ carbocyclyl or 4-6 membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more (*e.g.*, 1, 2, or 3)

substituents each of which is independently oxo, halo, OH, NH₂, C₁₋₄ alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C₁₋₄ heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F; or

- (9) two R³² are joined together with the intervening atom(s) to form an optionally substituted 3-7 membered ring; or

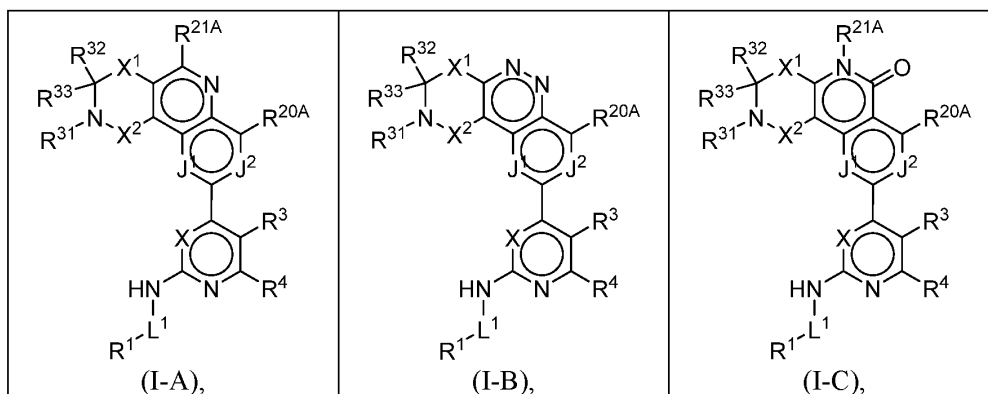
a R³¹ and an adjacent R³² are joined together with the intervening atom(s) to form an optionally substituted 3-7 membered ring;

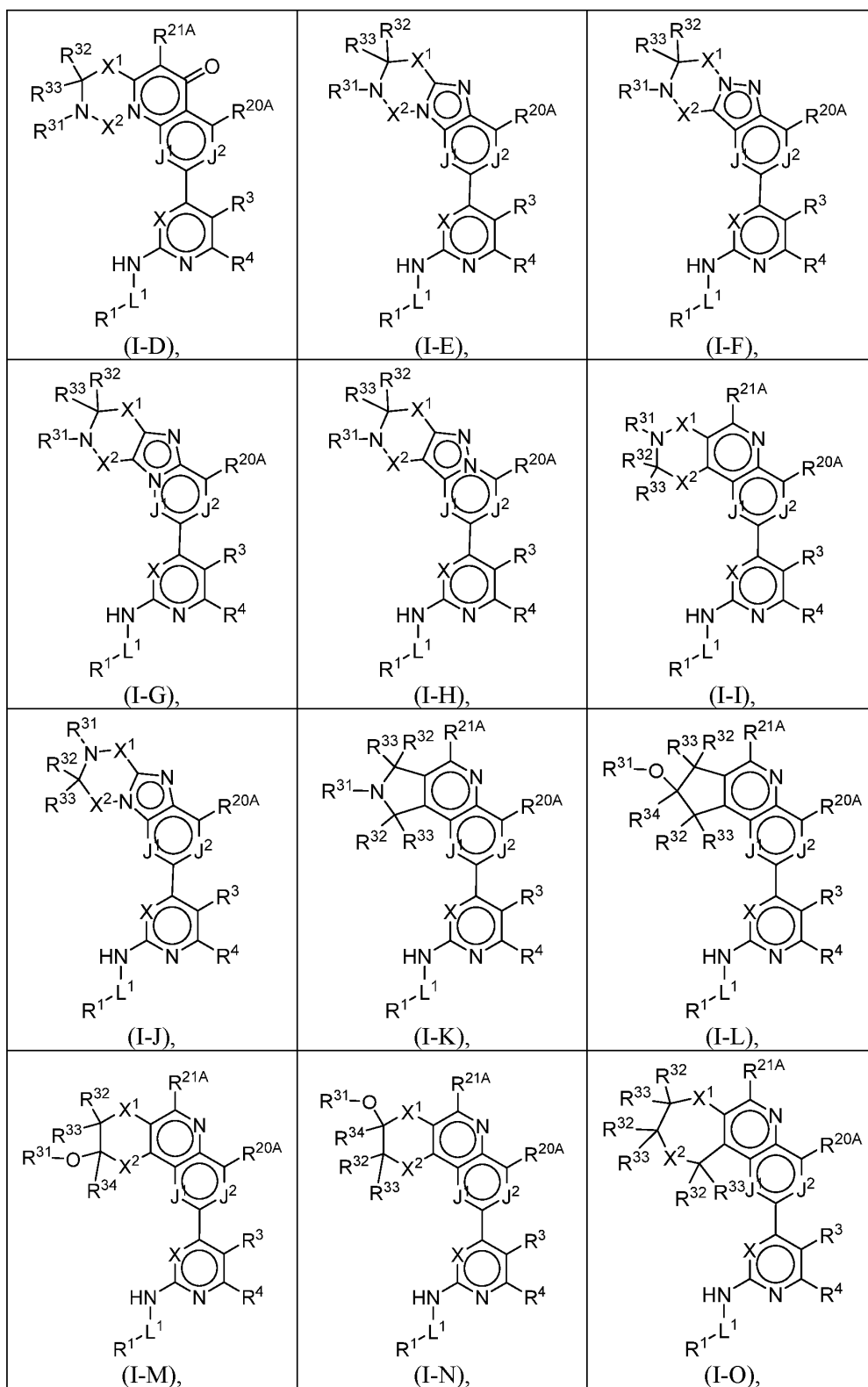
R³⁴ at each occurrence is independently hydrogen, C₁₋₄ alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, optionally substituted C₃₋₆ carbocyclyl, optionally substituted phenyl, optionally substituted 4-6 membered heterocyclyl, or optionally substituted 5- or 6-membered heteroaryl; or

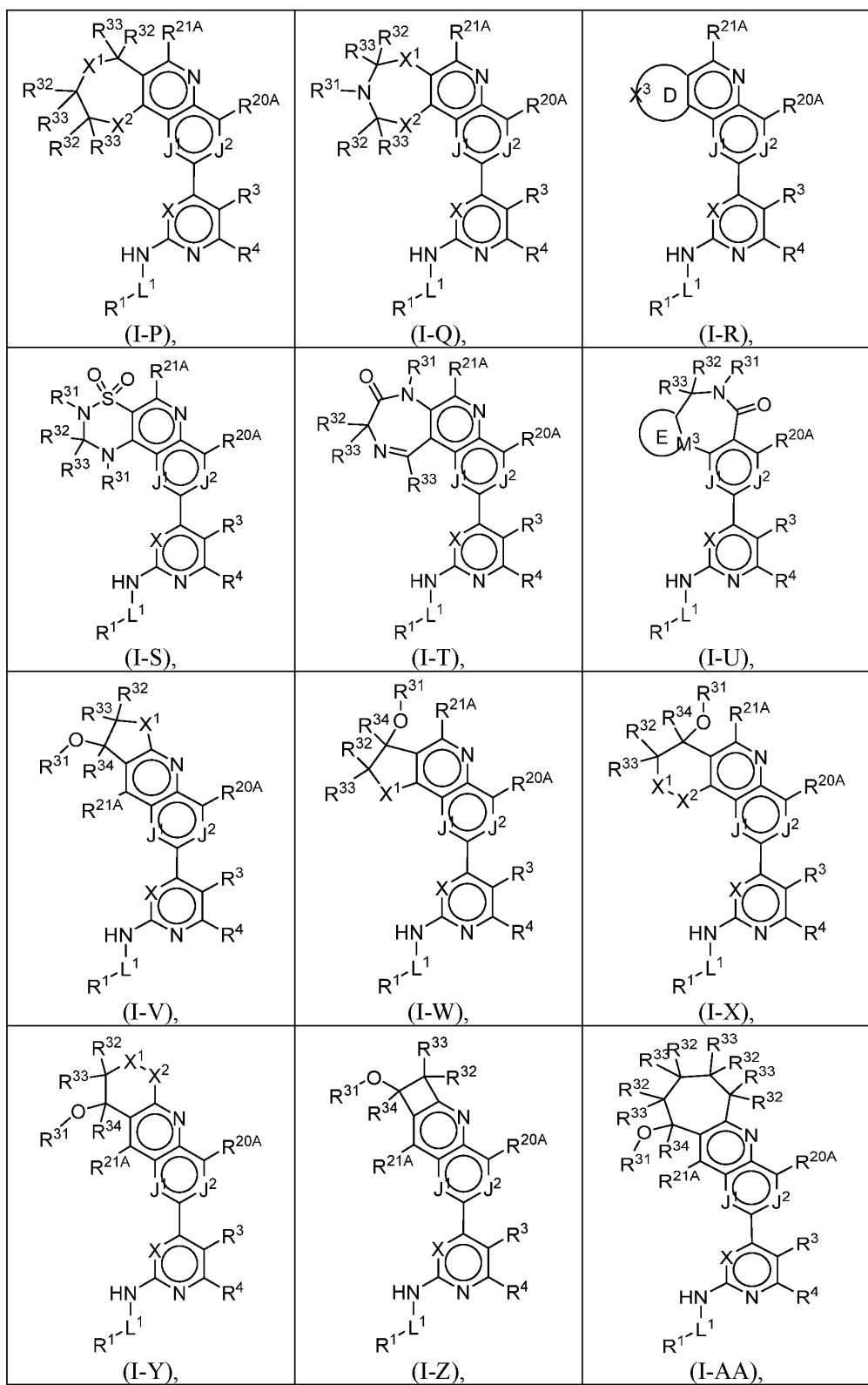
a R³⁴ and a R³² are joined together with the intervening atom(s) to form an optionally substituted 3-7 membered ring; and

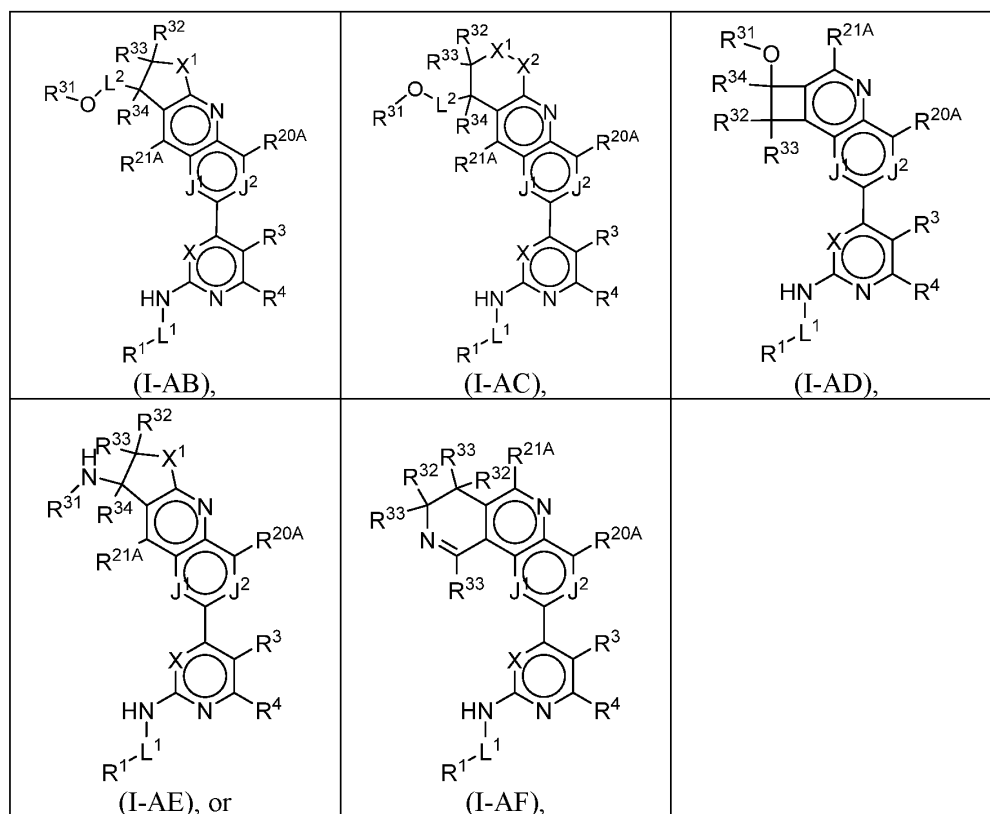
L² is an optionally substituted C₁₋₃ alkylene.

[0083] In some embodiments, the compound is a compound of Formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (I-I), (I-J), (I-K), (I-L), (I-M), (I-N), (I-O), (I-P), (I-Q), (I-R), (I-S), (I-T), (I-U), (I-V), (I-W), (I-X), (I-Y), (I-Z), (I-AA), (I-AB), (I-AC), (I-AD), (I-AE), or (I-AF):



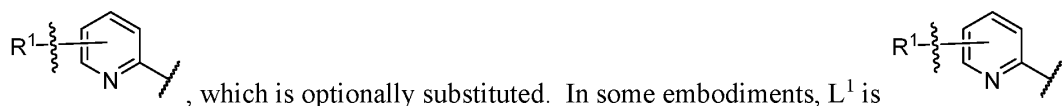




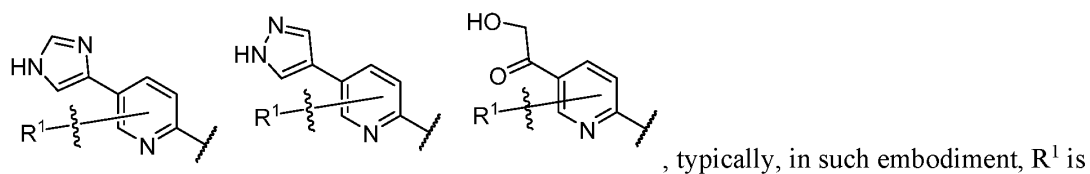


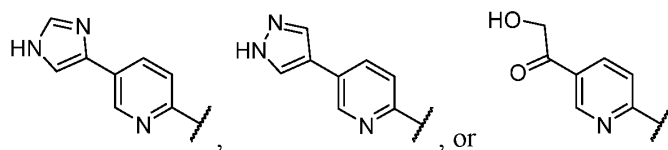
or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof.

[0084] In some embodiments, L^1 is an optionally substituted phenylene. In some embodiments, L^1 is an optionally substituted 5- or 6-membered heteroarylene, *e.g.*, those having 1-3 ring heteroatoms independently selected from N, O, and S, such as pyridylene, *e.g.*,



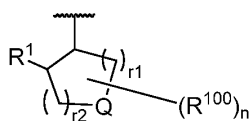
wherein the pyridylene is optionally substituted with a 5-membered heteroaryl, such as a pyrazole or imidazole. In some embodiments, L^1 is selected from:





hydrogen (*i.e.*, $-L^1-R^1$ is hydrogen). In some embodiments, L^1 is an optionally substituted 4- to 8-membered heterocyclene, *e.g.*, a monocyclic or bicyclic (*e.g.*, fused, bridged, or spiro bicyclic) 4- to 8-membered heterocyclene having 1-2 ring heteroatoms independently selected from N, O, and S. In some embodiments, L^1 is an optionally substituted C_{3-8} carbocyclene, *e.g.*, a monocyclic or bicyclic (*e.g.*, fused, bridged, or spiro bicyclic) carbocyclene.

[0085] In some embodiments, $-L^1-R^1$ has a structure of Formula (A):



Formula (A),

wherein:

Q is

- (1) O;
- (2) NR^{14} , wherein R^{14} is hydrogen, G^A , SO_2G^A , $SO_2NG^B G^C$, $S(O)(NH)G^A$, COG^A , $COOG^A$, or $C(O)NG^B G^C$;
- (3) $CR^{15}R^{16}$, wherein R^{15} and R^{16} are joined with the carbon atom they are attached to form an optionally substituted 4-6 membered heterocyclic ring having 1 or 2 ring heteroatoms independently selected from O and N; or
- (4) absent;

r_1 is 1, 2, or 3; and

r_2 is 0, 1, or 2;

n is 0, 1, 2, 3, or 4, as valency permits; and

- (i) R^{100} at each occurrence is independently selected from halogen (*e.g.*, F or Cl), CN, OH, COOH, G^A , OG^A , $NG^B G^C$, $NG^B G^C SO_2 G^A$, $NG^B G^C SO_2 NG^B G^C$, $NG^B G^C S(O)(NH)G^A$, $NG^B G^C COG^A$, $NG^B G^C COOG^A$, $NG^B G^C C(O)NG^B G^C$, $SO_2 G^A$, $SO_2 NG^B G^C$, $S(O)(NH)G^A$, COG^A , $COOG^A$, or $C(O)NG^B G^C$; or
- (ii) two instances of R^{100} are joined together with the intervening atom(s) to form an optionally substituted ring, such as an optionally substituted 3-6

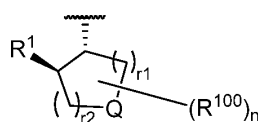
membered ring, and any remaining R^{100} at each occurrence is as defined in (i);

wherein:

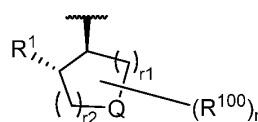
G^A at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl (e.g., 5- or 6-membered heteroaryl), or optionally substituted 4-10 membered heterocyclyl; and

each of G^B and G^C , at each occurrence, is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl (e.g., 5- or 6-membered heteroaryl), optionally substituted 4-10 membered heterocyclyl; or G^B and G^C can be joined to form an optionally substituted 4-10 membered heterocyclyl or 5- or 6-membered heteroaryl.

[0086] In some embodiments, the structure of Formula (A) has a stereochemistry as shown in Formula (A-S1) or (A-S2):



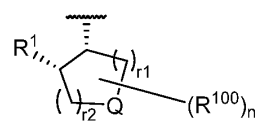
Formula (A-S1), or



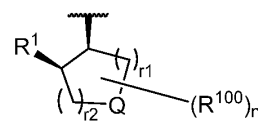
Formula (A-S2).

[0087] In some embodiments, the compound can exist as the stereoisomer of Formula (A-S1), such as having an ee of greater than about 60%, greater than about 80%, greater than about 90%, greater than about 95%, greater than about 98%, greater than about 99% ee, or with a non-detectable amount of the enantiomer according to Formula (A-S2).

[0088] In some embodiments, the structure of Formula (A) has a stereochemistry as shown in Formula (A-S3) or (A-S4):



Formula (A-S3), or

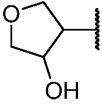
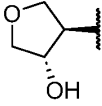
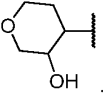
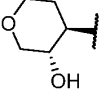
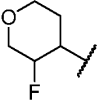
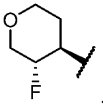
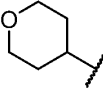


Formula (A-S4).

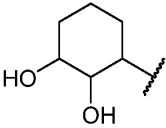
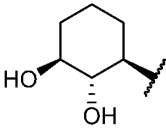
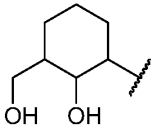
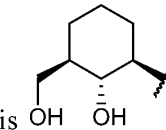
[0089] In some embodiments, Q is absent (*i.e.*, Q is a bond connecting the two carbon atoms adjacent to Q in Formula A). In some embodiments, Q is O. In some embodiments, Q is NR^{14} . In some embodiments, Q is $CR^{15}R^{16}$.

[0090] In some embodiments, r_1 is 1 and r_2 is 1. In some embodiments, r_1 is 2 and r_2 is 1. In some embodiments, r_1 is 1 and r_2 is 2. In some embodiments, r_1 is 2 and r_2 is 2. In some embodiments, r_1 is 1, r_2 is 1, and Q is O. In some embodiments, r_1 is 2, r_2 is 1, and Q is O.

[0091] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

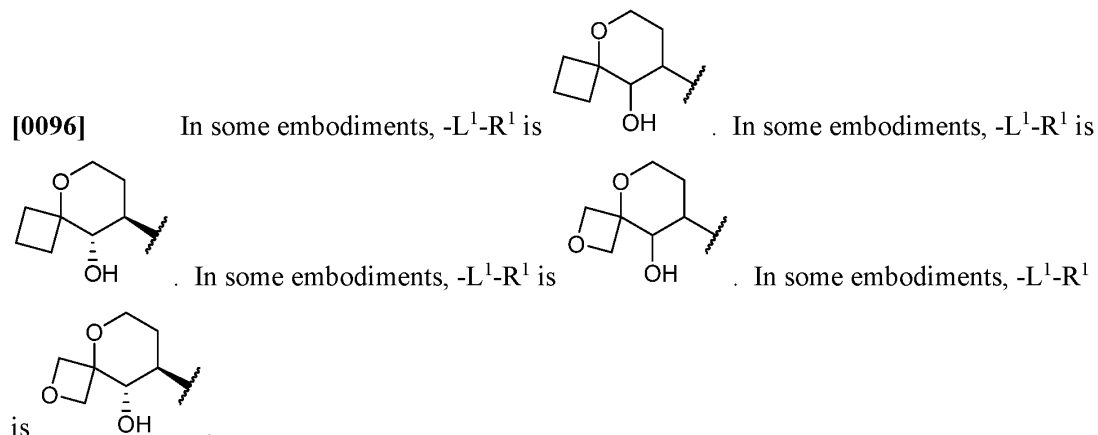
[0092] In some embodiments, $-L^1-R^1$ is . In some embodiments, $-L^1-R^1$ is . In some embodiments, $-L^1-R^1$ is . In some embodiments, $-L^1-R^1$ is . In some embodiments, $-L^1-R^1$ is . In some embodiments, $-L^1-R^1$ is . In some embodiments, $-L^1-R^1$ is .

[0093] In some embodiments, n is 1 or 2, and R^{100} at each occurrence is independently selected from F, Cl, CN, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F or OH, C_{1-4} alkoxy optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, and C_{1-4} heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, n is 1, and R^{100} is F, Cl, CN, OH, methyl, $-CH_2OH$, fluorine-substituted methyl such as CF_3 , methoxy, or fluorine-substituted methoxy.

[0094] In some embodiments, $-L^1-R^1$ is . In some embodiments, $-L^1-R^1$ is . In some embodiments, $-L^1-R^1$ is . In some embodiments, $-L^1-R^1$ is .

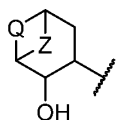
[0095] In some embodiments, n is 2, and two geminal R^{100} are joined together with the carbon atom they are attached to form an optionally substituted 3-6 membered ring. In some embodiments, the ring (formed by the two geminal R^{100} together with the carbon atom they are attached to) is a C_{3-6} cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, or cyclopentyl). In some embodiments, the ring is a 4-6 membered heterocyclyl (*e.g.*, oxetanyl). In some embodiments,

the ring is unsubstituted. In some embodiments, the ring is substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, halogen, CN, OH, or C₁₋₃ alkyl (*e.g.*, methyl).

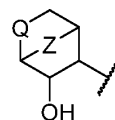


[0097] In some embodiments, n is 2, and two non-geminal R¹⁰⁰ are joined together with the intervening atom(s) to form an optionally substituted 4-6 membered ring. In some embodiments, the ring (formed by the two non-geminal R¹⁰⁰ together with the intervening atoms) is a C₄₋₆ cycloalkyl (*e.g.*, cyclobutyl, or cyclopentyl). In some embodiments, the ring is a 4-6 membered heterocyclyl. In some embodiments, the ring is unsubstituted. In some embodiments, the ring is substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, halogen, CN, OH, or C₁₋₃ alkyl (*e.g.*, methyl).

[0098] In some embodiments, -L¹-R¹ has a structure of Formula (A-1) or (A-2):



Formula (A-1), or



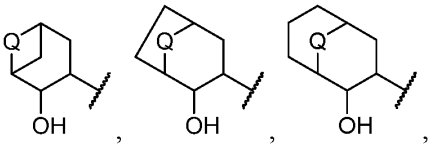
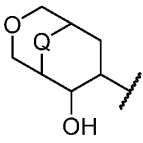
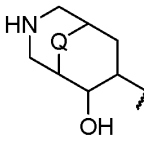
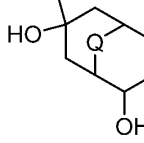
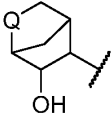
Formula (A-2),

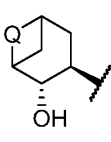
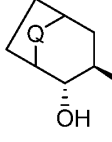
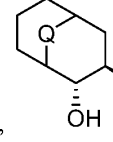
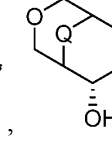
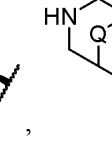
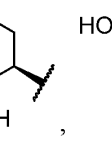
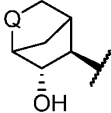
wherein Z is C₁₋₃ alkylene, wherein the non-terminal CH₂ is optionally replaced by O or NH, and wherein Z is optionally substituted with one or more (*e.g.*, 1 or 2) substituents each of which is independently halogen, OH, or C₁₋₄ alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F.

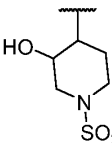
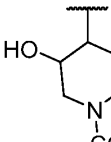
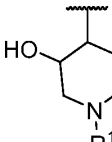
[0099] In some embodiments, Q is O, NH, NHR¹⁷, NHC(O)R¹⁷, or NHS(O)₂R¹⁷.

[0100] In some embodiments, Z is -CH₂-. In some embodiments, Z is -CH₂CH₂-. In some embodiments, Z is -CH₂CH₂CH₂-. In some embodiments, Z is -CH₂OCH₂-. In some embodiments, Z is -CH₂NHCH₂-.

[0101] In some embodiments, Z is unsubstituted. In some embodiments, Z is substituted with one or more (*e.g.*, 1 or 2) substituents each of which is independently OH or C₁₋₄ alkyl. In some embodiments, Z is -CH₂C(OH)(CH₃)CH₂-.

[0102] In some embodiments, -L¹-R¹ is , , , , or . In some embodiments, -L¹-R¹ is

, , , , , , or .

[0103] In some embodiments, -L¹-R¹ is . In some embodiments, -L¹-R¹ is . In some embodiments, -L¹-R¹ is . In some embodiments, R¹⁷ is an

optionally substituted C₁₋₄ alkyl, optionally substituted C₃₋₆ cycloalkyl, optionally substituted phenyl, optionally substituted 4-8 membered heterocyclic ring, or optionally substituted 5 or 6 membered heteroaryl.

[0104] In some embodiments, R¹⁷ is: (1) C₁₋₄ alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, and OH, such as CHF₂, CF₃, etc.; (2) phenyl, pyridyl, or pyrimidyl, each of which is optionally substituted with 1-3 substituents independently selected from deuterium, halogen, CN, OH, C₁₋₃ alkyl optionally substituted with F, or C₁₋₃ alkoxy optionally substituted with F; or (3) 5-membered heteroaryl optionally

substituted with 1-3 substituents independently selected from deuterium, halogen, CN, OH, C₁₋₃ alkyl optionally substituted with F, or C₁₋₃ alkoxy optionally substituted with F.

[0105] In some embodiments, R¹⁷ is C₁₋₄ alkyl, (C₁₋₄ alkylene)_j-C₃₋₆ cycloalkyl, (C₁₋₄ alkylene)_j-(4-8 membered monocyclic heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S), or (C₁₋₄ alkylene)_j-(5 or 6 membered heteroaryl having 1-3 ring heteroatoms independently selected from N, O, and S),

wherein j is 0 or 1, and the C₁₋₄ alkylene is straight or branched alkylene chain optionally substituted with F; and

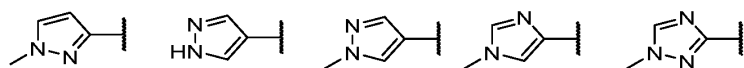
wherein each of the C₁₋₄ alkyl, C₃₋₆ cycloalkyl, 5 or 6 membered heteroaryl and 4-8 membered monocyclic heterocyclyl is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents independently selected from oxo (as valency permits), halo (*e.g.*, F), G¹, OH, O-G¹, NH₂, NH(G¹), and N(G¹)(G¹),

wherein G¹ at each occurrence is independently (1) a C₁₋₄ alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C₁₋₄ heteroalkyl, or (2) a C₃₋₆ cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C₁₋₄ heteroalkyl;

when substituted, the C₁₋₄ alkyl, C₃₋₆ cycloalkyl, 5 or 6 membered heteroaryl, or 4-8 membered monocyclic heterocyclyl is, *e.g.*, substituted with 1, 2, or 3 substituents each independently F, Cl, CN, OH, C₁₋₄ alkyl optionally substituted with F, or C₁₋₄ alkoxy optionally substituted with F, *e.g.*, with 1, 2, or 3 substituents each independently F, OH, methyl, fluorine-substituted methyl such as CF₃, methoxy, or fluorine-substituted methoxy.

[0106] In some embodiments, j is 0. In some embodiments, j is 1, and the C₁₋₄ alkylene is straight or branched alkylene chain, such as CH₂.

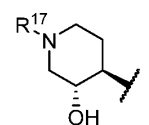
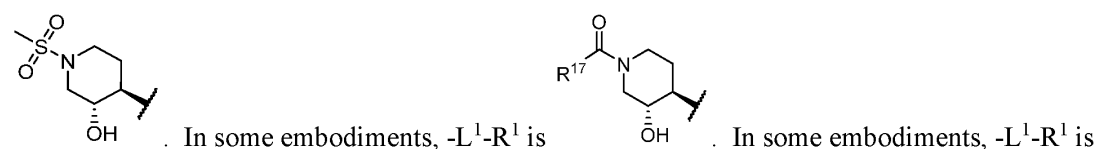
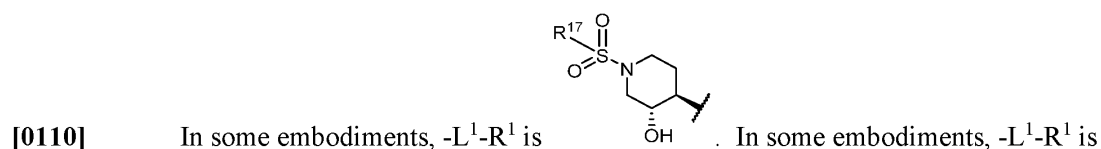
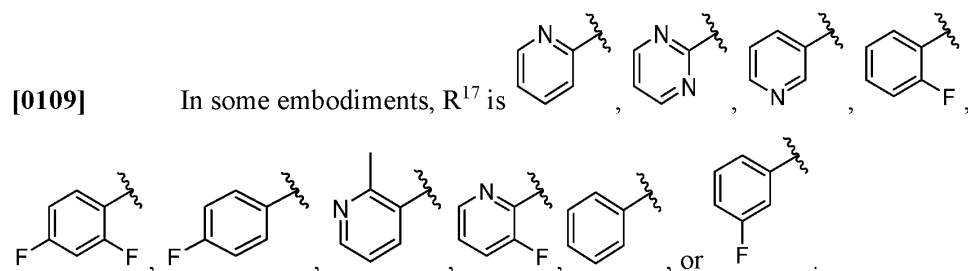
[0107] In some embodiments, R¹⁷ is C₁₋₄ alkyl, such as methyl, ethyl, isopropyl, etc. In some embodiments, R¹⁷ is C₁₋₄ alkyl optionally substituted with F. In some embodiments, R¹⁷ is C₃₋₆ cycloalkyl, which is optionally substituted, *e.g.*, with a substituent described herein. In some embodiments, R¹⁷ is 4-8 membered monocyclic heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S, which is optionally substituted, *e.g.*, with a substituent described herein. In some embodiments, R¹⁷ is a 5-membered heteroaryl, which is optionally substituted, such as with a C₁₋₄ alkyl, for example, R¹⁷ can be selected from:



[0108] In some embodiments, R^{17} is a phenyl or 6-membered heteroaryl having 1-3 ring nitrogen atoms, wherein the phenyl or 6-membered heteroaryl is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents independently selected from halo (*e.g.*, F), G^1 , OH, $O-G^1$, NH_2 , $NH(G^1)$, and $N(G^1)(G^1)$,

wherein G^1 at each occurrence is independently (1) a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or (2) a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl,

when substituted, the phenyl or 6-membered heteroaryl is, *e.g.*, substituted with 1, 2, or 3 substituents each independently F, Cl, CN, OH, C_{1-4} alkyl optionally substituted with F, C_{1-4} alkoxy optionally substituted with F, *e.g.*, with 1 or 2 substituents each independently F or methyl.



[0111] In some embodiments, when Ring C is a saturated ring directly substituted with -OH (*e.g.*, Formulas (I-V), (I-M), (I-N), (I-V), (I-W), (I-X), (I-Y), (I-Z), or (I-AA), or a sub-formula thereof), also provided herein are compounds where a L^2 is inserted between the -OH and the saturated ring. For example, for a compound of Formula (I-V) or a sub-formula thereof,

the corresponding compound of Formula (I-AB) or a sub-formula is also provided, even if Formula (I-AB) is not specifically displayed herein.

[0112] In some embodiments, L^2 is $-(CR^{32}R^{33})_{1-3}-$. In some embodiments, L^2 is $-CR^{32}R^{33}-$. In some embodiments, L^2 is CH_2 . In some embodiments, L^2 is $CH(C_{1-4} \text{ alkyl})$. In some embodiments, L^2 is $CH(CH_3)$. In some embodiments, L^2 is $C(C_{1-4} \text{ alkyl})_2$. In some embodiments, L^2 is $C(CH_3)_2$. In some embodiments, L^2 is $-CR^{32}R^{33}-$, wherein R^{32} and R^{33} , together with the carbon atom they are attached to, form a 3-4 membered ring (*e.g.*, cyclopropyl).

[0113] In some embodiments, R^1 is OH. In some embodiments, R^1 is NH_2 . In some embodiments, R^1 is $NHCH_3$. In some embodiments, R^1 is $N(CH_3)_2$. In some embodiments, R^1 is hydrogen.

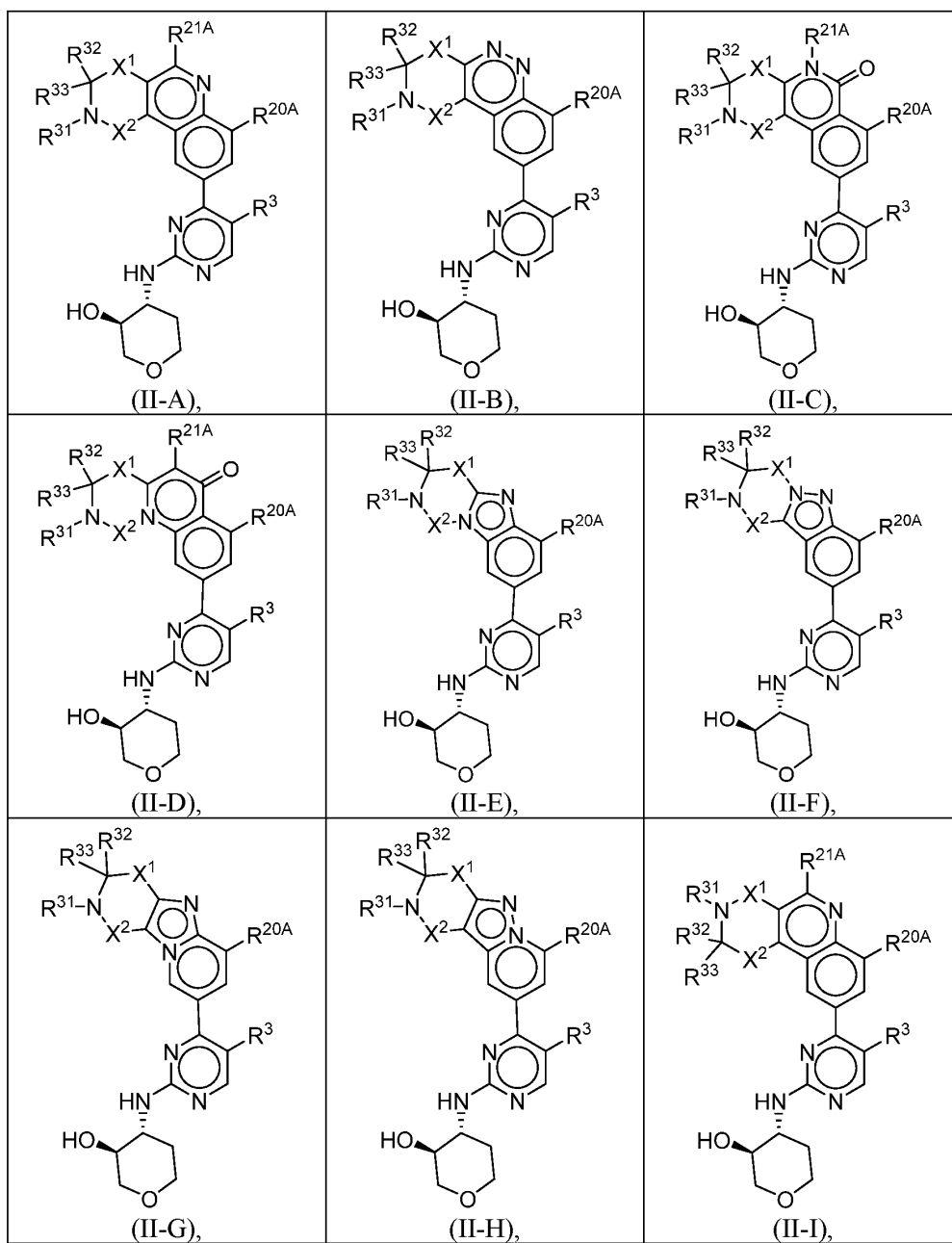
[0114] In some embodiments, X is N. In some embodiments, X is CR^{10} . In some embodiments, R^{10} is hydrogen (*i.e.*, X is CH). In some embodiments, R^{10} is halogen (*e.g.*, F), CN, or -OH.

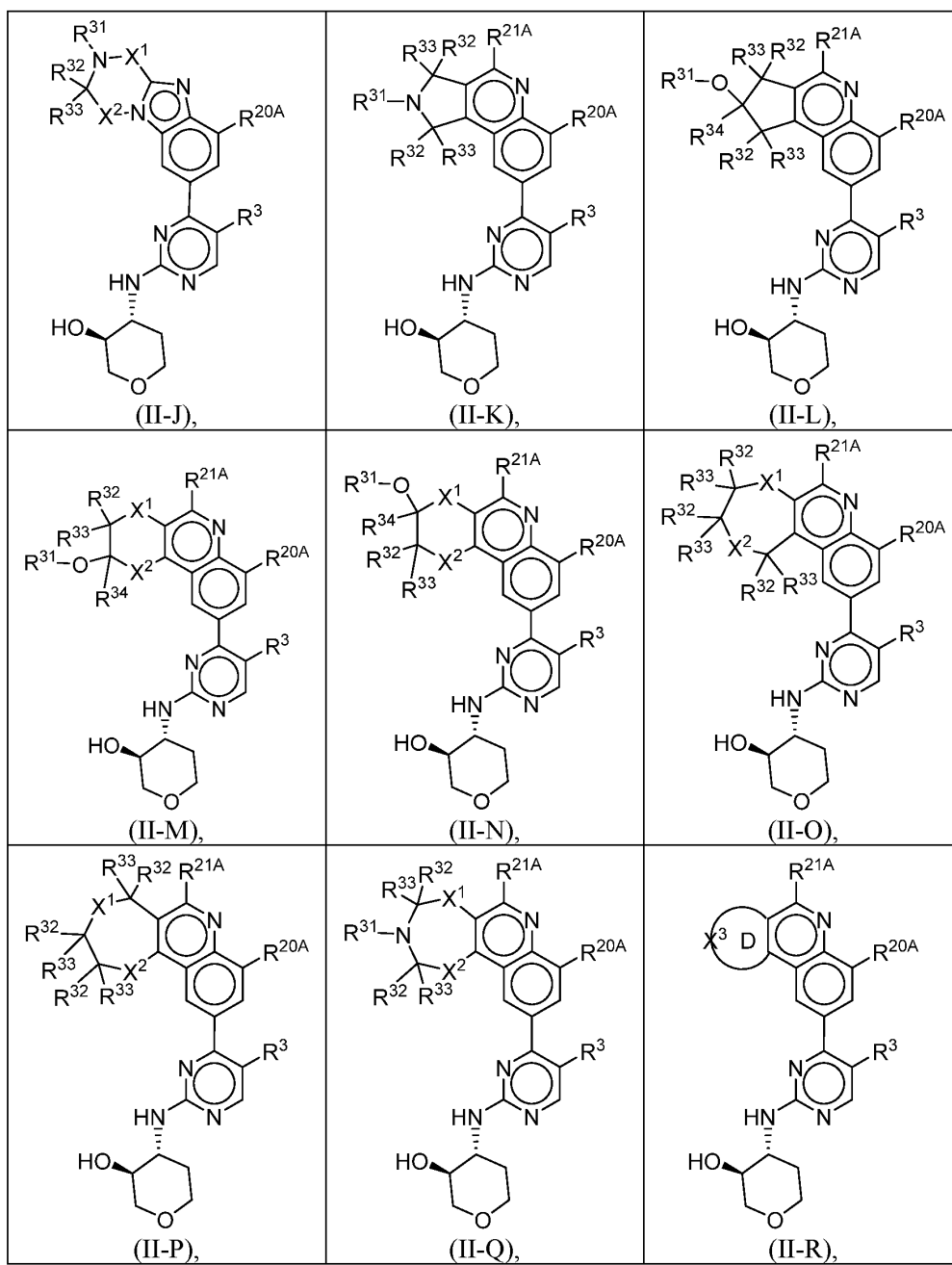
[0115] In some embodiments, J^1 is N. In some embodiments, J^1 is CR^{30} . In some embodiments, R^{30} is hydrogen (*i.e.*, J^1 is CH). In some embodiments, R^{30} is halogen (*e.g.*, F). In some embodiments, R^{30} is C_{1-4} alkyl (*e.g.*, methyl).

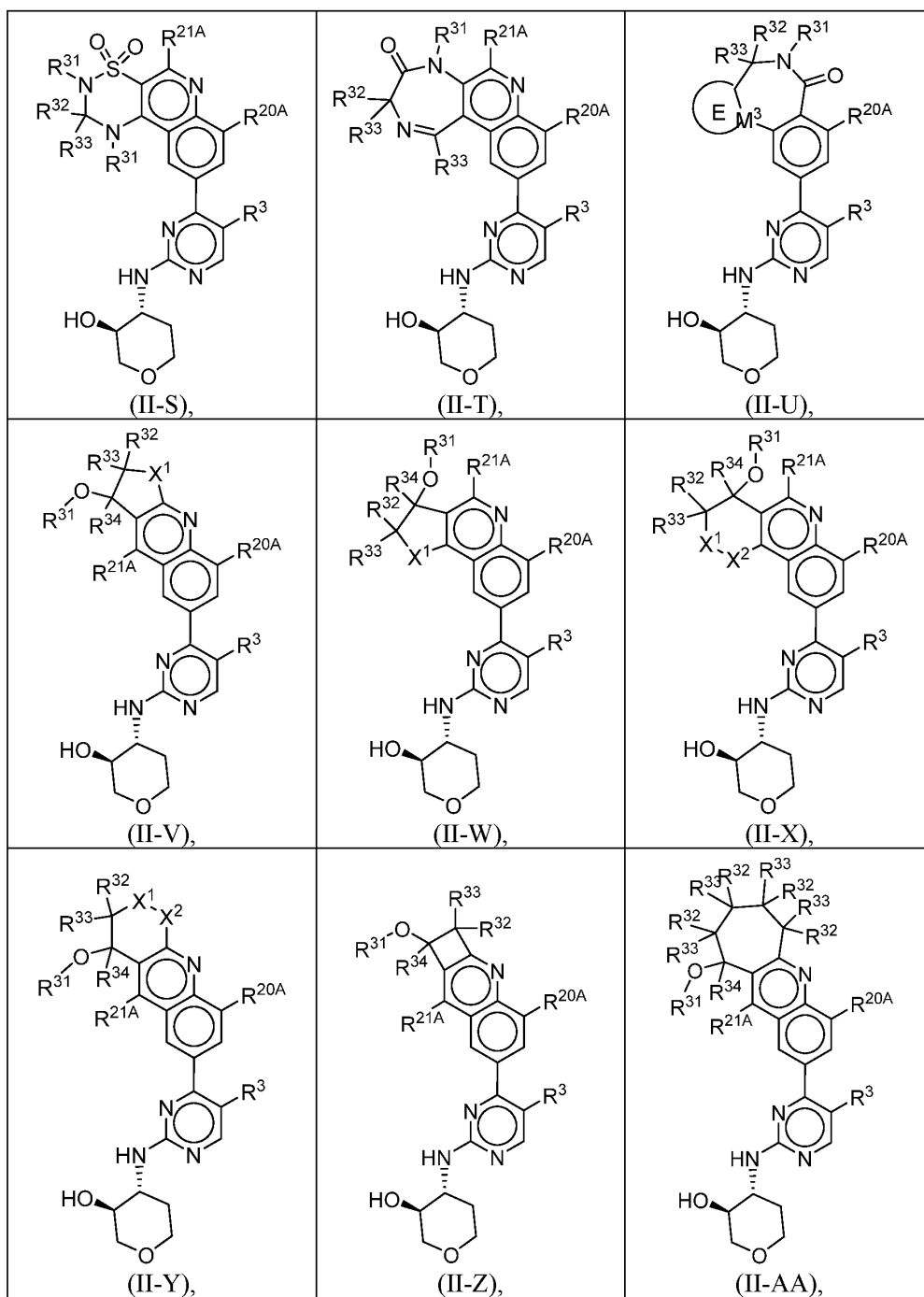
[0116] In some embodiments, J^2 is N. In some embodiments, J^2 is CR^{30} . In some embodiments, R^{30} is hydrogen (*i.e.*, J^2 is CH). In some embodiments, R^{30} is halogen (*e.g.*, F). In some embodiments, R^{30} is C_{1-4} alkyl (*e.g.*, methyl).

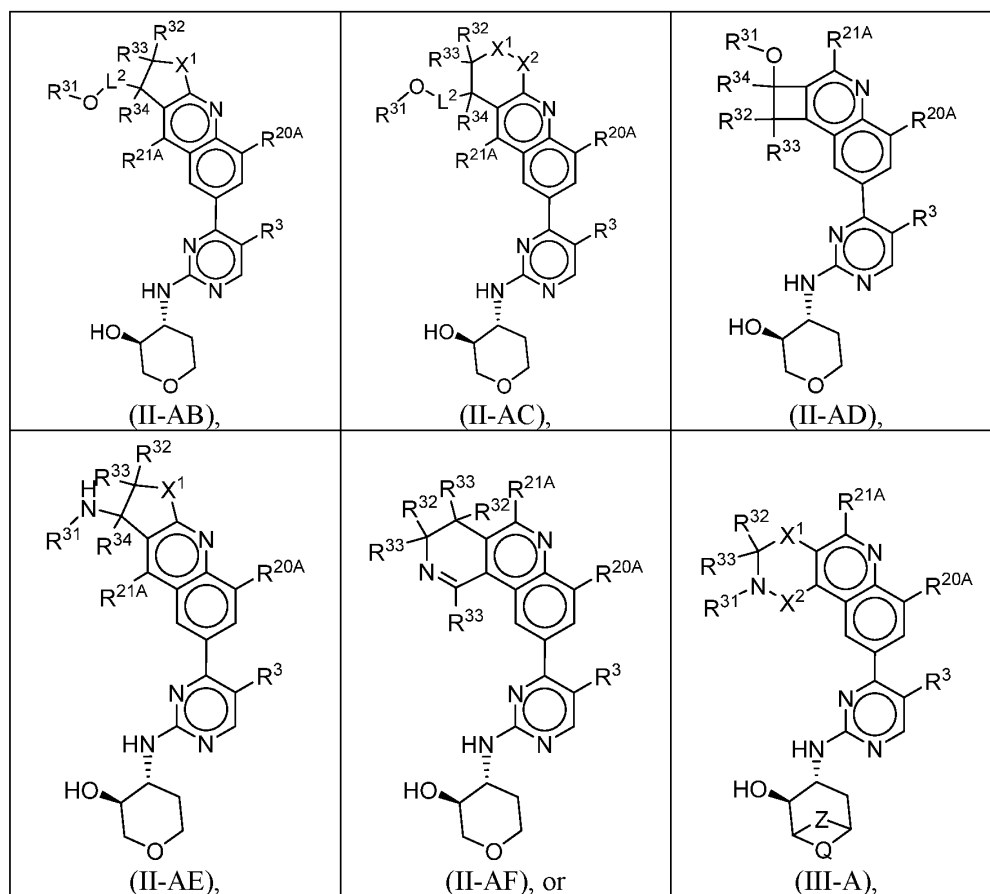
[0117] In some embodiments, J^1 is CR^{30} and J^2 is CR^{30} . In some embodiments, J^1 is CH and J^2 is CH. In some embodiments, J^1 and J^2 are not both N. In some embodiments, J^1 is N and J^2 is CR^{30} . In some embodiments, J^1 is CR^{30} and J^2 is N. In some embodiments, J^1 is N and J^2 is N.

[0118] In some embodiments, the compound is a compound of Formula (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), (II-H), (II-I), (II-J), (II-K), (II-L), (II-M), (II-N), (II-O), (II-P), (II-Q), (II-R), (II-S), (II-T), (II-U), (II-V), (II-W), (II-X), (II-Y), (II-Z), (II-AA), (II-AB), (II-AC), (II-AD), (II-AE), (II-AF), or (III-A):









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

[0119] In some embodiments, R^{20A} is hydrogen. In some embodiments, R^{20A} is halogen. In some embodiments, R^{20A} is F. In some embodiments, R^{20A} is Cl. In some embodiments, R^{20A} is CN. In some embodiments, R^{20A} is C_{1-4} alkyl optionally substituted with F. In some embodiments, R^{20A} is C_{1-4} alkyl. In some embodiments, R^{20A} is methyl. In some embodiments, R^{20A} is C_{1-4} heteroalkyl optionally substituted with F. In some embodiments, the C_{1-4} heteroalkyl has 1 or 2 heteroatoms independently N or O. In some embodiments, R^{20A} is an optionally substituted 3-6 membered ring structure (*e.g.*, cyclopropyl, cyclobutyl, 4-6 membered heterocyclic ring, or 5 membered heteroaryl). In some embodiments, R^{20A} is hydrogen, halogen (*e.g.*, F or Cl), or C_{1-4} alkyl (*e.g.*, methyl or ethyl).

[0120] In some embodiments, R^{21A} is hydrogen. In some embodiments, R^{21A} is deuterium. In some embodiments, R^{21A} is halogen. In some embodiments, R^{21A} is F. In some embodiments, R^{21A} is Cl. In some embodiments, R^{21A} is CN. In some embodiments, R^{21A} is OH.

In some embodiments, R^{21A} is C_{1-4} alkyl optionally substituted with F. In some embodiments, R^{21A} is C_{1-4} alkyl. In some embodiments, R^{21A} is methyl. In some embodiments, R^{21A} is ethyl. In some embodiments, R^{21A} is n-propyl. In some embodiments, R^{21A} is isopropyl. In some embodiments, R^{21A} is C_{1-4} heteroalkyl optionally substituted with F. In some embodiments, the C_{1-4} heteroalkyl has 1 or 2 heteroatoms independently N or O. In some embodiments, R^{21A} is C_{1-4} alkoxy optionally substituted with F. In some embodiments, R^{21A} is an optionally substituted 3-6 membered ring structure (*e.g.*, cyclopropyl, cyclobutyl, 4-6 membered heterocyclic ring, or 5 membered heteroaryl). In some embodiments, R^{21A} is cyclopropyl. In some embodiments, R^{21A} is hydrogen, halogen (*e.g.*, F or Cl), or C_{1-4} alkyl (*e.g.*, methyl or ethyl). In some embodiments, R^{21A} is hydrogen, deuterium, or methyl.

[0121] In some embodiments, X^1 is O. In some embodiments, X^1 is NR^{31} . In some embodiments, X^1 is $CR^{32}R^{33}$. In some embodiments, X^1 is C=O.

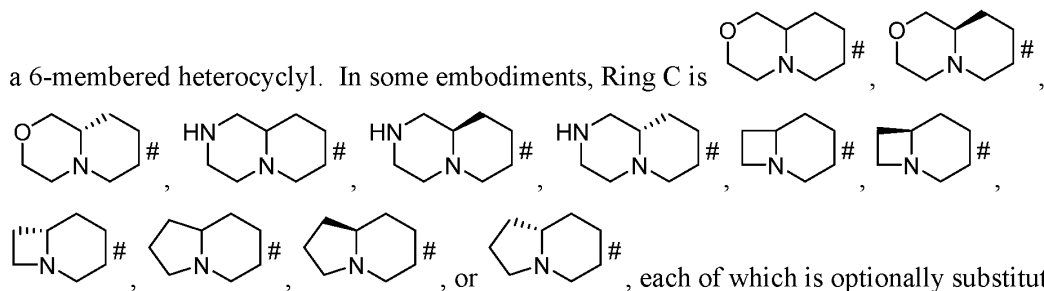
[0122] In some embodiments, X^2 is O. In some embodiments, X^2 is NR^{31} . In some embodiments, X^2 is $CR^{32}R^{33}$. In some embodiments, X^2 is C=O.

[0123] In some embodiments, R^{31} is hydrogen. In some embodiments, R^{31} is C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, R^{31} is methyl. In some embodiments, R^{31} is CF_3 . In some embodiments, R^{31} is CD_3 . In some embodiments, R^{31} is optionally substituted C_{3-6} carbocyclyl (*e.g.*, C_{3-6} cycloalkyl, *e.g.*, cyclopropyl). In some embodiments, R^{31} is optionally substituted phenyl. In some embodiments, R^{31} is optionally substituted 4-6 membered heterocyclyl (*e.g.*, oxetanyl). In some embodiments, R^{31} is optionally substituted 5- or 6-membered heteroaryl. In some embodiments, R^{31} is $SO_2(C_{1-4}$ alkyl). In some embodiments, R^{31} is SO_2Me .

[0124] In some embodiments, R^{31} at each occurrence is independently hydrogen or C_{1-4} alkyl. In some embodiments, R^{31} at each occurrence is independently hydrogen or methyl. In some embodiments, the R^{31} on the nitrogen that is not X^1 or X^2 is hydrogen. In some embodiments, the R^{31} on the nitrogen that is X^1 or X^2 is hydrogen. In some embodiments, the R^{31} on the nitrogen that is X^1 or X^2 is C_{1-3} alkyl (*e.g.*, methyl).

[0125] In some embodiments, a R^{31} and an adjacent R^{32} are joined together with the intervening atom(s) to form an optionally substituted 3-7 membered ring. In this situation, Ring C becomes a fused bicyclic ring. In some embodiments, the ring is a 4-membered heterocyclyl. In some embodiments, the ring is a 5-membered heterocyclyl. In some embodiments, the ring is

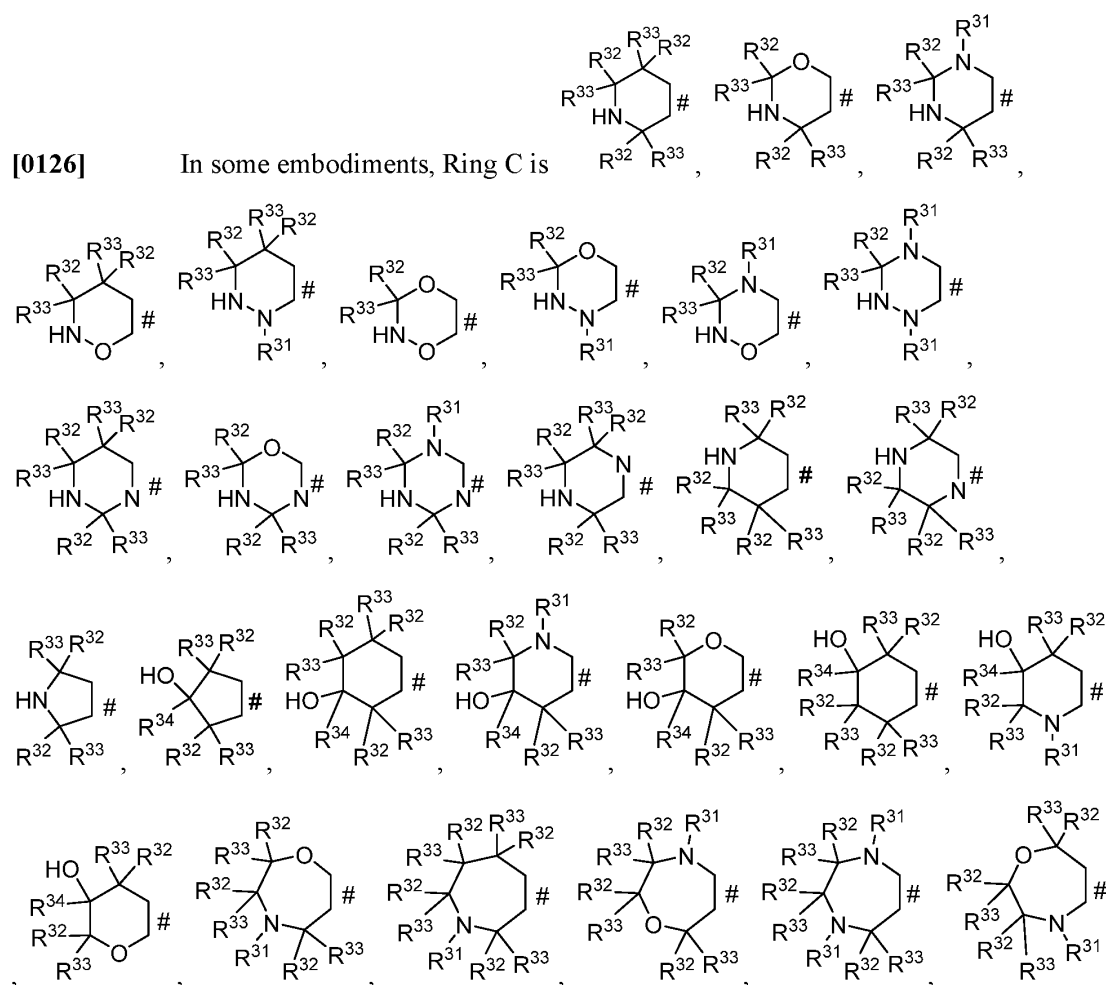
a 6-membered heterocyclyl. In some embodiments, Ring C is

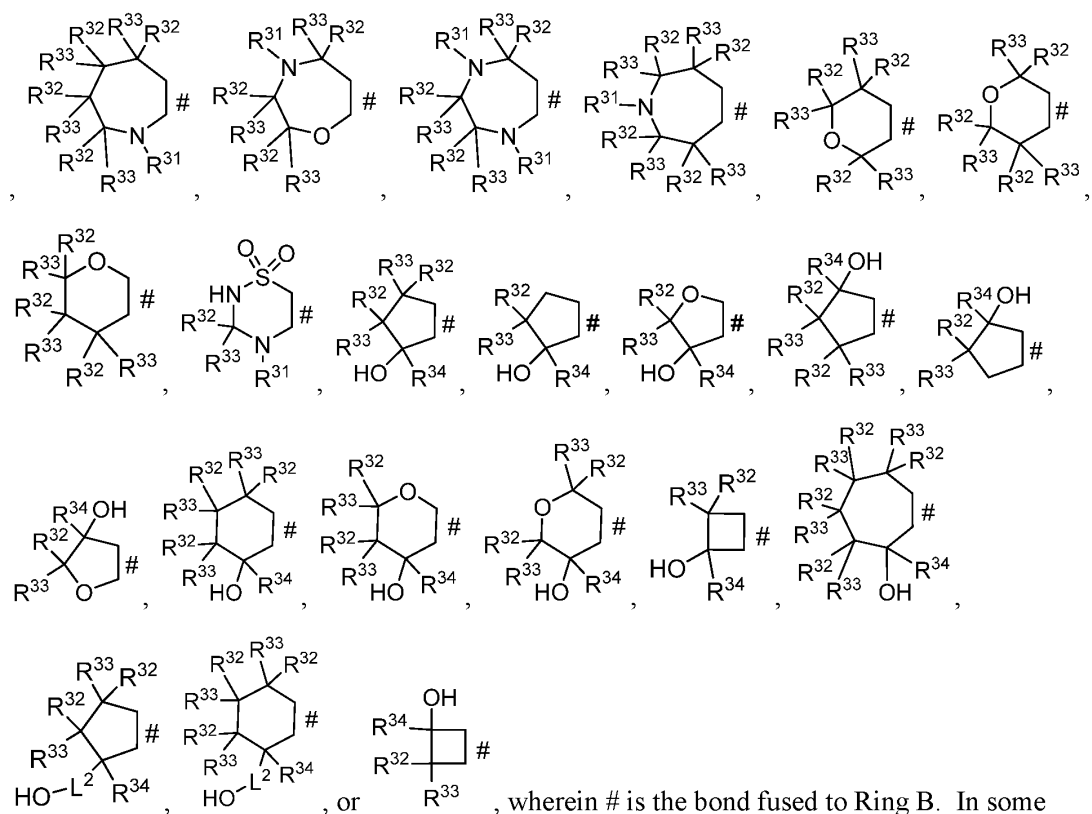


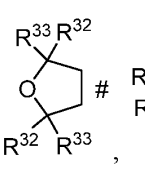
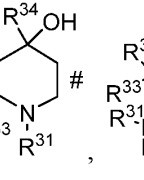
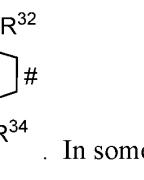
, each of which is optionally substituted (e.g., with one or more (e.g., 1, 2, or 3) substituents each of which is independently oxo, halo, OH, NH₂, C₁₋₄ alkyl optionally substituted with one or more (e.g., 1, 2, or 3) deuterium or F, or C₁₋₄ heteroalkyl optionally substituted with one or more (e.g., 1, 2, or 3) deuterium or F).

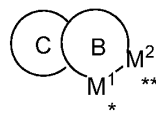
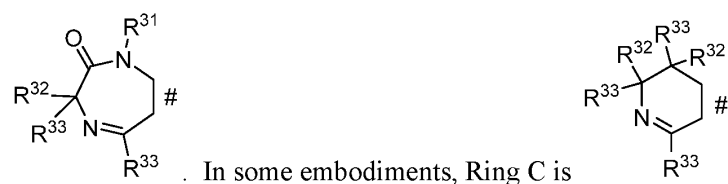
[0126]

In some embodiments, Ring C is

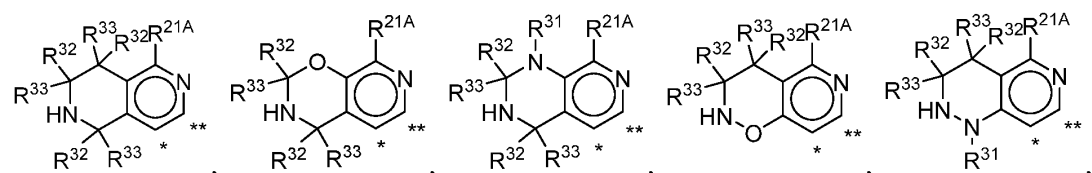


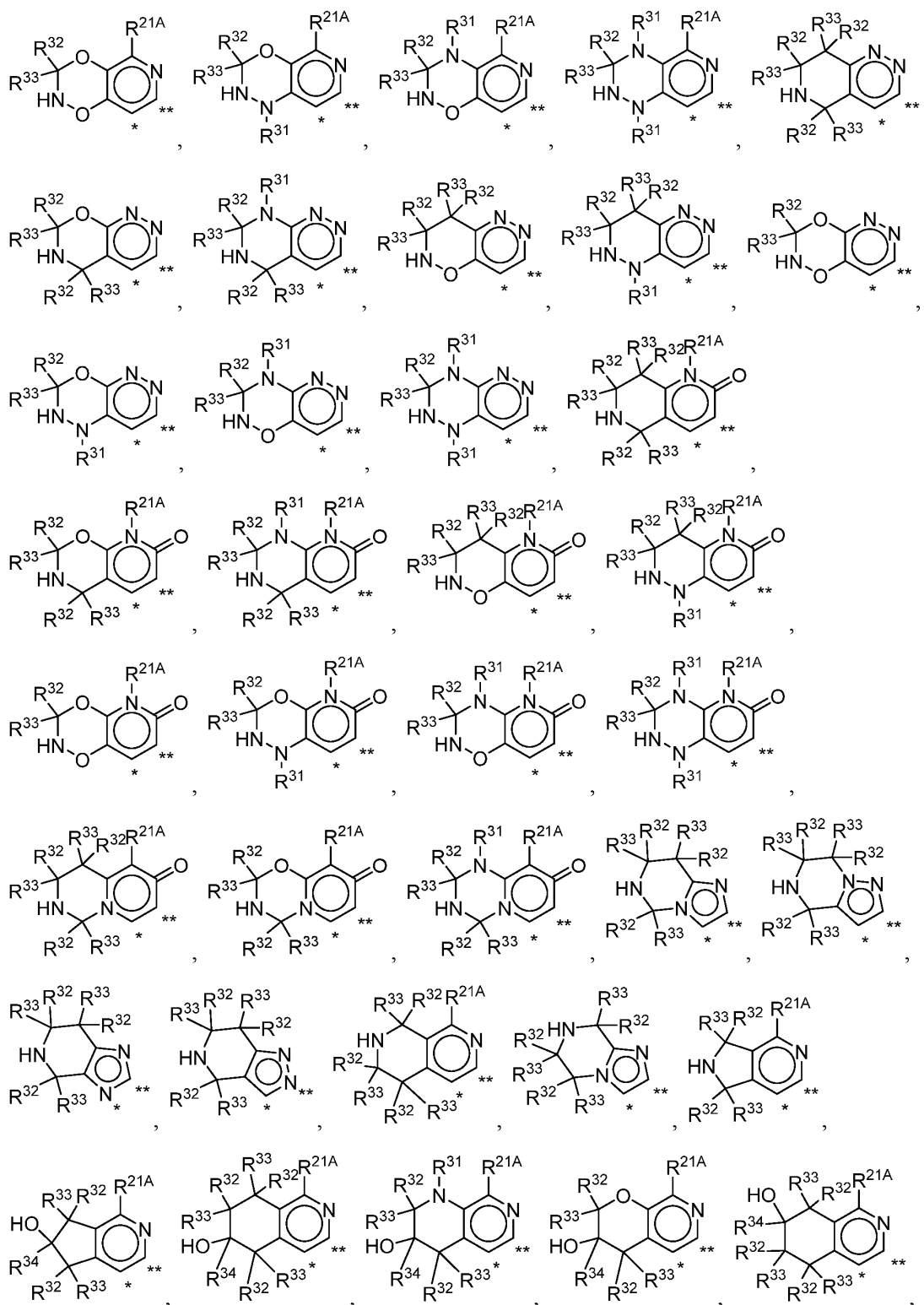


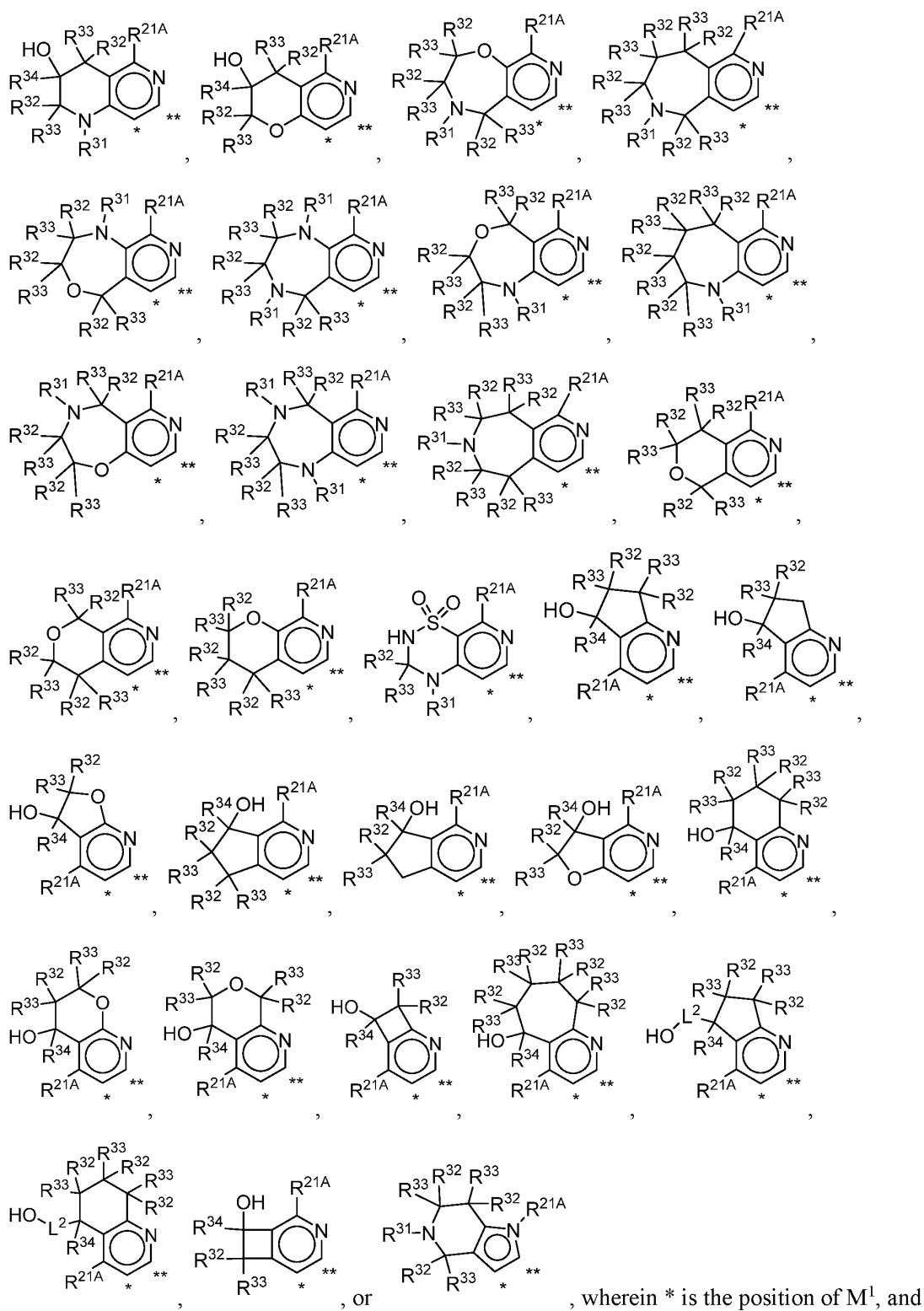
embodiments, Ring C is , , . In some embodiments, Ring C is

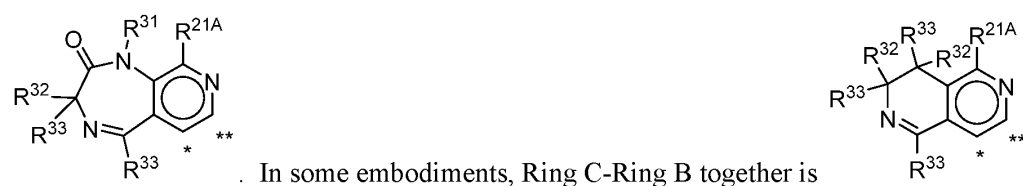
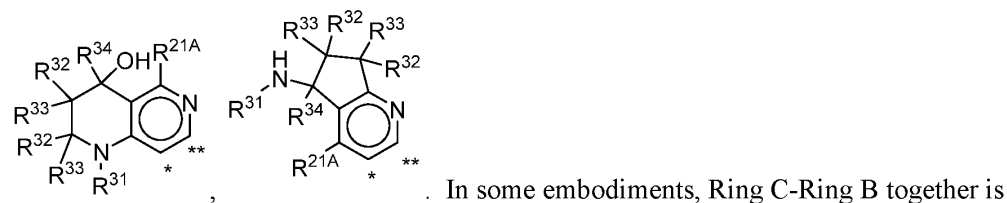
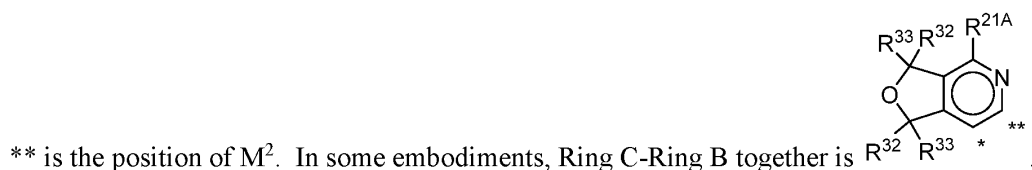


[0127] In some embodiments, Ring C-Ring B together, *i.e.*, , is









[0128] In some embodiments, when a ring carbon atom of Ring C is substituted with a hydroxy, an adjacent ring carbon atom of Ring C is substituted with non-hydrogen R^{32} (*e.g.*, C_{1-4} alkyl, *e.g.*, methyl), and non-hydrogen R^{33} (*e.g.*, C_{1-4} alkyl, *e.g.*, methyl, ethyl, or isopropyl). In some embodiments, when a ring carbon atom of Ring C is substituted with a hydroxy, R^{21A} is not hydrogen (*e.g.*, R^{21A} is C_{1-4} alkyl, *e.g.*, methyl, ethyl, or isopropyl).

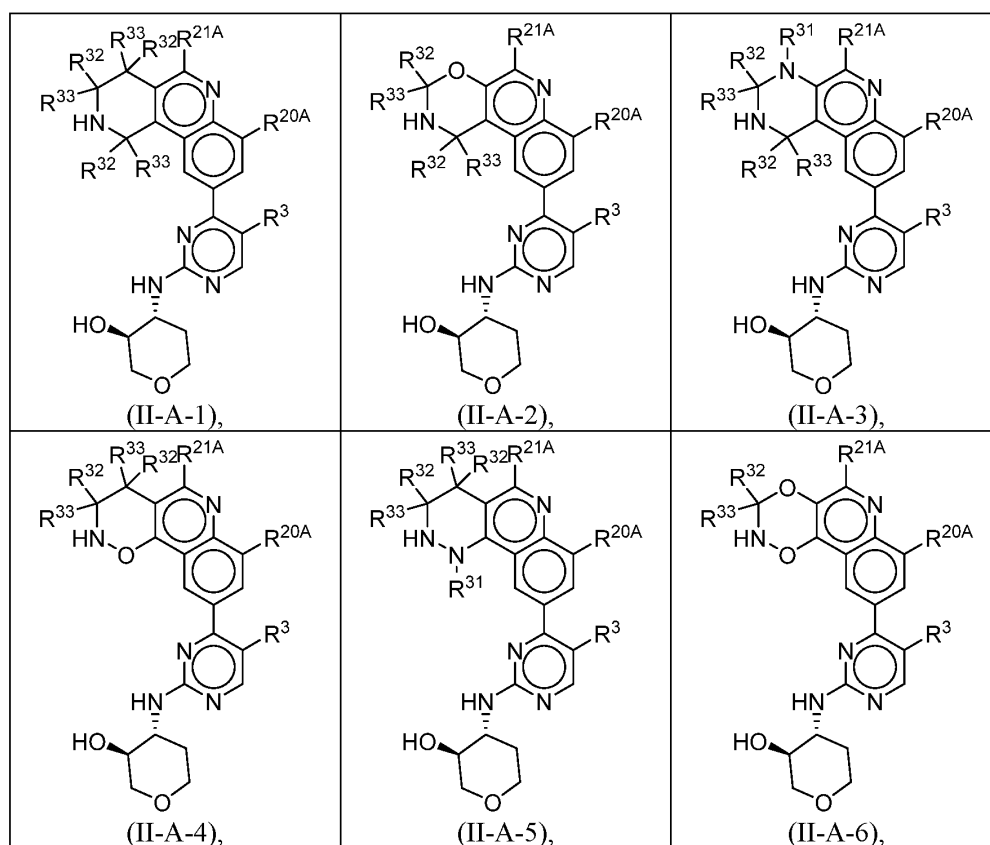
[0129] In some embodiments, Ring D is an optionally substituted 5-membered ring (*e.g.*, 5-membered heterocyclyl). In some embodiments, Ring D is an optionally substituted 6-membered ring (*e.g.*, 6-membered heterocyclyl).

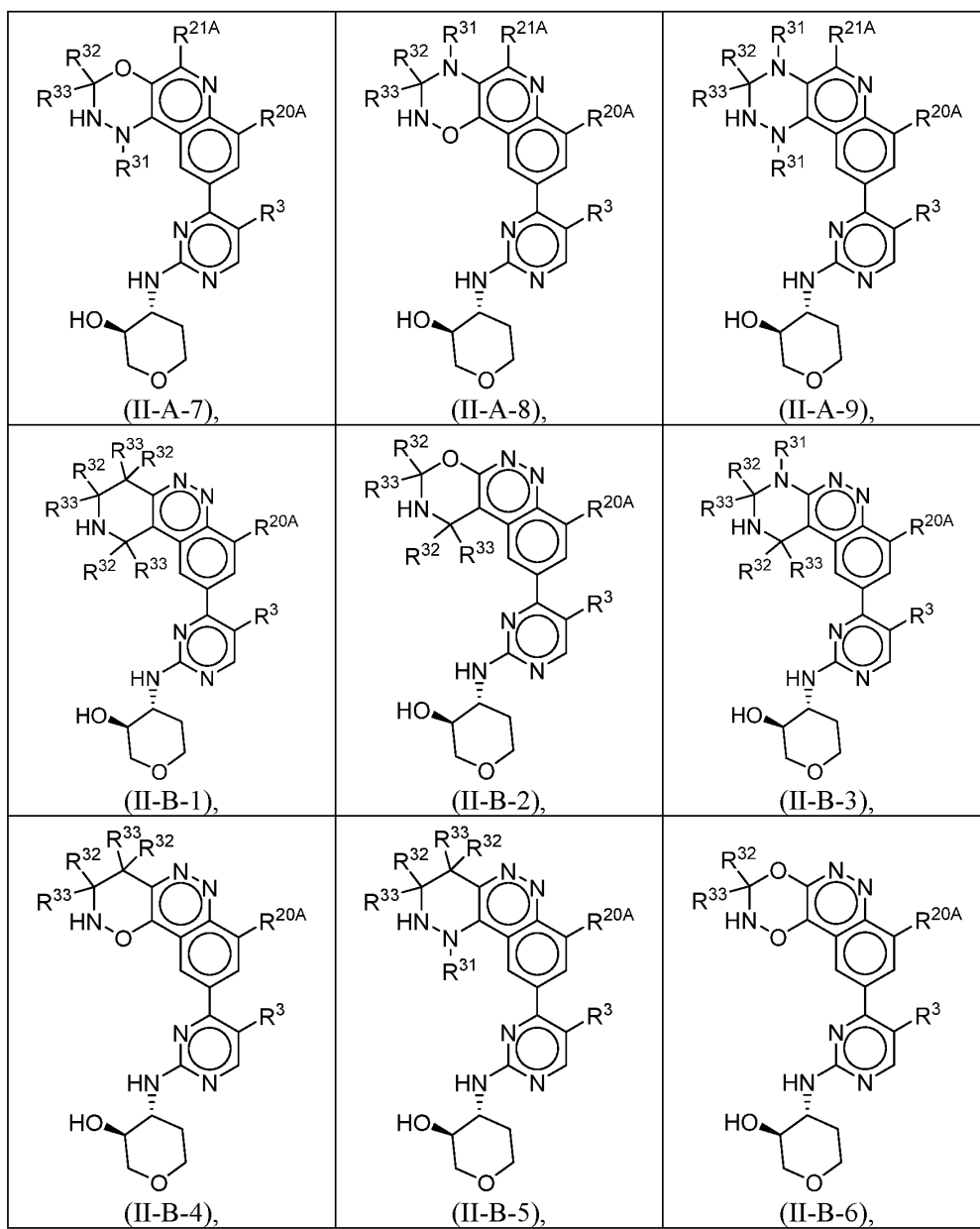
[0130] In some embodiments, X^3 is -O-. In some embodiments, X^3 is -S(O)-. In some embodiments, X^3 is -S(O)₂-. In some embodiments, X^3 is -S(O)₂-NR³¹-. In some embodiments, X^3 is -NR³¹-S(O)₂-. In some embodiments, X^3 is -S(O)(NH)-. In some embodiments, X^3 is -P(O)(R³⁴)-. In some embodiments, X^3 is -P(O)(R³⁴)-NR³¹-. In some embodiments, X^3 is -NR³¹-P(O)(R³⁴)-. Unless otherwise specified, the left side of the X^3 group provided here is to the direction that is further away from M^1 , and the right side of the X^3 group provided here is to the direction that is closer to M^1 .

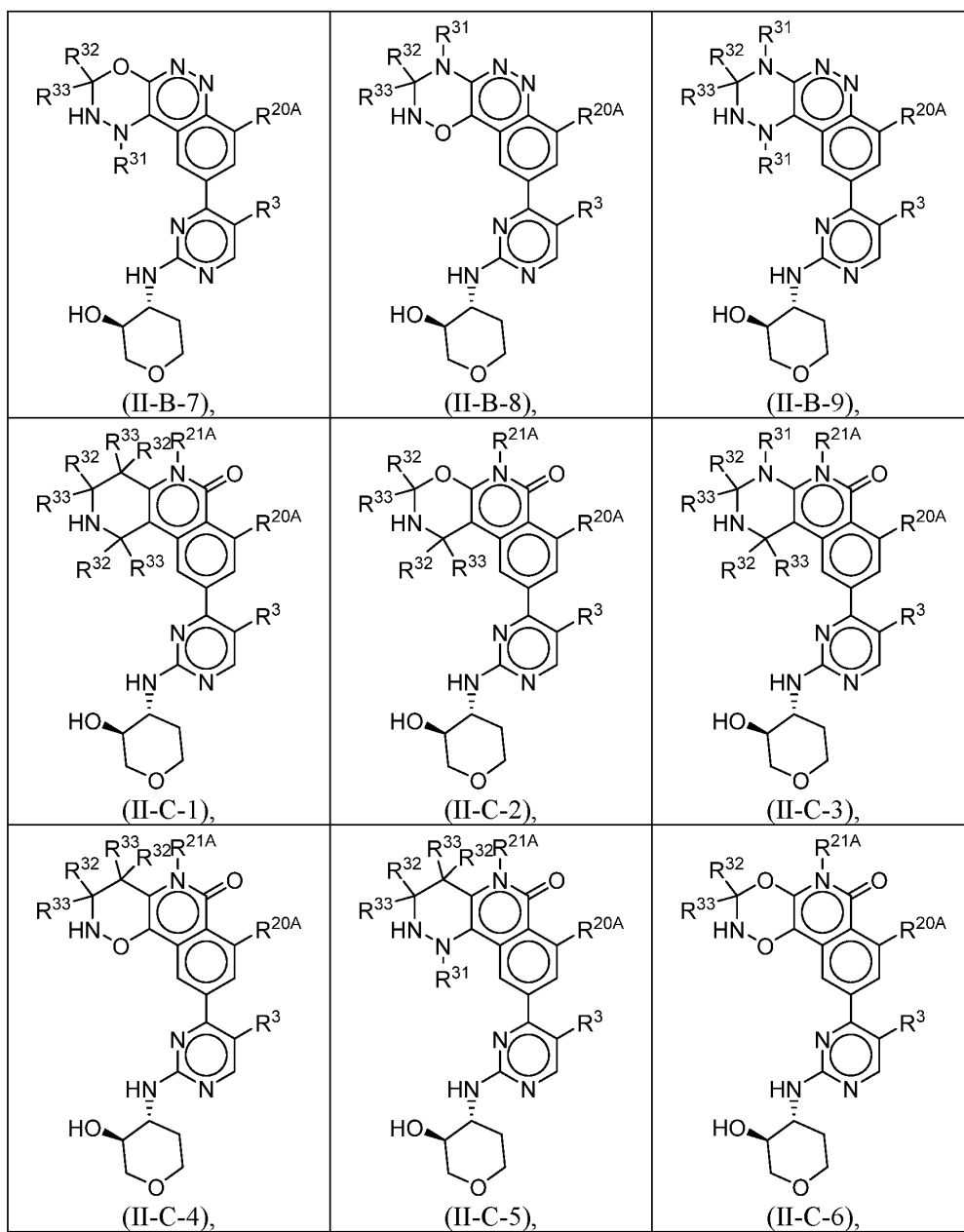
[0131] In some embodiments, M^3 is C. In some embodiments, M^3 is N.

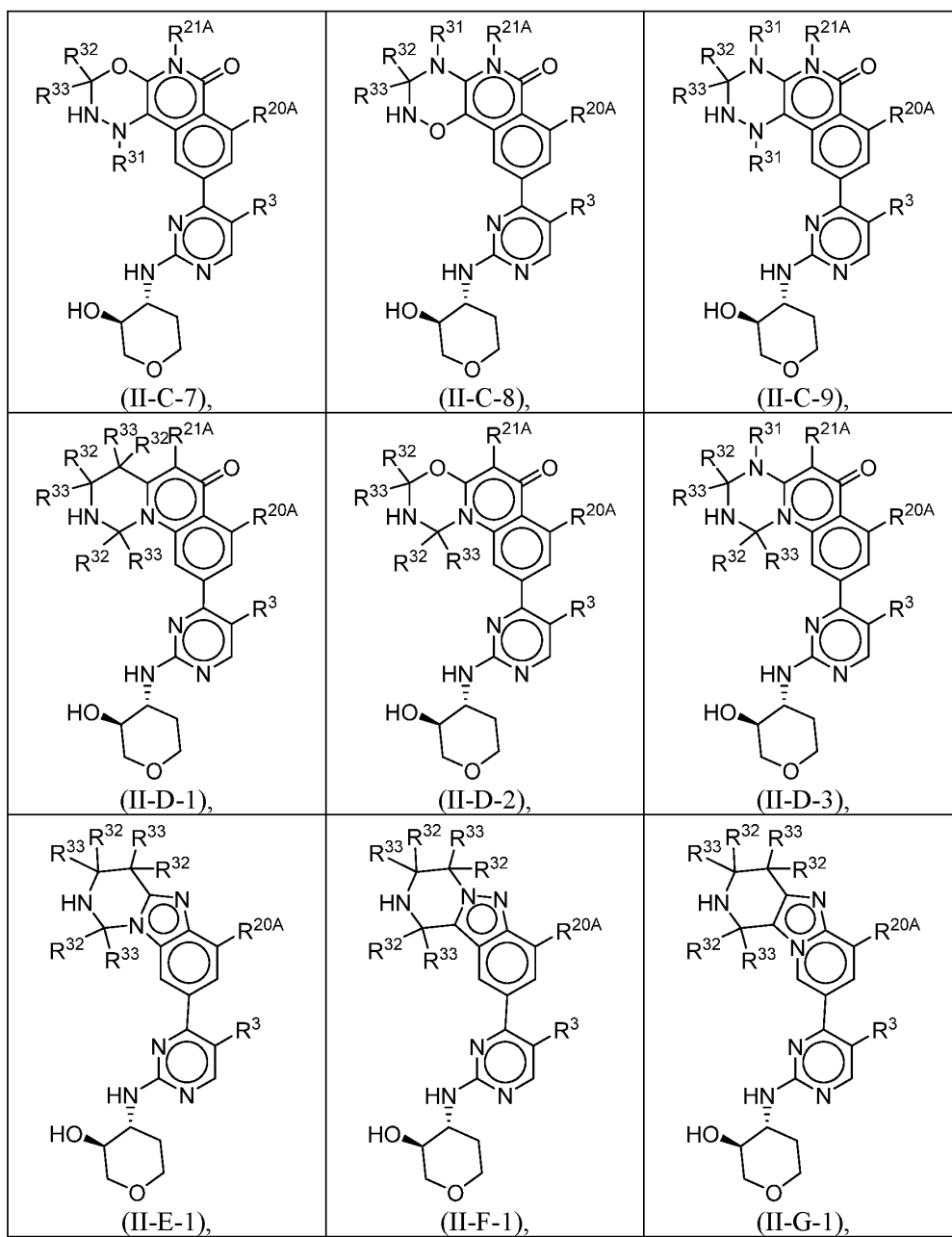
[0132] In some embodiments, Ring E is optionally substituted phenyl. In some embodiments, Ring E is optionally substituted 5-membered heteroaryl (*e.g.*, imidazolyl or pyrazolyl). In some embodiments, Ring E is optionally substituted 6-membered heteroaryl (*e.g.*, pyridinyl or pyrimidinyl).

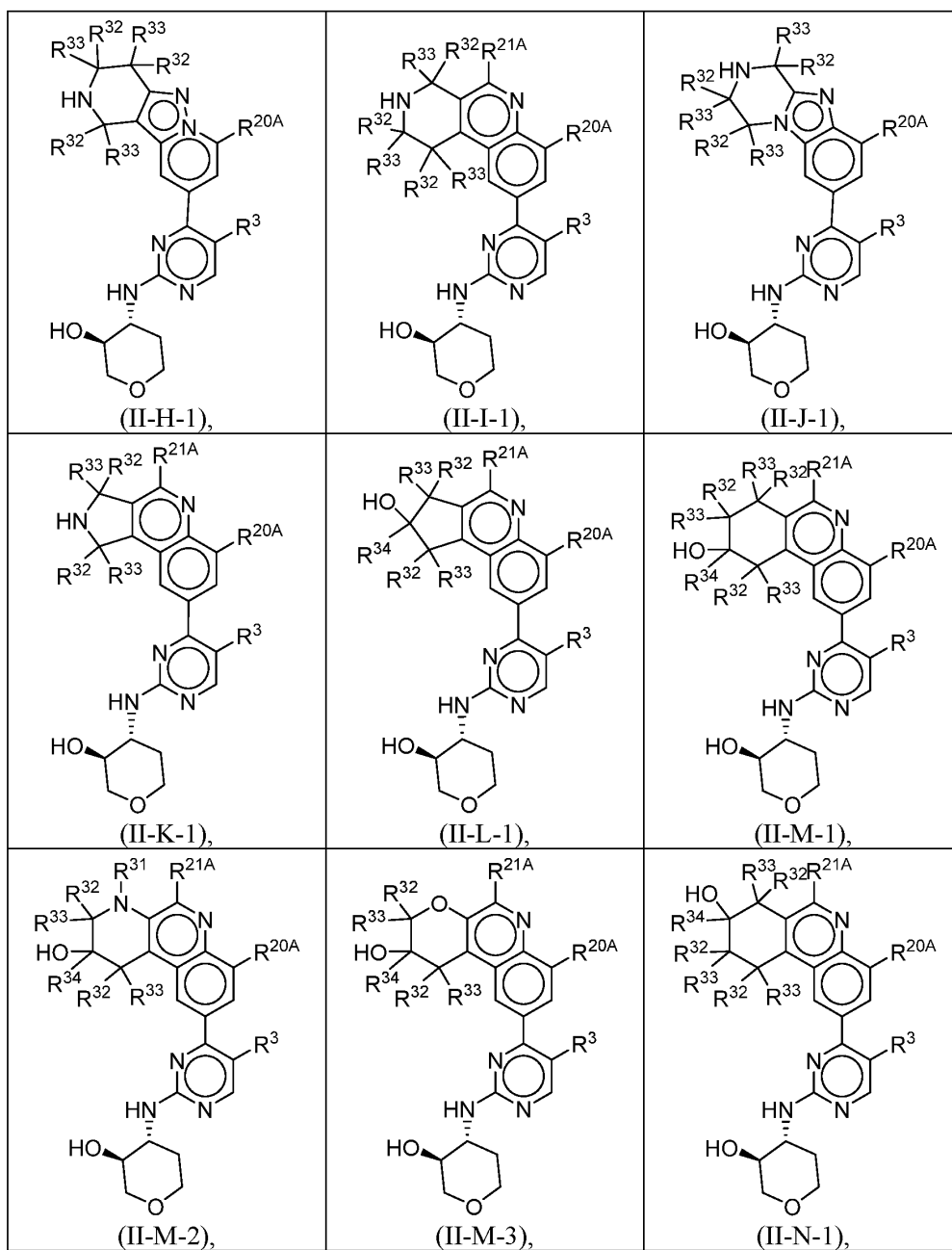
[0133] In some embodiments, the compound is a compound of Formula (II-A-1), (II-A-2), (II-A-3), (II-A-4), (II-A-5), (II-A-6), (II-A-7), (II-A-8), (II-A-9), (II-B-1), (II-B-2), (II-B-3), (II-B-4), (II-B-5), (II-B-6), (II-B-7), (II-B-8), (II-B-9), (II-C-1), (II-C-2), (II-C-3), (II-C-4), (II-C-5), (II-C-6), (II-C-7), (II-C-8), (II-C-9), (II-D-1), (II-D-2), (II-D-3), (II-E-1), (II-F-1), (II-G-1), (II-H-1), (II-I-1), (II-J-1), (II-K-1), (II-L-1), (II-M-1), (II-M-2), (II-M-3), (II-N-1), (II-N-2), (II-N-3), (II-O-1), (II-O-2), (II-O-3), (II-O-4), (II-P-1), (II-P-2), (II-P-3), (II-P-4), (II-Q-1), (II-R-1), (II-R-2), (II-R-3), (II-R-4), (II-R-5), (II-R-6), (II-R-7), (II-R-8), (II-R-9), (II-R-10), (II-S-1), (II-U-1), (II-U-2), (II-U-3), (II-U-4), (II-U-5), (II-U-6), (II-U-7), (II-V-1), (II-V-2), (II-V-3), (II-W-1), (II-W-2), (II-W-3), (II-X-1), (II-X-2), (II-X-3), (II-X-4), (II-Y-1), (II-Y-2), (II-Y-3), (II-Z-1), (II-AA-1), (II-AB-1), (II-AC-1), (II-AD-1), (II-AE-1), or (III-A-1):

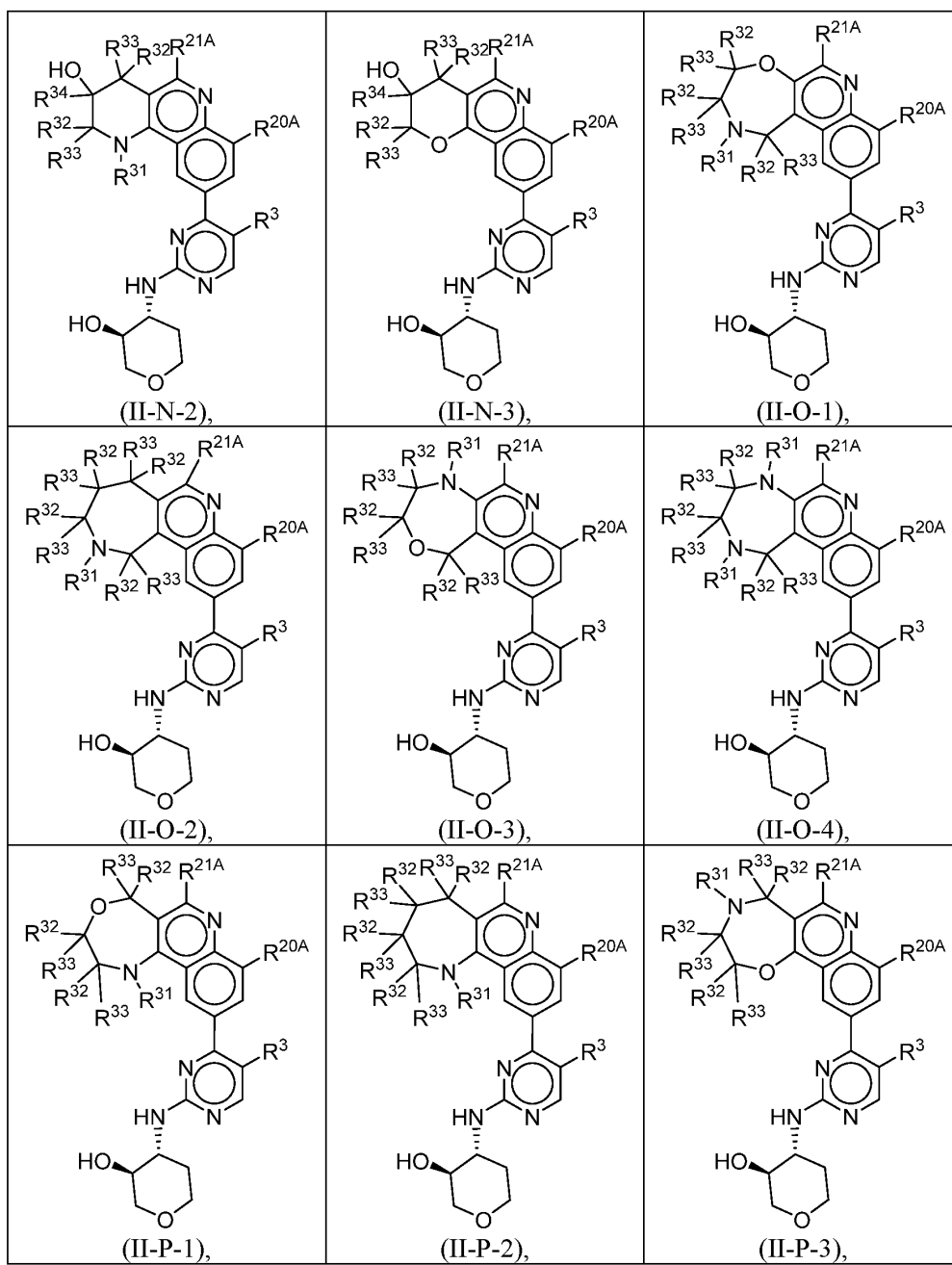


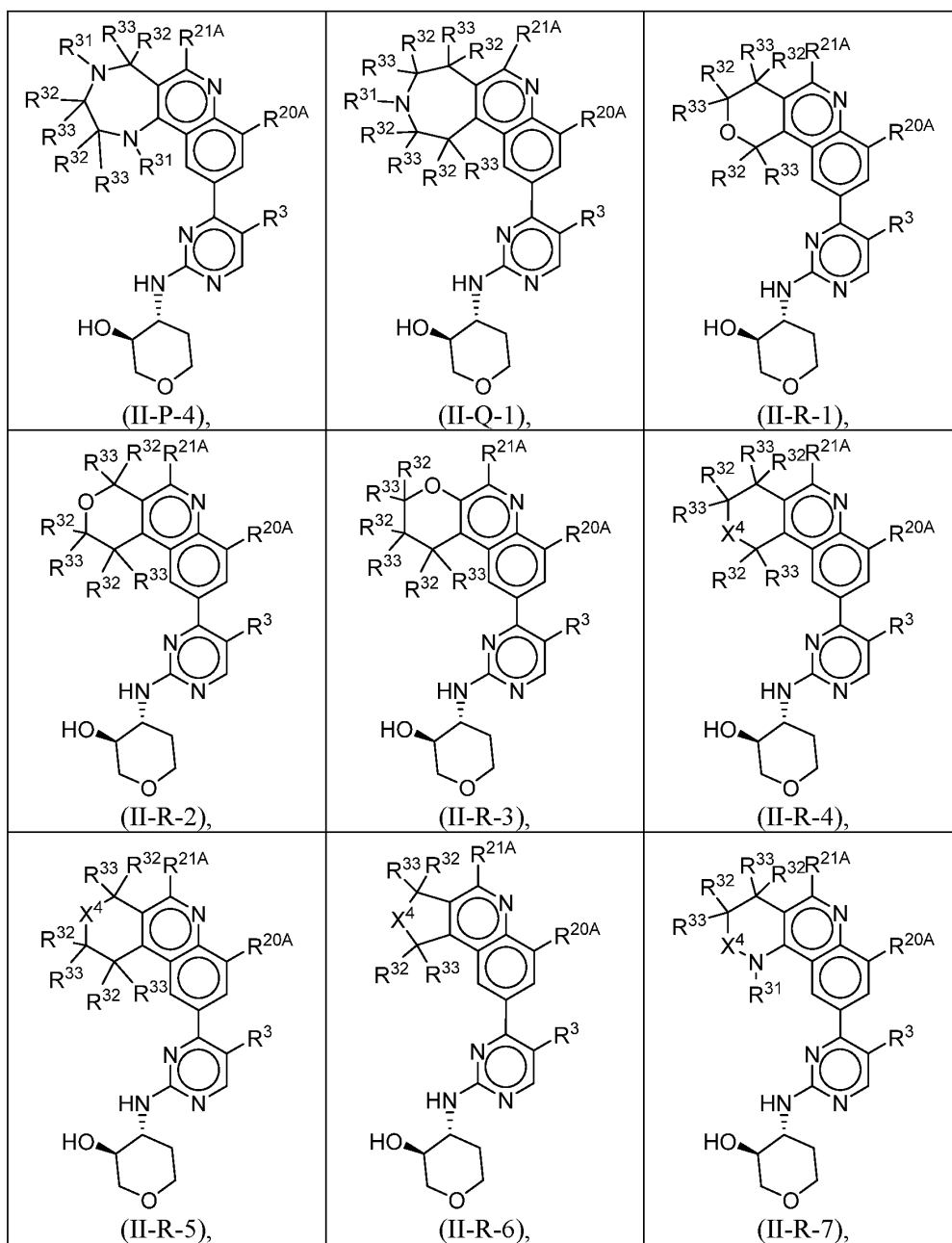


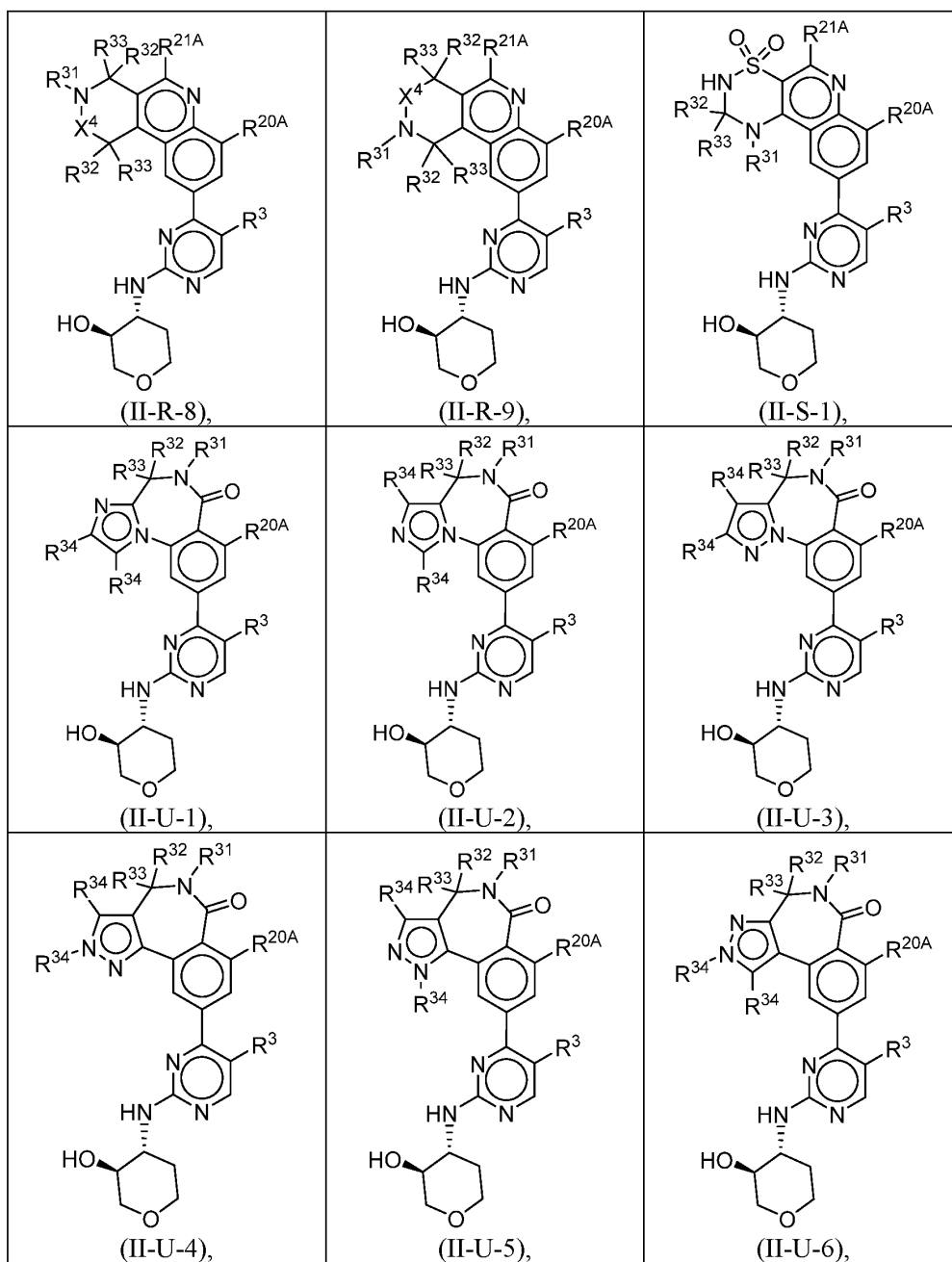


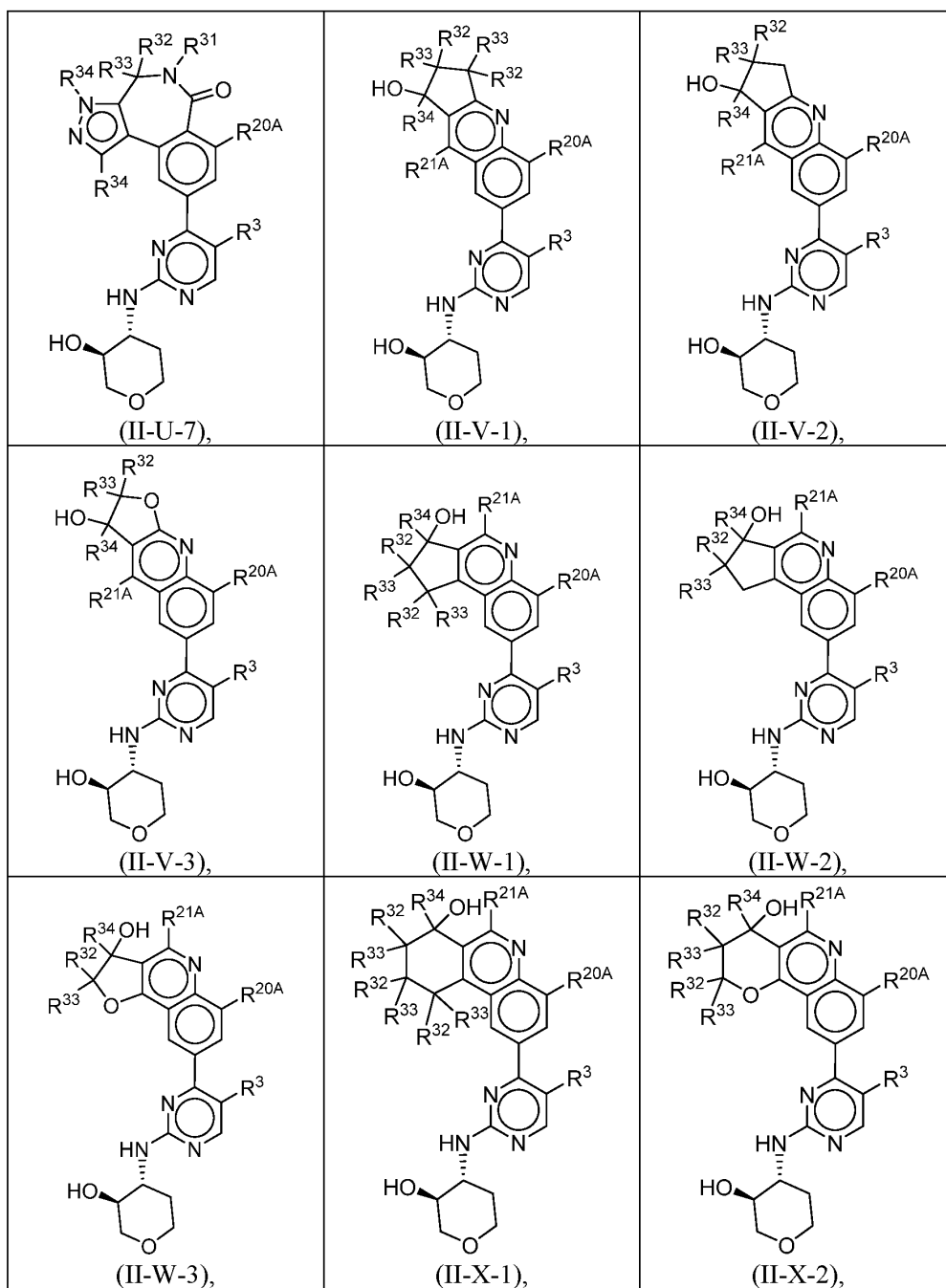


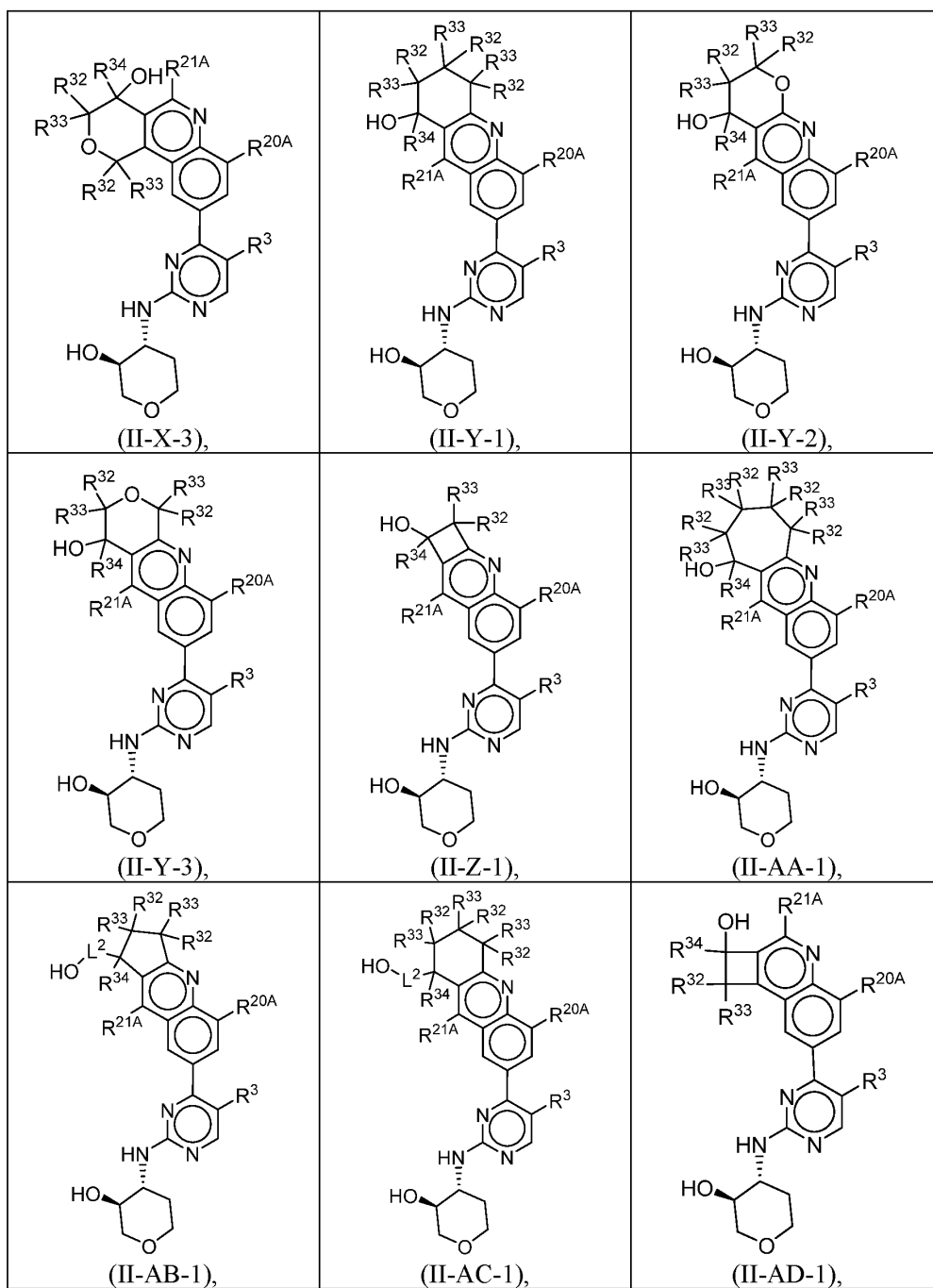


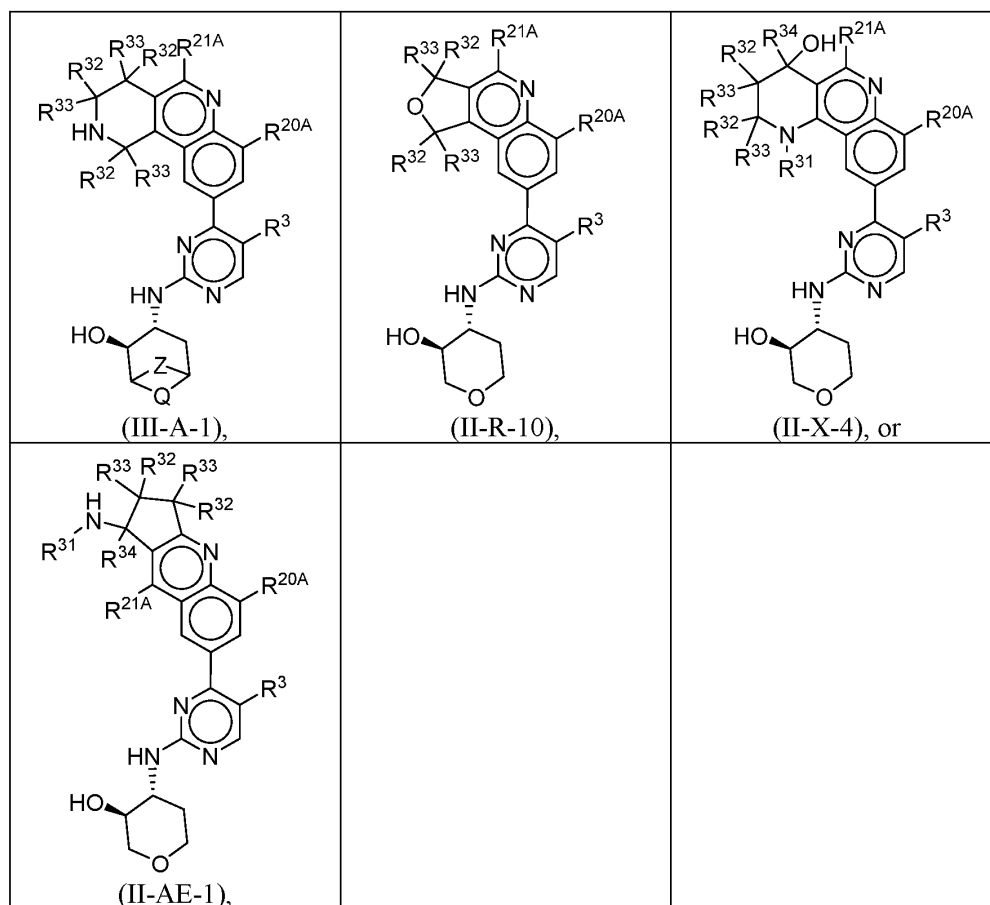












or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein:

X^4 is $-S(O)-$, $-S(O)_2-$, $-S(O)(NH)-$, or $-P(O)(R^{34})-$.

[0134] In some embodiments, X^4 is $-S(O)-$. In some embodiments, X^4 is $-S(O)_2-$. In some embodiments, X^4 is $-S(O)(NH)-$. In some embodiments, X^4 is $-P(O)(R^{34})-$.

[0135] In some embodiments, when a ring carbon atom of Ring C is substituted with a hydroxy (*e.g.*, Formula (II-V-1), (II-V-2), (II-V-3), (II-W-1), (II-W-2), (II-W-3), (II-X-1), (II-X-2), (II-X-3), (II-X-4), (II-Y-1), (II-Y-2), (II-Y-3), (II-Z-1), or (II-AA-1)), the R^{32} and R^{33} on the adjacent ring carbon atom of Ring C are both not hydrogen (*e.g.*, said R^{32} and R^{33} are independently C_{1-4} alkyl, *e.g.*, methyl, ethyl, or isopropyl). In some embodiments, when a ring carbon atom of Ring C is substituted with a hydroxy (*e.g.*, Formula (II-V-1), (II-V-2), (II-V-3), (II-W-1), (II-W-2), (II-W-3), (II-X-1), (II-X-2), (II-X-3), (II-X-4), (II-Y-1), (II-Y-2), (II-Y-3), (II-Z-1), or (II-AA-1)), R^{21A} is not hydrogen (*e.g.*, R^{21A} is C_{1-4} alkyl, *e.g.*, methyl, ethyl, or isopropyl).

[0136] In some embodiments, each of R^{32} and R^{33} at each occurrence is independently (1) hydrogen or deuterium; (2) halogen (*e.g.*, F or Cl) or cyano; (3) OH, NH_2 , $NH(C_{1-4} \text{ alkyl})$, or $N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$; (4) C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each of which is independently deuterium, F, OH, NH_2 , $NH(C_{1-4} \text{ alkyl})$, $N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, $NH(C_{3-6} \text{ cycloalkyl})$, $N(C_{1-4} \text{ alkyl})(C_{3-6} \text{ cycloalkyl})$, $N(C_{3-6} \text{ cycloalkyl})(C_{3-6} \text{ cycloalkyl})$, or $SO_2(C_{1-4} \text{ alkyl})$; (5) C_{1-4} alkoxy optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F; (6) an optionally substituted C_{3-6} carbocyclyl (*e.g.*, C_{3-6} cycloalkyl, *e.g.*, cyclopropyl or cyclobutyl), optionally substituted phenyl, optionally substituted 4-6 membered heterocyclyl, or optionally substituted 5- or 6-membered heteroaryl; (7) R^{32} and R^{33} , together with the carbon atom they are attached to, form a carbonyl (CO); or (8) R^{32} and R^{33} , together with the carbon atom they are attached to, form a C_{3-6} carbocyclyl (*e.g.*, C_{3-6} cycloalkyl, *e.g.*, cyclopropyl or cyclobutyl) or 4-6 membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each of which is independently oxo, halo, OH, NH_2 , C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, two R^{32} are joined together with the intervening atom(s) to form an optionally substituted 3-7 membered ring. In some embodiments, the ring (formed by the two R^{32} together with the intervening atoms) is a 4-6 membered heterocyclyl (including the nitrogen that is not X^1 or X^2). In some embodiments, the ring is unsubstituted (not counting the R^{31} on the nitrogen that is not X^1 or X^2). In some embodiments, the ring is substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, halogen, CN, OH, or C_{1-3} alkyl (*e.g.*, methyl) (not counting the R^{31} on the nitrogen that is not X^1 or X^2).

[0137] In some embodiments, R^{32} at each occurrence is independently hydrogen, halogen, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} alkoxy optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, and R^{33} at each occurrence is independently hydrogen, halogen, or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, R^{32} at each occurrence is independently hydrogen or methyl, and R^{33} at each occurrence is independently hydrogen or methyl. In some embodiments, R^{32} and R^{33} together with the carbon atom they are attached to form a carbonyl (CO). In some embodiments, R^{32} and R^{33} together with the carbon atom they are attached to form a C_{3-6} carbocyclyl (*e.g.*, C_{3-6} cycloalkyl, *e.g.*, cyclopropyl) or 4-6 membered

heterocyclyl (*e.g.*, oxetanyl). In some embodiments, R^{32} and R^{33} together with the carbon atom they are attached to form a cyclopropyl.

[0138] When more than one $CR^{32}R^{33}$ exist, the definition of each instant of $CR^{32}R^{33}$ is independently from each other. In some embodiments, for one instance of $CR^{32}R^{33}$, R^{32} is hydrogen or C_{1-4} alkyl (*e.g.*, methyl or ethyl) and R^{33} is hydrogen or C_{1-4} alkyl (*e.g.*, methyl or ethyl). In some embodiments, one instance of $CR^{32}R^{33}$ is CH_2 . In some embodiments, one instance of $CR^{32}R^{33}$ is $CH(CH_3)$. In some embodiments, one instance of $CR^{32}R^{33}$ is or $C(CH_3)_2$. In some embodiments, for one instance of $CR^{32}R^{33}$, R^{32} and R^{33} , together with the carbon atom they are attached to, form a carbonyl (CO). In some embodiments, for one instance of $CR^{32}R^{33}$, R^{32} and R^{33} , together with the carbon atom they are attached to, form a 3-4 membered ring (*e.g.*, cyclopropyl).

[0139] In some embodiments, for the $CR^{32}R^{33}$ that is not X^1 or X^2 , R^{32} and R^{33} are both C_{1-4} alkyl, or R^{32} and R^{33} together with the carbon atom they are attached to form a C_{3-6} carbocyclyl or 4-6 membered heterocyclyl. In some embodiments, for the $CR^{32}R^{33}$ that is not X^1 or X^2 , R^{32} and R^{33} are both methyl. In some embodiments, for the $CR^{32}R^{33}$ that is not X^1 or X^2 , R^{32} and R^{33} together with the carbon atom they are attached to form a cyclopropyl.

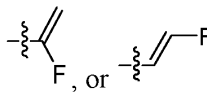
[0140] In some embodiments, R^{34} is hydrogen. In some embodiments, R^{34} is C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, R^{34} is methyl. In some embodiments, R^{34} is ethyl. In some embodiments, R^{34} is cyclopropyl.

[0141] In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is halogen. In some embodiments, R^3 is F. In some embodiments, R^3 is Cl. In some embodiments, R^3 is Br. In some embodiments, R^3 is CN. In some embodiments, R^3 is $C(O)NR^{11}R^{12}$. In some embodiments, R^3 is $C(O)NH_2$. In some embodiments, R^3 is C_{1-6} alkyl (*e.g.*, C_{1-4} alkyl) optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, R^3 is an optionally substituted C_{3-8} carbocyclyl. In some embodiments, R^3 is an optionally substituted 4-10 membered heterocyclyl having 1 or 2 ring heteroatoms independently selected from N, O, and S. In some embodiments, R^3 is an optionally substituted 5-10 membered heteroaryl having 1-4 ring heteroatoms independently selected from N, O, and S.

[0142] In some embodiments, R^3 is hydrogen, F, Cl, Br, CN, or C_{1-4} alkyl optionally substituted with F.

[0143] In some embodiments, R^3 is an optionally substituted C_{1-4} alkyl. In some embodiments, R^3 is C_{1-4} alkyl optionally substituted with one or more, such as 1-3 substituents

independently selected from deuterium, F, CN, or OR^{C} , wherein R^{C} at each occurrence is independently hydrogen, C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl. In some embodiments, R^3 is methyl, CD_3 , $\text{CH}_2\text{-OMe}$, $\text{CH}_2\text{-OCD}_3$, ethyl, CHF_2 , CF_2CH_3 , $\text{CH}_2\text{CH}_2\text{F}$, $\text{CH}_2\text{CF}_2\text{H}$, or CF_3 . In some embodiments, R^3 is CF_2CF_3 .

[0144] In some embodiments, R^3 is an optionally substituted C_{2-4} alkenyl, such as , , or . In some embodiments, R^3 is an optionally substituted C_{2-4} alkynyl, such as

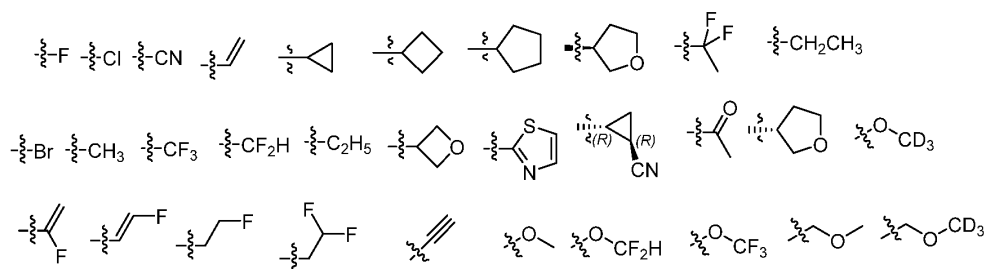


[0145] In some embodiments, R^3 is OR^{A} . In some embodiments, R^3 is OR^{A} , and R^{A} is hydrogen, C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

[0146] In some embodiments, R^3 is $\text{C}(\text{O})\text{R}^{\text{B}}$. In some embodiments, R^3 is $\text{C}(\text{O})\text{R}^{\text{B}}$ and R^{B} is hydrogen, C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

[0147] In some embodiments, R^3 is a C_{3-6} cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, etc.), 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, such as oxetanyl, tetrahydrofuranyl, or 5-6 membered heteroaryl having 1-4 ring heteroatoms independently selected from N, O, and S, such as thiazolyl, each of which is optionally substituted with 1-3 substituents independently selected from oxo (as applicable), deuterium, F, CN, G^1 , OH, O-G^1 , NH_2 , $\text{NH}(\text{G}^1)$, $\text{N}(\text{G}^1)(\text{G}^1)$, $\text{C}(\text{O})\text{-NH}_2$, $\text{C}(\text{O})\text{-NH}(\text{G}^1)$, and $\text{C}(\text{O})\text{-N}(\text{G}^1)(\text{G}^1)$, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

[0148] In some embodiments, R^3 is selected from:

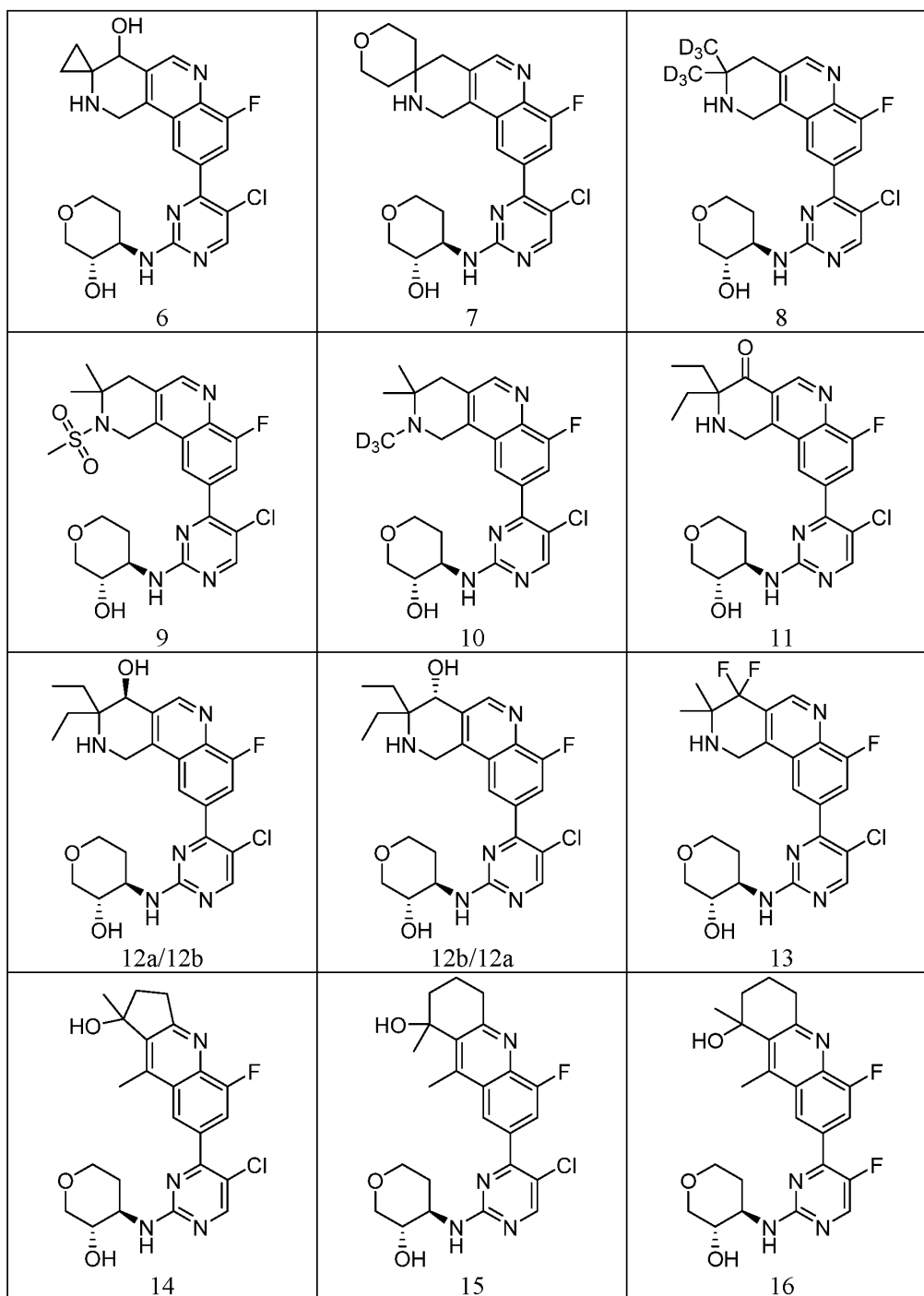


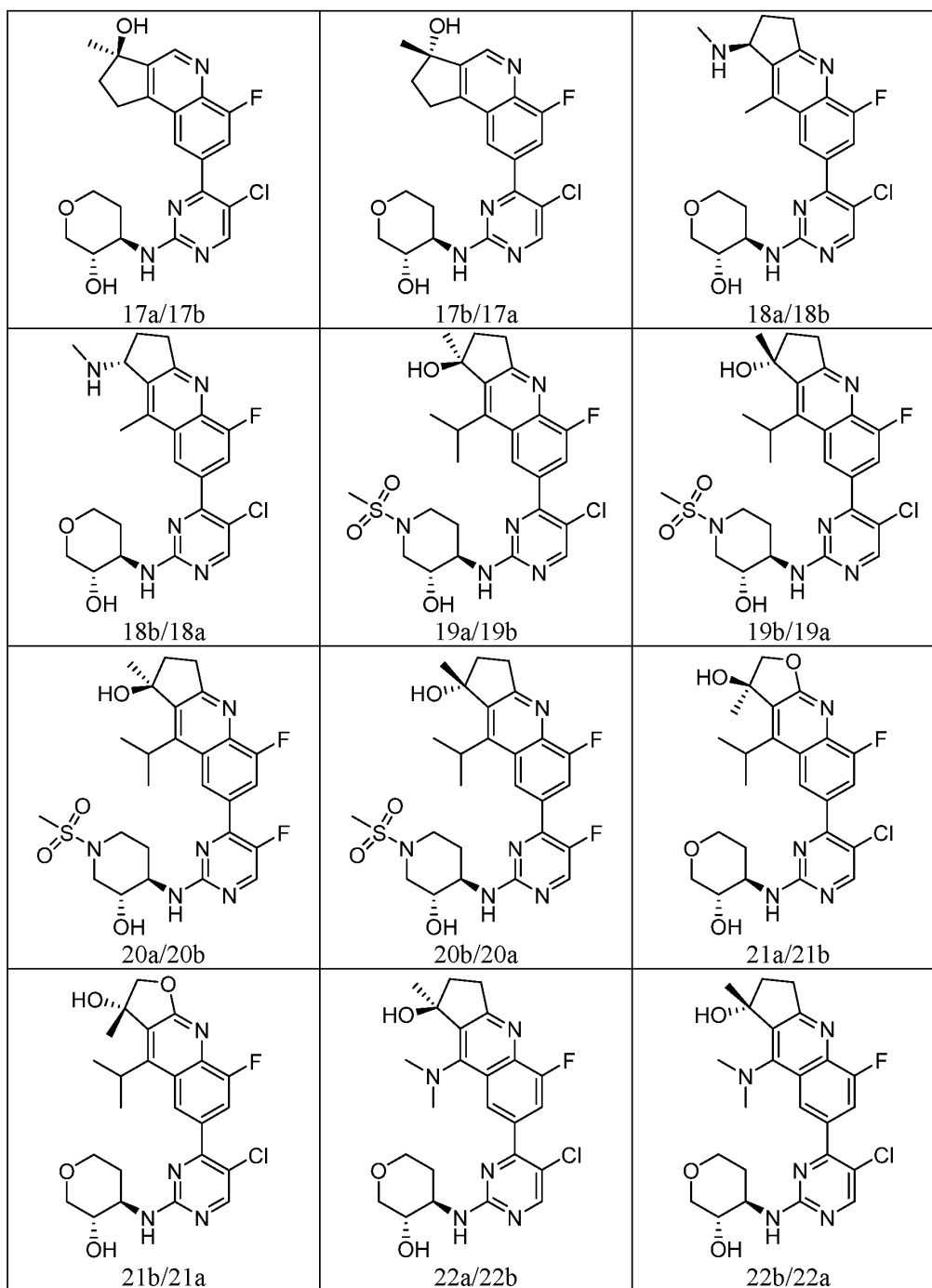
[0149] In some embodiments, R^4 is hydrogen. In some embodiments, R^4 is deuterium. In some embodiments, R^4 is halogen (*e.g.*, F), optionally substituted C_{1-6} alkyl, or $\text{NR}^{11}\text{R}^{12}$. In some embodiments, R^4 is NH_2 .

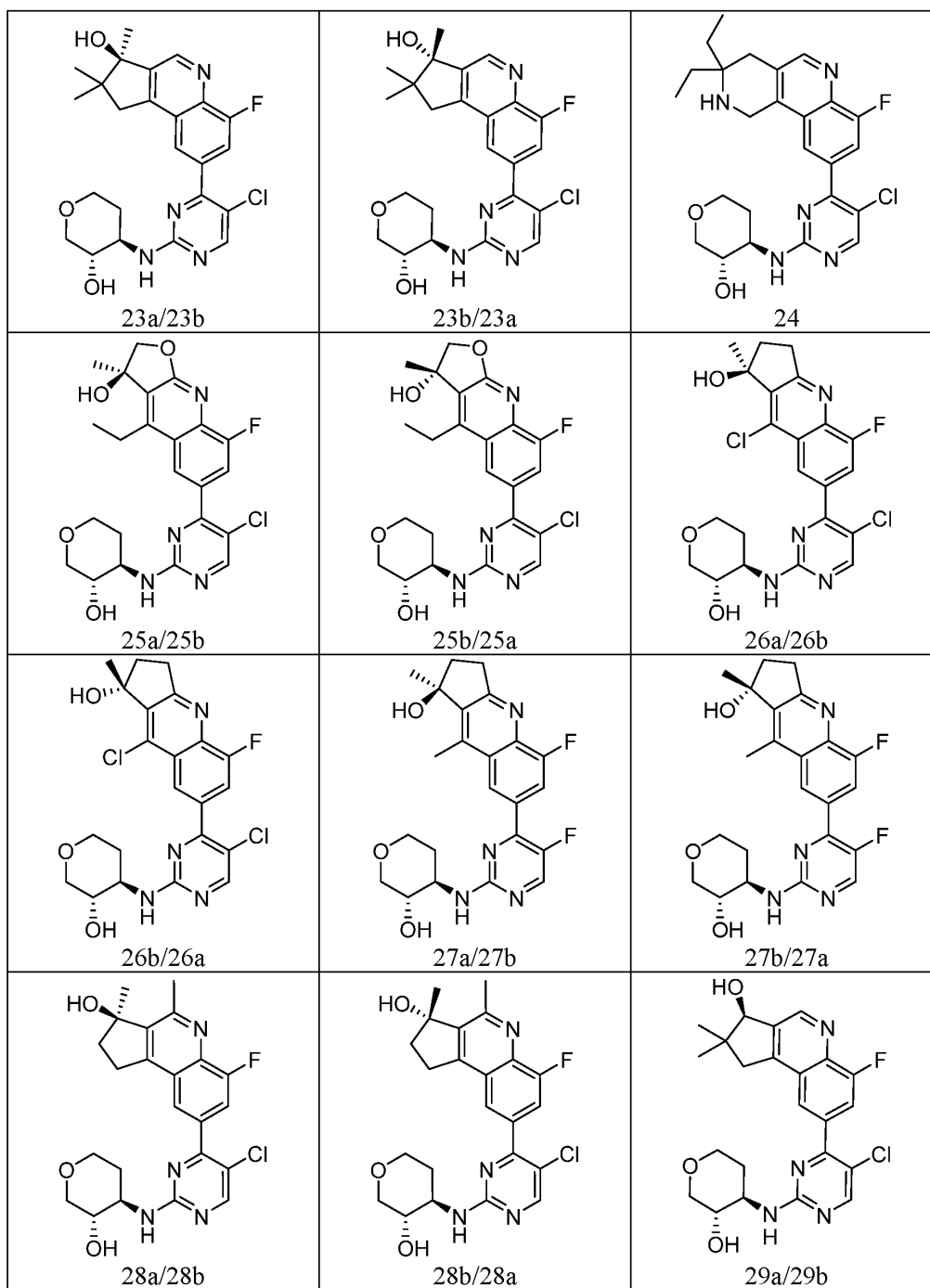
[0150] In some embodiments, provided herein is a compound of Table 1, or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof.

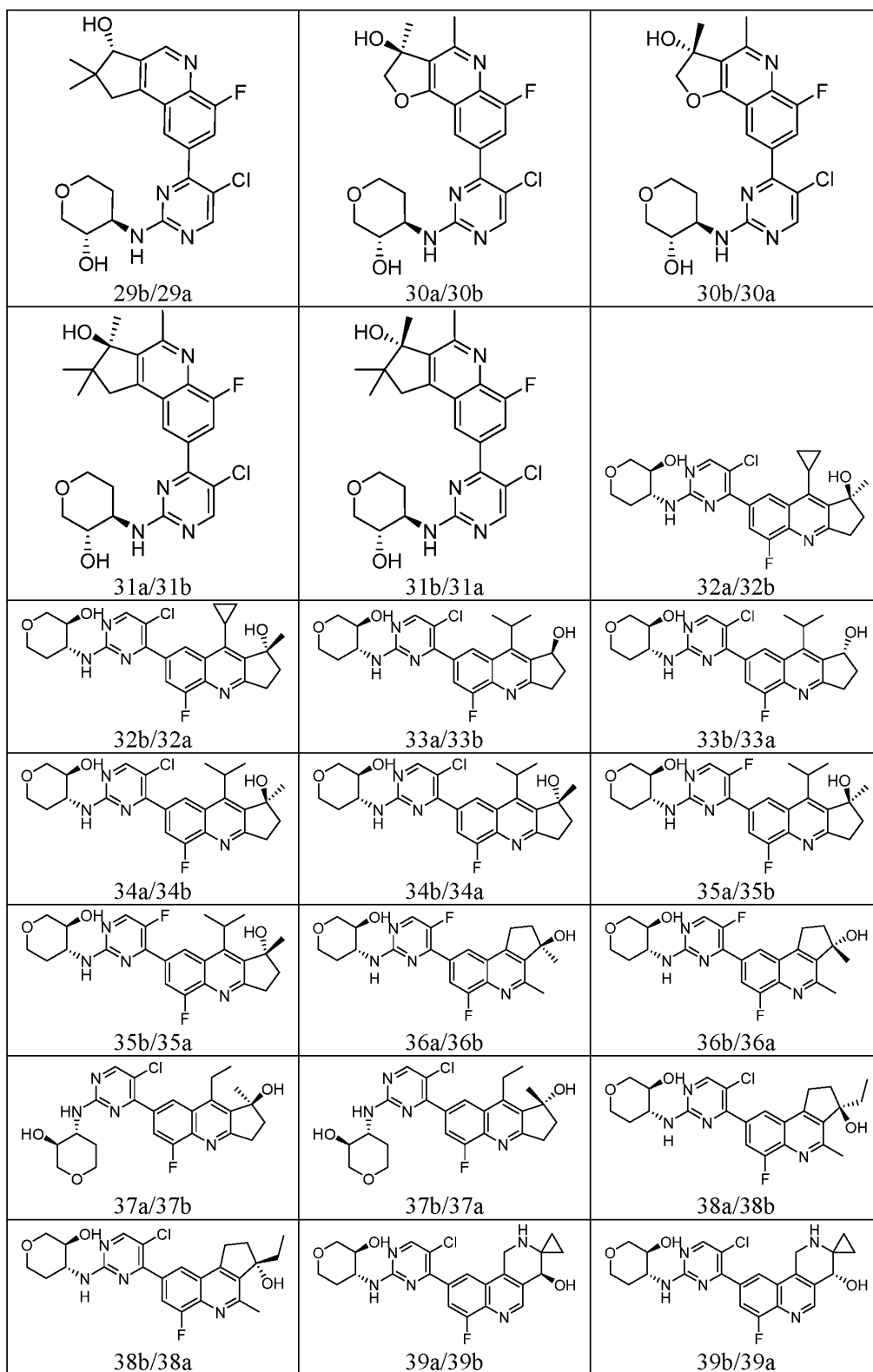
Table 1. List of Compounds

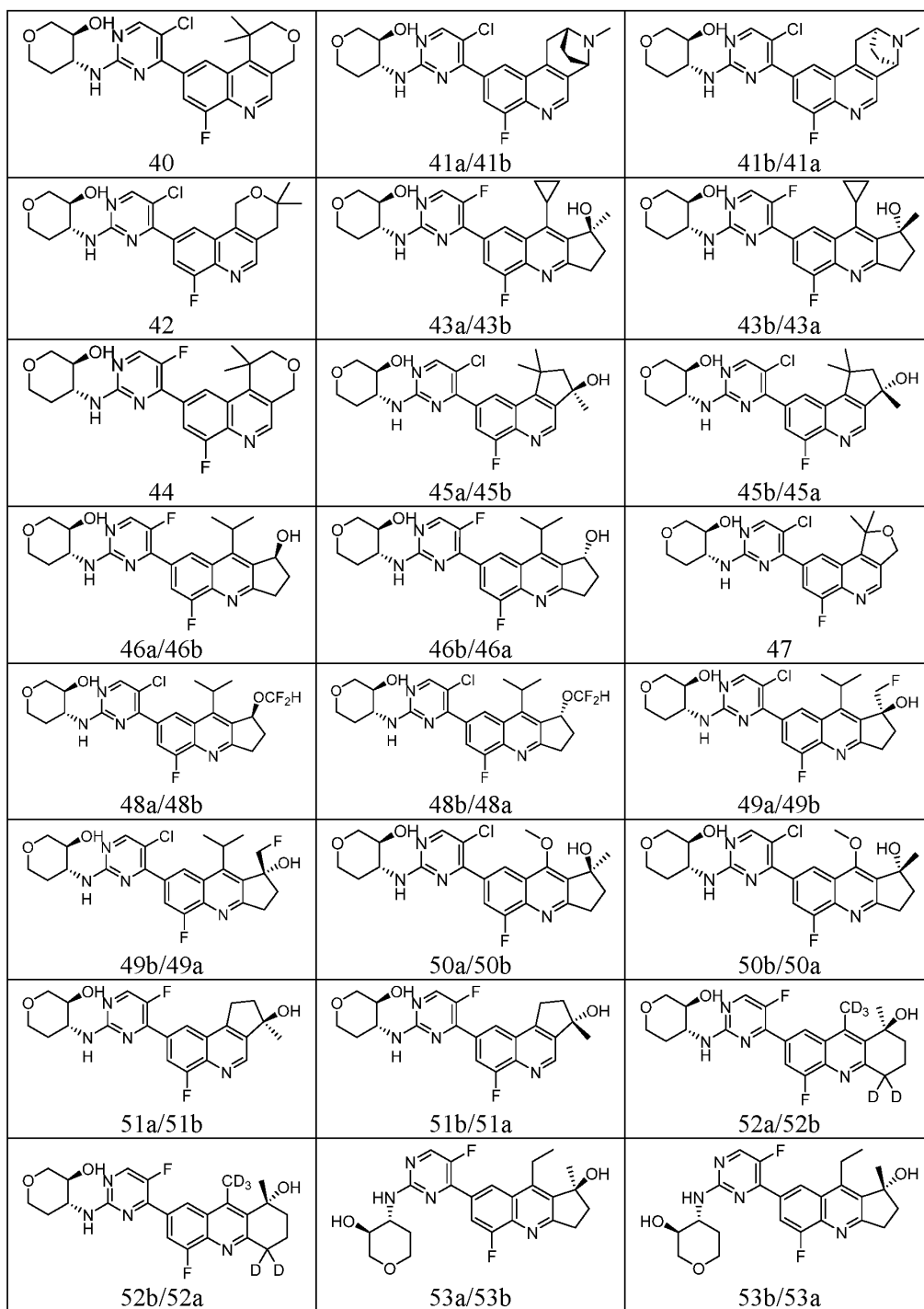
1	2	3
4	5a/5b	5b/5a

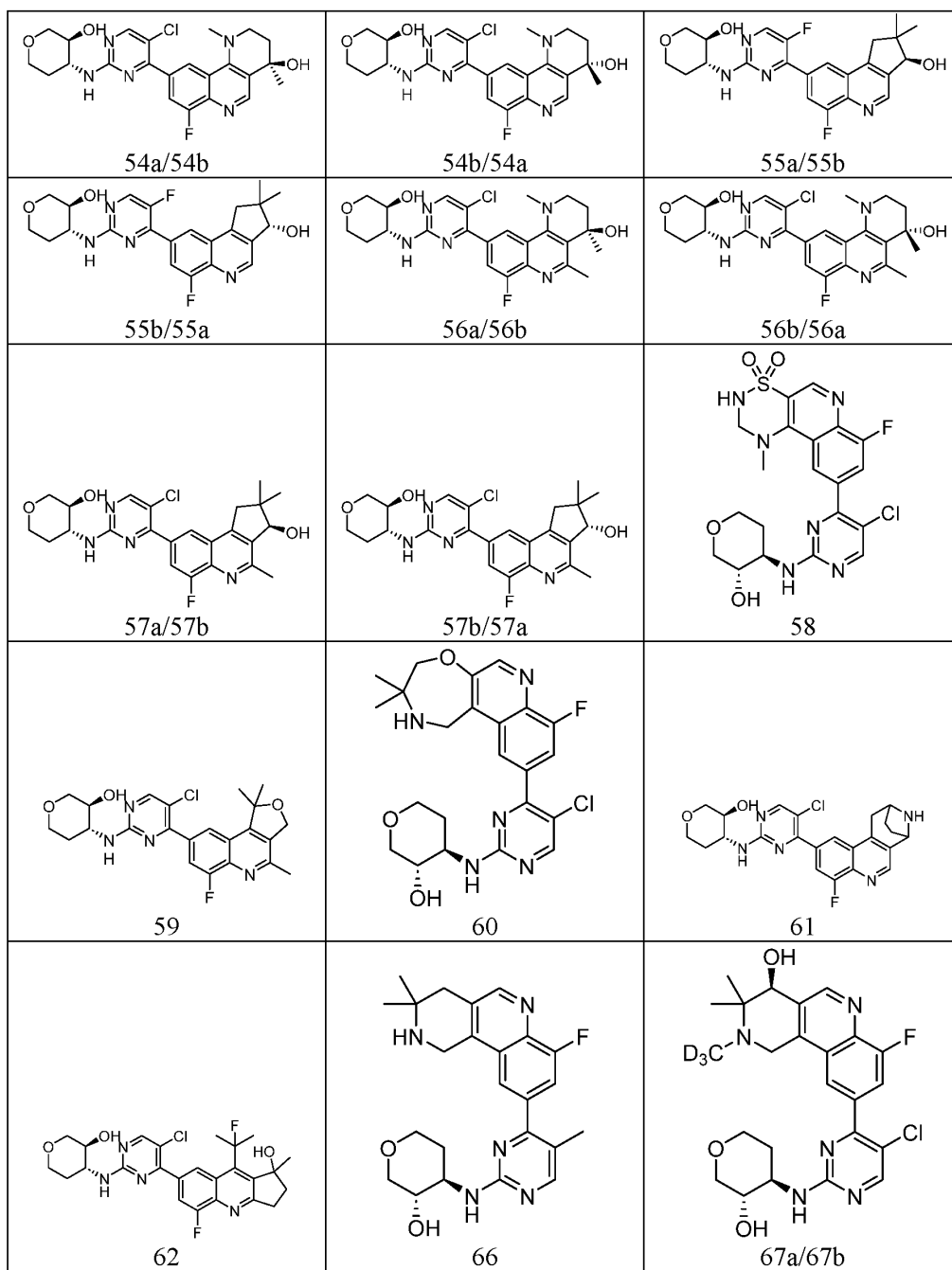


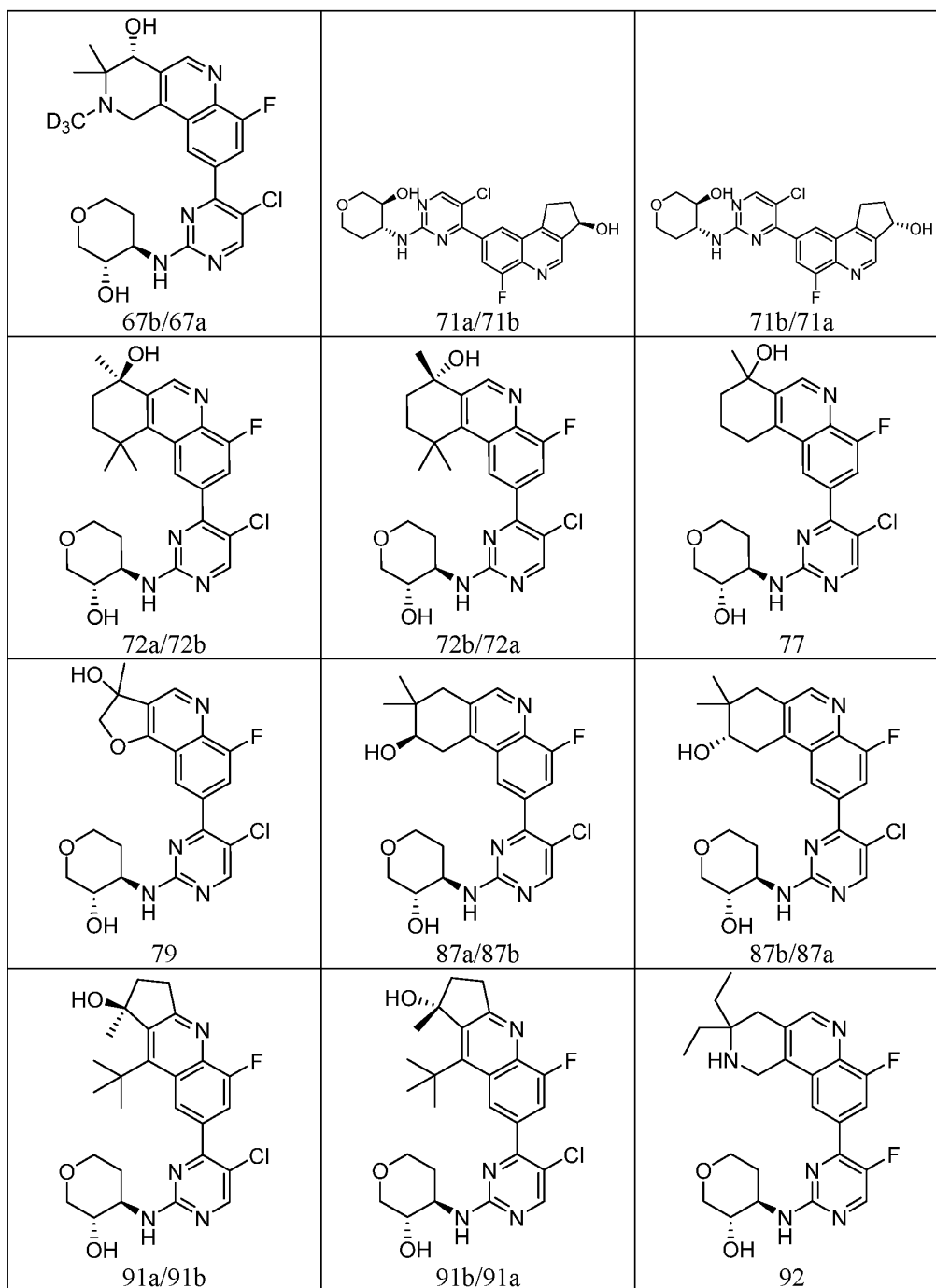


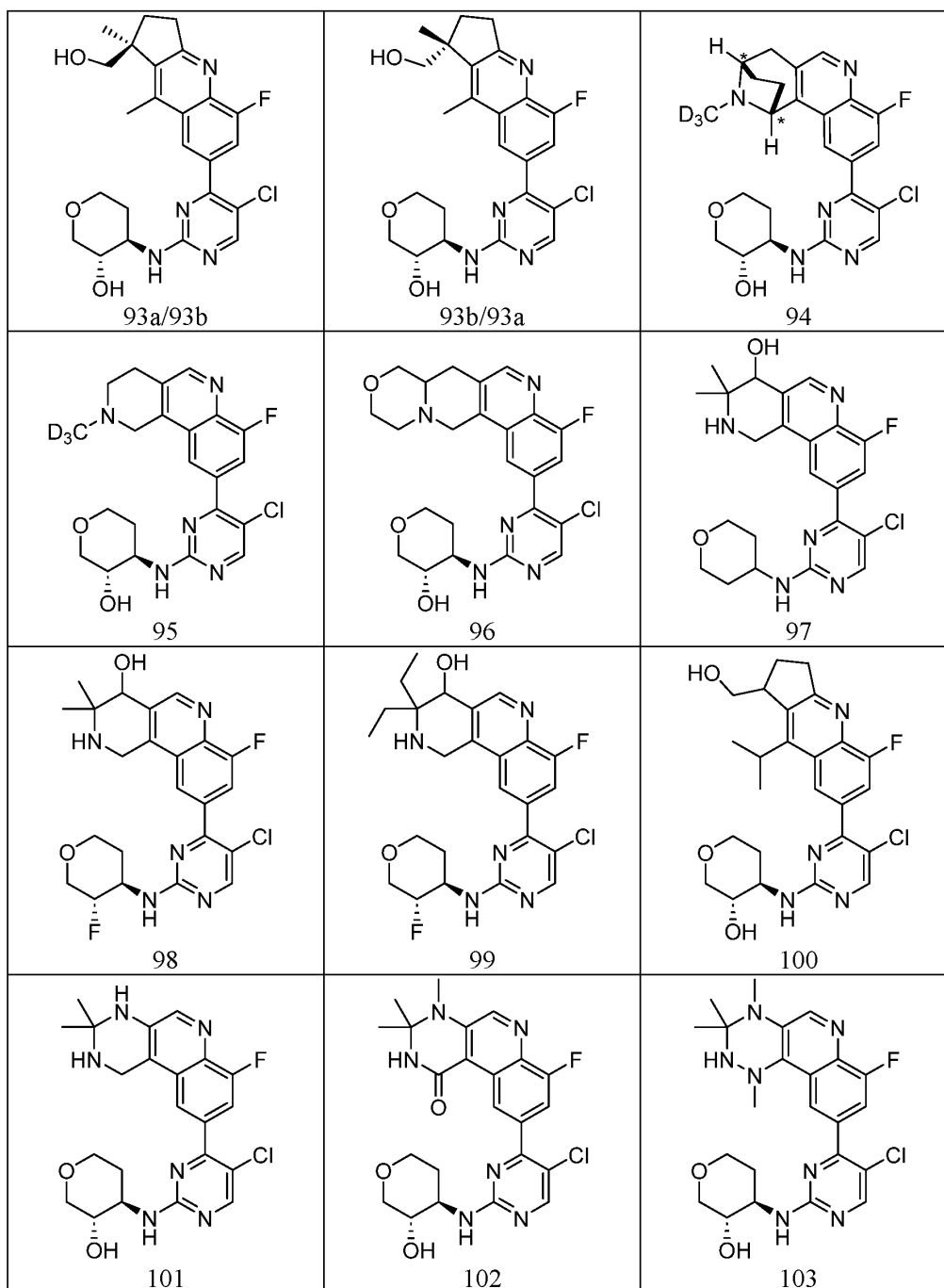


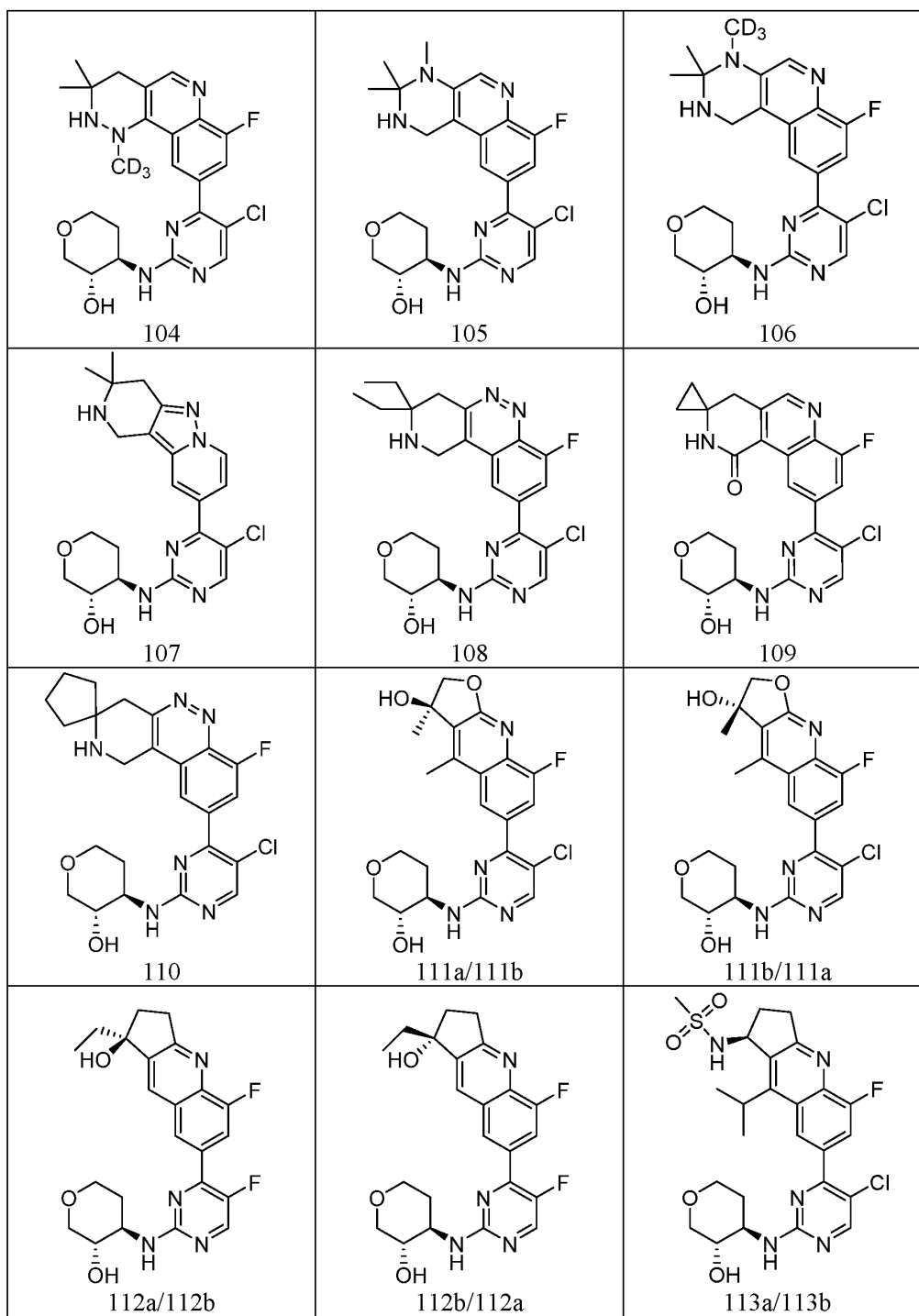


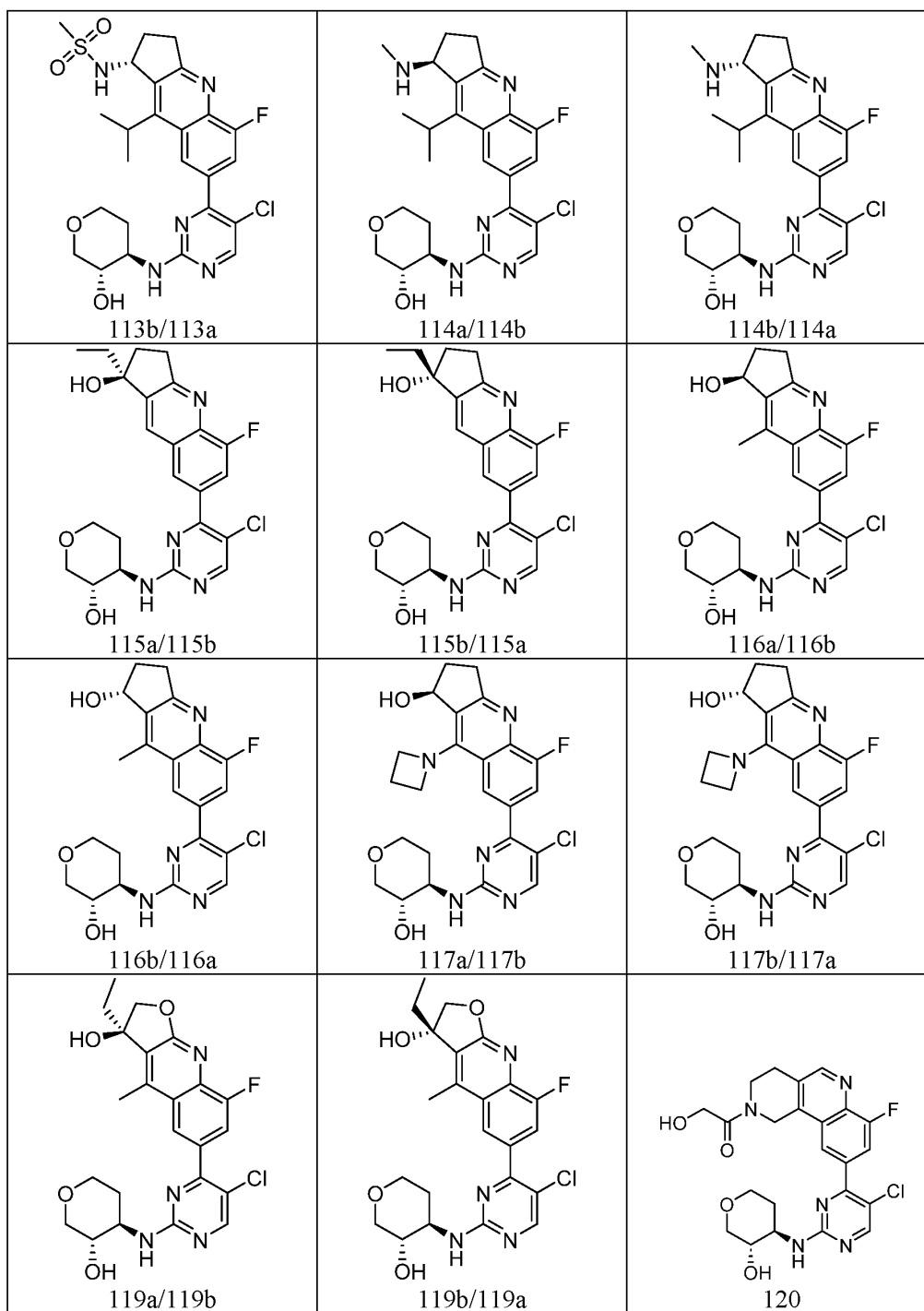


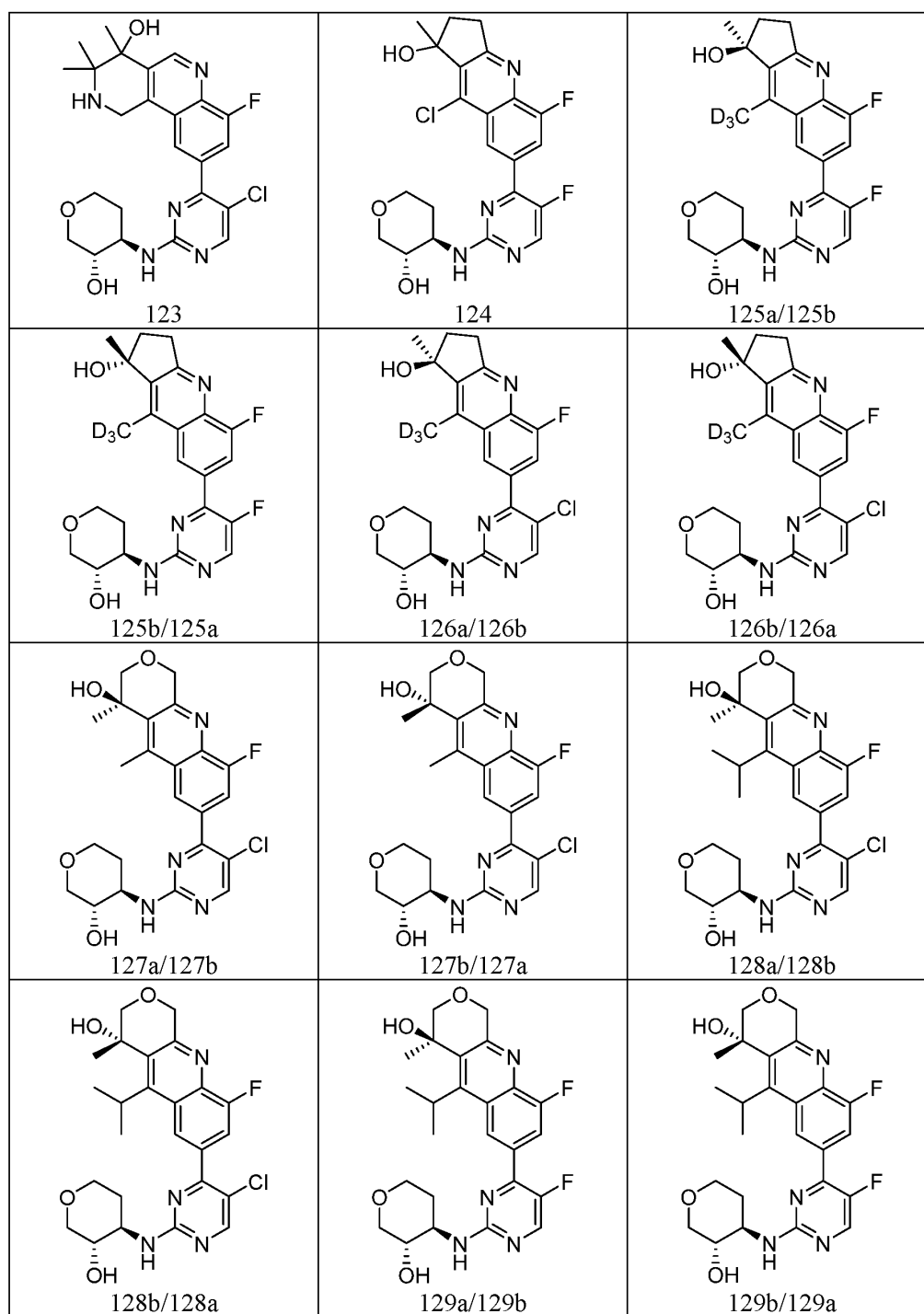


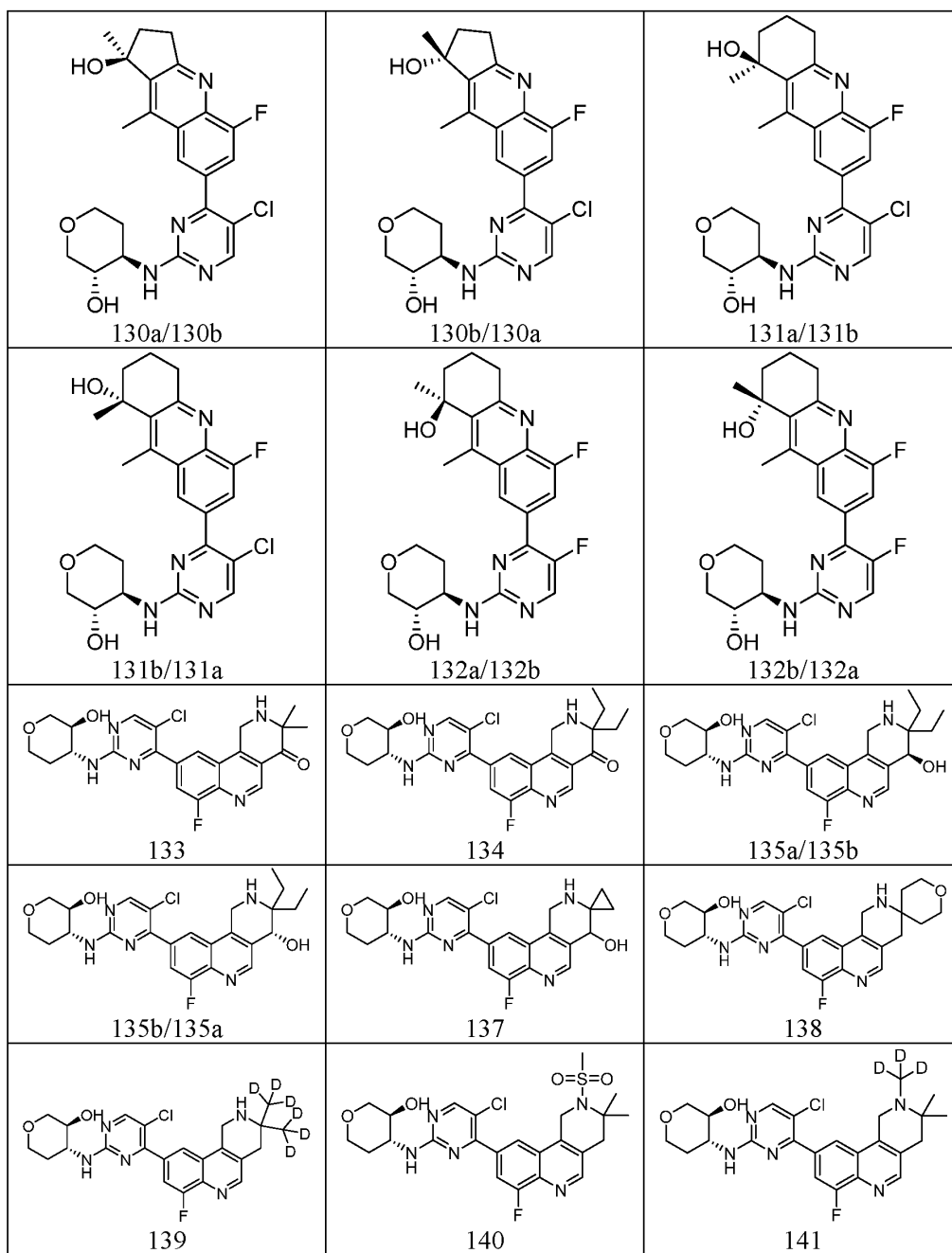


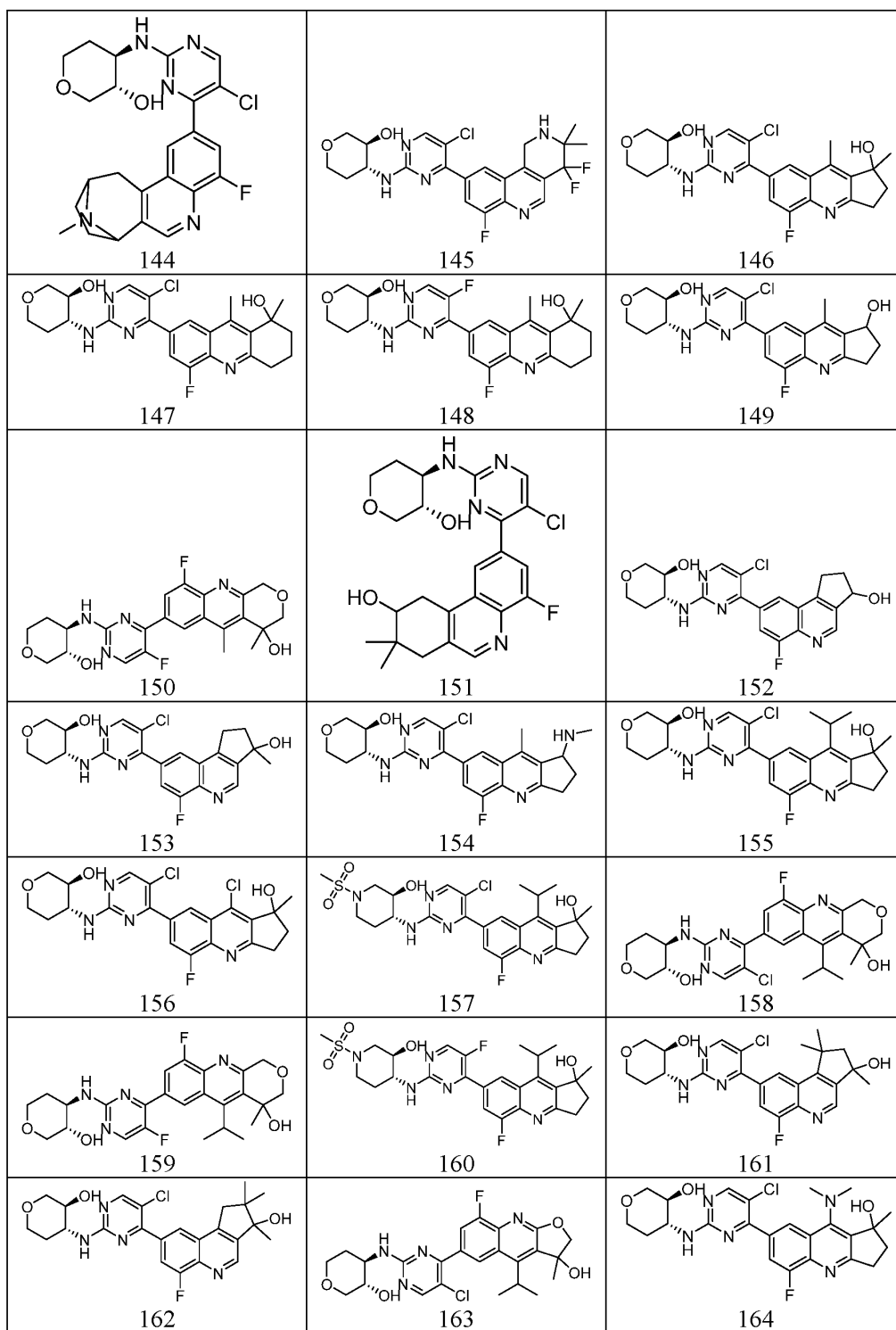


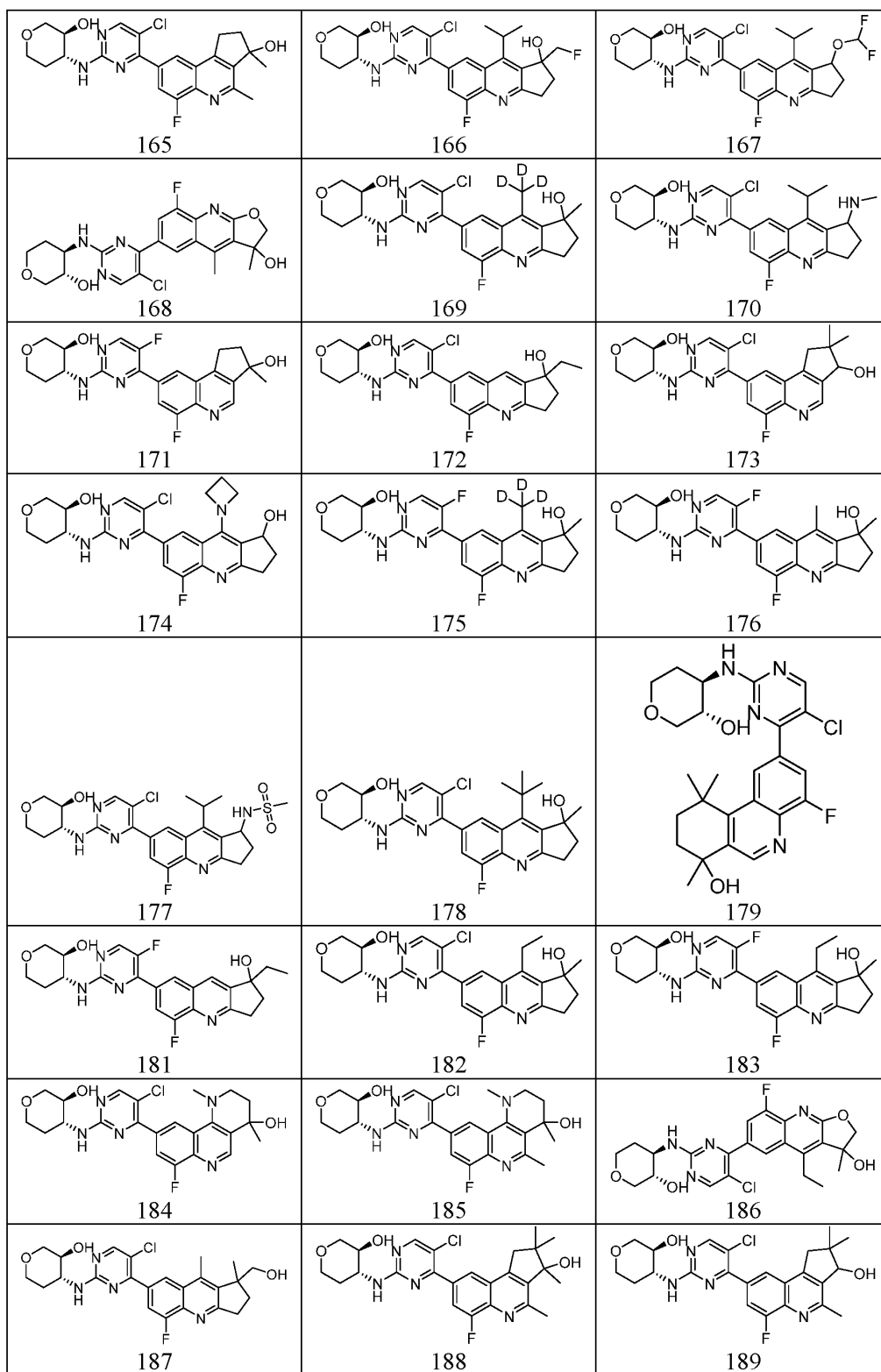


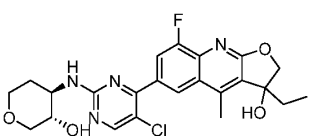
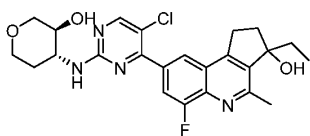
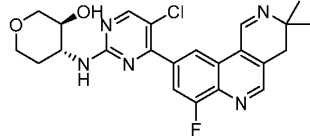
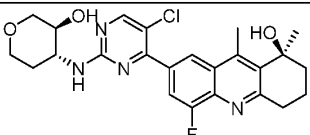
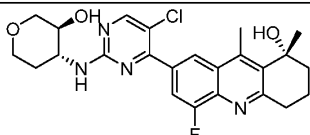
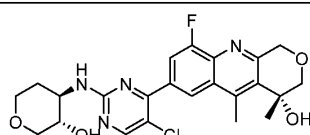
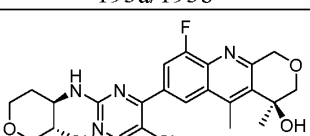
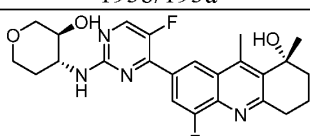
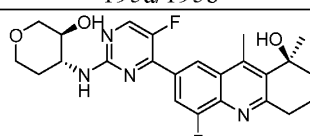
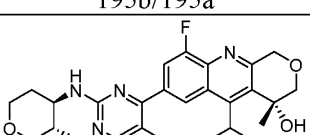
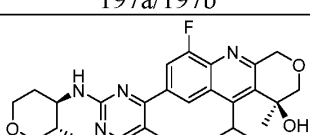
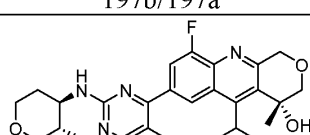
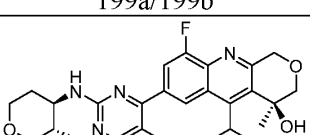






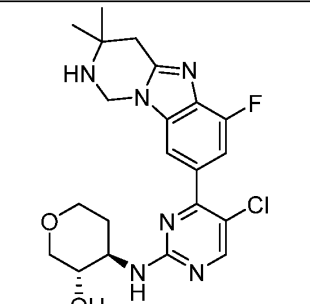
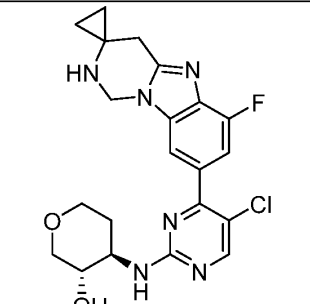
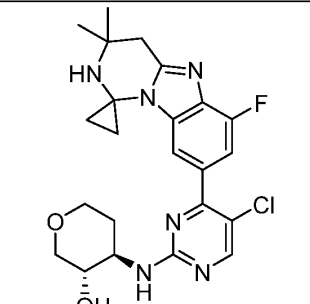


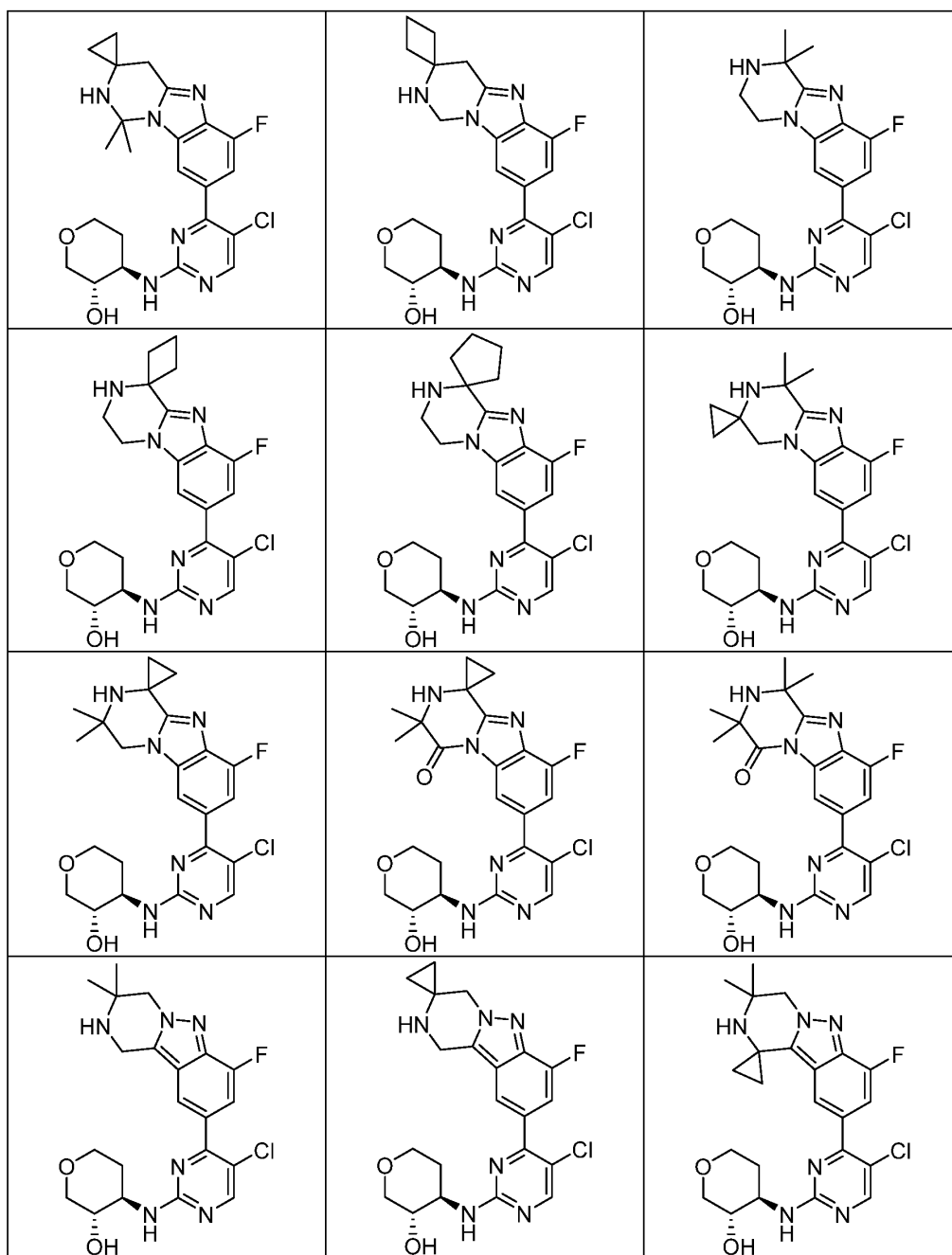


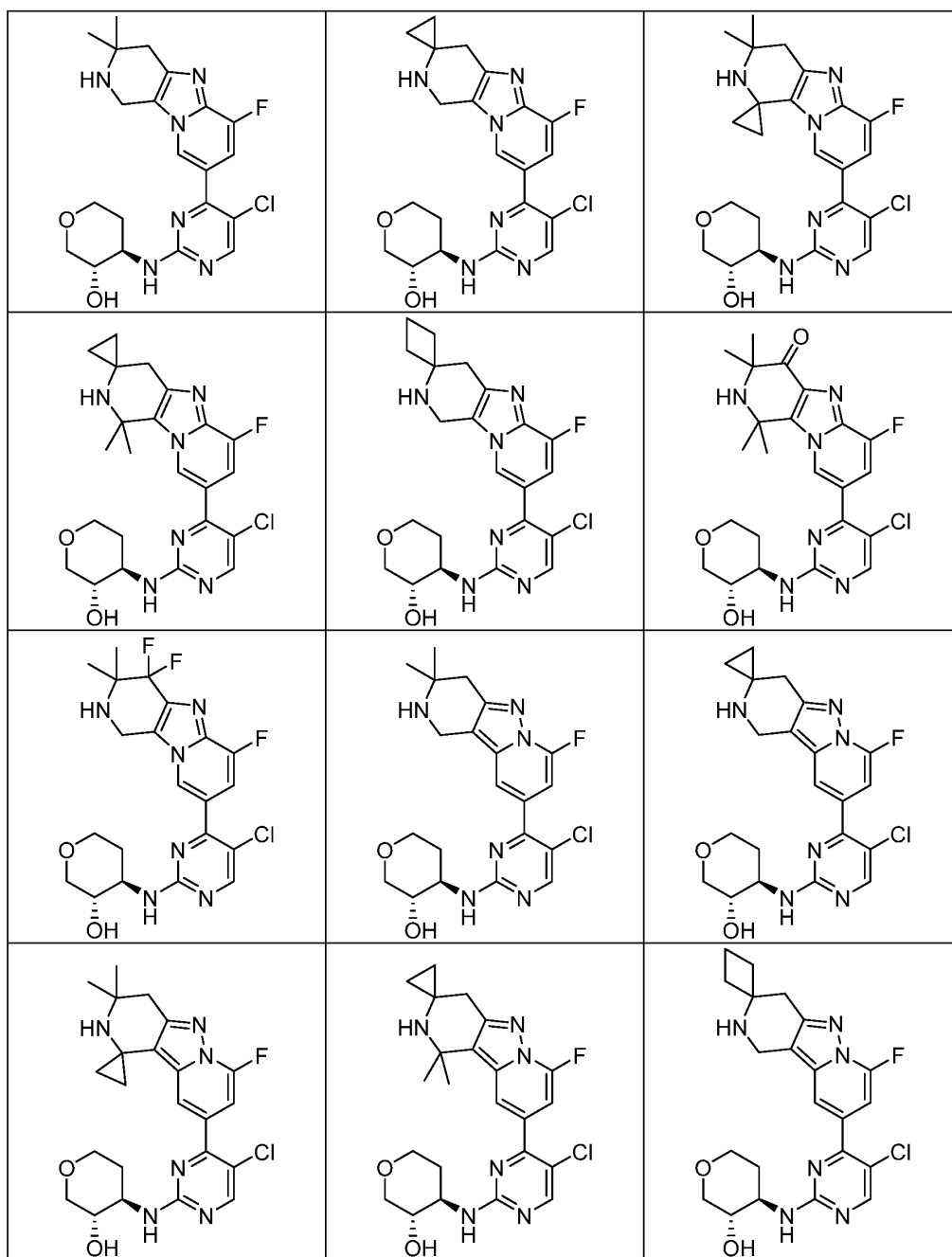
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 193a/193b	 193b/193a	 195a/195b
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 201b/201a		

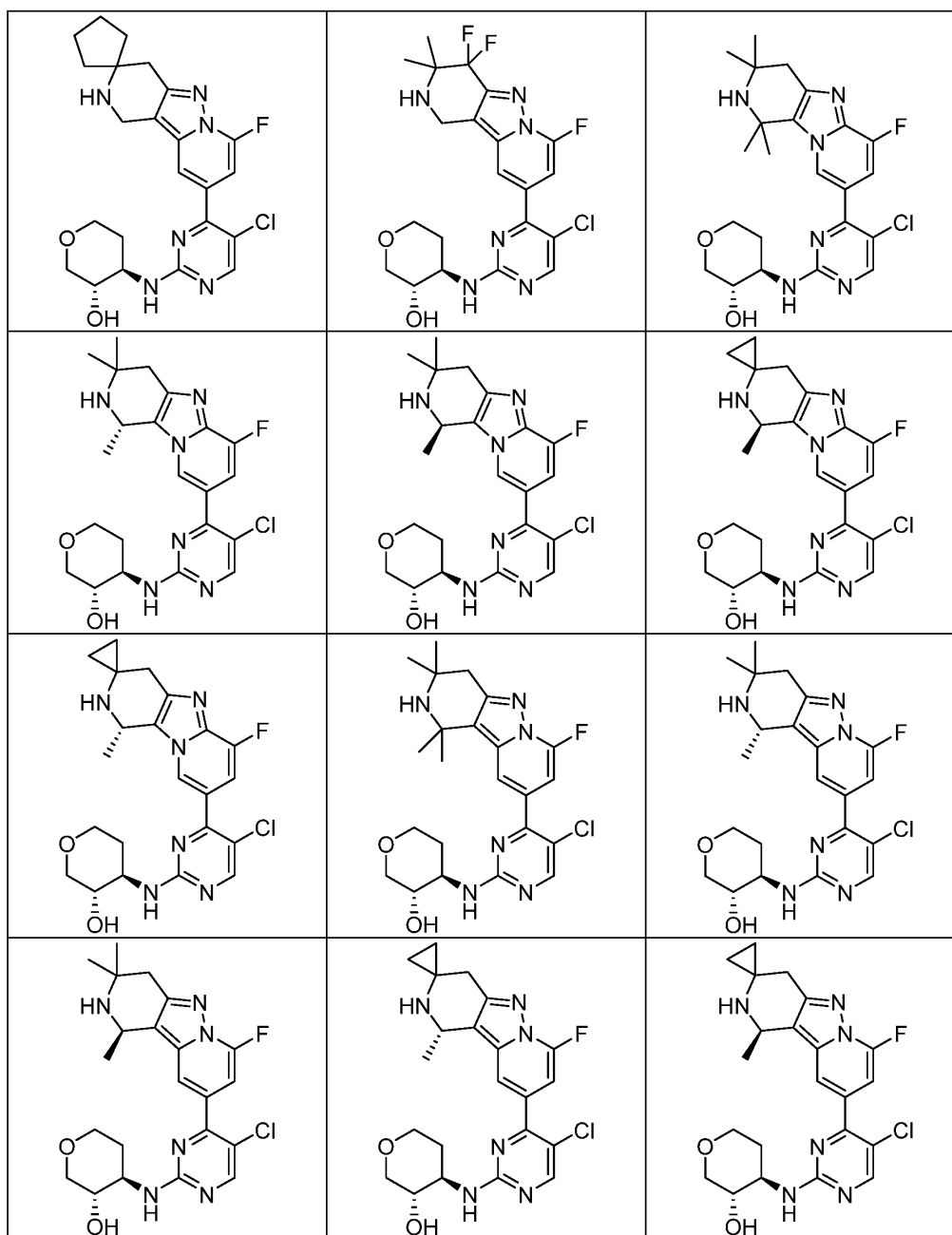
[0151] In some embodiments, provided herein is a compound of Table 1A, or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof.

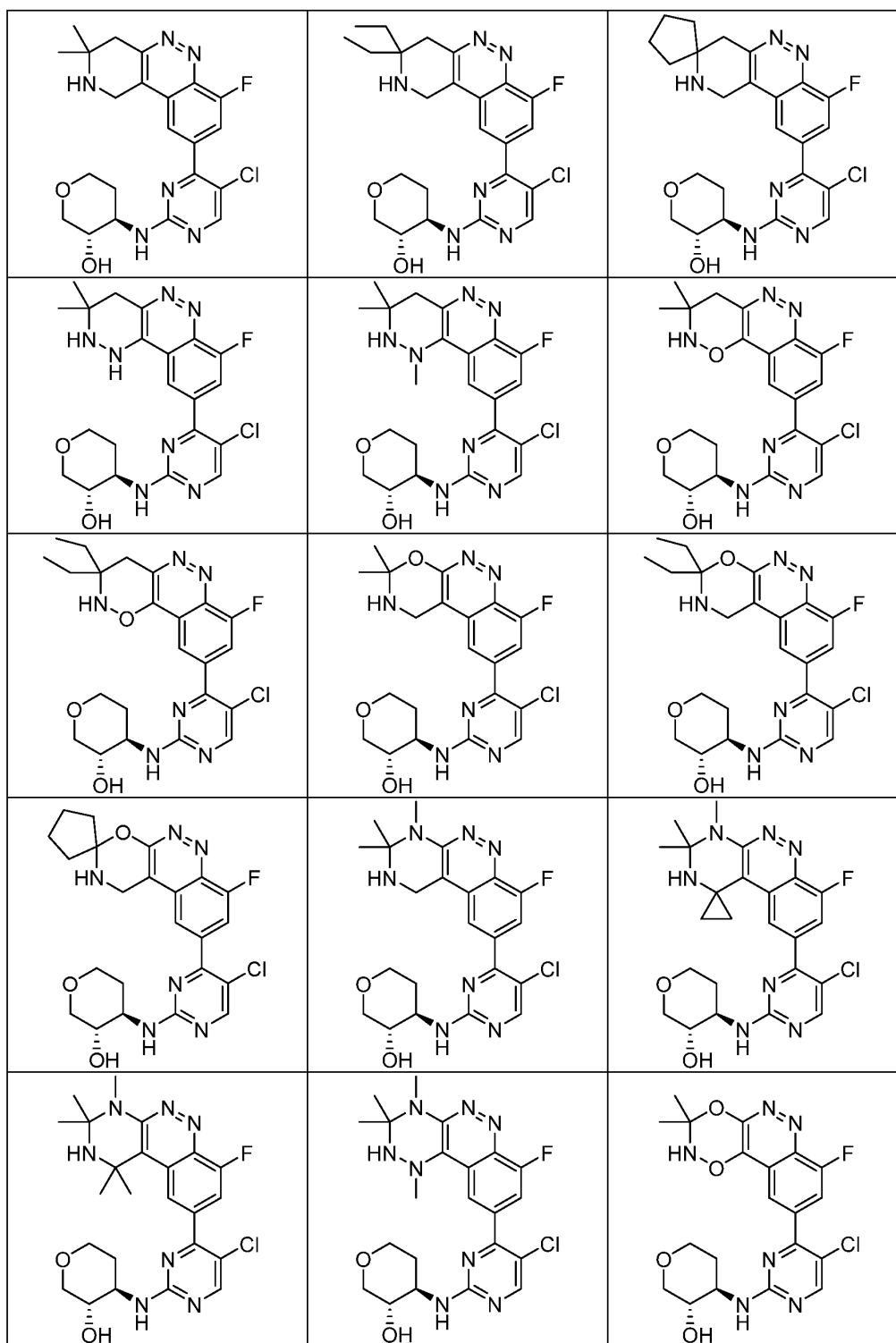
Table 1A. List of Compounds

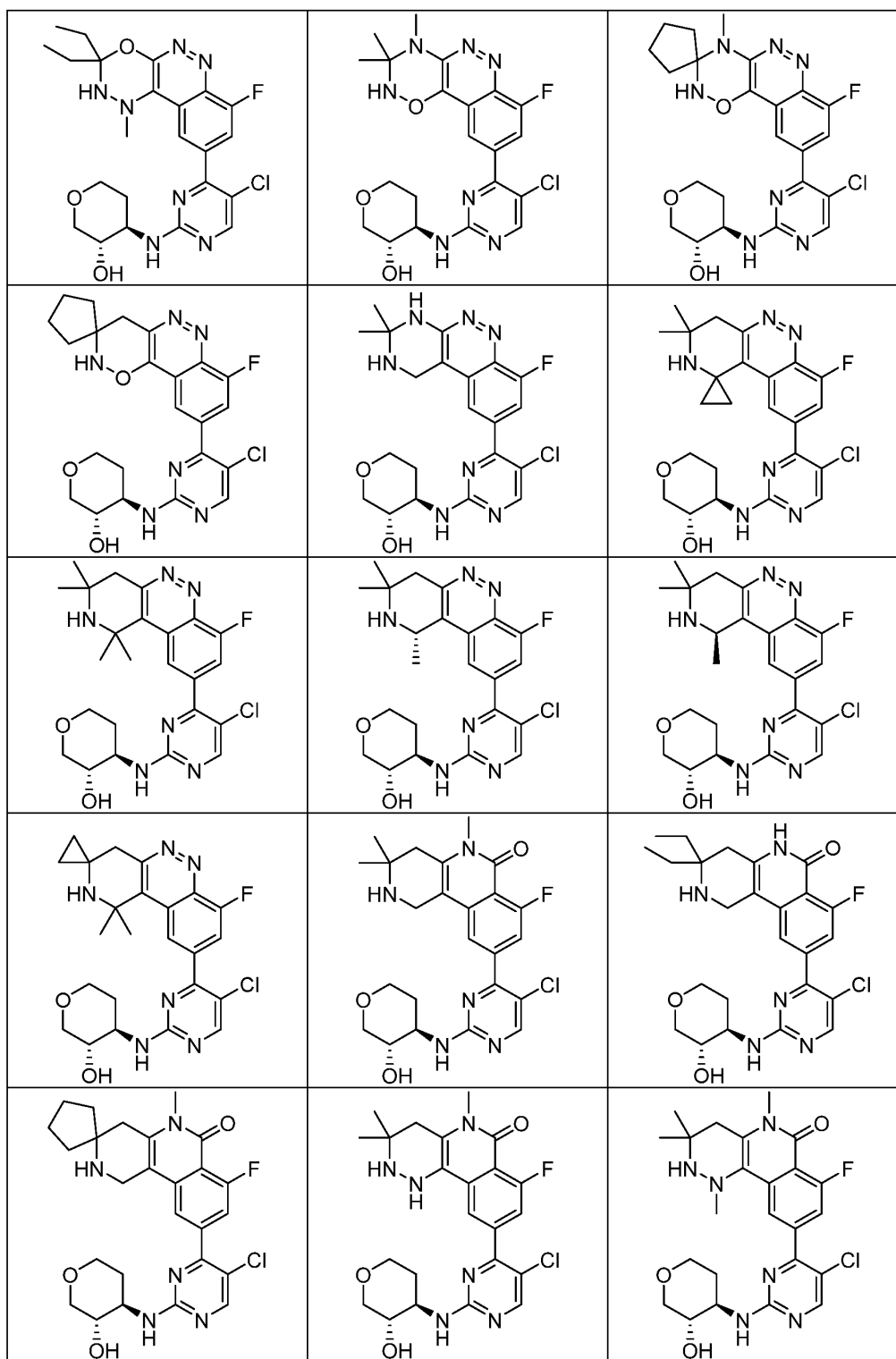
		
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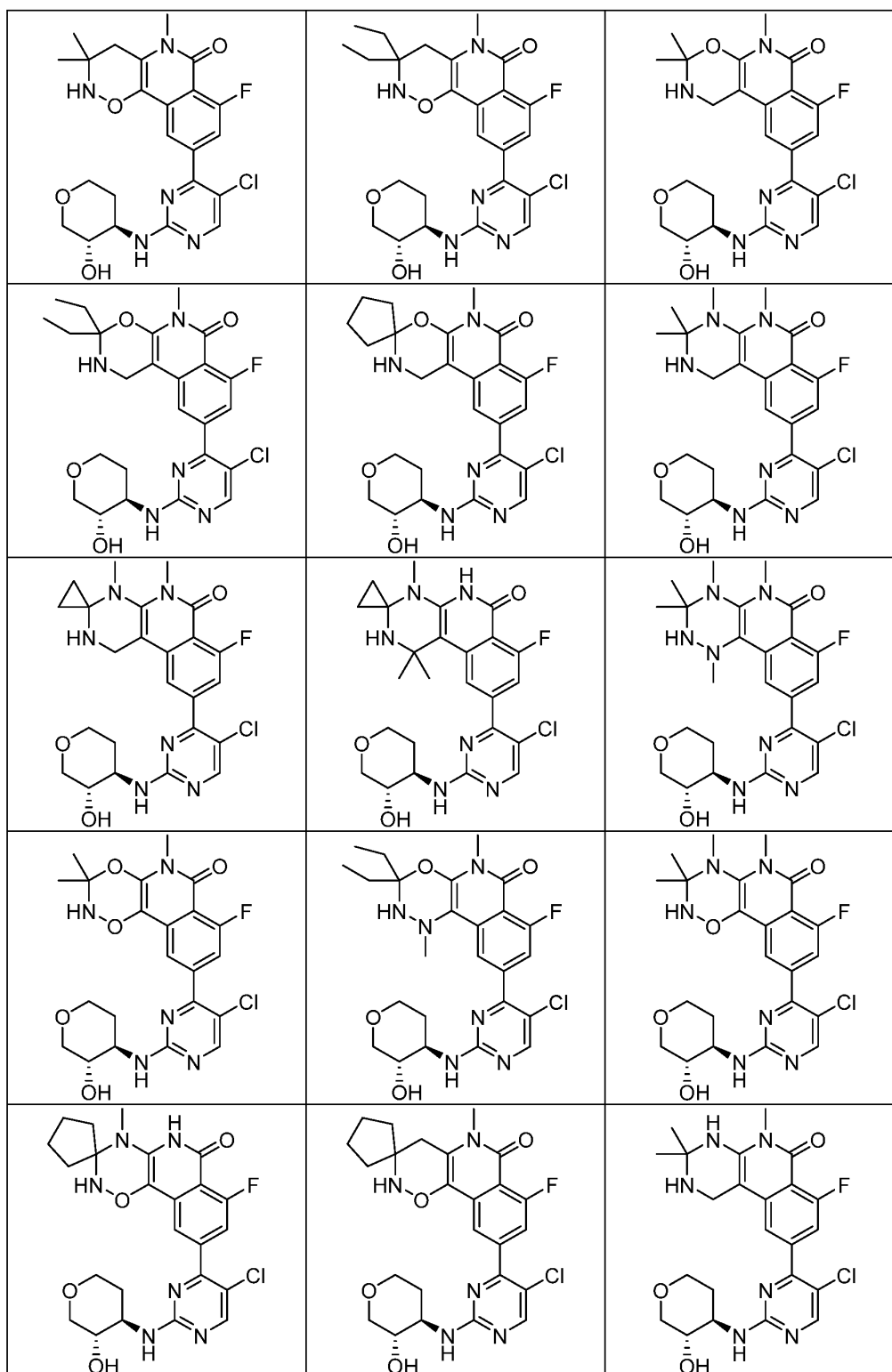


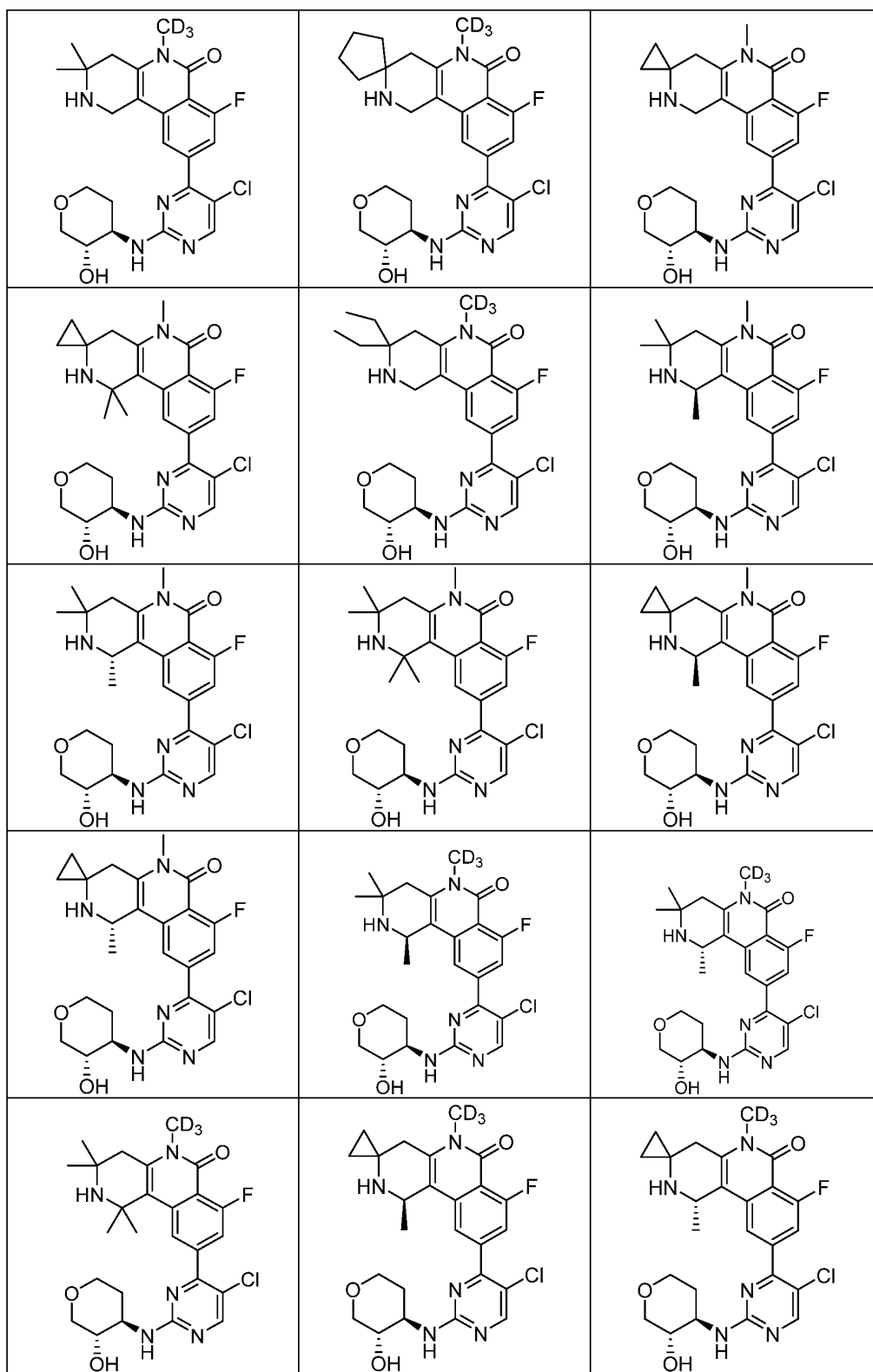


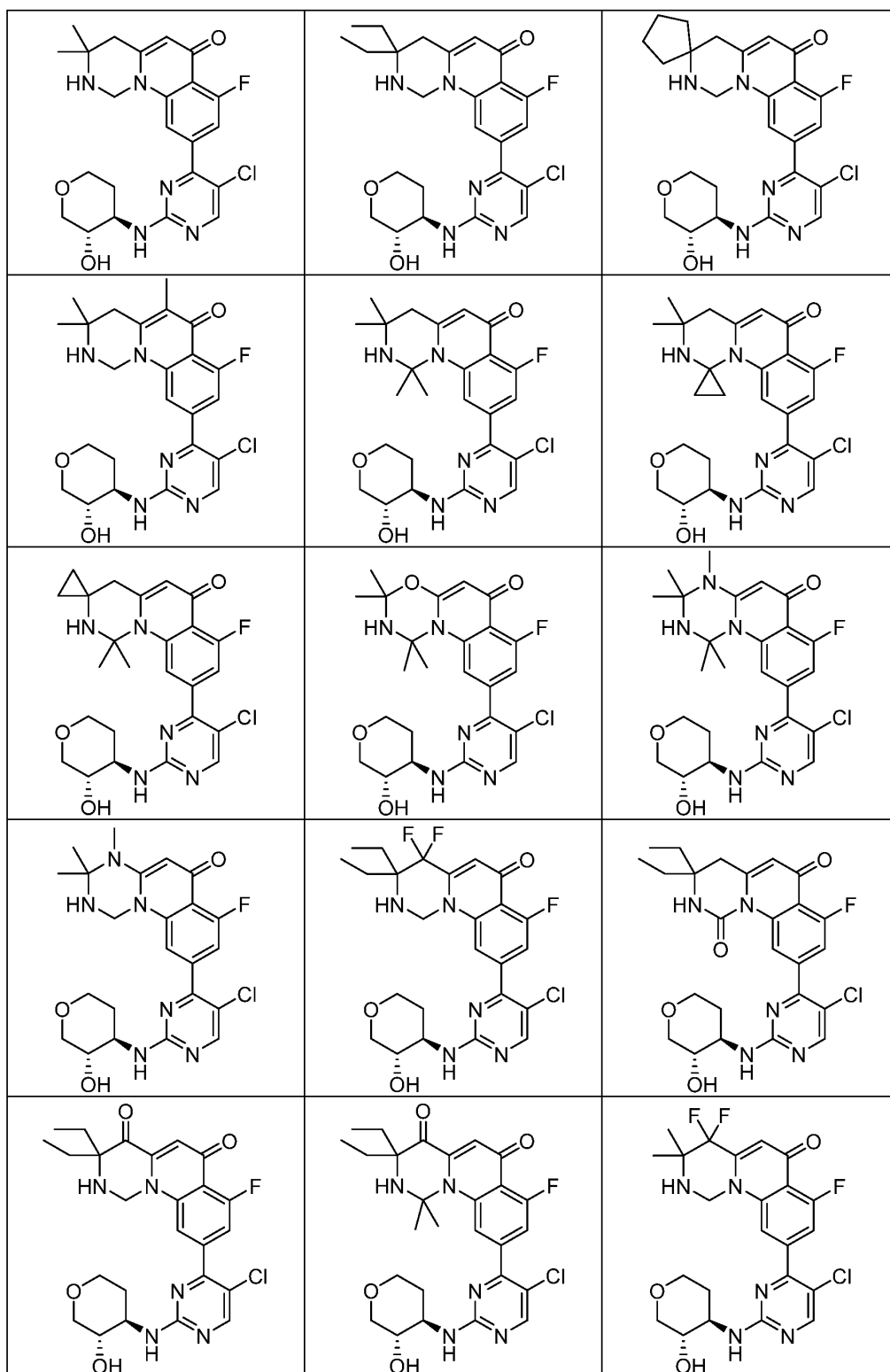


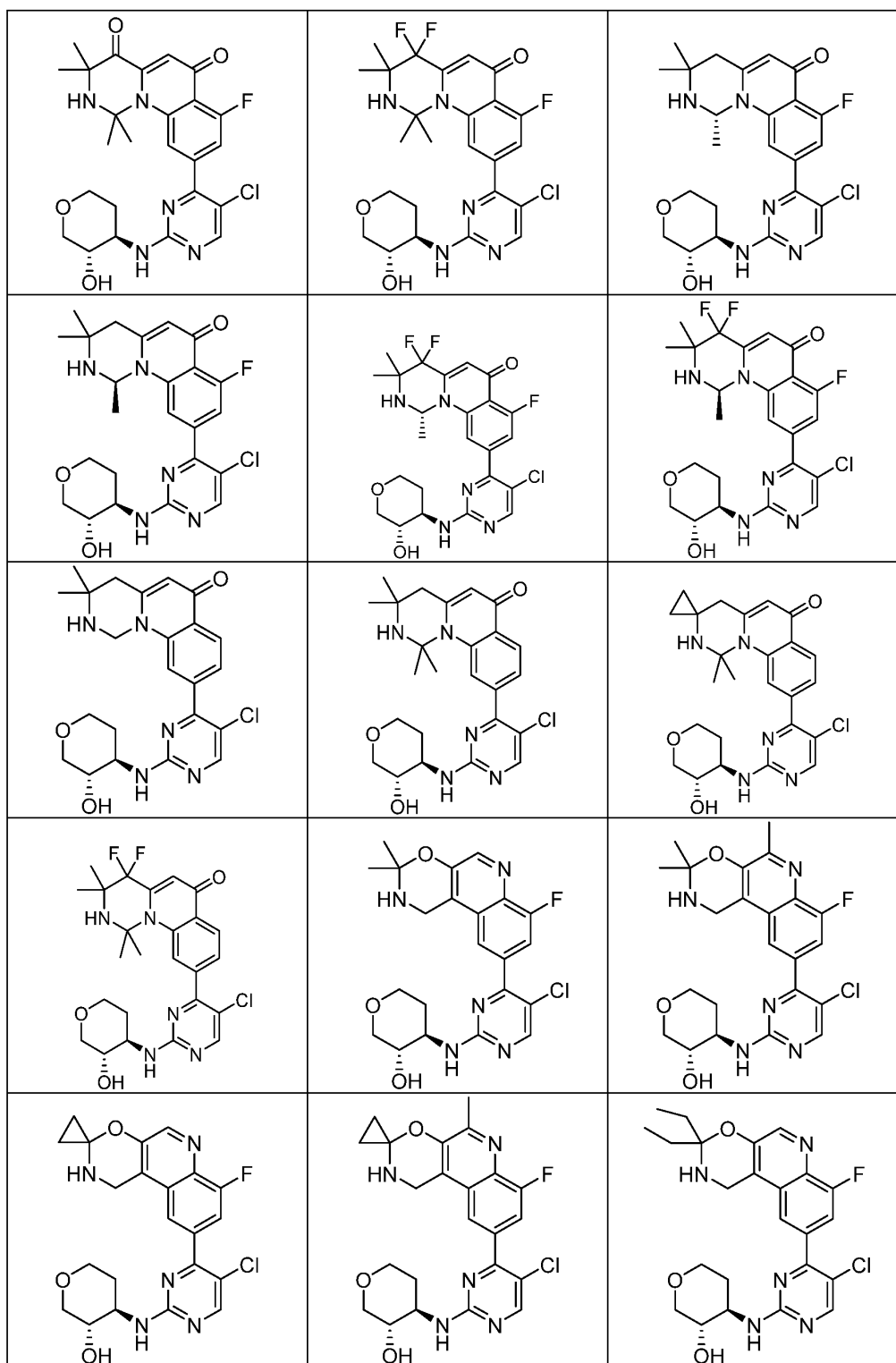


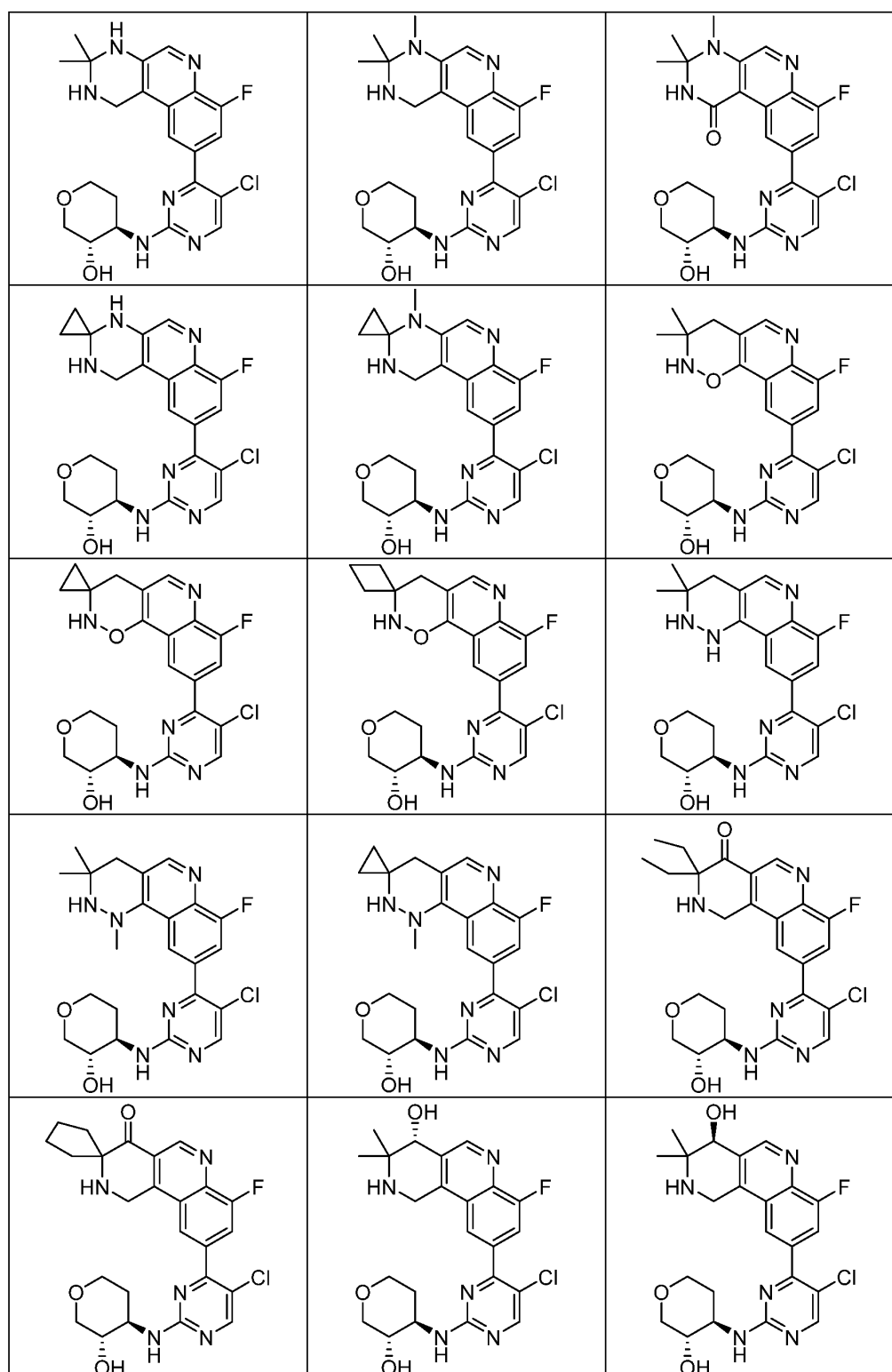


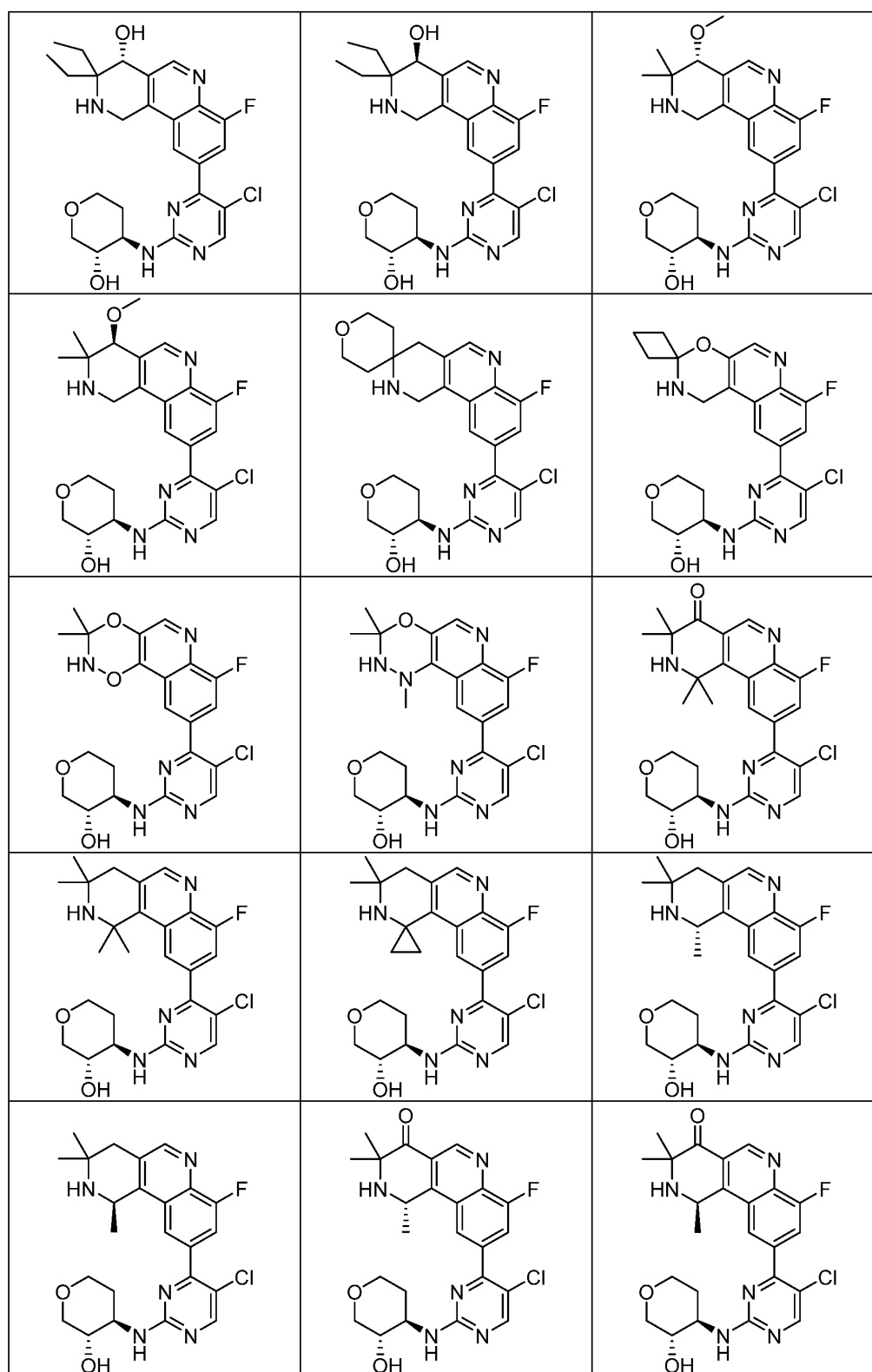


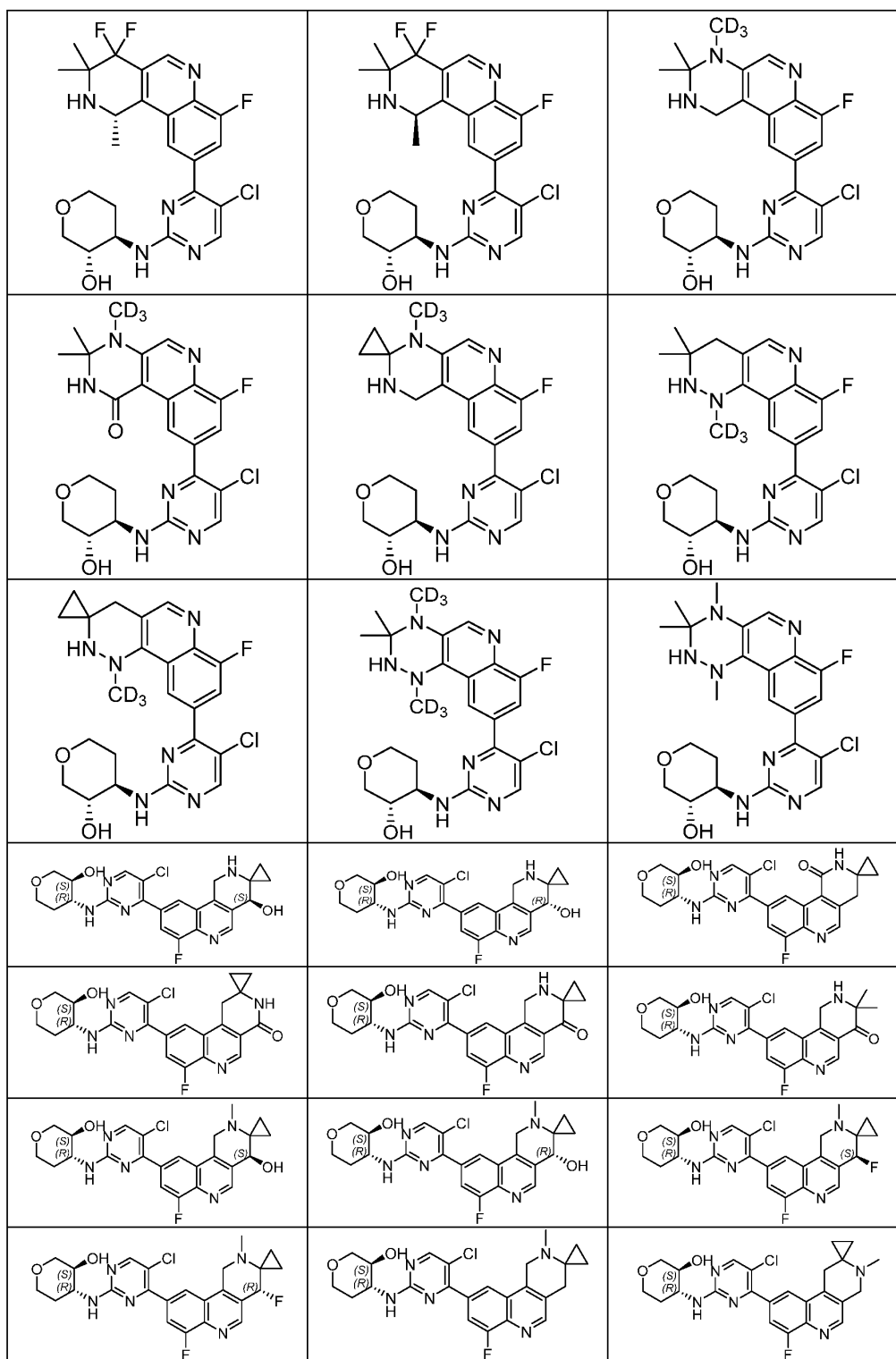


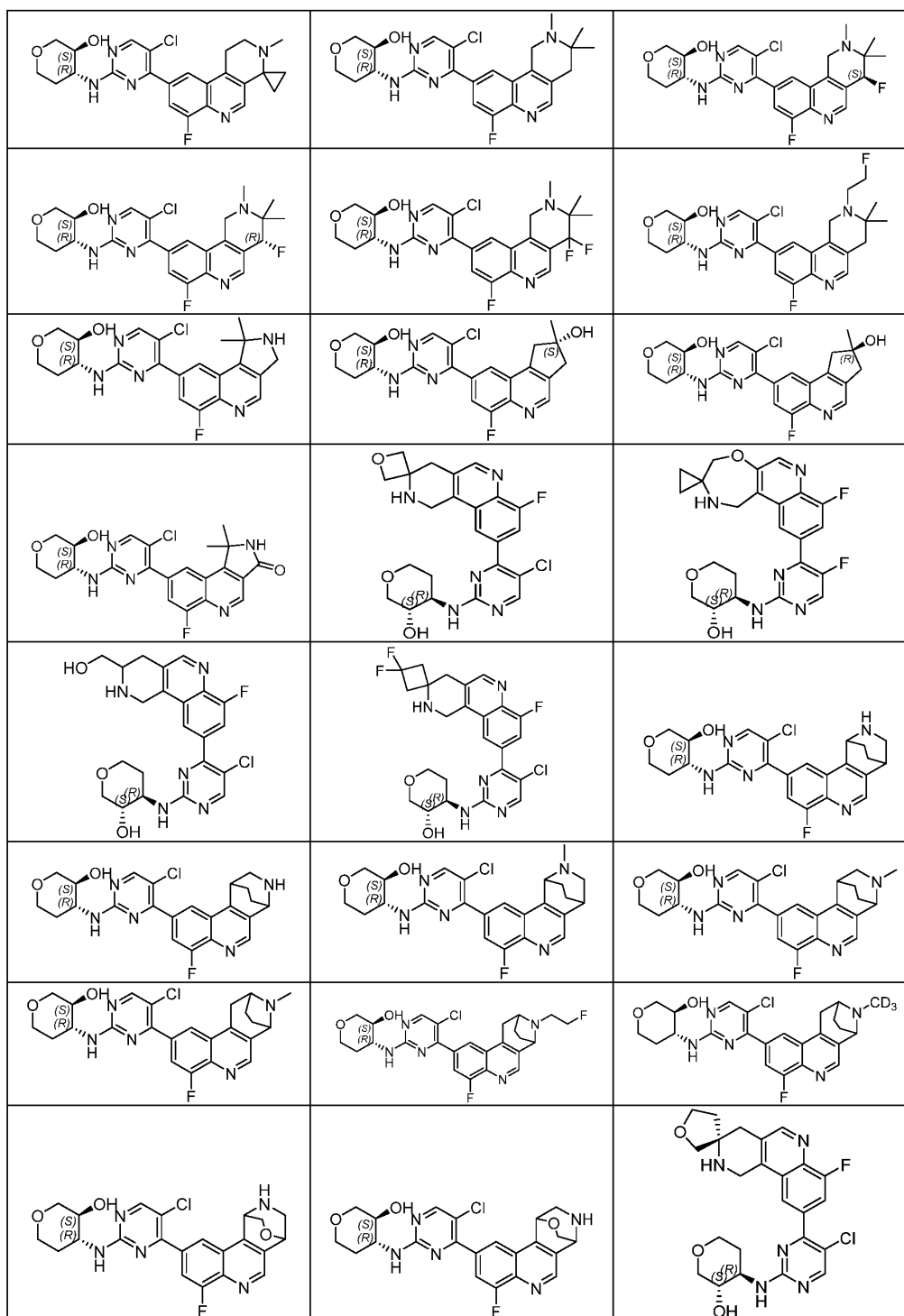


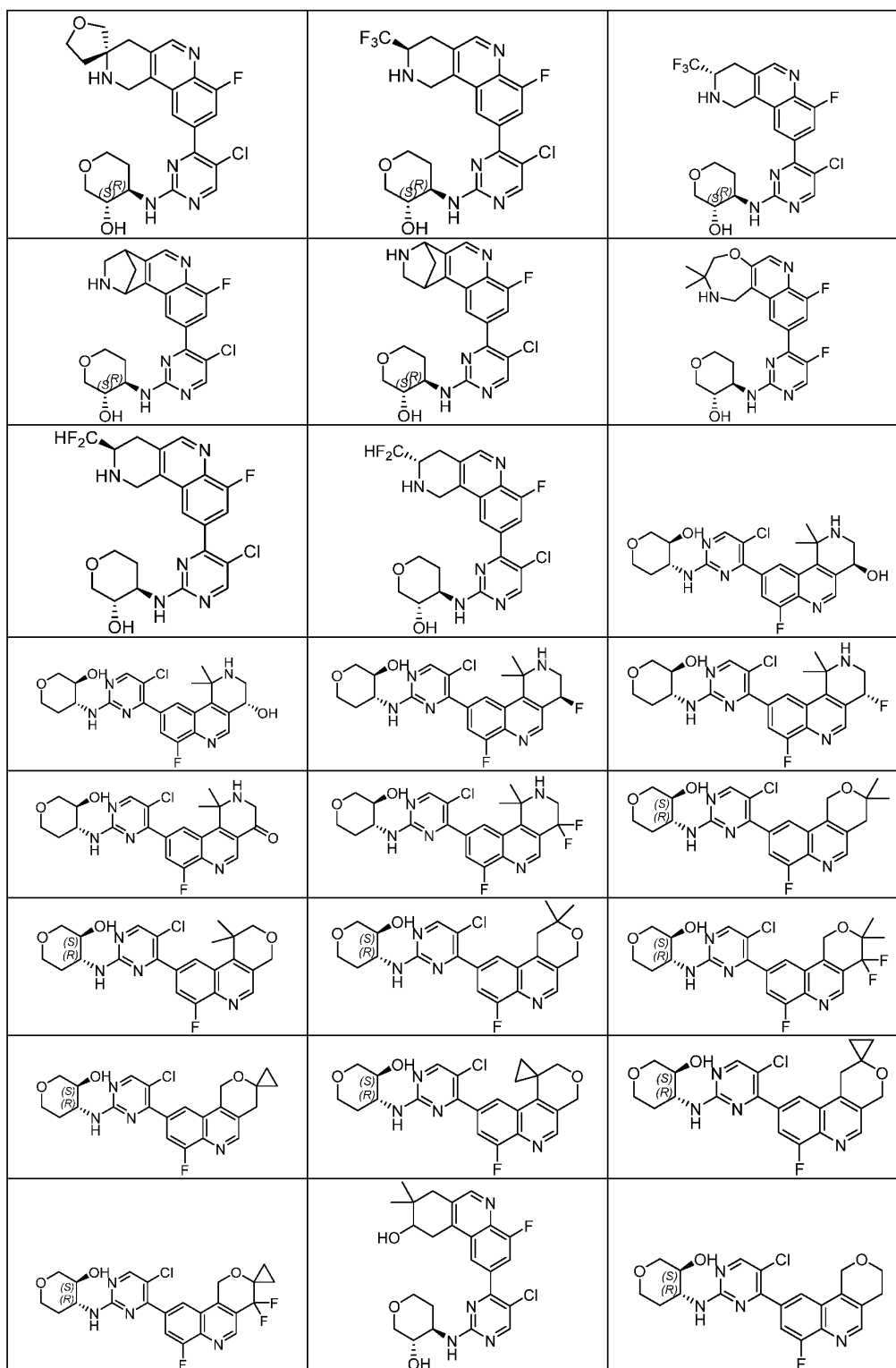


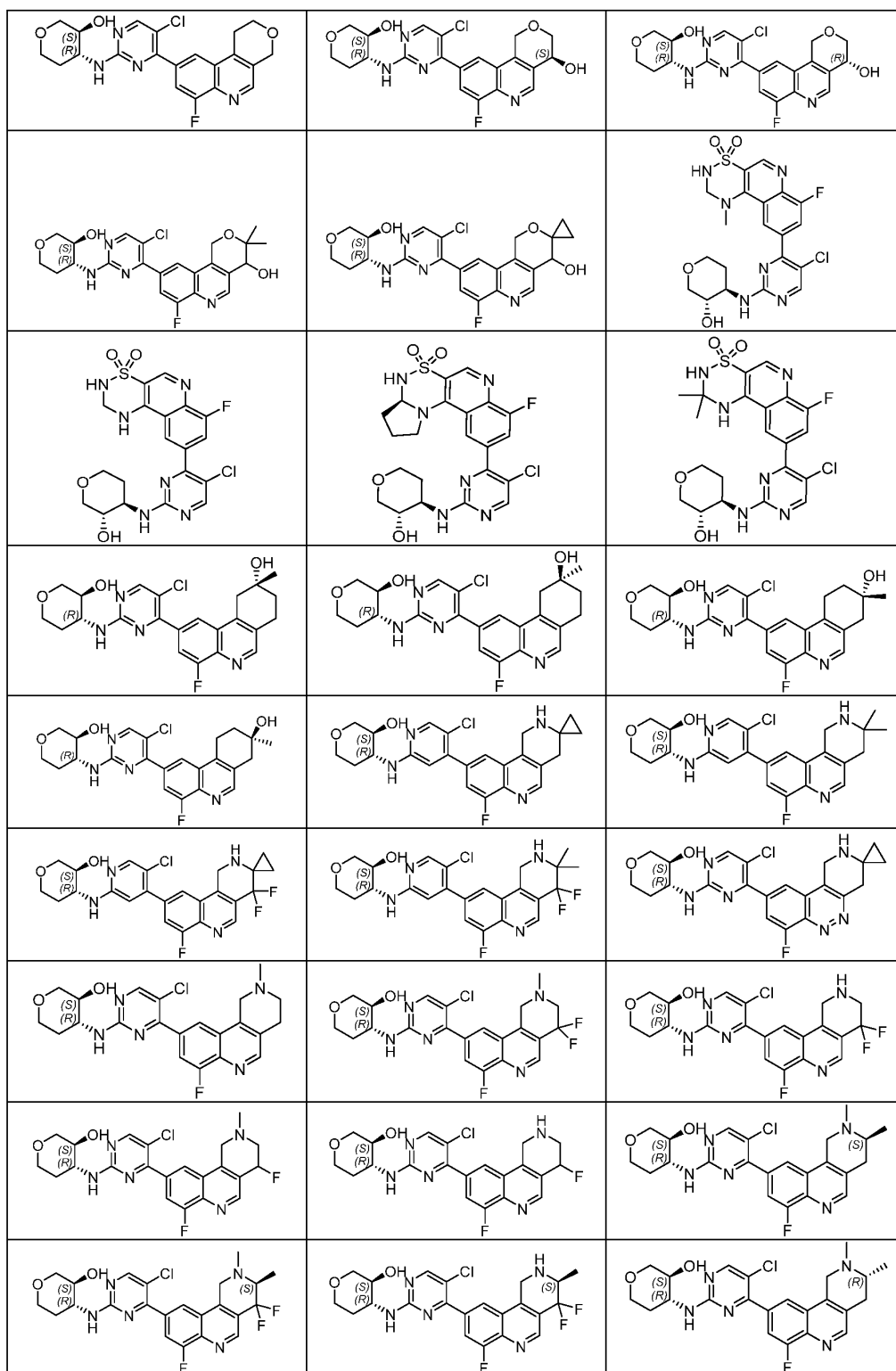


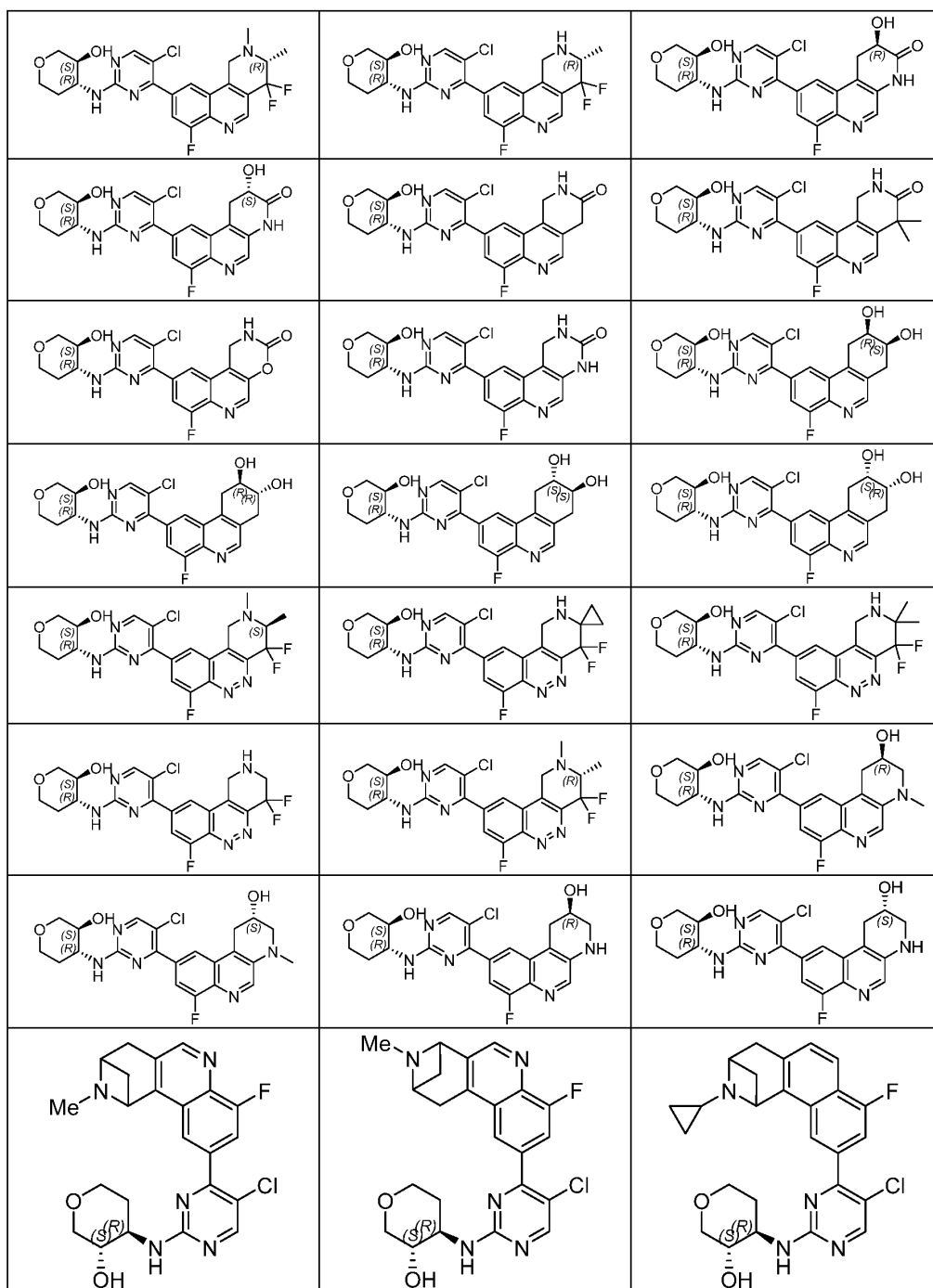


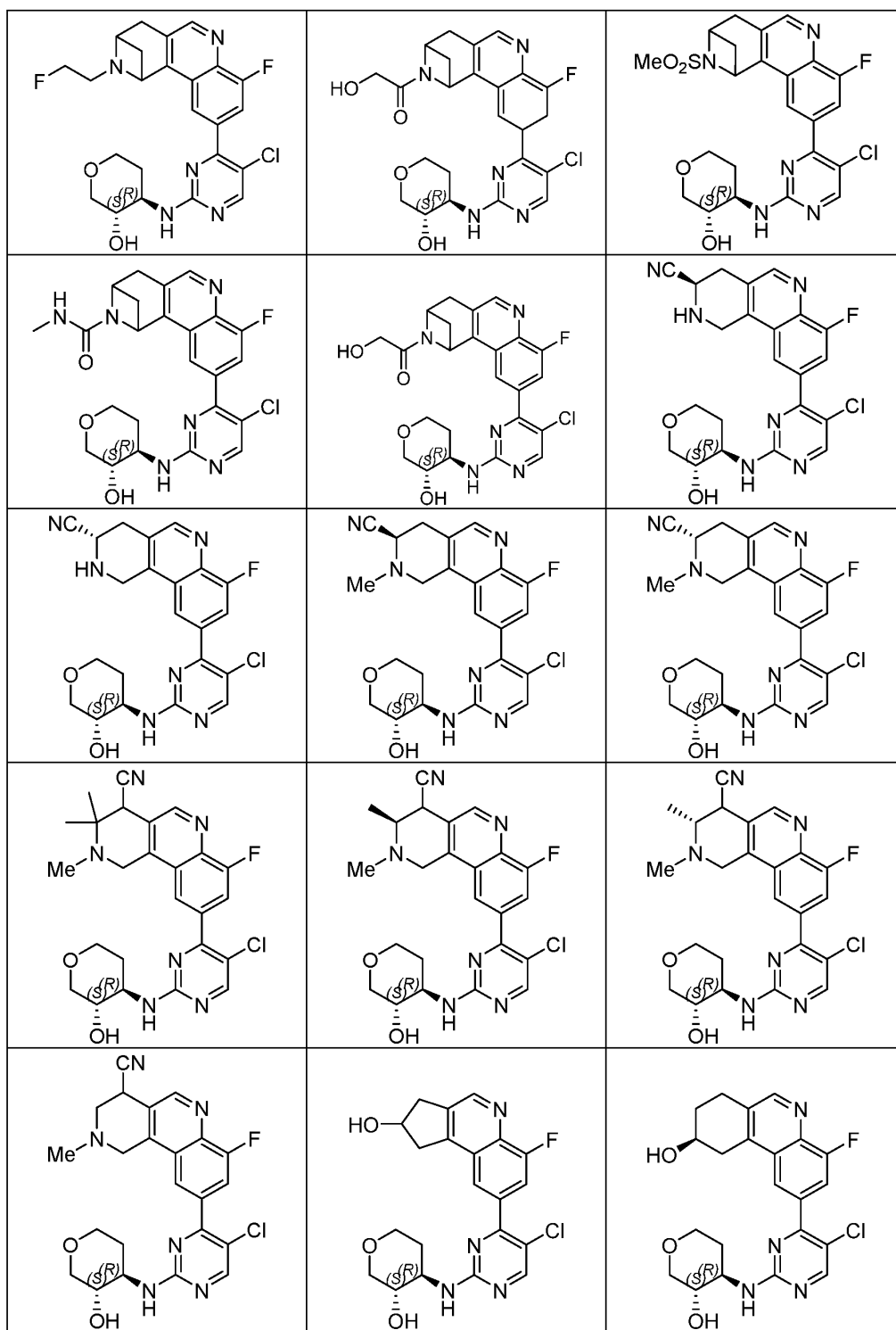


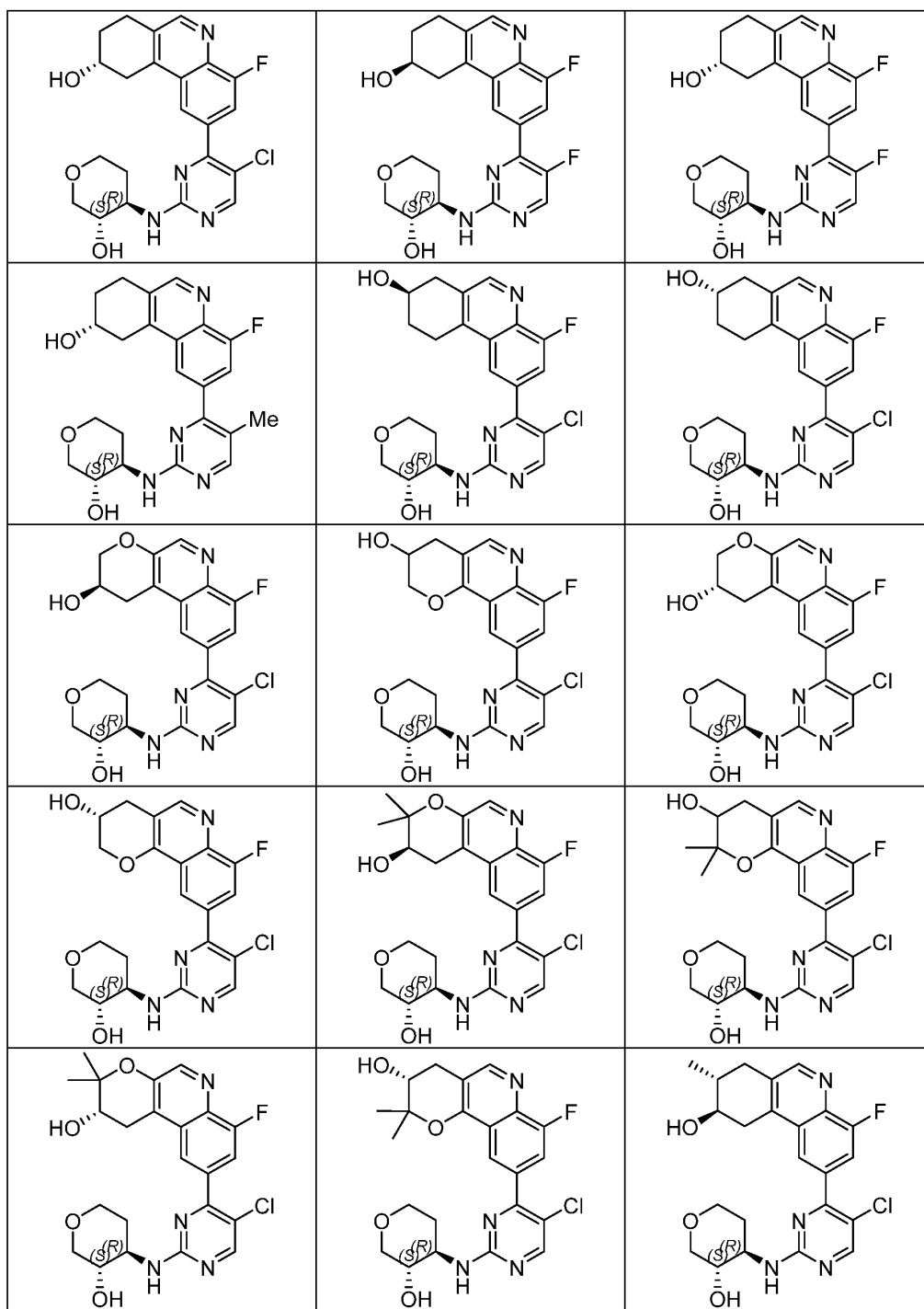


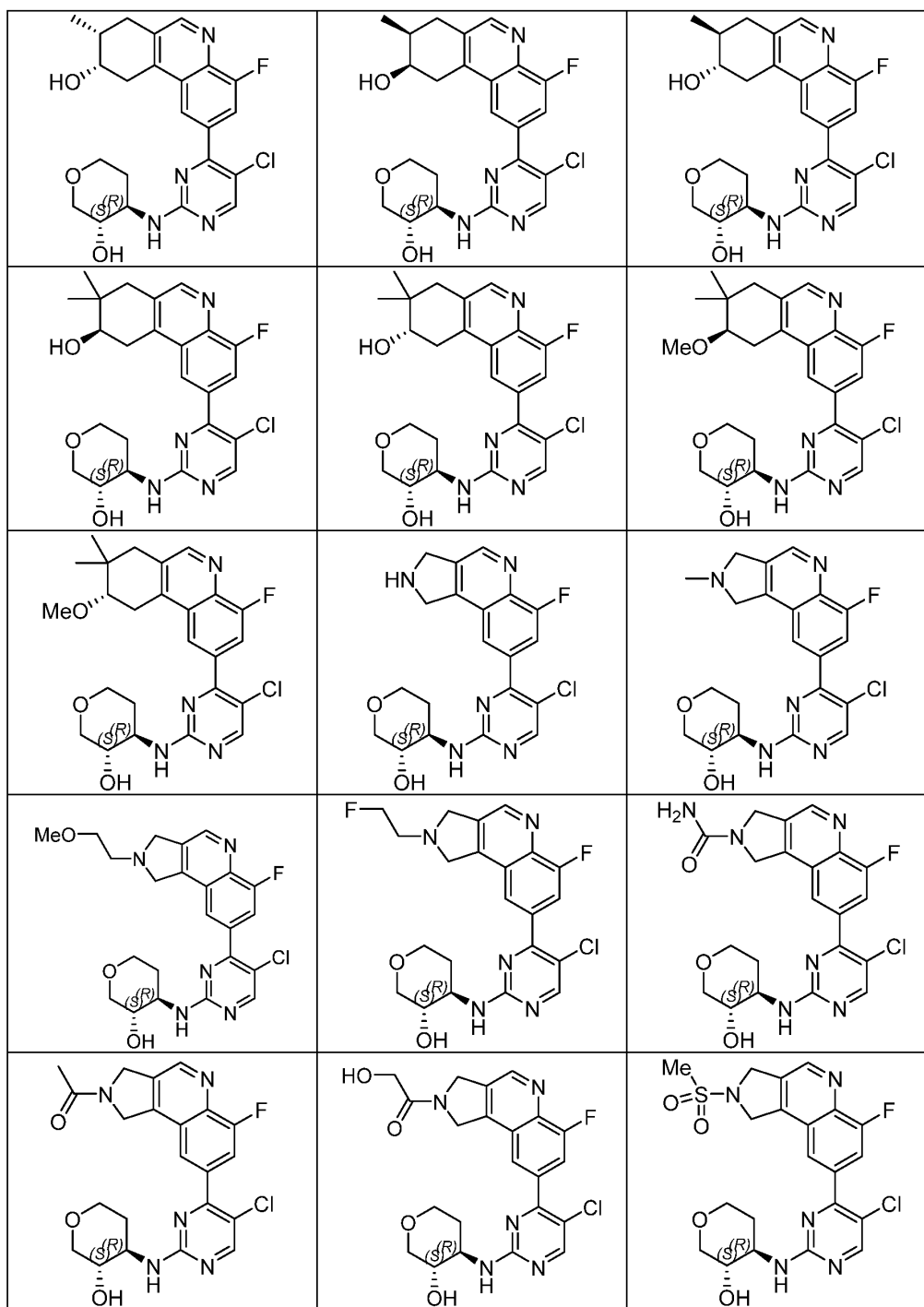


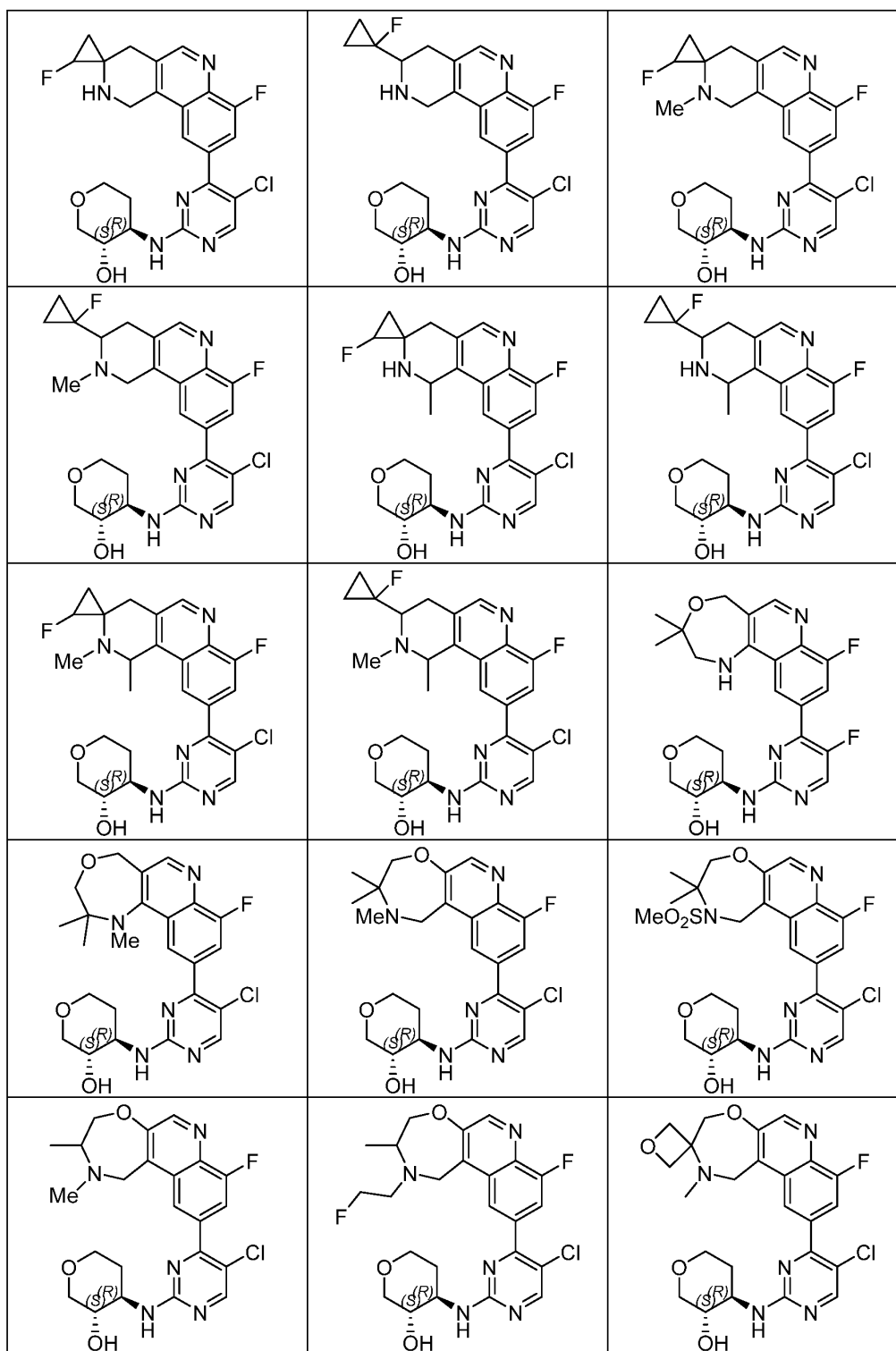


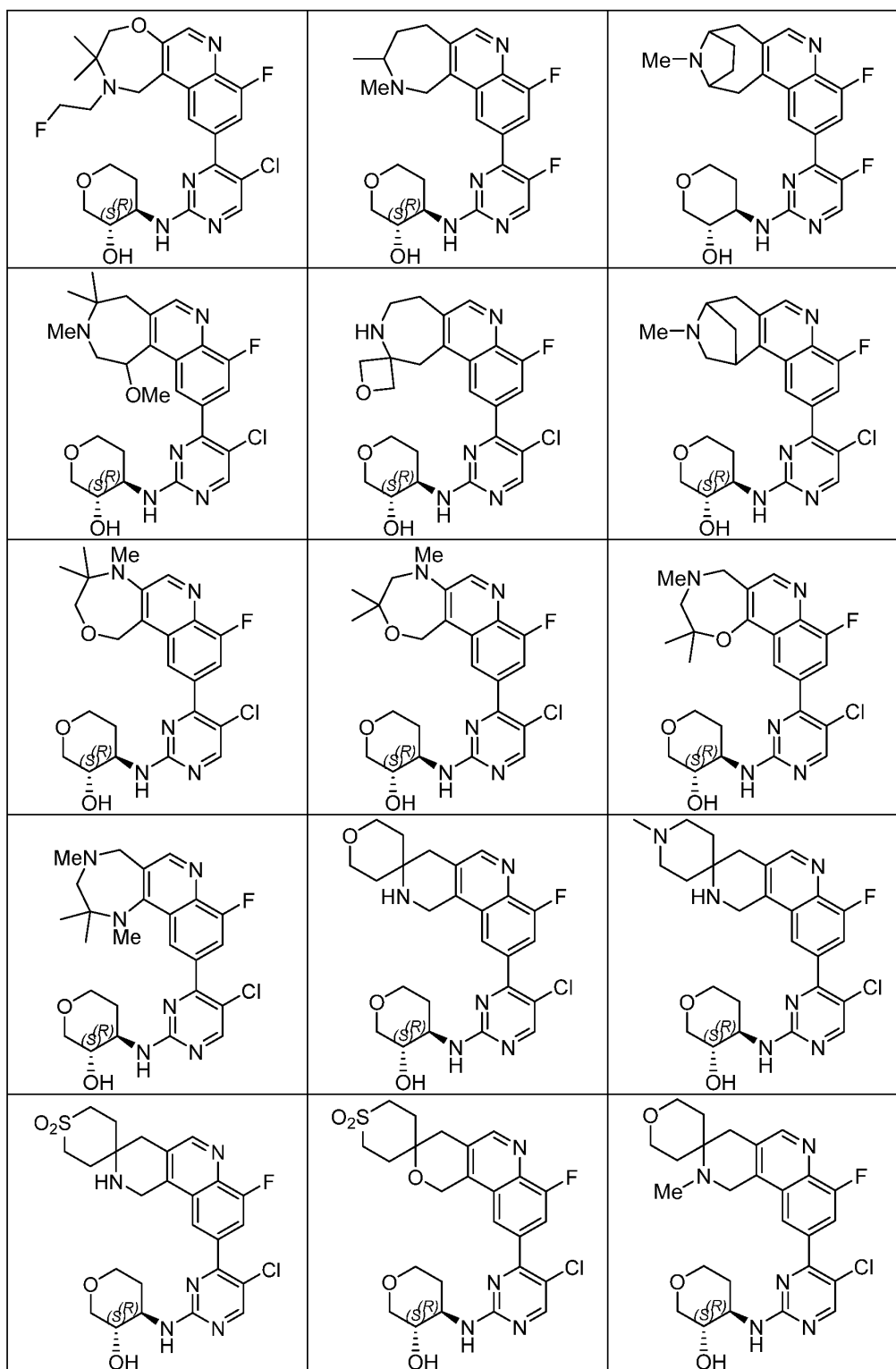


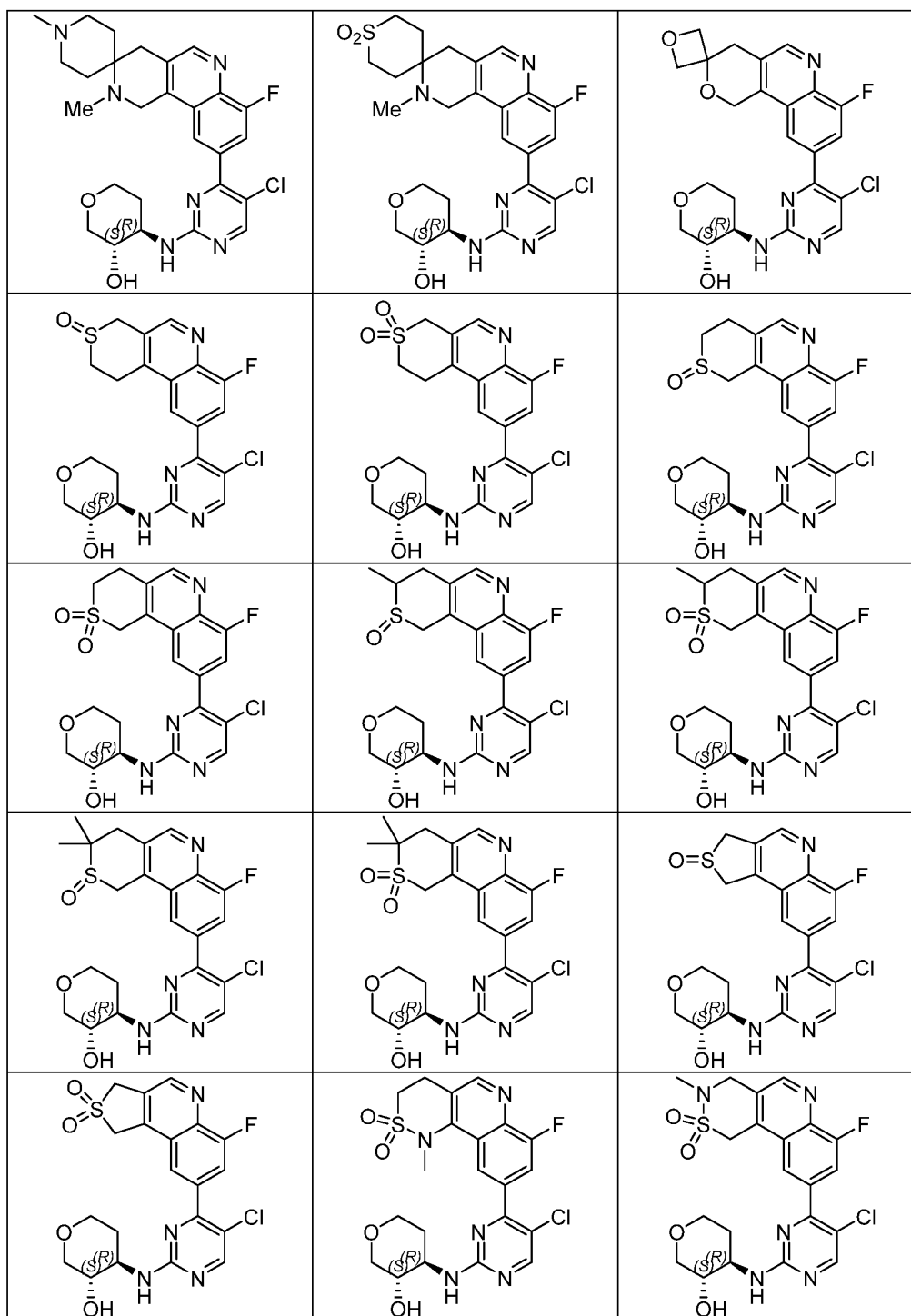


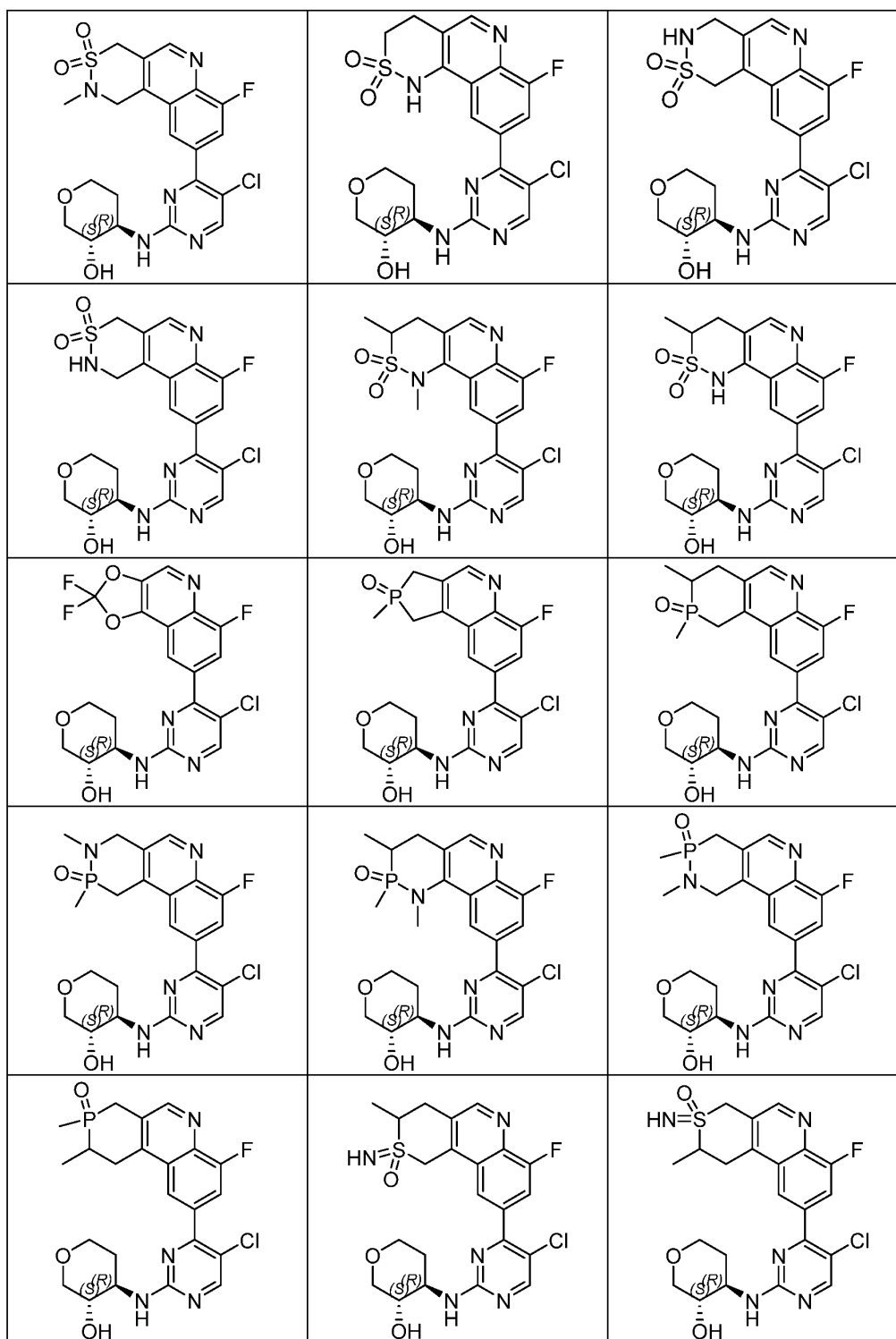


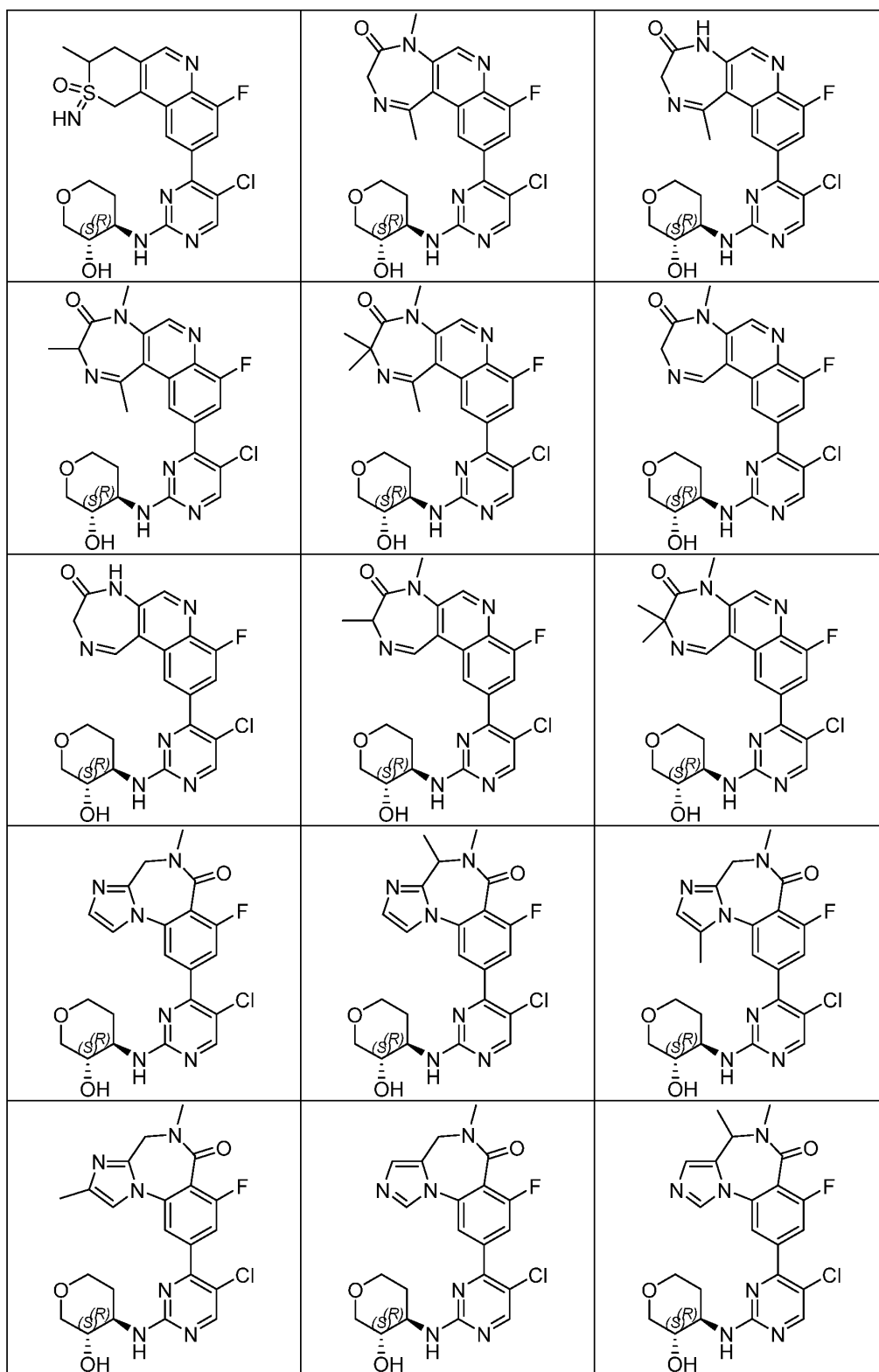


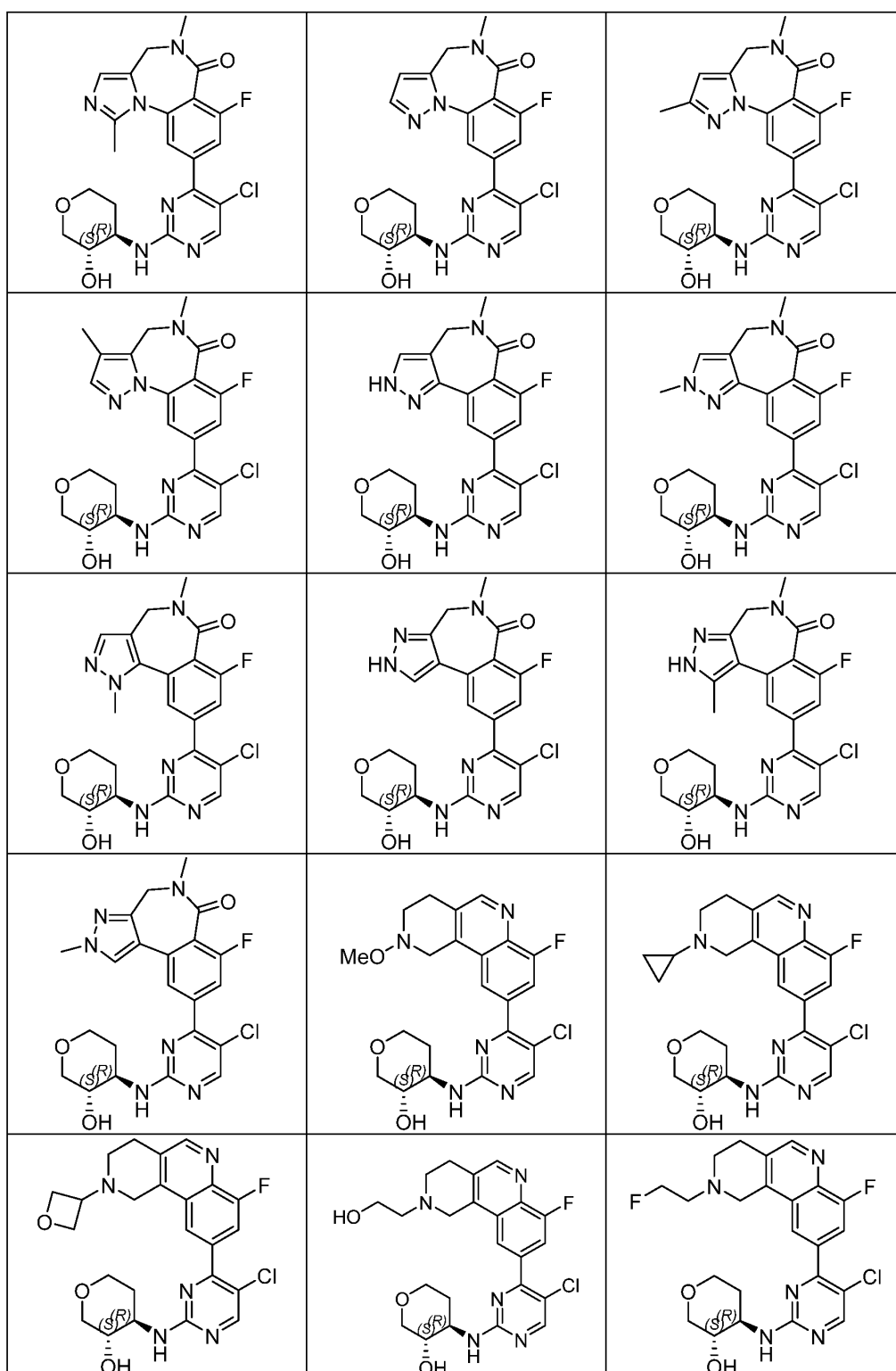


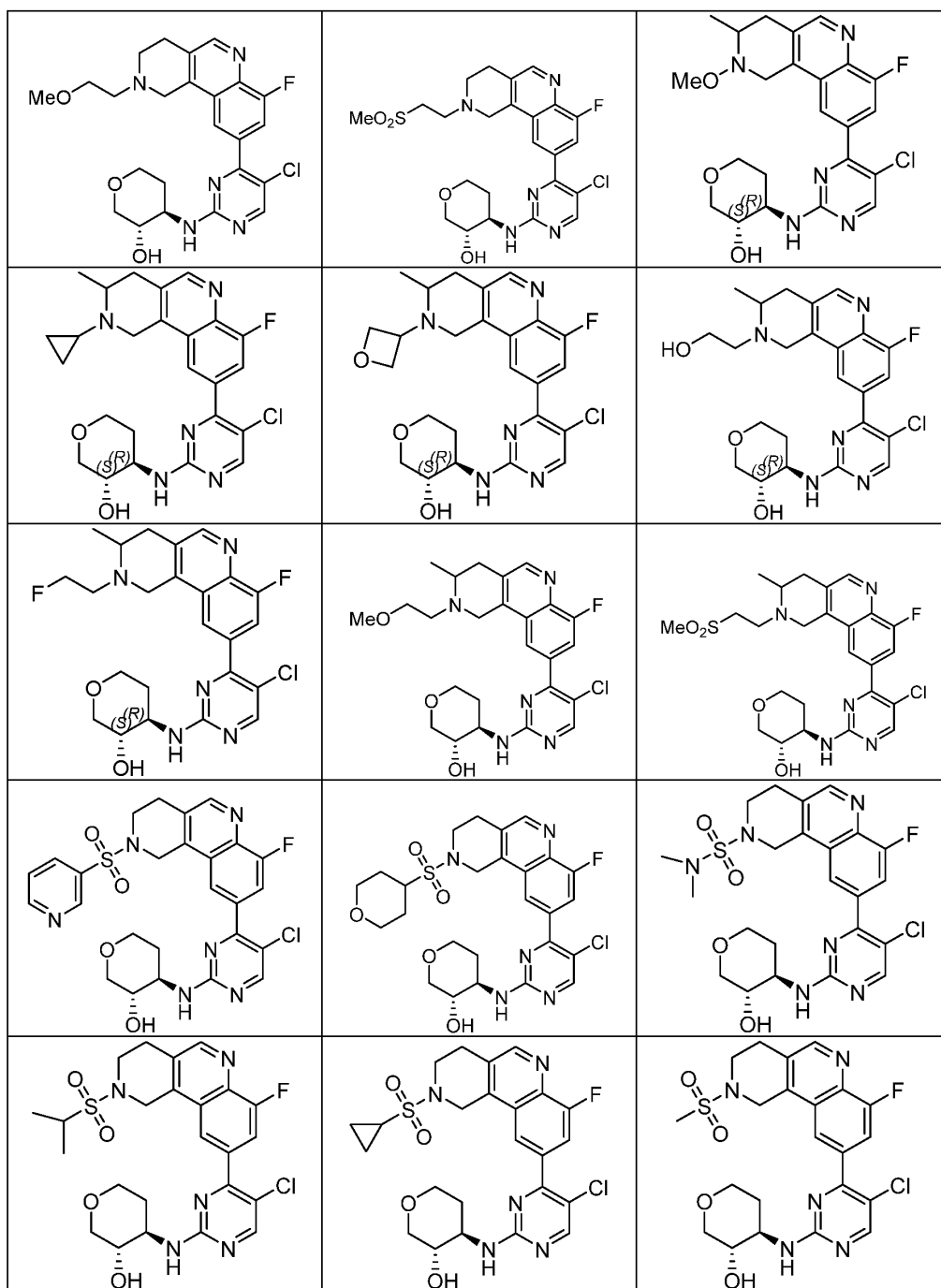


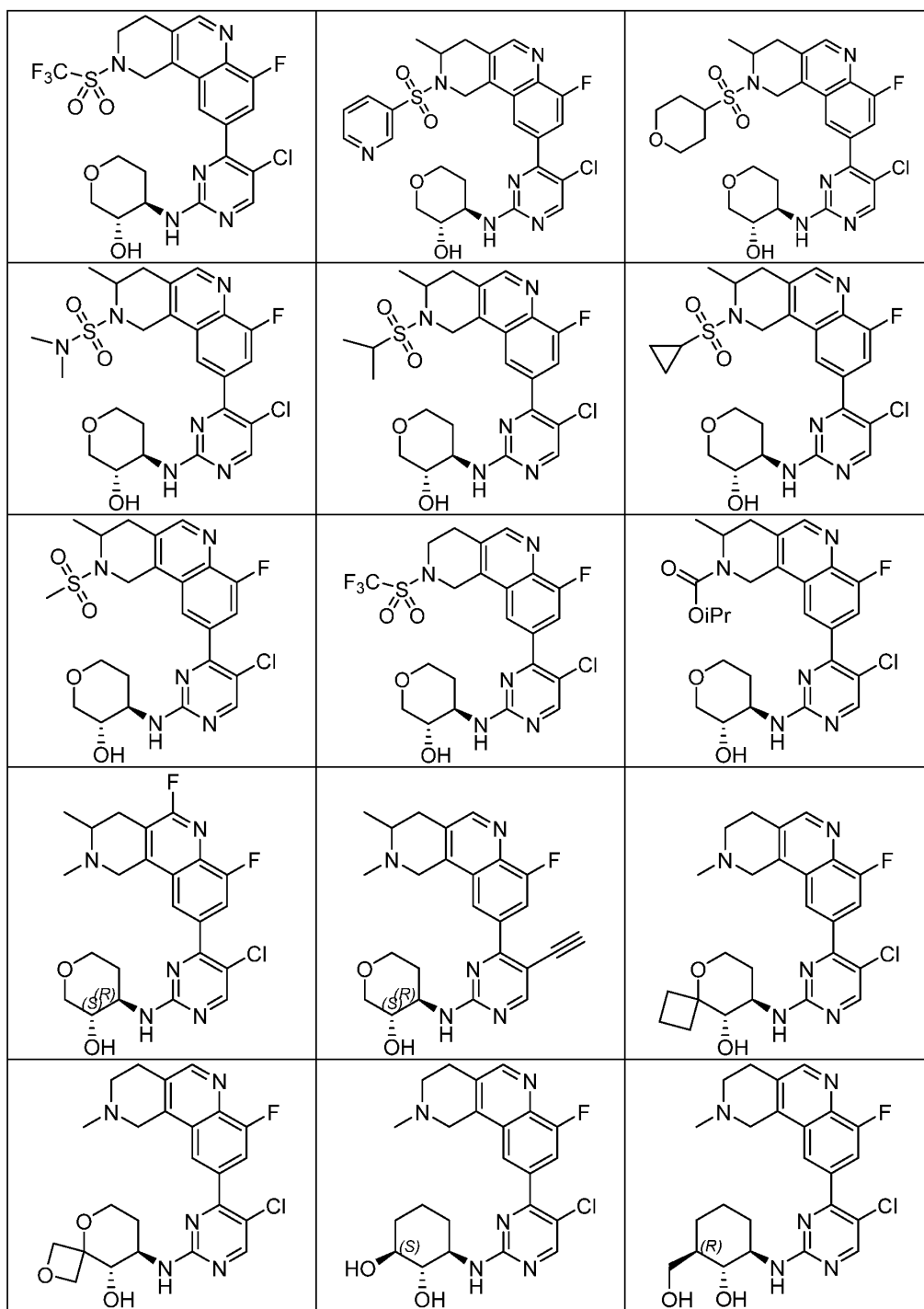


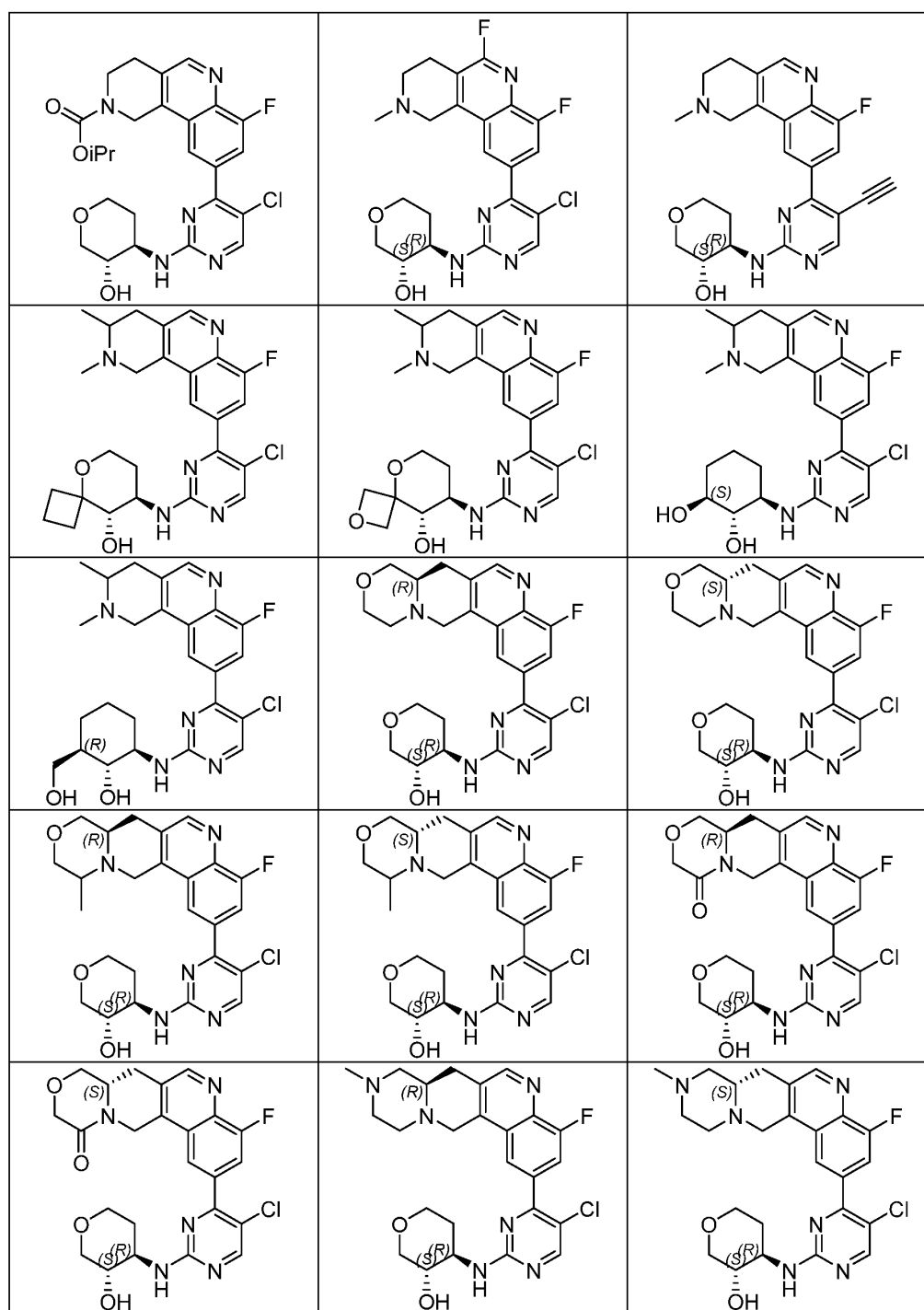


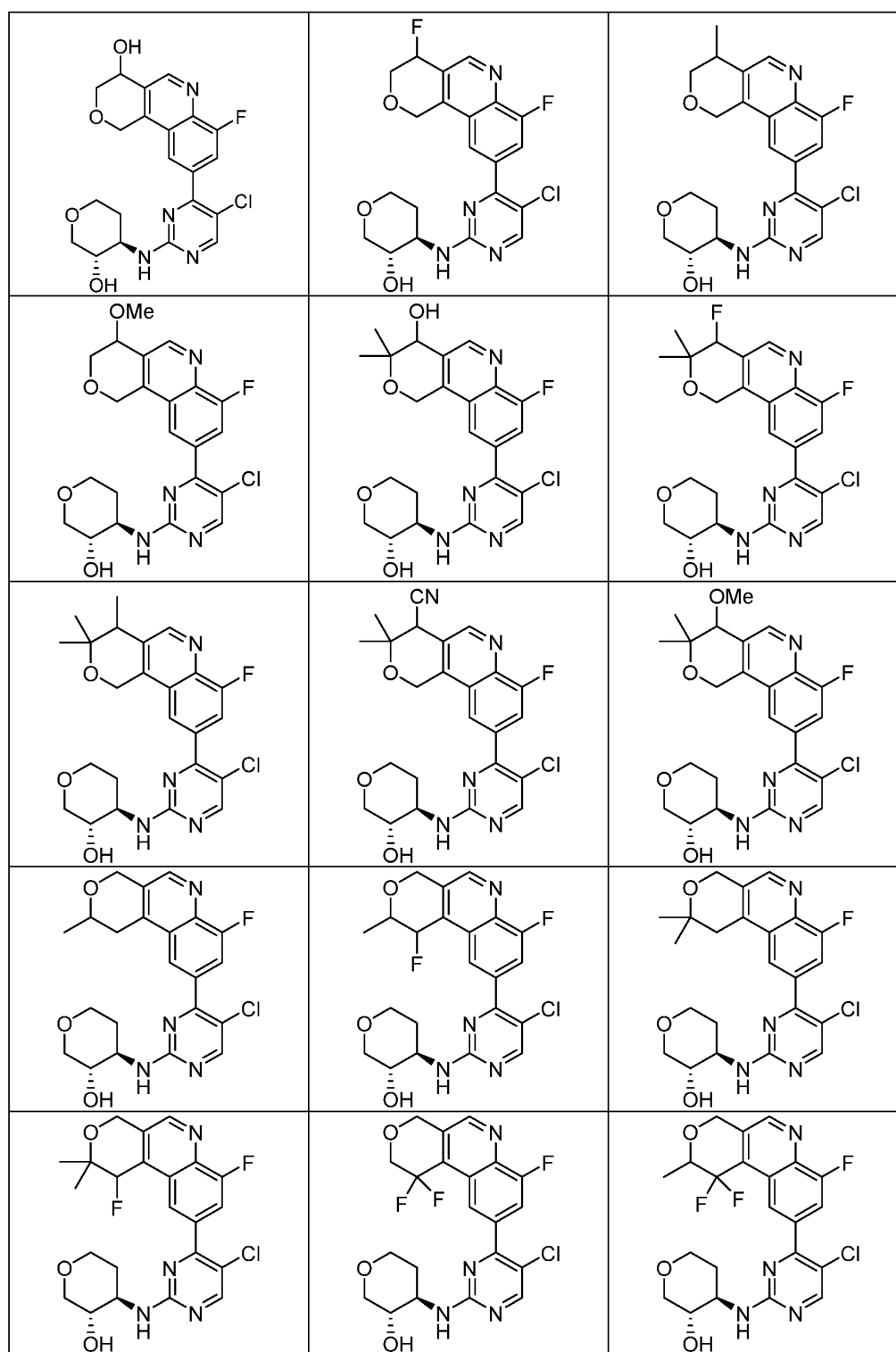


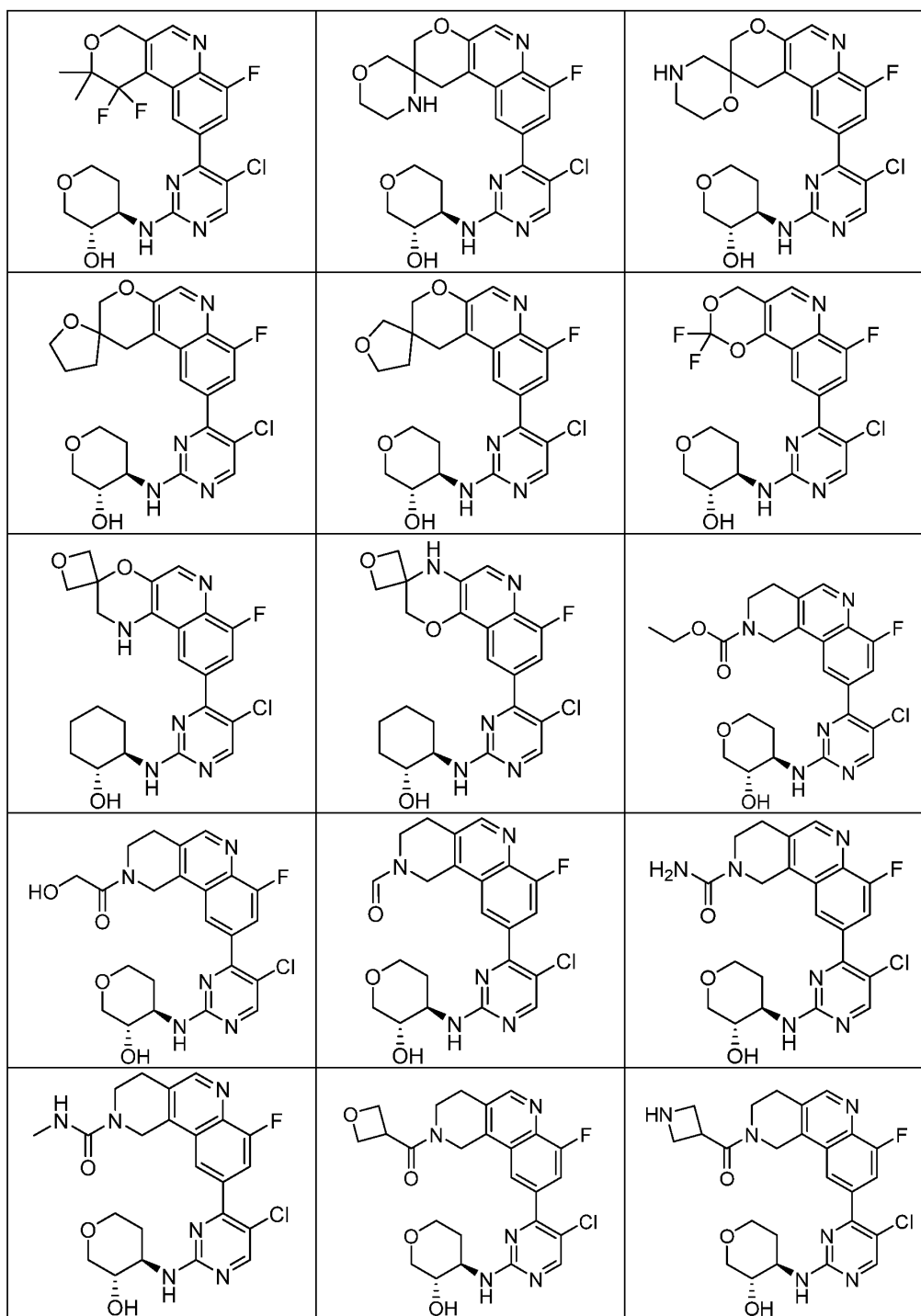


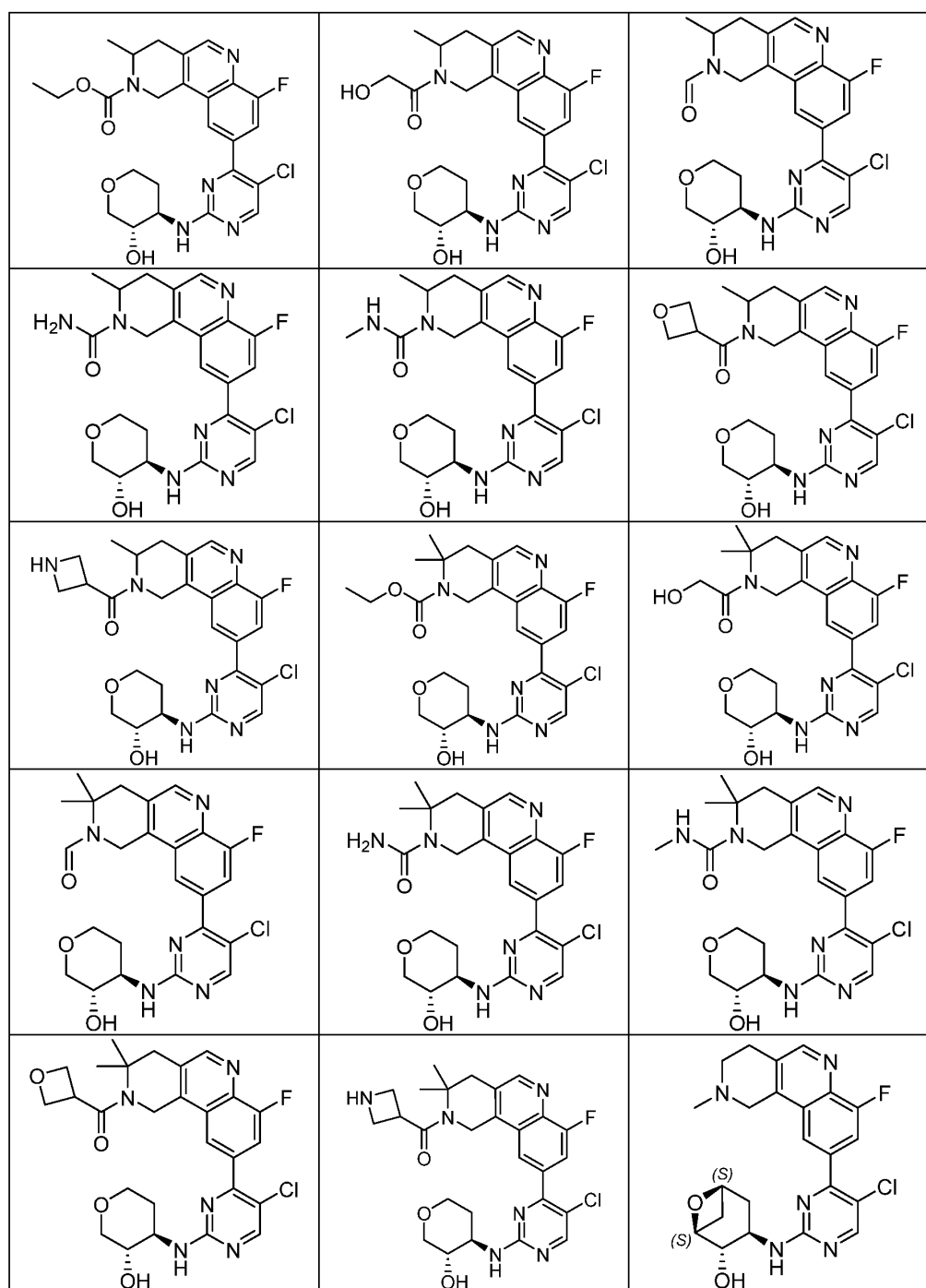


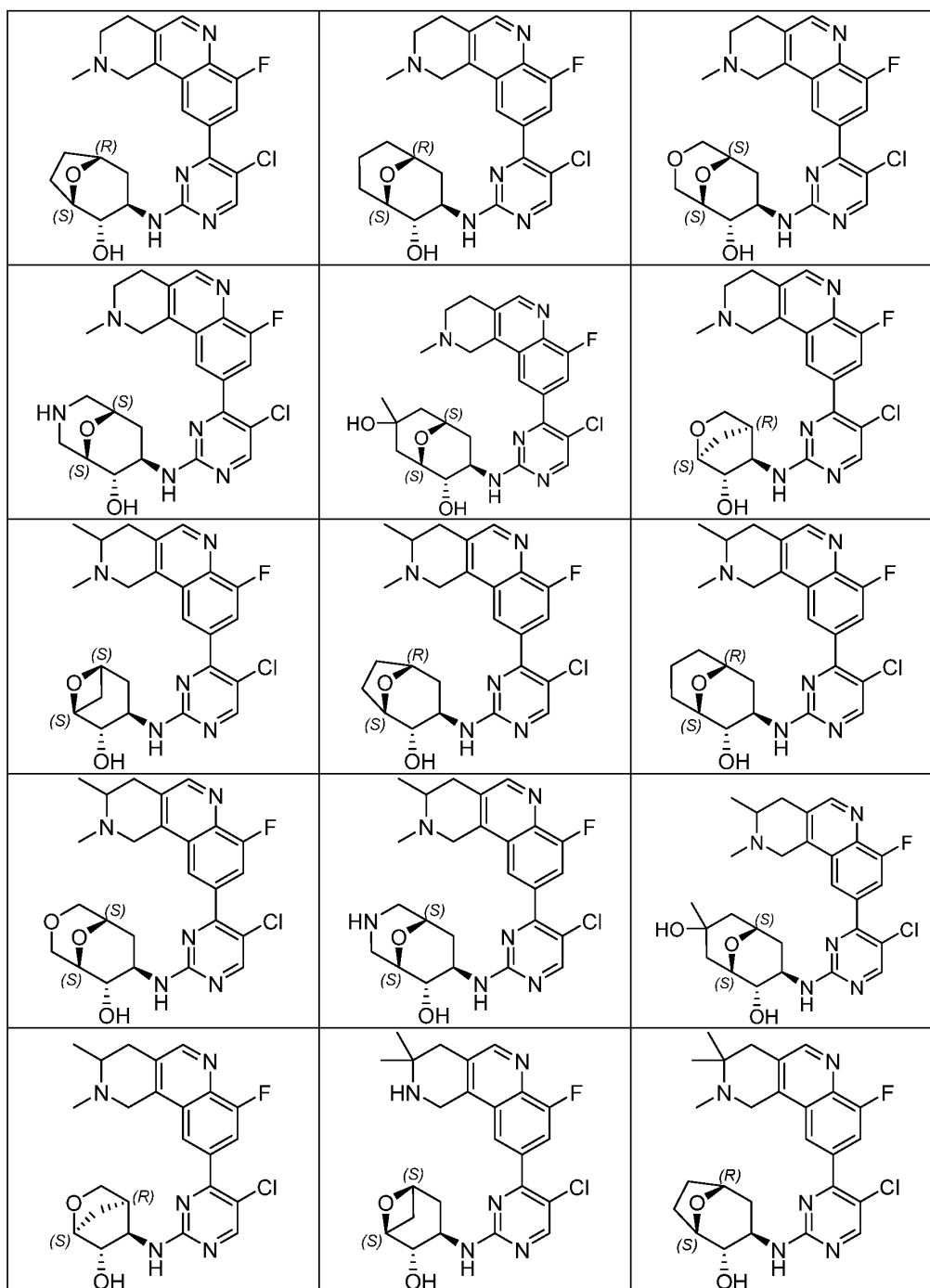


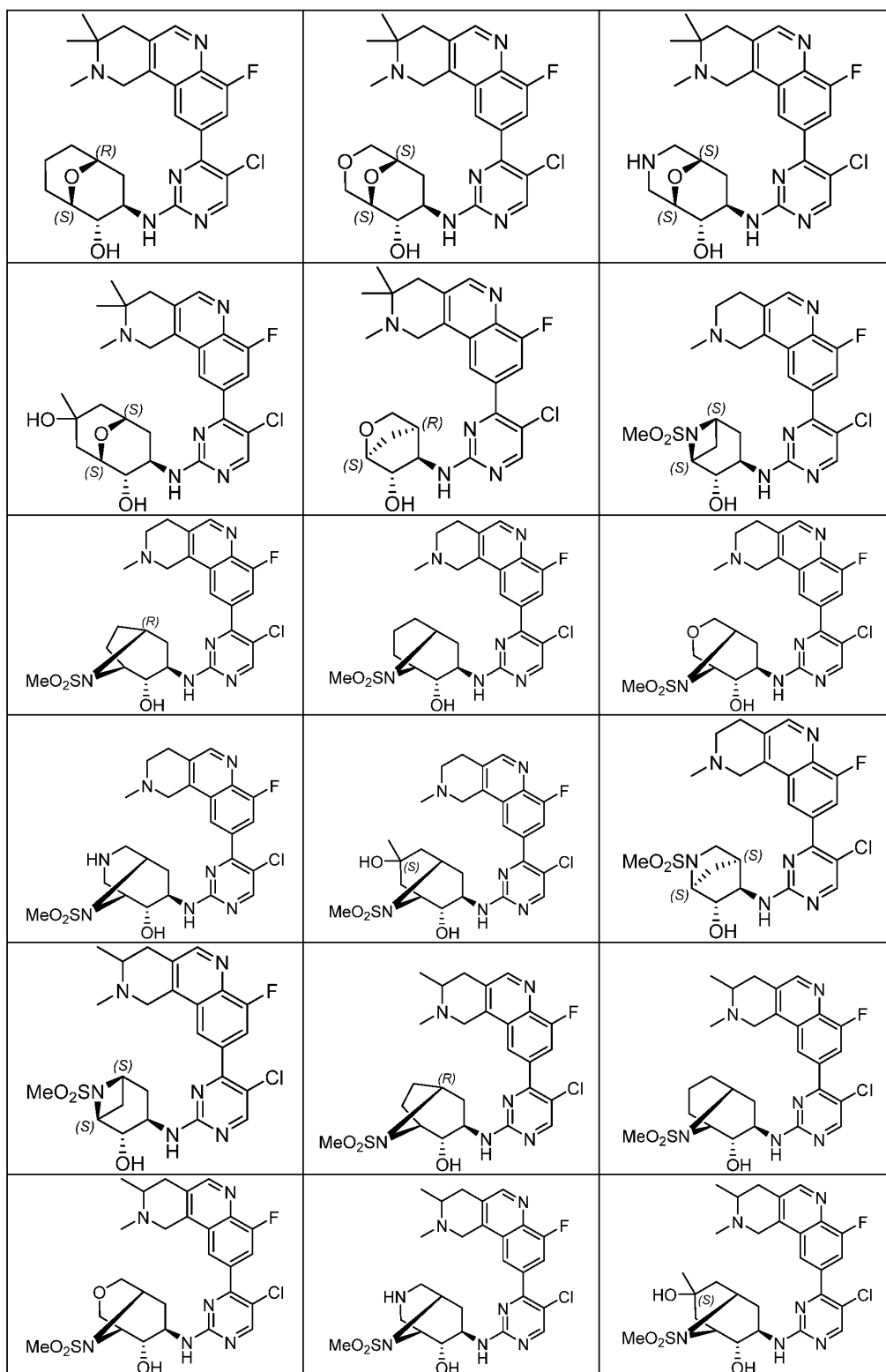


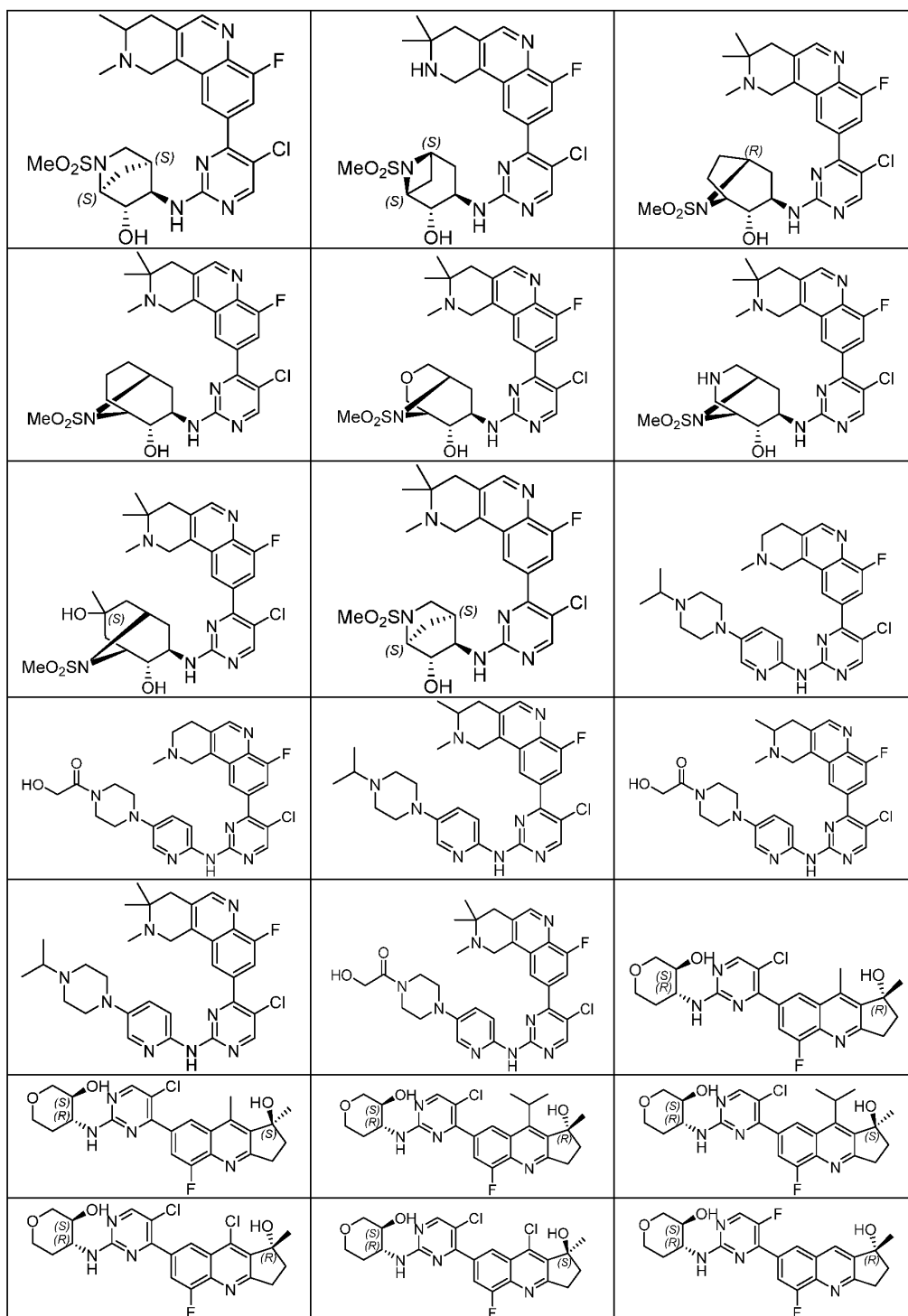


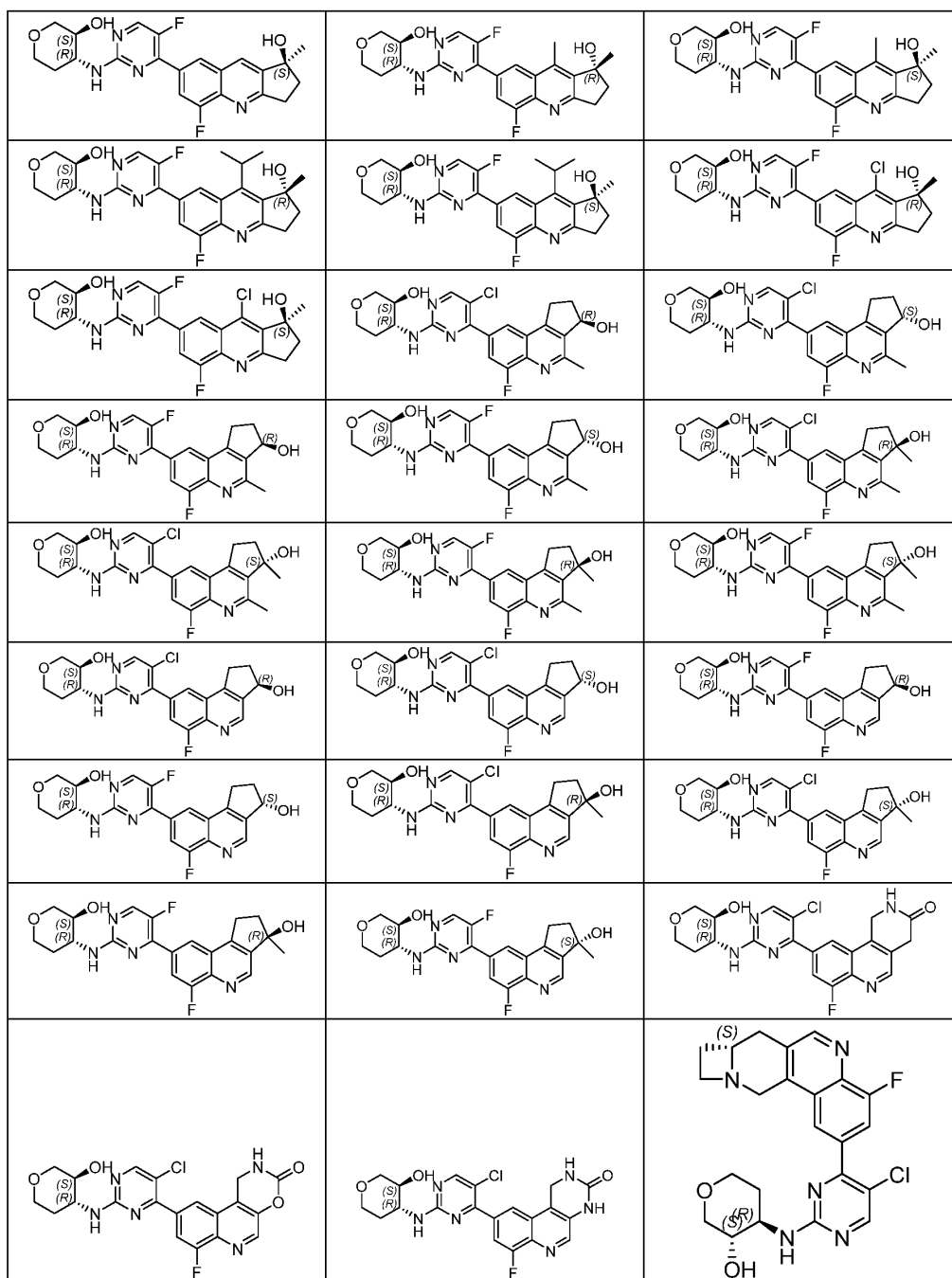


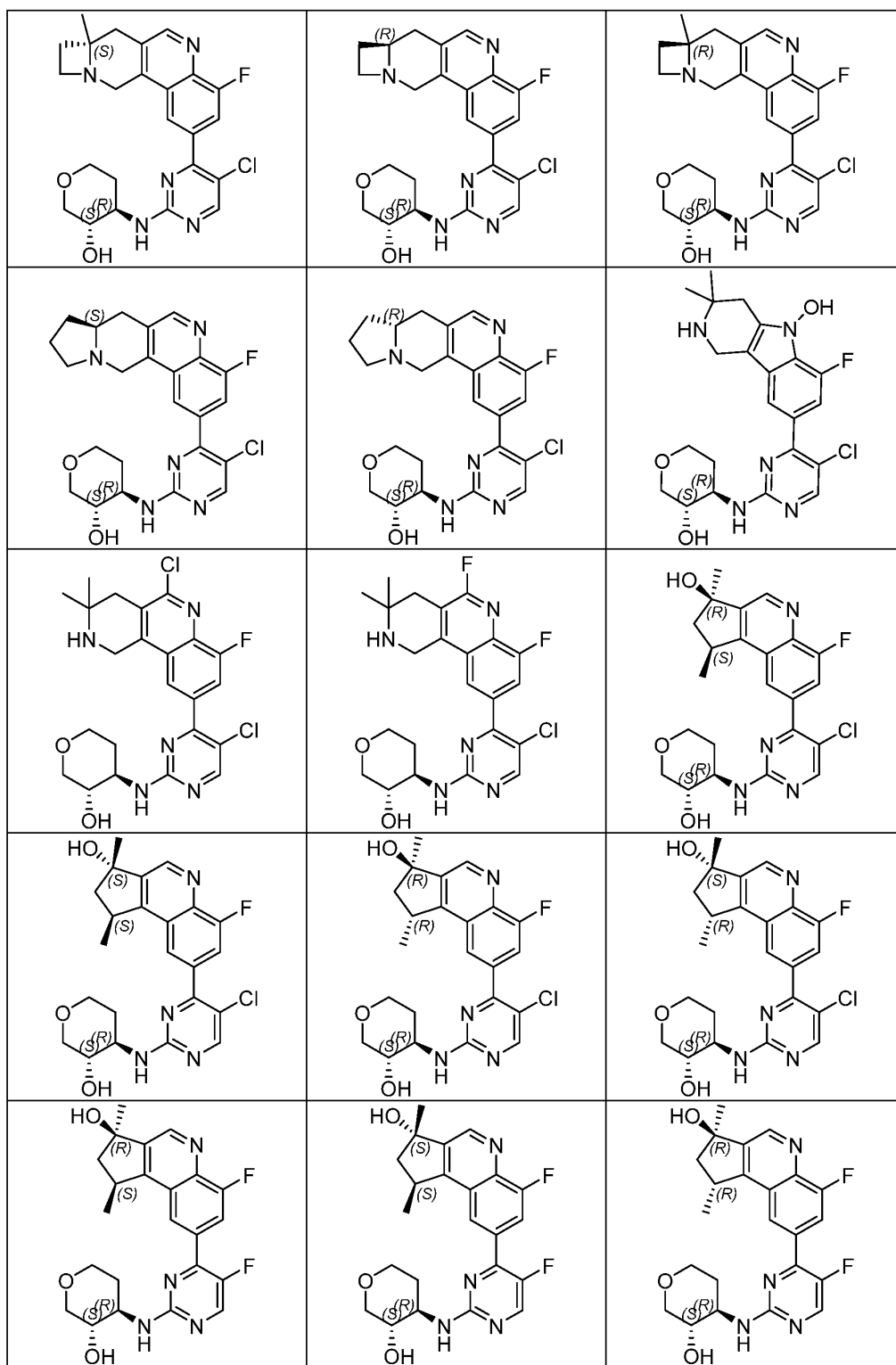


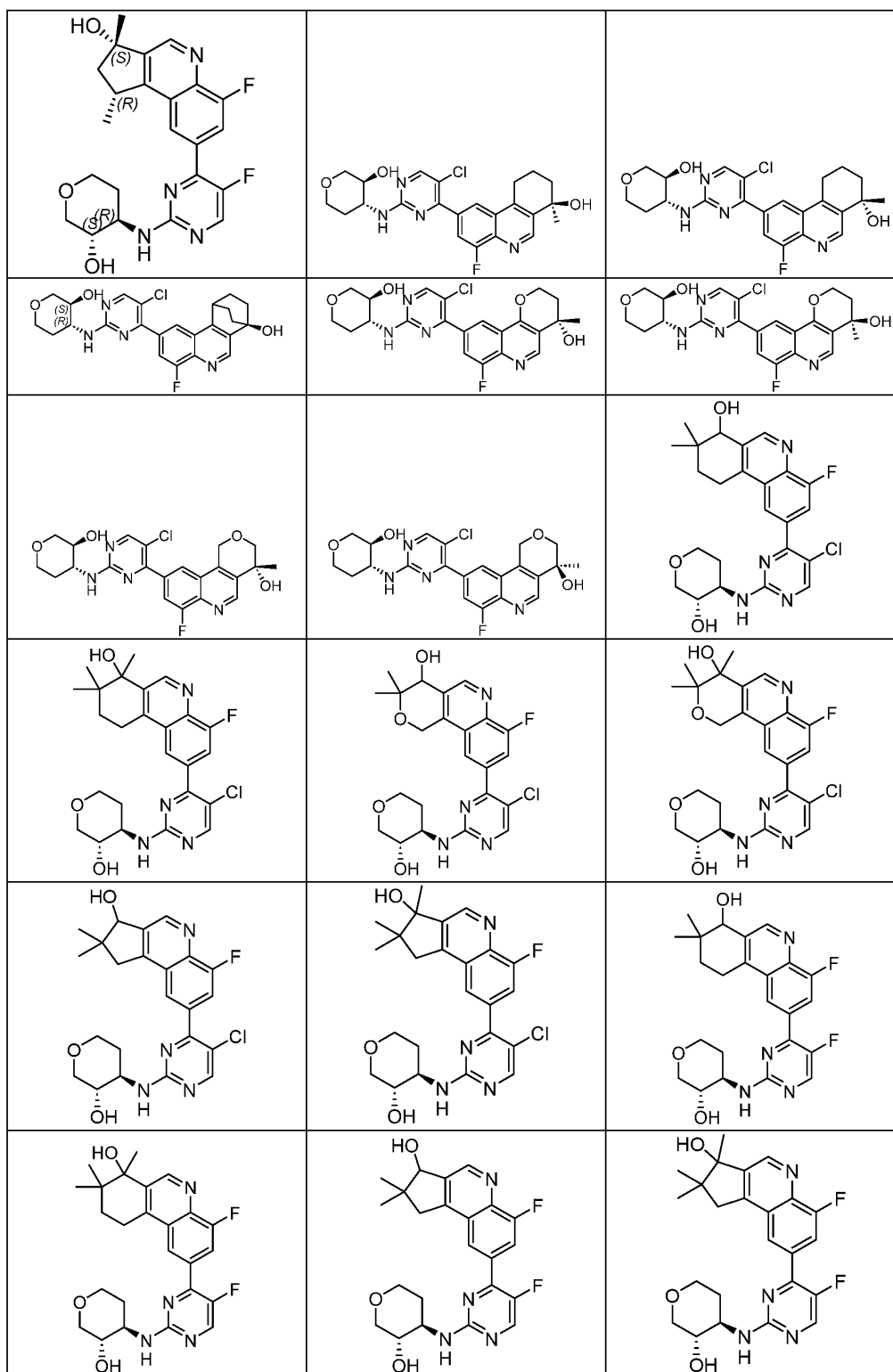


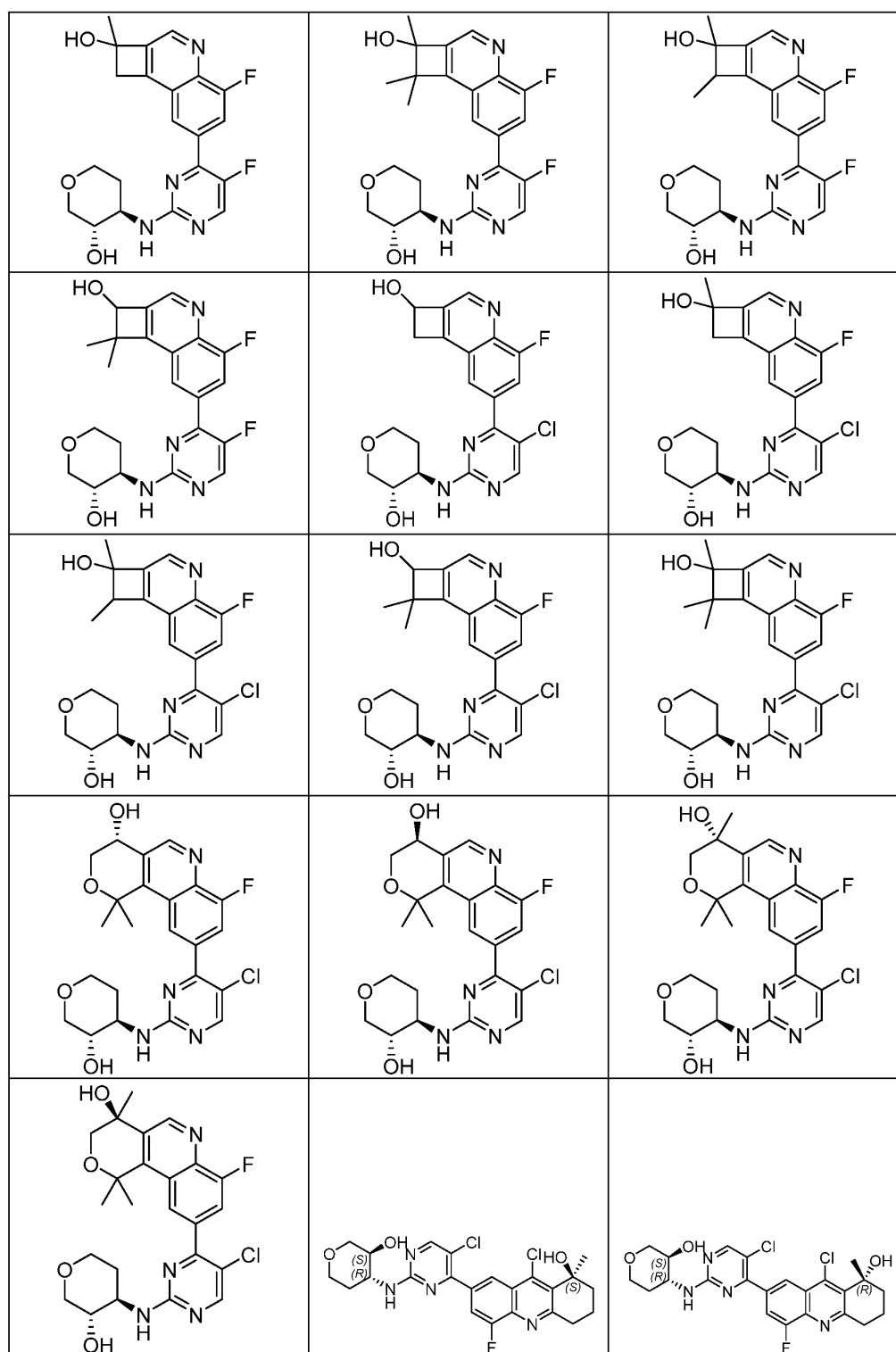


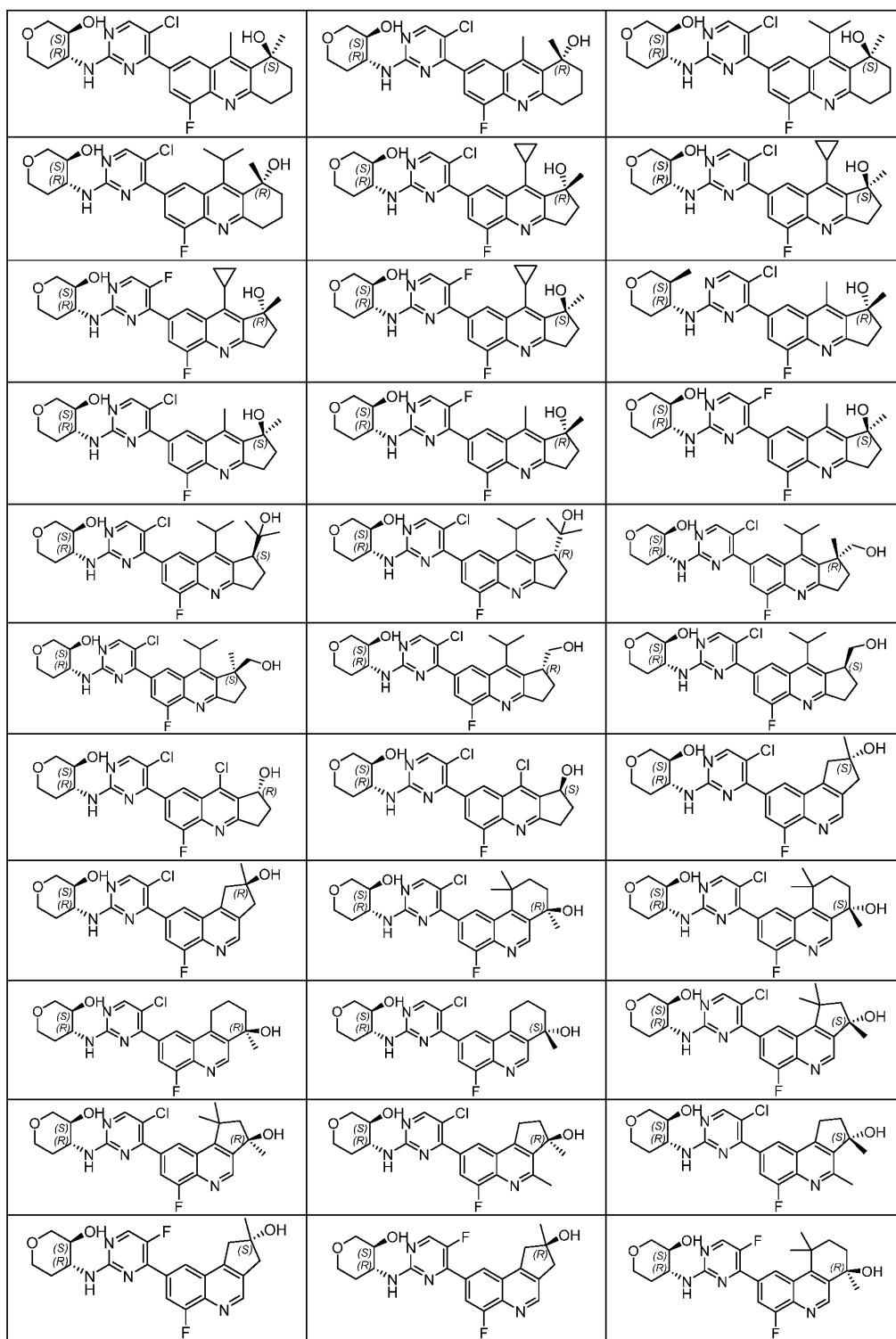


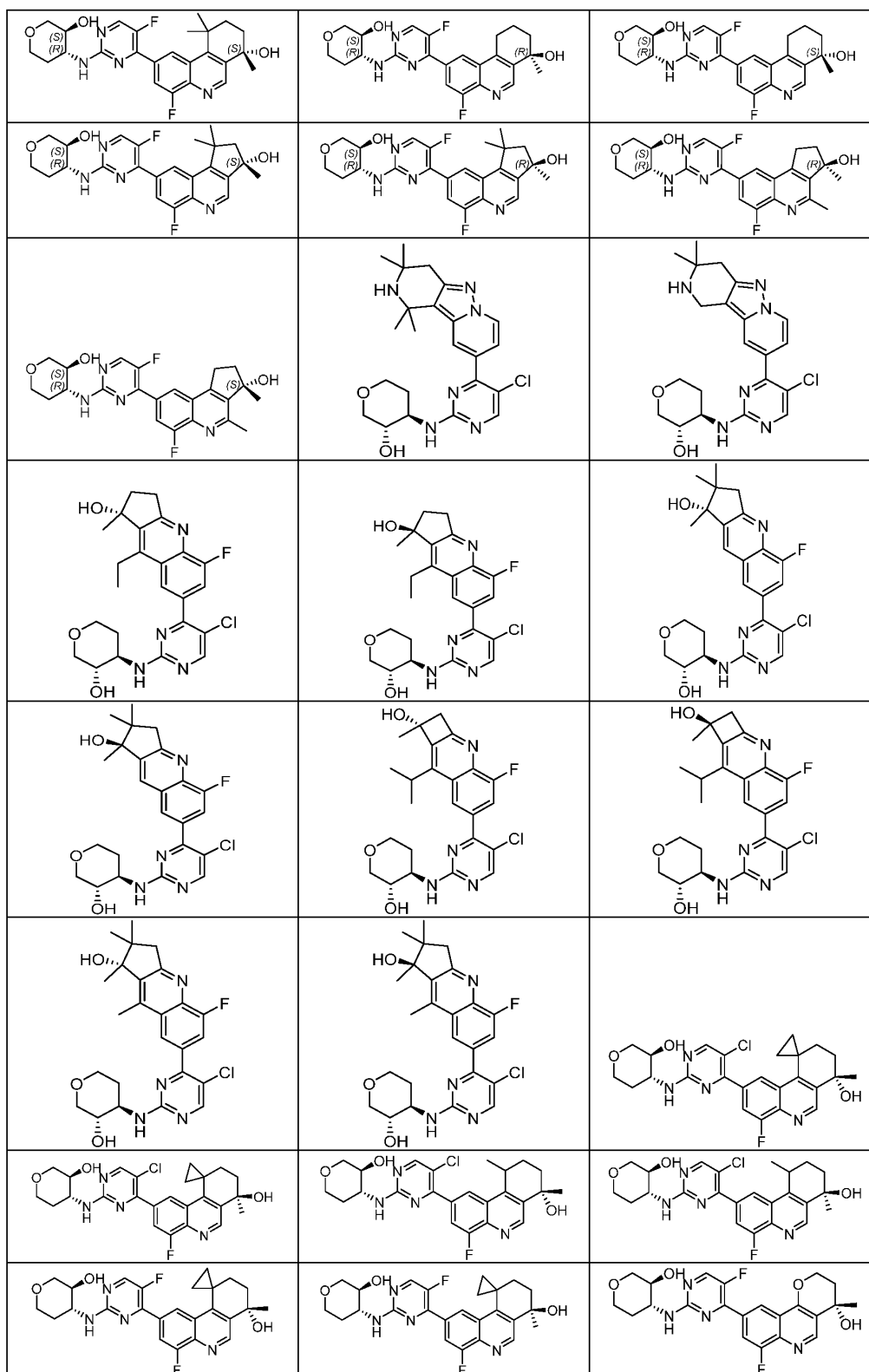


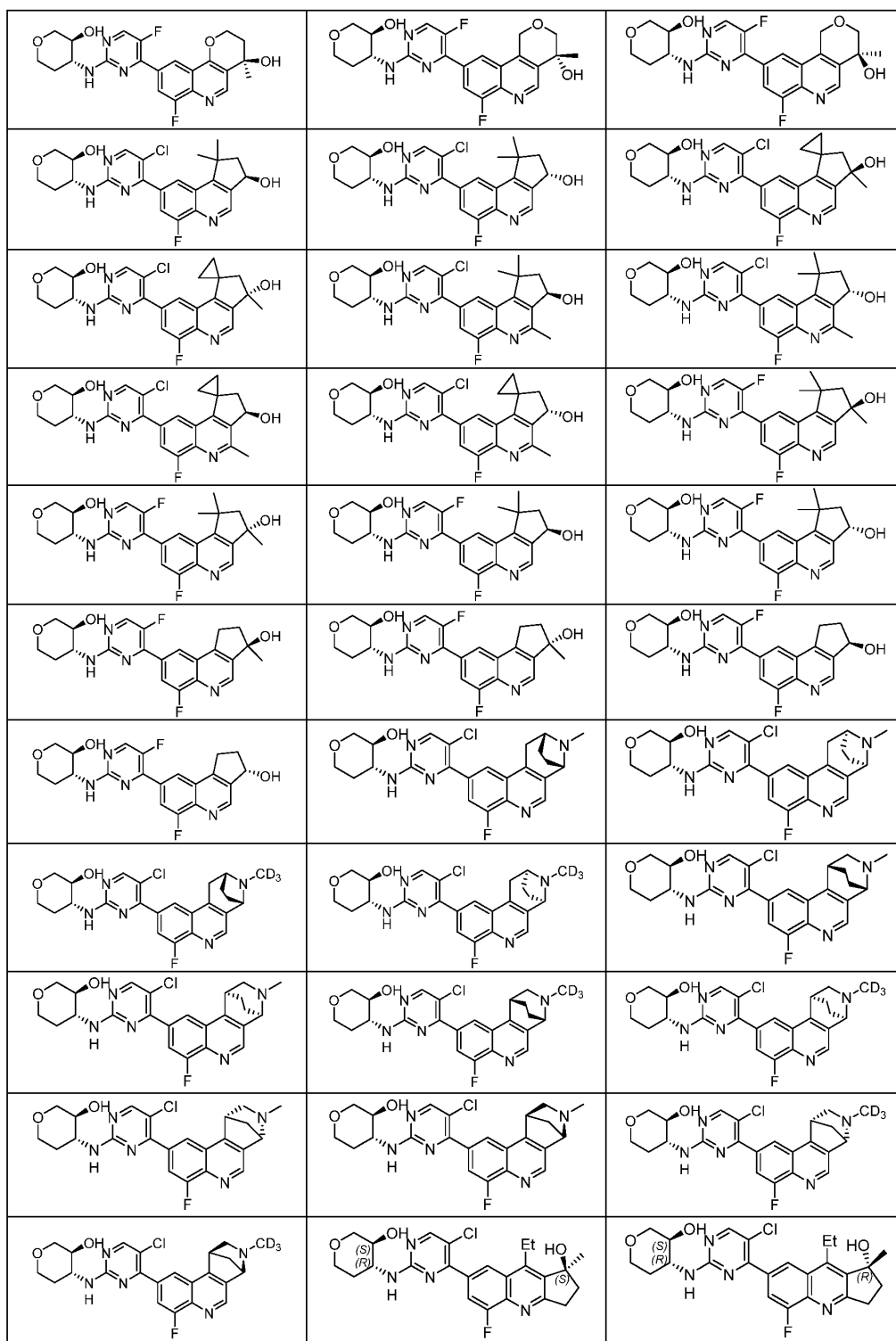


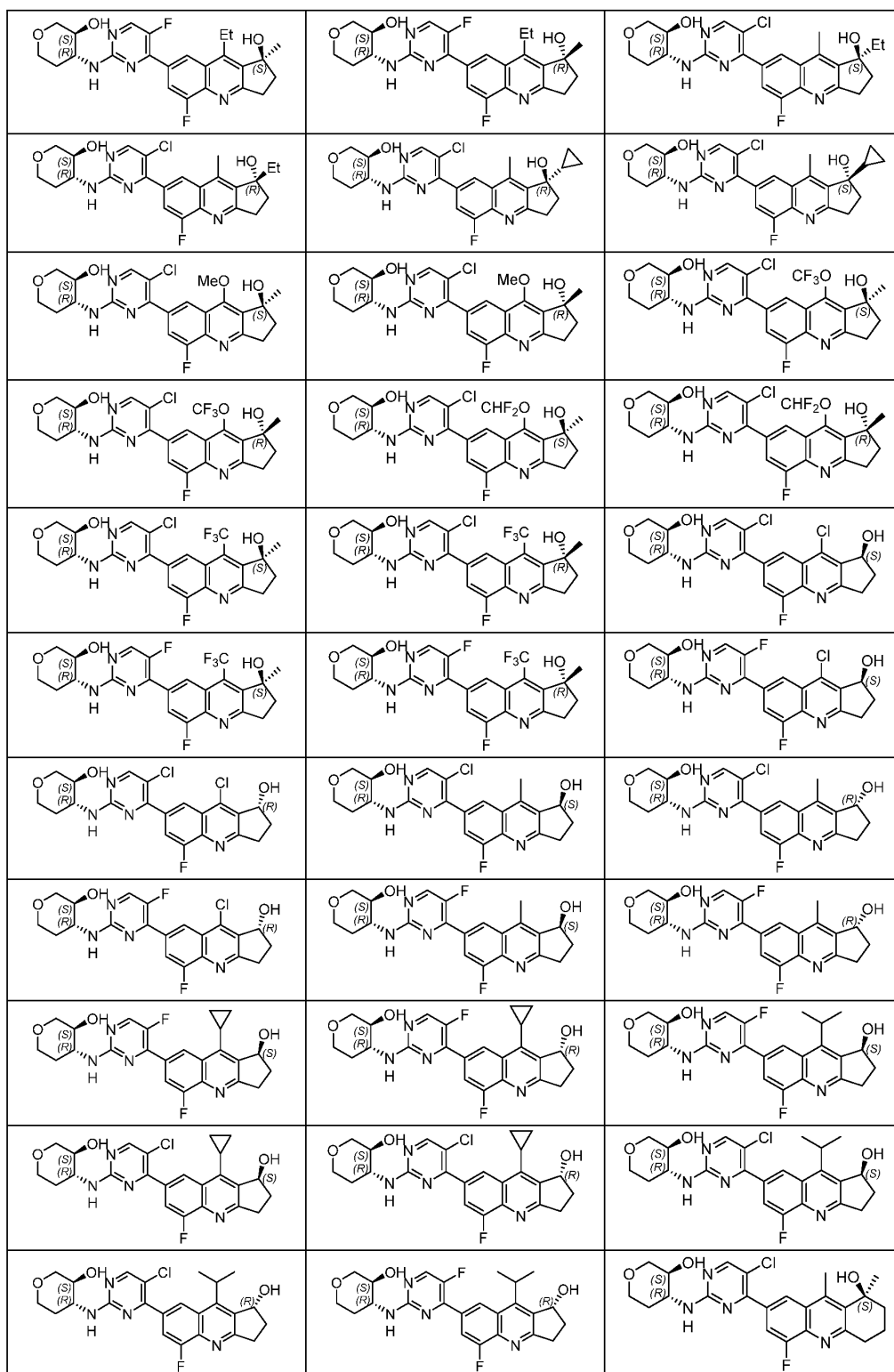


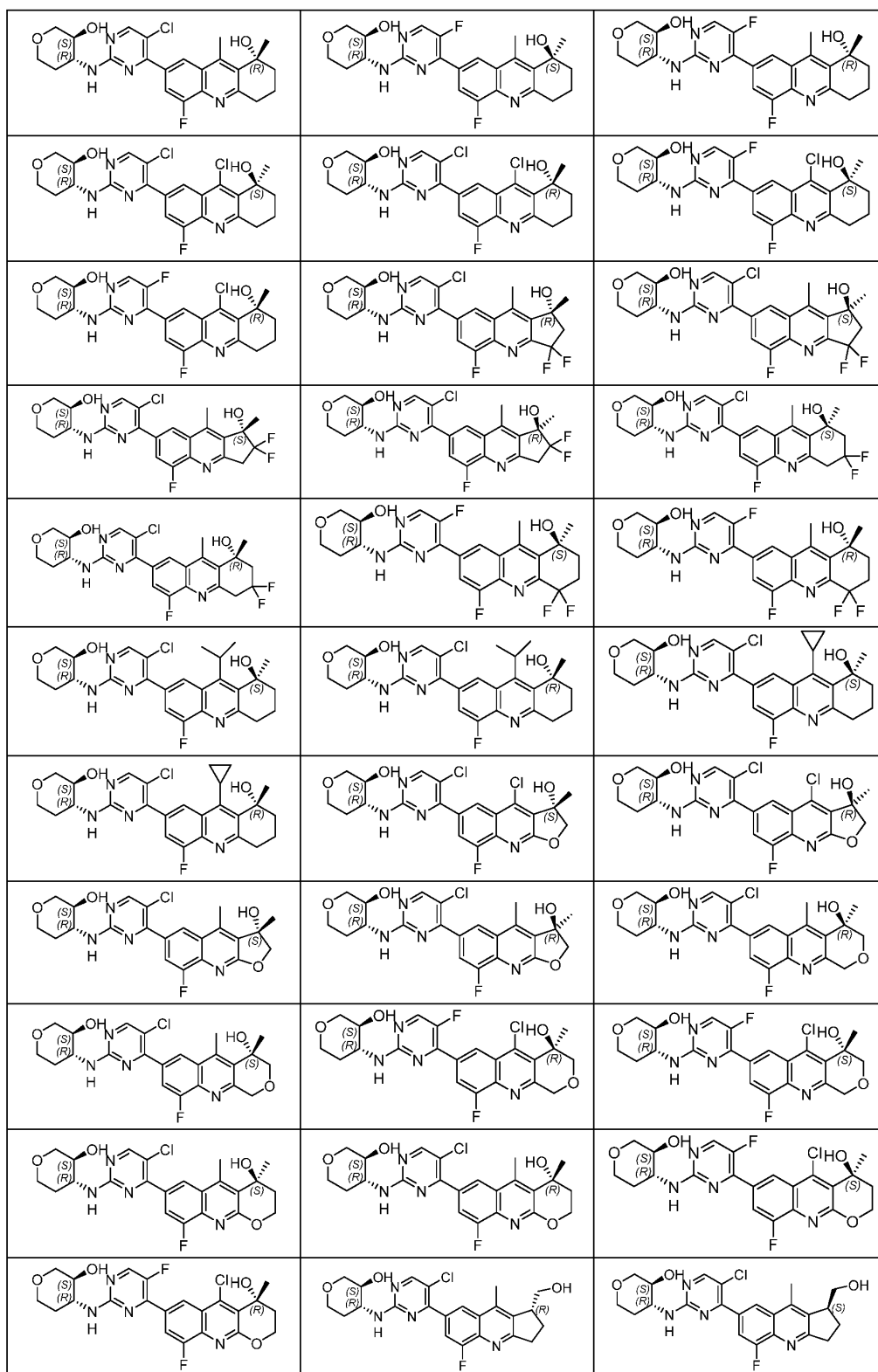


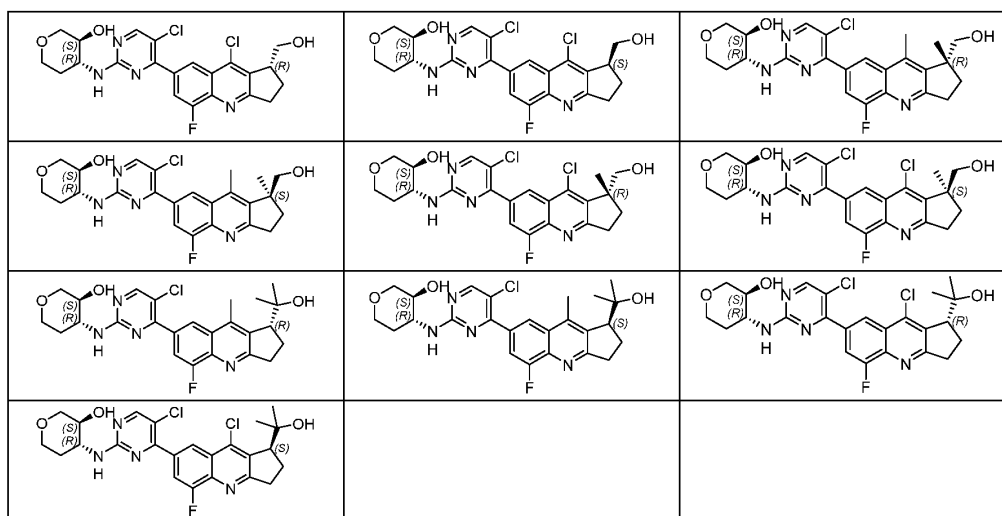












[0152] Compounds of Table 1 or Table 1A can exist in various stereoisomeric forms, such as individual isomer, an individual enantiomer and/or diastereomer, as applicable, or a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomers. In some embodiments, when applicable, a compound shown Table 1 or Table 1A can have an enantiomeric excess (“ee”) of greater than about 60%, such as having greater than about 80% ee, greater than about 90% ee, greater than about 90% ee, greater than about 95% ee, greater than about 98% ee, greater than about 99% ee, or with the other enantiomer in a non-detectable amount. In some embodiments, when applicable, a compound shown Table 1 or Table 1A can also exist as a mixture of stereoisomers in any ratio, such as a racemic mixture.

[0153] In some embodiments, to the extent applicable, the genus of compounds provided herein also excludes any specifically known single compounds prior to this disclosure. In some embodiments, to the extent applicable, any sub-genus or species of compounds prior to this disclosure that are entirely within a genus of compounds provided herein can also be excluded from such genus provided herein.

[0154] The compounds provided herein can be readily synthesized by those skilled in the art in view of the information provided herein and synthetic knowledge in the art. Exemplified synthesis are also shown in the Examples section.

[0155] As will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous

protecting groups are described in "Protective Groups in Organic Synthesis", 4th ed. P. G. M. Wuts; T. W. Greene, John Wiley, 2007, and references cited therein. The reagents for the reactions described herein are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the reagents are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplemental (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (Wiley, 7th Edition), and Larock's Comprehensive Organic Transformations (Wiley-VCH, 1999), and any of available updates as of this filing.

5.3 *Pharmaceutical Compositions*

[0156] Also provided herein is a pharmaceutical composition comprising one or more compounds provided herein.

[0157] The pharmaceutical composition can optionally contain one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition comprises a compound provided herein and one or more pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients are known in the art. Non-limiting suitable excipients include, for example, encapsulating materials or additives such as antioxidants, binders, buffers, carriers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof. *See also* Remington's The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, Md., 2005; incorporated herein by reference), which describes various excipients used in formulating pharmaceutical compositions and known techniques for the preparation thereof.

[0158] The pharmaceutical composition can include any one or more of the compounds provided herein. In some embodiments, the pharmaceutical composition comprises a compound provided herein in a therapeutically effective amount. In any of the embodiments described herein, the pharmaceutical composition can comprise a therapeutically effective amount (*e.g.*, for treating breast cancer or ovarian cancer) of a compound provided herein. In some embodiments,

the pharmaceutical composition can comprise a compound selected from the compounds provided herein that have a CDK4/CyclinD1 IC50 level designated as "A" or "B", in some embodiments, "A" in Table 2 provided herein.

[0159] The pharmaceutical composition herein can be formulated for delivery via any of the known routes of delivery, which include but not limited to administering orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally or parenterally.

[0160] In some embodiments, the pharmaceutical composition is formulated for oral administration. The oral formulations can be presented in discrete units, such as capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Excipients for the preparation of compositions for oral administration are known in the art. Non-limiting suitable excipients include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and mixtures thereof.

[0161] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (such as intravenous injection or infusion, subcutaneous or intramuscular injection). The parenteral formulations can be, for example, an aqueous solution, a suspension, or an emulsion. Excipients for the preparation of parenteral formulations are known in the art. Non-limiting suitable excipients include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof.

[0162] Compounds provided herein can be used alone, in combination with each other, or in combination with one or more additional therapeutic agents, *e.g.*, in combination with an additional anticancer therapeutic agent, such as mitotic inhibitors, alkylating agents, antimetabolites, antitumor antibiotics, anti-angiogenesis agents, topoisomerase I and II inhibitors, plant alkaloids, hormonal agents and antagonists, growth factor inhibitors, radiation, signal transduction inhibitors, such as inhibitors of protein tyrosine kinases and/or serine/threonine kinases, cell cycle inhibitors, biological response modifiers, enzyme inhibitors, antisense oligonucleotides or oligonucleotide derivatives, cytotoxics, immuno-oncology agents, and the like. In some embodiments, one or more compounds provided herein can be used in combination with one or more targeted agents, such as inhibitors of PI3 kinase, mTOR, PARP, IDO, TDO, ALK, ROS, MEK, VEGF, FLT3, AXL, ROR2, EGFR, FGFR, Src/Abl, RTK/Ras, Myc, Raf, PDGF, AKT, c-Kit, erbB, CDK2, CDK5, CDK7, CDK9, SMO, CXCR4, HER2, GLS1, EZH2 or Hsp90, or immunomodulatory agents, such as PD-1 or PD-L1 antagonists, OX40 agonists or 4-1BB agonists. In some embodiments, one or more compounds provided herein can be used in combination with a standard of care agent, such as tamoxifen, docetaxel, paclitaxel, cisplatin, capecitabine, gemcitabine, vinorelbine, exemestane, letrozole, fulvestrant, anastrozole or trastuzumab. Suitable additional anticancer therapeutic agent include any of those known in the art, such as those approved for the appropriate cancer by a regulatory agency such as the U.S. Food and Drug Administration. Some examples of suitable additional anticancer therapeutic agents also include those described as suitable for combined use with a CDK inhibitor in WO2019/207463, WO2020/224568, etc., the content of each of which is herein incorporated by reference in its entirety.

[0163] When used in combination with one or more additional therapeutic agents, compounds provided herein or pharmaceutical compositions provided herein can be administered to the subject either concurrently or sequentially in any order with such additional therapeutic agents. In some embodiments, the pharmaceutical composition can comprise one or more compounds provided herein and the one or more additional therapeutic agents in a single composition. In some embodiments, the pharmaceutical composition comprising one or more compounds provided herein can be included in a kit which also comprises a separate pharmaceutical composition comprising the one or more additional therapeutic agents.

[0164] The pharmaceutical composition can include various amounts of the compounds provided herein, depending on various factors such as the intended use and potency and

selectivity of the compounds. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a compound provided herein. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of the compound provided herein and one or more pharmaceutically acceptable excipients. As used herein, a therapeutically effective amount of a compound provided herein is an amount effective to treat a disease or disorder provided herein, such as breast cancer or ovarian cancer, which can depend on the recipient of the treatment, the disorder, condition or disease being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered.

5.4 *Method of Use*

[0165] Without being limited by a particular theory, compounds provided herein have various utilities. For example, compounds provided herein can be used as therapeutic active substances for the treatment and/or prophylaxis of a CDK4-mediated disease or disorder. Accordingly, also provided herein are methods of using one or more compounds provided herein or pharmaceutical compositions provided herein for treating or preventing a CDK4-mediated disease or disorder in a subject in need thereof, such as for treating cancer in a subject in need thereof.

[0166] In some embodiments, provided herein is a method of inhibiting abnormal cell growth in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of provided herein or a pharmaceutical composition provided herein. In some embodiments, the abnormal cell growth is cancer associated with CDK4.

[0167] In some embodiments, provided herein is a method of inhibiting CDK activity in a subject or biological sample. In some embodiments, provided herein is a method of inhibiting CDK4 activity in a subject or biological sample, which comprises contacting the subject or biological sample with an effective amount of the compound provided herein or a pharmaceutical composition provided herein.

[0168] In some embodiments, provided herein is a method of treating or preventing a CDK mediated, in particular CDK4-mediated disease or disorder in a subject in need thereof. In some embodiments, the method comprises administering to the subject an effective amount of a compound provided herein or an effective amount of a pharmaceutical composition provided herein. In some embodiments, the CDK4-mediated disease or disorder is cancer.

[0169] In some embodiments, provided herein is a method of treating or preventing cancer in a subject in need thereof, which comprises administering to the subject an effective amount of a compound provided herein or an effective amount of a pharmaceutical composition provided herein.

[0170] In some embodiments, provided herein is use of a compound provided herein or a pharmaceutical composition provided herein in the manufacture of a medicament for treating cancer. In some embodiments, provided herein is use of a compound provided herein or a pharmaceutical composition provided herein for treating cancer. In some embodiments, provided herein is a compound provided herein or a pharmaceutical composition provided herein for use in the treatment of cancer. In some embodiments, provided herein is a compound provided herein or a pharmaceutical composition provided herein for use in a method of treating cancer, wherein the method comprises administering to a subject in need thereof an effective amount of a compound provided herein or a pharmaceutical composition provided herein.

[0171] In some embodiments, the cancer is selected from breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer (including NSCLC, SCLC, squamous cell carcinoma or adenocarcinoma), esophageal cancer, head and neck cancer, colorectal cancer, kidney cancer (including RCC), liver cancer (including HCC), pancreatic cancer, stomach (i.e., gastric) cancer, thyroid cancer, and combinations thereof. In some embodiments of the methods provided herein, the cancer is breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer, esophageal cancer, liver cancer, pancreatic cancer and/or stomach cancer.

[0172] In some embodiments, the cancer is breast cancer, such as ER-positive/HR-positive, HER2-negative breast cancer; ER-positive/HR-positive, HER2- positive breast cancer; triple negative breast cancer (TNBC); or inflammatory breast cancer. In some embodiments, the breast cancer can be endocrine resistant breast cancer, trastuzumab resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/CDK6 inhibition. In some embodiments, the breast cancer can be advanced or metastatic breast cancer.

[0173] In some embodiments, the cancer is ovarian cancer.

[0174] In some embodiments, the compound provided herein is administered as first line therapy. In other embodiments, the compound provided herein is administered as second (or later) line therapy. In some embodiments, the compound provided herein is administered as second (or later) line therapy following treatment with an endocrine therapeutic agent and/or a

CDK4/CDK6 inhibitor. In some embodiments, the compound provided herein is administered as second (or later) line therapy following treatment with an endocrine therapeutic agent, *e.g.*, an aromatase inhibitor, a SERM or a SERD. In some embodiments, the compound provided herein is administered as second (or later) line therapy following treatment with a CDK4/CDK6 inhibitor. In some embodiments, the compound provided herein is administered as second (or later) line therapy following treatment with one or more chemotherapy regimens, *e.g.*, including taxanes or platinum agents. In some embodiments, the compound provided herein is administered as second (or later) line therapy following treatment with HER2 targeted agents, *e.g.*, trastuzumab.

[0175] In some embodiments, provided herein is a method of treating breast cancer in a subject in need thereof, which comprises administering to the subject a therapeutically effective amount of a compound provided herein or an effective amount of a pharmaceutical composition provided herein. In some embodiments, the breast cancer is selected from ER-positive/HR-positive, HER2-negative breast cancer; ER-positive/HR-positive, HER2- positive breast cancer; triple negative breast cancer (TNBC); and inflammatory breast cancer. In some embodiments, the breast cancer is selected from endocrine resistant breast cancer, trastuzumab resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/CDK6 inhibition. In some embodiments, the breast cancer is advanced or metastatic breast cancer.

[0176] In some embodiments, the compound provided herein for the methods provided herein has a CDK4/CyclinD1 IC₅₀ of less than 100 nM, or less than 10 nM, measured/calculated according to the Biological Example 1 herein. In some embodiments, the compound provided herein for the methods provided herein is selected from the compounds provided herein that have a CDK4/CyclinD1 IC₅₀ level designated as "A" or "B", in some embodiments, "A", in Table 2 herein.

[0177] In some embodiments, the compound provided herein for the methods provided herein are selective for CDK4 over CDK6. In some embodiments, the compound provided herein for the methods provided herein can also be selective for CDK4 over other CDKs. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 5, greater than a factor of about 10, greater than a factor of about 25, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 300, greater than a factor of about 400, greater than a factor of about 500, greater than a factor of about 600, greater than a factor of about 800, or greater than a factor of about 1000,

where selectivity can be measured by ratio of IC₅₀ values, among other means. In some embodiments, the selectivity of CDK4 over CDK6 (or other CDKs) is measured by the ratio of the IC₅₀ value against CDK6 (or other CDKs) to the IC₅₀ value against CDK4.

[0178] In some embodiments, provided herein is a method of inhibiting cancer cell proliferation in a subject, comprising administering to the subject a compound provided herein, or a pharmaceutically acceptable salt thereof, in an amount effective to inhibit cell proliferation.

[0179] In some embodiments, provided herein is a method of inhibiting cancer cell invasiveness in a subject, comprising administering to the subject a compound provided herein, or a pharmaceutically acceptable salt thereof, in an amount effective to inhibit cell invasiveness.

[0180] In some embodiments, provided herein is a method of inducing apoptosis in cancer cells in a subject, comprising administering to the subject a compound provided herein, or a pharmaceutically acceptable salt thereof, in an amount effective to induce apoptosis.

[0181] In some embodiments, provided herein is a method of inhibiting cancer cell metastasis in a subject, comprising administering to the subject a compound provided herein, or a pharmaceutically acceptable salt thereof, in an amount effective to inhibit cell metastasis.

[0182] The administering in the methods provided herein is not limited to any particular route of administration. For example, in some embodiments, the administering can be orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In some embodiments, the administering is orally. In some embodiments, the administering is a parenteral injection, such as an intravenous injection.

[0183] Compounds provided herein can be used as a monotherapy or in a combination therapy. In some embodiments according to the methods provided herein, one or more compounds provided herein can be administered as the only active ingredient(s). In some embodiments according to the methods provided herein, one or more compounds provided herein can also be co-administered with an additional therapeutic agent, either concurrently or sequentially in any order, to the subject in need thereof. The additional therapeutic agent can typically be an additional anticancer therapeutic agent, such as mitotic inhibitors, alkylating agents, antimetabolites, antitumor antibiotics, anti-angiogenesis agents, topoisomerase I and II inhibitors, plant alkaloids, hormonal agents and antagonists, growth factor inhibitors, radiation, signal transduction inhibitors, such as inhibitors of protein tyrosine kinases and/or serine/threonine kinases, cell cycle inhibitors, biological response modifiers, enzyme inhibitors,

antisense oligonucleotides or oligonucleotide derivatives, cytotoxics, immuno-oncology agents, and the like. In some embodiments, the additional anticancer agent is an endocrine agent, such as an aromatase inhibitor, a SERD or a SERM. In some embodiments, one or more compounds provided herein can be administered in combination with one or more targeted agents, such as inhibitors of PI3 kinase, mTOR, PARP, IDO, TDO, ALK, ROS, MEK, VEGF, FLT3, AXL, ROR2, EGFR, FGFR, Src/Abl, RTK/Ras, Myc, Raf, PDGF, AKT, c-Kit, erbB, CDK2, CDK5, CDK7, CDK9, SMO, CXCR4, HER2, GLS1, EZH2 or Hsp90, or immunomodulatory agents, such as PD-1 or PD-L1 antagonists, OX40 agonists or 4-1BB agonists. In some embodiments, one or more compounds provided herein can be administered in combination with a standard of care agent, such as tamoxifen, docetaxel, paclitaxel, cisplatin, capecitabine, gemcitabine, vinorelbine, exemestane, letrozole, fulvestrant, anastrozole or trastuzumab. Suitable additional anticancer therapeutic agent include any of those known in the art, such as those approved for the appropriate cancer by a regulatory agency such as the U.S. Food and Drug Administration. Some examples of suitable additional anticancer therapeutic agents also include those described as suitable for combined use with a CDK inhibitor in WO2019/207463, WO2020/224568, etc., the contents of each of which is incorporated by reference herein in their entirety.

[0184] Dosing regimen including doses for the methods provided herein can vary and be adjusted, which can depend on the recipient of the treatment, the disorder, condition or disease being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered.

6. EXAMPLES

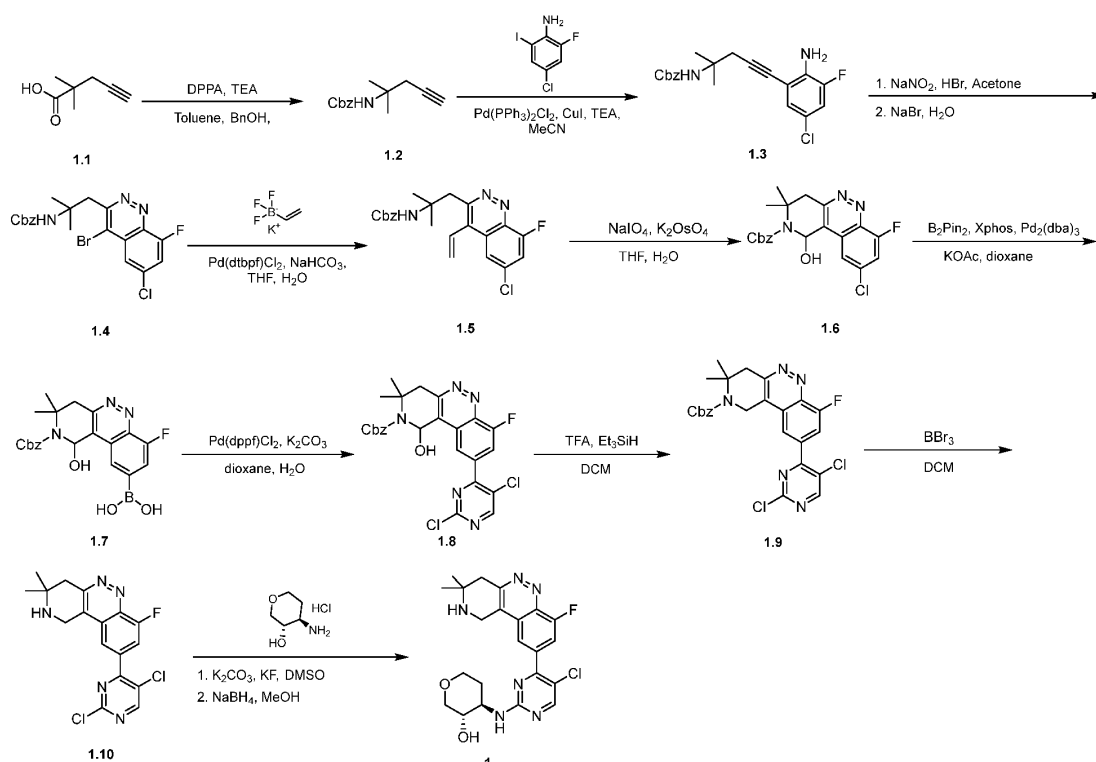
[0185] The various starting materials, intermediates, and compounds provided herein can be isolated and purified where appropriate using conventional techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Characterization of these compounds can be performed using conventional methods such as by melting point, mass spectrum, nuclear magnetic resonance, and various other spectroscopic analyses. The abbreviations used in the Examples section should be understood as having their ordinary meanings in the art unless specifically indicated otherwise or obviously contrary from context. The examples are illustrative only and do not limit the claimed invention in any way.

[0186] Exemplary embodiments of steps for performing the synthesis of products provided herein are described in greater detail infra. Some of the Examples discussed herein can

be prepared by separating from the corresponding racemic mixtures. As would be understood by a person of ordinary skill in the art, the compounds described in the Examples section immediately prior to the chiral separation step, *e.g.*, by supercritical fluid chromatography (SFC), exist in racemic and/or stereoisomeric mixture forms, the bolded but not wedged bonds are used in the chemical structure drawings to indicate relative stereochemistry. It should be understood that the enantiomeric excesses ("ee") and/or diastereomeric excesses ("de") reported for these examples are only representative from the exemplified procedures provided herein and not limiting; those skilled in the art would understand that such enantiomers with a different ee and/or de, such as a higher ee and/or higher de, can be obtained in view of the information provided herein.

[0187] In some illustrative examples, the synthesis of a deuterated compound is shown. To the extent applicable, it should be understood that the corresponding non-deuterated (*i.e.*, with natural abundance) compound was prepared through the same method except by using a corresponding non-deuterated starting material or intermediate.

Example 1. (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-3,3-dimethyl-1,2,3,4-tetrahydropyrido[4,3-*c*]cinnolin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**1**)



[0188] To a solution of 2,2-dimethylpent-4-ynoic acid (**1.1**, 4.00 g, 31.7 mmol) in toluene (40 mL) at 0 °C were added triethylamine (4.81 g, 47.5 mmol, 6.62 mL) and diphenylphosphoryl azide (17.4 g, 63.4 mmol, 13.7 mL). The mixture was stirred at 80 °C for 2 hrs followed by addition of benzyl alcohol (13.7 g, 126 mmol, 13.1 mL), and the resulting mixture was stirred at 90 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford benzyl (2-methylpent-4-yn-2-yl)carbamate (**1.2**, 5.00 g, 68.2%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃-*d*) δ = 7.37 - 7.32 (m, 5H), 5.08 (s, 2H), 4.88 (br s, 1H), 2.63 (d, *J* = 1.5 Hz, 2H), 2.03 (s, 1H), 1.41 (s, 6H).

[0189] To a solution of benzyl (2-methylpent-4-yn-2-yl)carbamate (**1.2**, 5.00 g, 21.6 mmol) and 4-chloro-2-fluoro-6-iodo-aniline (5.10 g, 18.8 mmol) in acetonitrile (24 mL) were added bis(triphenylphosphine)palladium(II) chloride (659 mg, 940 μmol), cuprous iodide (322 mg, 1.69 mmol) and triethylamine (19.0 g, 188 mmol, 26.2 mL). The resulting mixture was stirred at 50 °C for 4 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (40 mL × 3). The combined organic layers were washed with brine (50 mL) and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford benzyl (5-(2-amino-5-chloro-3-fluorophenyl)-2-methylpent-4-yn-2-yl)carbamate (**1.3**, 6.10 g, 86.6%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃-*d*) δ = 7.38 - 7.31 (m, 5H), 7.03 - 6.93 (m, 2H), 5.09 (s, 2H), 4.88 (br s, 1H), 2.94 (s, 2H), 1.45 (s, 6H).

[0190] To a solution of benzyl (5-(2-amino-5-chloro-3-fluorophenyl)-2-methylpent-4-yn-2-yl)carbamate (**1.3**, 5.90 g, 15.7 mmol) in acetone (130 mL) were added HBr (109 g, 215 mmol, 73 mL, 16 wt.%) and NaNO₂ (1.19 g, 17.3 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 mins followed by addition of NaBr (32.4 g, 314 mmol, 10 mL) in water (50 mL). The resulting mixture was stirred at 45 °C for 1 hr. The mixture was concentrated in vacuum and extracted with dichloromethane (60 mL × 2). The combined organic layers were concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford benzyl (1-(4-bromo-6-chloro-8-fluorocinnolin-3-yl)-2-methylpropan-2-yl)carbamate (**1.4**, 4.60 g, 62.6%) as a yellow solid. LC-MS (ESI) *m/z* 466.1 [M+H]⁺.

[0191] To a solution of benzyl (1-(4-bromo-6-chloro-8-fluorocinnolin-3-yl)-2-methylpropan-2-yl)carbamate (**1.4**, 2.00 g, 4.29 mmol) in THF (20 mL) and H₂O (2 mL) were added NaHCO₃ (720 mg, 8.57 mmol, 333 μL), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (279 mg, 428 μmol) and potassium vinyltrifluoroborate (574 mg, 4.29

mmol). The mixture was stirred at 80 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was quenched with water (100 mL) and then extracted with ethyl acetate (60 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford benzyl (1-(6-chloro-8-fluoro-4-vinylcinnolin-3-yl)-2-methylpropan-2-yl)carbamate (**1.5**, 970 mg, 54.7%) as a yellow solid. **LC-MS (ESI)** *m/z* 414.1 [M+H]⁺.

[0192] To a solution of benzyl (1-(6-chloro-8-fluoro-4-vinylcinnolin-3-yl)-2-methylpropan-2-yl)carbamate (**1.5**, 1.30 g, 3.14 mmol) in THF (100 mL) and H₂O (20 mL) were added NaIO₄ (3.36 g, 15.7 mmol) and K₂OsO₄·2H₂O (115 mg, 314 μmol) at 0 °C. The mixture was stirred at 20 °C for 12 hrs followed by addition of NaIO₄ (3.36 g, 15.7 mmol) and K₂OsO₄·2H₂O (57.8 mg, 157 μmol) at 0 °C, and the resulting mixture was stirred at 20 °C for 4 hrs. The reaction mixture was quenched with water (150 mL) and then extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated with dichloromethane/ethyl acetate/methyl *tert*-butyl ether (1/1/8) at 20 °C for 20 mins to afford benzyl 9-chloro-7-fluoro-1-hydroxy-3,3-dimethyl-3,4-dihydropyrido[4,3-*c*]cinnoline-2(1*H*)-carboxylate (**1.6**, 920 mg, 70.4%) as a white solid. **LC-MS (ESI)** *m/z* 416.0 [M+H]⁺.

[0193] To a solution of benzyl 9-chloro-7-fluoro-1-hydroxy-3,3-dimethyl-3,4-dihydropyrido[4,3-*c*]cinnoline-2(1*H*)-carboxylate (**1.6**, 600 mg, 1.44 mmol) and bis(pinacolato)diboron (476 mg, 1.88 mmol) in dioxane (10 mL) were added XPhos (137 mg, 288 μmol), Pd₂(dba)₃ (132 mg, 144 μmol) and KOAc (424 mg, 4.33 mmol). The mixture was stirred at 100 °C for 1.5 hrs under nitrogen atmosphere. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford (2-((benzyloxy)carbonyl)-7-fluoro-1-hydroxy-3,3-dimethyl-1,2,3,4-tetrahydropyrido[4,3-*c*]cinnolin-9-yl)boronic acid (**1.7**, 1.92 g, crude). **LC-MS (ESI)** *m/z* 426.0 [M+H]⁺.

[0194] To a solution of (2-((benzyloxy)carbonyl)-7-fluoro-1-hydroxy-3,3-dimethyl-1,2,3,4-tetrahydropyrido[4,3-*c*]cinnolin-9-yl)boronic acid (**1.7**, 1.92 g, crude) and 2,4,5-trichloropyrimidine (423 mg, 2.31 mmol) in dioxane (15 mL) and H₂O (3 mL) were added Pd(dppf)Cl₂ (105 mg, 144 μmol) and K₂CO₃ (398 mg, 2.88 mmol). The mixture was stirred at 100 °C for 1 h under nitrogen atmosphere. The reaction mixture was quenched with water (50 mL) and then extracted with ethyl acetate (30 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to

silica gel column chromatography to afford benzyl 9-(2,5-dichloropyrimidin-4-yl)-7-fluoro-1-hydroxy-3,3-dimethyl-3,4-dihydropyrido[4,3-*c*]cinnoline-2(1*H*)-carboxylate (**1.8**, 460 mg) as a white solid. **LC-MS (ESI)** *m/z* 528.2 [M+H]⁺.

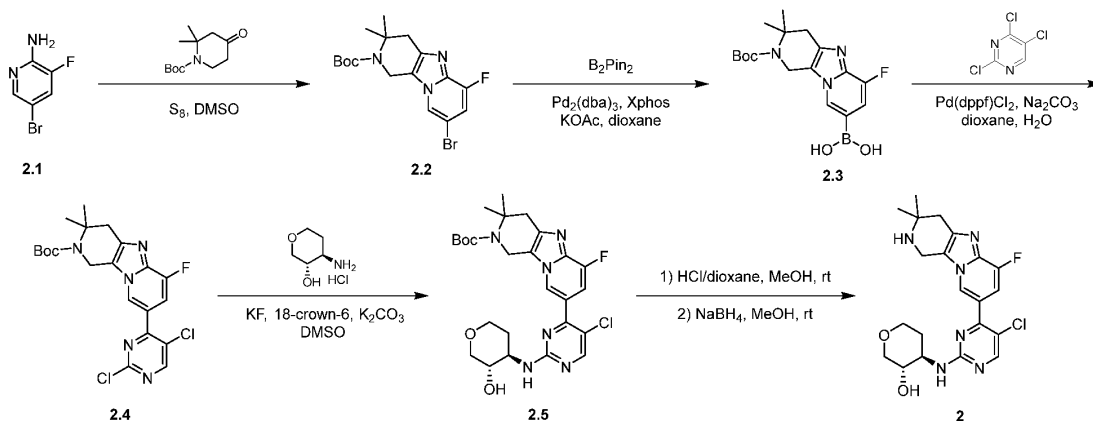
[0195] To a solution of benzyl 9-(2,5-dichloropyrimidin-4-yl)-7-fluoro-1-hydroxy-3,3-dimethyl-3,4-dihydropyrido[4,3-*c*]cinnoline-2(1*H*)-carboxylate (**1.8**, 100 mg, 189 μmol) in dichloromethane (2 mL) were added trifluoroacetic acid (767 mg, 6.73 mmol, 0.5 mL) and Et₃SiH (182 mg, 1.57 mmol, 0.25 mL), and the mixture was stirred at 0 °C for 15 mins. The reaction mixture was concentrated under reduced pressure, diluted with water (10 mL) and then extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give benzyl 9-(2,5-dichloropyrimidin-4-yl)-7-fluoro-3,3-dimethyl-3,4-dihydropyrido[4,3-*c*]cinnoline-2(1*H*)-carboxylate (**1.9**, 90.0 mg, crude) as a brown oil. **LC-MS (ESI)** *m/z* 512.2 [M+H]⁺.

[0196] To a solution of benzyl 9-(2,5-dichloropyrimidin-4-yl)-7-fluoro-3,3-dimethyl-3,4-dihydropyrido[4,3-*c*]cinnoline-2(1*H*)-carboxylate (**1.9**, 90.0 mg, crude) in dichloromethane (5 mL) was added BBr₃ (263 μL, 2 M) dropwise at -70 °C, and the mixture was stirred at -70 °C for 1 hr under nitrogen atmosphere. The reaction mixture was quenched with water (5 mL) at -70 °C and then extracted with dichloromethane (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 9-(2,5-dichloropyrimidin-4-yl)-7-fluoro-3,3-dimethyl-1,2,3,4-tetrahydropyrido[4,3-*c*]cinnoline (**1.10**, 66.0 mg, crude) as a brown oil. **LC-MS (ESI)** *m/z* 378.1 [M+H]⁺.

[0197] To a solution of 9-(2,5-dichloropyrimidin-4-yl)-7-fluoro-3,3-dimethyl-1,2,3,4-tetrahydropyrido[4,3-*c*]cinnoline (**1.10**, 66.0 mg, crude) and (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (80.4 mg, 523 μmol) in DMSO (2 mL) were added K₂CO₃ (144 mg, 1.05 mmol), KF (60.8 mg, 1.05 mmol) and 18-crown-6 (18.4 mg, 69.8 μmol). The mixture was stirred at 120 °C for 45 mins. The reaction mixture was cooled to room temperature followed by addition of NaBH₄ (9.94 mg, 262 μmol) and stirred at 20 °C for 10 mins. The resulting mixture was filtered and the filtrate was subjected to prep-HPLC to afford (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-3,3-dimethyl-1,2,3,4-tetrahydropyrido[4,3-*c*]cinnolin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**1**, 13.0 mg) as a light-yellow solid. **LC-MS (ESI)** *m/z* 459.1 [M+H]⁺. ¹H NMR (400 MHz, CD₃CN-*d*₃) δ = 8.42 (s, 1H), 8.23 (s, 1H), 7.88 (br d, *J* = 10.8 Hz, 1H), 6.06 (br d, *J* = 7.6 Hz, 1H), 4.44 (s, 2H), 3.94 - 3.84 (m, 3H), 3.55 (br d, *J* = 6.6 Hz, 1H),

3.42 (br d, $J = 2.2$ Hz, 1H), 3.21 (s, 2H), 3.16 - 3.09 (m, 1H), 2.06 - 2.02 (m, 1H), 1.65 - 1.56 (m, 1H), 1.23 (s, 6H).

Example 2. (3*S*,4*R*)-4-((5-chloro-4-(6-fluoro-3,3-dimethyl-1,2,3,4-tetrahydroimidazo[1,2- α :5,4- c']dipyridin-8-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**2**)



[0198] A mixture of 5-bromo-3-fluoropyridin-2-amine (**2.1**, 3.20 g, 16.8 mmol), *tert*-butyl 2,2-dimethyl-4-oxopiperidine-1-carboxylate (5.70 g, 25.2 mmol) and elemental sulfur (2.70 g, 84.0 mmol) in DMSO (4.20 g) was stirred in a sealed tube at 120 °C for 16 hrs. The mixture was concentrated under reduced pressure, subjected to silica gel column chromatography and further purified by Prep-TLC (PE:EA = 3:1) to afford *tert*-butyl 8-bromo-6-fluoro-3,3-dimethyl-3,4-dihydroimidazo[1,2- α :5,4- c']dipyridine-2(1*H*)-carboxylate (**2.2**, 135 mg, 1.8%) as a yellow solid. **LC-MS (ESI)** m/z 398.2 ($M+H$)⁺. **¹H NMR** (400 MHz, CDCl₃) δ 7.78 (s, 1H), 7.02 (d, $J = 9.6$ Hz, 1H), 4.72 (s, 2H), 2.95 (s, 2H), 1.55 (s, 6H), 1.49 (s, 9H).

[0199] To a mixture of *tert*-butyl 8-bromo-6-fluoro-3,3-dimethyl-3,4-dihydroimidazo[1,2- α :5,4- c']dipyridine-2(1*H*)-carboxylate (**2.2**, 135 mg, 0.34 mmol), (4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (172 mg, 0.68 mmol) and potassium acetate (66.5 mg, 0.68 mmol) in 1,4-dioxane (12 mL) were added Pd₂(dba)₃ (15.0 mg, 0.034 mmol) and Xphos (32.0 mg, 0.068 mmol). The resulting mixture was stirred at 90 °C for 4 hrs under nitrogen atmosphere. The reaction mixture was filtered and the filtrate were concentrated under reduced pressure to afford (2-(*tert*-butoxycarbonyl)-6-fluoro-3,3-dimethyl-1,2,3,4-tetrahydroimidazo[1,2- α :5,4- c']dipyridin-8-yl)boronic acid (**2.3**, 360 mg, crude) as a brown oil. **LC-MS (ESI)** m/z 364.1 ($M+H$)⁺.

[0200] A mixture of (2-(*tert*-butoxycarbonyl)-6-fluoro-3,3-dimethyl-1,2,3,4-tetrahydroimidazo[1,2- α :5,4- c']dipyridin-8-yl)boronic acid (**2.3**, 360 mg, crude), 2,4,5-

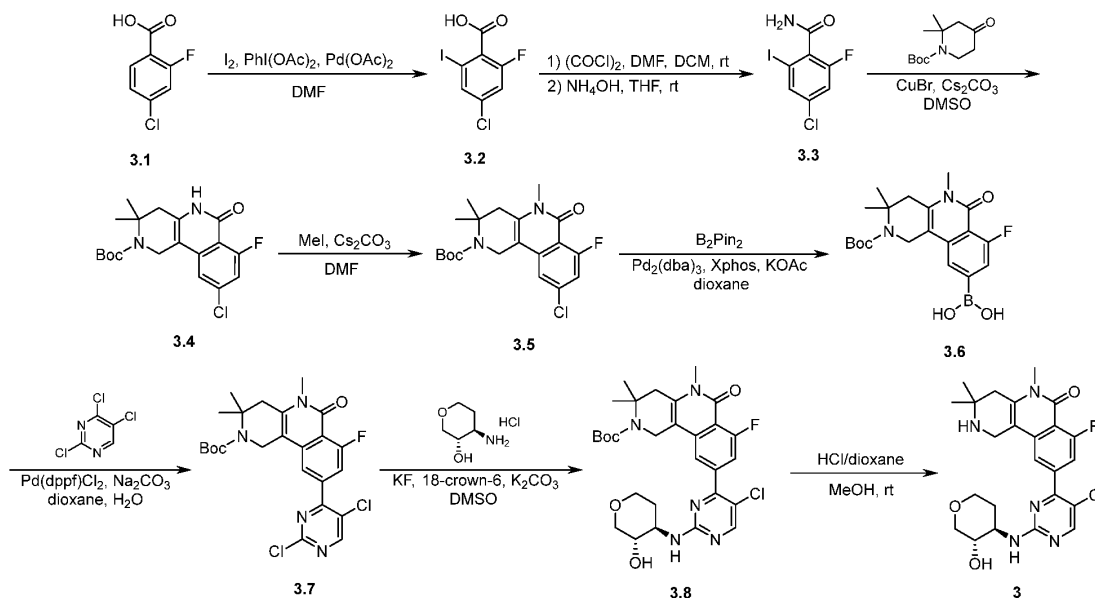
trichloropyrimidine (75.0 mg, 0.41 mmol), Pd(dppf)Cl₂ (26.0 mg, 0.034 mmol) and Na₂CO₃ (73.0 mg, 0.68 mmol) in 1,4-dioxane (8 mL) and H₂O (1 mL) was stirred at 90 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford *tert*-butyl 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-3,3-dimethyl-3,4-dihydroimidazo[1,2-*a*:5,4-*c'*]dipyridine-2(1*H*)-carboxylate (**2.4**, 55.0 mg, 35% for two steps) as a yellow solid. **LC-MS (ESI)** *m/z* 466.2 (M+H)⁺.

[0201] A mixture of *tert*-butyl 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-3,3-dimethyl-3,4-dihydroimidazo[1,2-*a*:5,4-*c'*]dipyridine-2(1*H*)-carboxylate (**2.4**, 55.0 mg, 0.12 mmol), (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (**7**, 21.4 mg, 0.14 mmol), 18-crown-6 (6.20 mg, 0.024 mmol), potassium fluoride (21.0 mg, 0.36 mmol) and potassium carbonate (16 mg, 0.12 mmol) in DMSO (2 mL) was stirred at 105 °C for 1 hr under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with water (10 mL × 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to Prep-TLC to afford *tert*-butyl 8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3,3-dimethyl-3,4-dihydroimidazo[1,2-*a*:5,4-*c'*]dipyridine-2(1*H*)-carboxylate (**2.5**, 60.0 mg, 93%) as a yellow solid. **LC-MS (ESI)** *m/z* 547.0 (M+H)⁺.

[0202] To a solution of *tert*-butyl 8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3,3-dimethyl-3,4-dihydroimidazo[1,2-*a*:5,4-*c'*]dipyridine-2(1*H*)-carboxylate (**2.5**, 60.0 mg, 0.11 mmol) in methanol (3 mL) was added hydrochloric acid (3 mL, 4 M in dioxane), and the mixture was stirred at room temperature for 3 hrs. The reaction mixture was concentrated under reduced pressure, adjusted to pH 7 with saturated sodium bicarbonate solution and then concentrated under reduced pressure. The residue was dissolved in methanol (2 mL) followed by addition of NaBH₄ (4 mg, 0.11 mmol). The mixture was stirred at room temperature for 10 mins and filtered. the filtrate was subjected to Prep-HPLC to afford (3*S*,4*R*)-4-((5-chloro-4-(6-fluoro-3,3-dimethyl-1,2,3,4-tetrahydroimidazo[1,2-*a*:5,4-*c'*]dipyridin-8-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**2**, 10.9 mg, 22%) as white solid. **LC-MS (ESI)** *m/z* 447.2 (M+H)⁺. ¹H NMR (400 MHz, CD₃OD-*d*₄) δ 8.66 (s, 1H), 8.43 (s, 1H), 8.37 (s, 1H), 7.66 (d, *J* = 11.6 Hz, 1H), 4.42 (s, 2H), 4.08

- 3.84 (m, 3H), 3.65-3.55 (m, 1H), 3.53 - 3.43 (m, 1H), 3.21 (t, $J = 11.2$, 1H), 2.95 (s, 2H), 2.18 - 2.02 (m, 1H), 1.70-1.55 (m, 1H), 1.42 (s, 6H).

Example 3. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3,5-trimethyl-1,3,4,5-tetrahydrobenzo[*c*][1,6]naphthyridin-6(2*H*)-one (**3**)



[0203] To a solution of 4-chloro-2-fluorobenzoic acid (**3.1**, 4.00 g, 22.9 mmol) in DMF (60 mL) were added (diacetoxyiodo)benzene (8.10 g, 25.2 mmol), I_2 (6.40 g, 25.2 mmol) and $Pd(OAc)_2$ (0.26 g, 1.14 mmol). The resulting mixture was stirred at 120 °C for 48 hrs under nitrogen atmosphere. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with EtOAc (300 mL) and washed with sat. aq. $Na_2S_2O_3$ (30 mL $\times$ 3), 1 N aq. HCl (30 mL $\times$ 3) and brine (50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated to 4-chloro-2-fluoro-6-iodobenzoic acid (**3.2**, 3.80 g, 44%) as a dark brown oil. **LC-MS (ESI) m/z 298.7 (M-H)⁺.**

[0204] To a solution of 4-chloro-2-fluoro-6-iodobenzoic acid (**3.2**, 2.50 g, 8.30 mmol) in DCM (30 mL) were added oxalyl chloride (3.20 g, 24.9 mmol) and DMF (5 drops). The resulting mixture was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in THF (40 mL) followed by addition of ammonium hydroxide (15 mL). The resulting mixture was stirred at room temperature for 1 hr under nitrogen atmosphere. The reaction mixture was concentrated in vacuum and diluted with brine (50 mL). The mixture was then adjust to pH 3 ~ 4 with 1 N aq. HCl and extracted with

ethyl acetate (200 mL $\times$ 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 4-chloro-2-fluoro-6-iodobenzamide (**3.3**, 1.60 g, 64%) as a white solid.

LC-MS (ESI) m/z 299.8 (M+H)⁺.

[0205] A mixture of 4-chloro-2-fluoro-6-iodobenzamide (**3.3**, 1.20 g, 4.00 mmol), *tert*-butyl 2,2-dimethyl-4-oxopiperidine-1-carboxylate (1.40 g, 6.00 mmol), CuBr (57.0 mg, 0.40 mmol) and Cs₂CO₃ (2.60 g, 8.00 mmol) in DMSO (25 mL) was stirred at 80 °C for 24 hrs under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with brine (30 mL $\times$ 4). The organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford *tert*-butyl 9-chloro-7-fluoro-3,3-dimethyl-6-oxo-3,4,5,6-tetrahydrobenzo[*c*][1,6]naphthyridine-2(1*H*)-carboxylate (**3.4**, 240 mg, 16%) as a white solid.

LC-MS (ESI) m/z 381.0 (M+H)⁺. **¹H NMR** (400 MHz, CDCl₃) δ 11.31 (brs, 1H), 7.36 (s, 1H), 7.11 (d, J = 10.4 Hz, 1H), 4.54 (s, 2H), 2.76 (s, 2H), 1.52 (s, 9H), 1.25 (s, 6H).

[0206] To a mixture of *tert*-butyl 9-chloro-7-fluoro-3,3-dimethyl-6-oxo-3,4,5,6-tetrahydrobenzo[*c*][1,6]naphthyridine-2(1*H*)-carboxylate (**3.4**, 320 mg, 0.84 mmol) and Cs₂CO₃ (547 mg, 1.68 mmol, 2.0 equiv.) in DMF (10 mL) was added iodomethane (179 mg, 1.26 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 hr under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with brine (10 mL $\times$ 4). The organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford *tert*-butyl 9-chloro-7-fluoro-3,3,5-trimethyl-6-oxo-3,4,5,6-tetrahydrobenzo[*c*][1,6]naphthyridine-2(1*H*)-carboxylate (**3.5**, 201 mg, 60%) as a white solid. **LC-MS (ESI)** m/z 395.2 (M+H)⁺. **¹H NMR** (400 MHz, CDCl₃) δ 7.35 (s, 1H), 7.10 (d, J = 11.2 Hz, 1H), 4.54 (s, 2H), 3.58 (s, 3H), 2.82 (s, 2H), 1.51 (s, 9H), 1.49 (s, 6H).

[0207] To a mixture of *tert*-butyl 9-chloro-7-fluoro-3,3,5-trimethyl-6-oxo-3,4,5,6-tetrahydrobenzo[*c*][1,6]naphthyridine-2(1*H*)-carboxylate (**3.5**, 170 mg, 0.43 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (164 mg, 0.64 mmol) and potassium acetate (85.0 mg, 0.86 mmol) in 1,4-dioxane (10 mL) were added Pd₂(dba)₃ (40.0 mg, 0.043 mmol) and Xphos (42.0 mg, 0.086 mmol). The resulting mixture was stirred at 90 °C for 2 hs under nitrogen atmosphere. The reaction mixture was cooled to room temperature and filtered. The filtrates were concentrated under reduced pressure to afford (2-

(*tert*-butoxycarbonyl)-7-fluoro-3,3,5-trimethyl-6-oxo-1,2,3,4,5,6-hexahydrobenzo[*c*][1,6]naphthyridin-9-yl)boronic acid (**3.6**, 220 mg, crude) as a brown oil. **LC-MS (ESI)** *m/z* 405.0 (M+H)⁺.

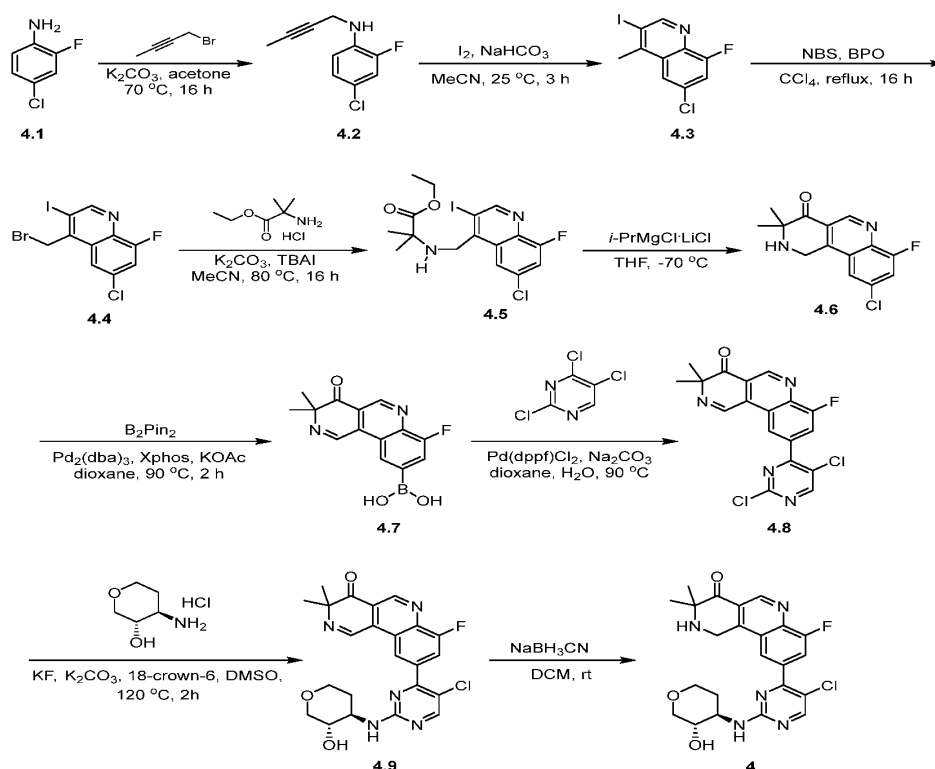
[0208] A mixture of crude (2-(*tert*-butoxycarbonyl)-7-fluoro-3,3,5-trimethyl-6-oxo-1,2,3,4,5,6-hexahydrobenzo[*c*][1,6]naphthyridin-9-yl)boronic acid (**3.6**, 220 mg, crude), 2,4,5-trichloropyrimidine (95.0 mg, 0.52 mmol), Pd(dppf)Cl₂ (33.0 mg, 0.044 mmol) and Na₂CO₃ (95.0 mg, 0.88 mmol) in 1,4-dioxane (8 mL) and water (1 mL) was stirred at 90 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford *tert*-butyl 9-(2,5-dichloropyrimidin-4-yl)-7-fluoro-3,3,5-trimethyl-6-oxo-3,4,5,6-tetrahydrobenzo[*c*][1,6]naphthyridine-2(1*H*)-carboxylate (**3.7**, 210 mg) as a yellow solid. **LC-MS (ESI)** *m/z* 507.0 (M+H)⁺.

[0209] A mixture of *tert*-butyl 9-(2,5-dichloropyrimidin-4-yl)-7-fluoro-3,3,5-trimethyl-6-oxo-3,4,5,6-tetrahydrobenzo[*c*][1,6]naphthyridine-2(1*H*)-carboxylate (**3.7**, 175 mg, 0.34 mmol), (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (48.0 mg, 0.41 mmol) 18-crown-6 (18.0 mg, 0.068 mmol), potassium carbonate (48.0 mg, 0.34 mmol) and potassium fluoride (60.0 mg, 1.02 mmol) in DMSO (4 mL) was stirred at 110 °C for 1 hr under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with water (10 mL × 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to Prep-TLC to afford *tert*-butyl 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3,5-trimethyl-6-oxo-3,4,5,6-tetrahydrobenzo[*c*][1,6]naphthyridine-2(1*H*)-carboxylate (**3.8**, 163 mg, 82%) as a yellow solid. **LC-MS (ESI)** *m/z* 588.0 (M+H)⁺.

[0210] To a solution of *tert*-butyl 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3,5-trimethyl-6-oxo-3,4,5,6-tetrahydrobenzo[*c*][1,6]naphthyridine-2(1*H*)-carboxylate (**3.8**, 163 mg, 0.28 mmol) in methanol (5 mL) was added hydrochloric acid (5 mL, 4 M in dioxane), and the mixture was stirred at room temperature for 3 hrs. The reaction mixture was concentrated under reduced pressure, dissolved in methanol (5 mL) and then adjusted to pH 8 with saturated sodium bicarbonate solution (0.3 mL). The resulting mixture was filtered and the filtrates were subjected to Prep-HPLC to afford 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-

3,3,5-trimethyl-1,3,4,5-tetrahydrobenzo[*c*][1,6]naphthyridin-6(2*H*)-one (**3**, 37.9 mg, 28%) as a yellow solid. **LC-MS (ESI)** *m/z* 488.0 (M+H)⁺. **¹H NMR** (400 MHz, CD₃OD-*d*₄) δ 8.38 (s, 1H), 7.82 (s, 1H), 7.58 (d, *J* = 12.4 Hz, 1H), 4.02 (s, 2H), 3.99 - 3.87 (m, 3H), 3.61 (dt, *J* = 9.2, 4.4 Hz, 1H), 3.56 (s, 3H), 3.48 (t, *J* = 11.6 Hz, 1H), 3.21 (t, *J* = 11.6 Hz, 1H), 2.69 (s, 2H), 2.15 - 2.07 (m, 1H), 1.70 - 1.54 (m, 1H), 1.27 (s, 6H).

Example 4. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3-dimethyl-2,3-dihydrobenzo[*c*][2,6]naphthyridin-4(1*H*)-one (**4**)



[0211] To a mixture of 4-chloro-2-fluoroaniline (**4.1**, 500 g, 3.44 mol) and K₂CO₃ (523 g, 3.79 mol) in acetone (5 L) was added 1-bromobut-2-yne (455 g, 3.44 mol), and the resulting mixture was stirred for 16 hrs at 70 °C under nitrogen atmosphere. The reaction mixture was filtered and the filtrates were concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford *N*-(but-2-yn-1-yl)-4-chloro-2-fluoroaniline (**4.2**, 550 g, 81%) as a yellow oil. **LC-MS (ESI)** *m/z* 198.2 (M+H)⁺.

[0212] To a mixture of *N*-(but-2-yn-1-yl)-4-chloro-2-fluoroaniline (**4.2**, 550 g, 2.79 mol,) and NaHCO₃ (469 g, 5.58 mol) in acetone (5 L) was added iodine (1417 g, 5.58 mol), and the resulting mixture was stirred at room temperature for 3 hrs under nitrogen atmosphere. The

reaction mixture was quenched with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (1 L) and extracted with ethyl acetate (4 L $\times$ 3). The organic layers were washed with brine (2 L), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 6-chloro-8-fluoro-3-iodo-4-methylquinoline (**4.3**, 130 g, 14%) as a brown solid. **LC-MS (ESI)** m/z 322.5 ($\text{M}+\text{H}$)⁺.

[0213] To a solution of 6-chloro-8-fluoro-3-iodo-4-methylquinoline (**4.3**, 20.0 g, 62.3 mmol) in CCl_4 (250 mL) were added *N*-bromosuccinimide (22.1 g, 124 mmol) and benzoyl peroxide (3.00 g, 12.4 mmol). The resulting mixture was stirred at 90 °C for 16 hrs under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and then subjected to silica gel column chromatography to afford 4-(bromomethyl)-6-chloro-8-fluoro-3-iodoquinoline (**4.4**, 11.5 g, 46%) as a brown solid. **LC-MS (ESI)** m/z 400.1 ($\text{M}+\text{H}$)⁺.

[0214] To a solution of 4-(bromomethyl)-6-chloro-8-fluoro-3-iodoquinoline (**4.4**, 11.5 g, 28.7 mmol) and ethyl 2-amino-2-methylpropanoate hydrochloride (7.20 g, 43.1 mmol) in acetonitrile (120 mL) were added K_2CO_3 (9.90 g, 71.9 mmol) and TBAI (1.00 g, 2.87 mmol). The resulting mixture was stirred at 80 °C for 16 hrs under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and then subjected to silica gel column chromatography to afford ethyl 2-(((6-chloro-8-fluoro-3-iodoquinolin-4-yl)methyl)amino)-2-methylpropanoate (**4.5**, 6.20 g, 48%) as a yellow solid. **LC-MS (ESI)** m/z 451.2 ($\text{M}+\text{H}$)⁺.

[0215] To a solution of ethyl 2-(((6-chloro-8-fluoro-3-iodoquinolin-4-yl)methyl)amino)-2-methylpropanoate (**4.5**, 6.20 g, 13.8 mmol) in THF (60 mL) was added *i*-PrMgCl·LiCl (21.2 mL, 27.5 mmol, 1.30 N) dropwise at -70 °C, and the resulting mixture was stirred at -70 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was quenched with sat. aq. NH_4Cl (50 mL) and extracted with ethyl acetate (150 mL $\times$ 3). The organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 9-chloro-7-fluoro-3,3-dimethyl-2,3-dihydrobenzo[*c*][2,6]naphthyridin-4(1*H*)-one (**4.6**, 2.20 g, 57%) as a yellow solid. **LC-MS (ESI)** m/z 279.3 ($\text{M}+\text{H}$)⁺.

[0216] To a mixture of 9-chloro-7-fluoro-3,3-dimethyl-2,3-dihydrobenzo[*c*][2,6]naphthyridin-4(1*H*)-one (**4.6**, 600 mg, 2.15 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (600 mg, 2.37 mmol) and potassium acetate (423 mg, 4.31 mmol) in 1,4-dioxane (10 mL) were added $\text{Pd}_2(\text{dba})_3$ (197 mg, 0.21 mmol) and Xphos (205 mg, 0.43 mmol). The resulting mixture was stirred at 90 °C for 2 hrs

under nitrogen atmosphere. The reaction mixture was filtered and the filtrates were concentrated under reduced pressure to afford (7-fluoro-3,3-dimethyl-4-oxo-3,4-dihydrobenzo[*c*][2,6]naphthyridin-9-yl)boronic acid (**4.7**, 800 mg, crude) as a brown oil. **LC-MS (ESI)** m/z 287.3 (M+H)⁺.

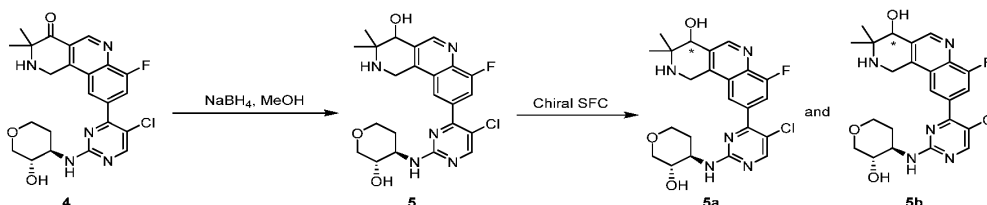
[0217] A mixture of (7-fluoro-3,3-dimethyl-4-oxo-3,4-dihydrobenzo[*c*][2,6]naphthyridin-9-yl)boronic acid (**4.7**, 800 mg, crude), 2,4,5-trichloropyrimidine (468 mg, 2.58 mmol), Pd(dppf)Cl₂ (157 mg, 0.21 mmol) and Na₂CO₃ (457 mg, 4.31 mmol) in 1,4-dioxane (10 mL) and H₂O (2 mL) was stirred at 90 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 9-(2,5-dichloropyrimidin-4-yl)-7-fluoro-3,3-dimethylbenzo[*c*][2,6]naphthyridin-4(3*H*)-one (**4.8**, 150 mg, 18% for two steps) as a yellow solid. **LC-MS (ESI)** m/z 389.2 (M+H)⁺.

[0218] A mixture of 9-(2,5-dichloropyrimidin-4-yl)-7-fluoro-3,3-dimethylbenzo[*c*][2,6]naphthyridin-4(3*H*)-one (**4.8**, 150 mg, 0.38 mmol), (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (70.0 mg, 0.46 mmol), 18-crown-6 (20.0 mg, 0.07 mmol), potassium carbonate (48.0 mg, 0.34 mmol) and potassium fluoride (66.0 mg, 1.14 mmol) in DMSO (4 mL) was stirred at 110 °C for 1 hr under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to prep-TLC (DCM/MeOH = 10/1) to afford 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3-dimethylbenzo[*c*][2,6]naphthyridin-4(3*H*)-one (**4.9**, 80.0 mg, 44%) as a yellow solid. **LC-MS (ESI)** m/z 470.1 (M+H)⁺.

[0219] To a solution of 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3-dimethylbenzo[*c*][2,6]naphthyridin-4(3*H*)-one (**4.9**, 80.0 mg, 0.17 mmol) in DCM (3 mL) was added NaBH₃CN (11.0 mg, 0.17 mmol). The resulting mixture was stirred at room temperature for 0.5 hr under nitrogen atmosphere. The reaction mixture was subjected to prep-HPLC to afford 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3-dimethyl-2,3-dihydrobenzo[*c*][2,6]naphthyridin-4(1*H*)-one (**4**, 10.8 mg, 13%) as a white solid. **LC-MS (ESI)** m/z 472.0 (M+H)⁺. ¹H NMR (400 MHz, Methanol-*d*₄) δ 9.34 (s, 1H), 8.45 (s, 1H), 8.39 (s, 1H), 8.09 (d, *J* = 11.2 Hz, 1H), 4.66 (s,

2H), 4.06 - 3.83 (m, 3H), 3.66 - 3.56 (m, 1H), 3.47 (t, $J = 11.2$ Hz, 1H), 3.20 (t, $J = 10.4$ Hz, 1H), 2.10 (d, $J = 13.2$ Hz, 1H), 1.62 (d, $J = 11.6$ Hz, 1H), 1.38 (s, 6H).

Example 5. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3-dimethyl-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-4-ol (**5a**) and 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3-dimethyl-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-4-ol (**5b**)



[0220] To a solution of 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3-dimethyl-2,3-dihydrobenzo[*c*][2,6]naphthyridin-4(1*H*)-one (**4**, 90.0 mg, 0.19 mmol) in methanol (4 mL) was added NaBH₄ (14.4 mg, 0.38 mmol), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure and the residue was subjected to prep-HPLC to give 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3-dimethyl-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-4-ol (**5**, 45.9 mg, 51%) as a white solid, which was further separated by chiral SFC to afford:

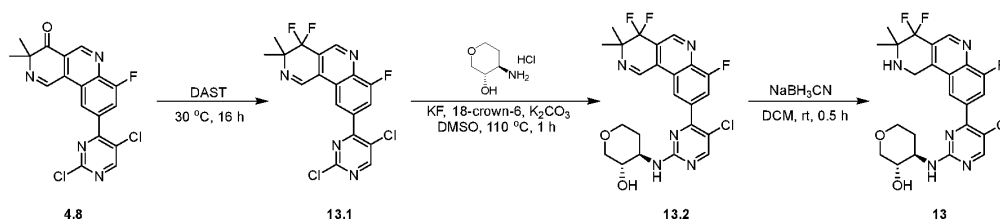
[0221] **Isomer 1: (5a, 100% de); Retention time:** 1.445 min; **LC-MS (ESI):** m/z 474.1 $[M+H]^+$; **¹H NMR** (500 MHz, DMSO-*d*₆) δ 9.01 (s, 1H), 8.47 (s, 1H), 8.26 - 8.11 (m, 1H), 7.97 - 7.79 (m, 1H), 7.67 - 7.44 (m, 1H), 5.66 (d, $J = 7.2$ Hz, 1H), 4.94 (d, $J = 5.8$ Hz, 1H), 4.38 (d, $J = 6.0$ Hz, 1H), 4.35 - 4.14 (m, 2H), 3.92 - 3.70 (m, 4H), 3.53 - 3.37 (m, 2H), 3.05 (t, $J = 10.4$ Hz, 1H), 2.07 - 1.83 (m, 1H), 1.58 - 1.40 (m, 1H), 1.11 (s, 3H), 0.98 (s, 3H).

[0222] **Isomer 2: (5b, 99% de); Retention time:** 1.570 min; **LC-MS (ESI):** m/z 474.1 $[M+H]^+$; **¹H NMR** (500 MHz, DMSO-*d*₆) δ 9.01 (s, 1H), 8.47 (s, 1H), 8.26 - 8.10 (m, 1H), 7.93 - 7.80 (m, 1H), 7.71 - 7.46 (m, 1H), 5.66 (d, $J = 7.0$ Hz, 1H), 4.94 (d, $J = 5.5$ Hz, 1H), 4.39 (d, $J = 6.6$ Hz, 1H), 4.34 - 4.17 (m, 2H), 3.91 - 3.74 (m, 3H), 3.59 - 3.36 (m, 3H), 3.05 (t, $J = 10.4$ Hz, 1H), 2.07 - 1.84 (m, 1H), 1.60 - 1.39 (m, 1H), 1.11 (s, 3H), 0.98 (s, 3H).

[0223] **Analytical method:** column: ChiralPak IG, 250 × 4.6 mm I.D., 5 μ m; mobile phase: A for CO₂ and B for MeOH (0.05% DEA); gradient: 8 min @ B 40%; flow rate: 2.0 mL/min; back pressure: 100 bar; column temperature: 40 °C.

[0224] Preparative separation method: Instrument: Waters SFC150AP preparative SFC; Column: DAICEL CHIRALCEL OD (250 mm * 30 mm, 10 μ m); Mobile phase: A for CO₂ and B for IPA (0.1% NH₃·H₂O); gradient: B% = 50% isocratic elution mode; flow rate: 70 g/min; Wavelength: 220 nm; column temperature: 35 degrees centigrade; system back pressure: 120 bar.

Example 6. (3*S*,4*R*)-4-((5-chloro-4-(4,4,7-trifluoro-3,3-dimethyl-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**13**)



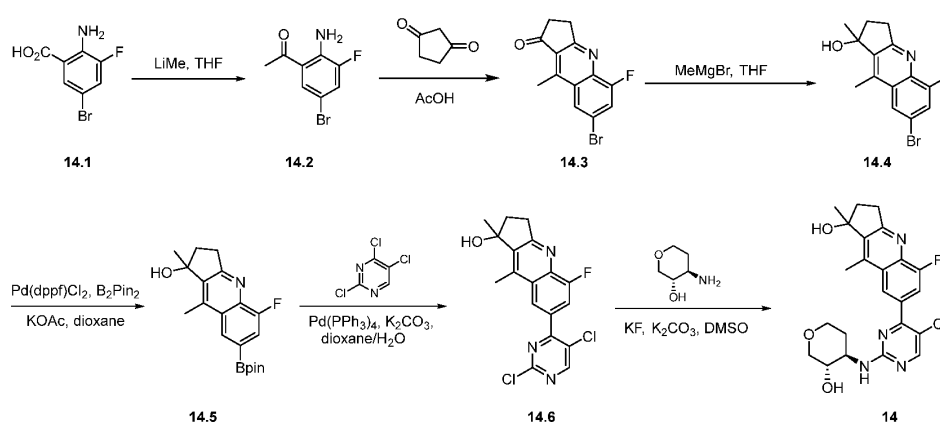
[0225] A mixture of 9-(2,5-dichloropyrimidin-4-yl)-7-fluoro-3,3-dimethylbenzo[*c*][2,6]naphthyridin-4(3*H*)-one (**4.8**, 30.0 mg, 0.10 mmol) and diethylaminosulphur trifluoride (1 mL) was stirred at 70 °C for 16 hrs under nitrogen atmosphere. The reaction mixture was quenched with sat. aq. NaHCO₃ (20 mL) and extracted with dichloromethane (20 mL $\times$ 3). The organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to prep-TLC (EtOAc/PE = 1/1) to afford 9-(2,5-dichloropyrimidin-4-yl)-4,4,7-trifluoro-3,3-dimethyl-3,4-dihydrobenzo[*c*][2,6]naphthyridine (**13.1**, 15.0 mg, 47%) as a white solid. **LC-MS (ESI):** *m/z* 411.3 (M+H)⁺.

[0226] A mixture of 9-(2,5-dichloropyrimidin-4-yl)-4,4,7-trifluoro-3,3-dimethyl-3,4-dihydrobenzo[*c*][2,6]naphthyridine (**13.1**, 15.0 mg, 0.04 mmol), (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (14.0 mg, 0.09 mmol), 18-crown-6 (1.00 mg, 0.01 mmol), potassium carbonate (12.6 mg, 0.09 mmol) and potassium fluoride (5.30 mg, 0.09 mmol) in DMSO (3 mL) was stirred at 110 °C for 1 hr under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (30 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford (3*S*,4*R*)-4-((5-chloro-4-(4,4,7-trifluoro-3,3-dimethyl-3,4-dihydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**13.2**, 30.0 mg, crude) as a yellow solid. **LC-MS (ESI):** *m/z* 492.1 (M+H)⁺.

[0227] To a solution of (3*S*,4*R*)-4-((5-chloro-4-(4,4,7-trifluoro-3,3-dimethyl-3,4-dihydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**13.2**, 30.0 mg, crude) in dichloromethane (3 mL) was added NaBH₃CN (1.9 mg, 0.03 mmol), and the

mixture was stirred at room temperature for 0.5 hr. The reaction mixture was subjected to prep-HPLC to afford (3*S*,4*R*)-4-((5-chloro-4-(4,4,7-trifluoro-3,3-dimethyl-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**13**, 6.40 mg, 35% for two steps) as a white solid. **LC-MS (ESI)**: m/z 494.0 ($M+H$)⁺. **¹H NMR** (400 MHz, Methanol-*d*₄) δ 9.13 (s, 1H), 8.37 (d, J = 13.2 Hz, 2H), 8.05 (d, J = 11.2 Hz, 1H), 4.53 (s, 2H), 4.04 - 3.86 (m, 3H), 3.65 - 3.55 (m, 1H), 3.47 (t, J = 11.6 Hz, 1H), 3.19 (t, J = 10.4 Hz, 1H), 2.10 (d, J = 13.2 Hz, 1H), 1.62 (d, J = 10.0 Hz, 1H), 1.31 (s, 6H).

Example 7. 7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-1,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**14**)



[0228] To a solution of 2-amino-5-bromo-3-fluorobenzoic acid (**14.1**, 10.0 g, 42.7 mmol) in THF (60 mL) was added CH₃Li (107 mL, 1.6 mol/L in diethyl ether) at 0 °C, and the mixture was stirred at 0 °C for 3 hrs under nitrogen atmosphere. The reaction mixture was quenched with saturated aqueous NH₄Cl, diluted with water (30 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 1-(2-amino-5-bromo-3-fluorophenyl)ethan-1-one (**14.2**, 8.60 g, 86.7%). **LC-MS (ESI)**: m/z 232.1 [$M+H$]⁺.

[0229] A mixture of 1-(2-amino-5-bromo-3-fluorophenyl)ethan-1-one (**14.2**, 1.00 g, 4.31 mmol) and cyclopentane-1,3-dione (507 mg, 5.17 mmol) in acetic acid (6 mL) was stirred at 110 °C for 10 hrs. The mixture was concentrated in vacuum to remove acetic acid, redissolved with ethyl acetate (30 mL) and washed with brine (15 mL × 3). The organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was

subjected to silica gel column chromatography to afford 7-bromo-5-fluoro-9-methyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-one (**14.3**, 178 mg, 14%). **LC-MS (ESI):** *m/z* 294.1 [M+H]⁺.

[0230] To a solution of 7-bromo-5-fluoro-9-methyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-one (**14.3**, 178 mg, 0.60 mmol) in THF (5 mL) was added CH₃MgBr (1.21 mL, 1 mol/L in THF) at 0 °C, and the mixture was stirred at 0 °C for 3 hrs under nitrogen atmosphere. The reaction mixture was quenched with saturated aqueous NH₄Cl, extracted with ethyl acetate (10 mL × 3) and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-bromo-5-fluoro-1,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**14.4**, 85.0 mg, 45.3%). **LC-MS (ESI):** *m/z* 310.0 [M+H]⁺.

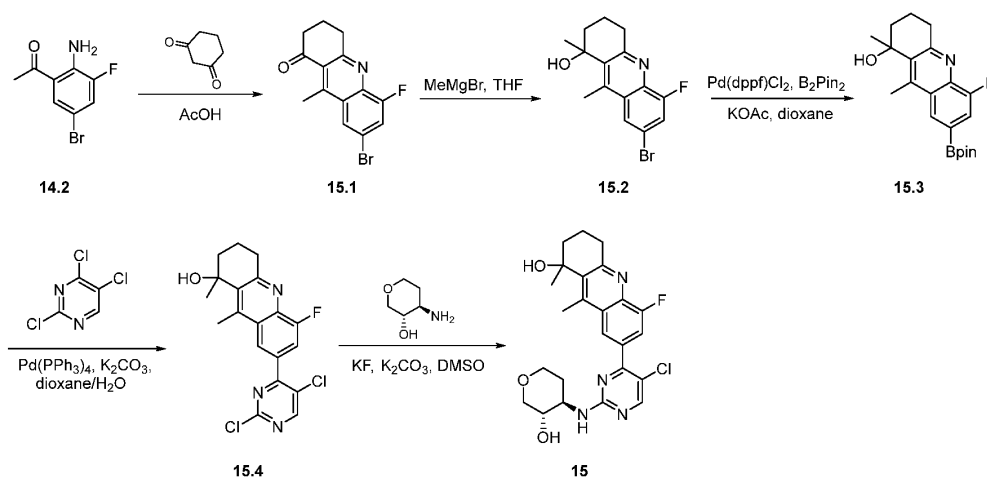
[0231] To a mixture of 7-bromo-5-fluoro-1,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**14.4**, 85.0 mg, 0.27 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (83.5 mg, 0.33 mmol) in dioxane (5 mL) were added Pd(dppf)Cl₂ (20.3 mg, 0.03 mmol) and KOAc (80.6 mg, 0.82 mmol), and the resulting mixture was stirred at 100 °C for 3 hrs under nitrogen atmosphere. The reaction mixture was filtered and the filtrates were concentrated under reduced pressure to give 5-fluoro-1,9-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**14.5**, 120 mg, crude). **LC-MS (ESI):** *m/z* 358.2 [M+H]⁺.

[0232] To a mixture of 2,4,5-trichloropyrimidine (0.031 mL, 0.27 mmol) and 5-fluoro-1,9-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**14.5**, 97.9 mg, crude) in dioxane (6 mL) and H₂O (1 mL) were added Pd(PPh₃)₄ (31.6 mg, 0.027 mmol) and K₂CO₃ (75.7 mg, 0.55 mmol), and the resulting mixture was stirred at 100 °C for 3 hrs under nitrogen atmosphere. The reaction mixture was diluted with brine (10 mL), extracted with ethyl acetate (10 mL × 3) and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-1,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**14.6**, 69.0 mg). **LC-MS (ESI):** *m/z* 378.1 [M+H]⁺.

[0233] To a mixture of 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-1,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**14.6**, 69.0 mg, 0.18 mmol) and (3*S*,4*R*)-4-aminotetrahydropyran-3-ol hydrochloride (42.0 mg, 0.24 mmol) in DMSO (3 mL) were added KF (21.1 mg, 0.36 mmol) and K₂CO₃ (50.4 mg, 0.36 mmol). The resulting mixture was stirred at 100 °C for 3 hrs. The reaction mixture was filtered and the filtrates were subjected to prep-HPLC to afford 7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-

yl)amino)pyrimidin-4-yl)-5-fluoro-1,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**14**, 22.0 mg, 26.3%) as a white solid. **LC-MS (ESI)**: m/z 459.2 $[M+H]^+$. **¹H NMR** (500 MHz, DMSO-*d*₆) δ 8.47 (s, 1H), 8.41 - 8.29 (m, 1H), 7.90 - 7.79 (m, 1H), 7.63 - 7.48 (m, 1H), 5.56 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 3.87 - 3.80 (m, 3H), 3.53 - 3.46 (m, 1H), 3.37 - 3.30 (m, 1H), 3.08 - 3.01 (m, 3H), 2.83 (s, 3H), 2.27 - 2.17 (m, 2H), 2.05 - 1.90 (m, 1H), 1.56 - 1.44 (m, 4H).

Example 8. 7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-1,9-dimethyl-1,2,3,4-tetrahydroacridin-1-ol (**15**)



[0234] To a solution of 1-(2-amino-5-bromo-3-fluorophenyl)ethan-1-one (**14.2**, 1.00 g, 4.31 mmol) in acetic acid (6 mL) was added cyclohexane-1,3-dione (579 mg, 5.17 mmol), and the mixture was stirred at 110 °C for 10 hrs. The mixture was concentrated in vacuum to remove acetic acid, redissolved with ethyl acetate (30 mL) and washed with brine (15 mL $\times$ 3). The organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-bromo-5-fluoro-9-methyl-1,2,3,4-tetrahydroacridin-1-one (**15.1**, 352 mg, 26.5%). **LC-MS (ESI)**: m/z 308.0 $[M+H]^+$.

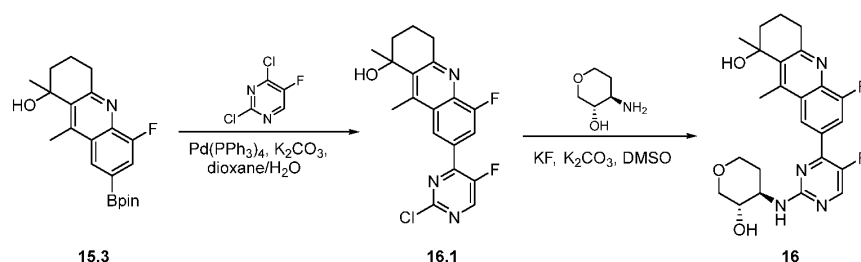
[0235] To a solution of 7-bromo-5-fluoro-9-methyl-1,2,3,4-tetrahydroacridin-1-one (**15.1**, 352 mg, 1.14 mmol) in THF (5 mL) was added CH₃MgBr (2.28 mL, 1 mol/L in THF) at 0 °C, and the mixture was stirred at 0 °C for 3 hrs under nitrogen atmosphere. The reaction mixture was quenched with saturated aqueous NH₄Cl, extracted with ethyl acetate (10 mL $\times$ 3) and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-bromo-5-fluoro-1,9-dimethyl-1,2,3,4-tetrahydroacridin-1-ol (**15.2**, 189 mg, 51%). **LC-MS (ESI)**: m/z 324.1 $[M+H]^+$.

[0236] To a mixture of 7-bromo-5-fluoro-1,9-dimethyl-1,2,3,4-tetrahydroacridin-1-ol (**15.2**, 189 mg, 0.583 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (177 mg, 0.70 mmol) in dioxane (10 mL) were added Pd(dppf)Cl₂ (43.2 mg, 0.058 mmol) and KOAc (171 mg, 1.75 mmol). The resulting mixture was stirred at 100 °C for 3 hrs under nitrogen atmosphere. The reaction mixture was filtered and the filtrates were concentrated under reduced pressure to give 5-fluoro-1,9-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydroacridin-1-ol (**15.3**, 250 mg, crude). **LC-MS (ESI):** *m/z* 372.2 [M+H]⁺.

[0237] To a mixture of 2,4,5-trichloropyrimidine (0.033 mL, 0.29 mmol) and 5-fluoro-1,9-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydroacridin-1-ol (**15.3**, 107 mg, crude) in dioxane (6 mL) and H₂O (1 mL) were added Pd(PPh₃)₄ (33.5 mg, 0.03 mmol) and K₂CO₃ (80.1 mg, 0.58 mmol), and the resulting mixture was stirred at 100 °C for 3 hrs under nitrogen atmosphere. The reaction mixture was diluted with brine (10 mL), extracted with ethyl acetate (10 mL × 3) and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-1,9-dimethyl-1,2,3,4-tetrahydroacridin-1-ol (**15.4**, 70.0 mg). **LC-MS (ESI):** *m/z* 392.1 [M+H]⁺.

[0238] To a mixture of 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-1,9-dimethyl-1,2,3,4-tetrahydroacridin-1-ol (**15.4**, 70.0 mg, 0.18 mmol) and (3*S*,4*R*)-4-aminotetrahydropyran-3-ol hydrochloride (42.0 mg, 0.24 mmol) in DMSO (3 mL) were added KF (20.7 mg, 0.36 mmol) and K₂CO₃ (49.3 mg, 0.36 mmol). The resulting mixture was stirred at 100 °C for 3 hrs. The reaction mixture was filtered and the filtrates were subjected to prep-HPLC to afford 7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-1,9-dimethyl-1,2,3,4-tetrahydroacridin-1-ol (**15**, 26.0 mg, 30.8%) as a white solid. **LC-MS (ESI):** *m/z* 473.2 [M+H]⁺. **¹H NMR** (500 MHz, DMSO-*d*₆) δ 8.46 (s, 1H), 8.43 - 8.32 (m, 1H), 7.88 - 7.76 (m, 1H), 7.62 - 7.49 (m, 1H), 5.28 (s, 1H), 4.94 (d, *J* = 5.4 Hz, 1H), 3.92 - 3.77 (m, 3H), 3.56 - 3.47 (m, 1H), 3.33 - 3.29 (m, 1H), 3.10 - 3.01 (m, 3H), 3.03 (s, 3H), 2.05 - 1.84 (m, 5H), 1.57 (s, 3H), 1.55 - 1.45 (m, 1H).

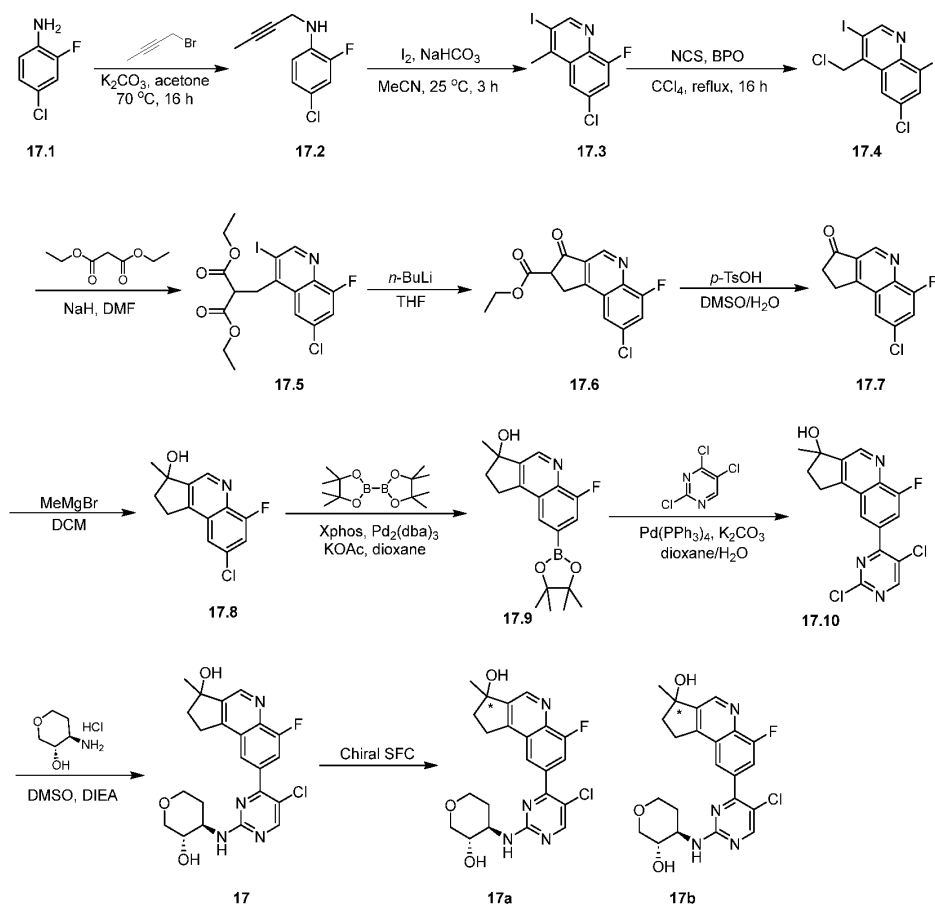
Example 9. 5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-1,9-dimethyl-1,2,3,4-tetrahydroacridin-1-ol (**16**)



[0239] To a mixture of 2,4-dichloro-5-fluoropyrimidine (40.4 mg, 0.24 mmol) and 5-fluoro-1,9-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydroacridin-1-ol (**15.3**, 90.0 mg, crude) in dioxane (6 mL) and H₂O (1 mL) were added Pd(PPh₃)₄ (27.9 mg, 0.024 mmol) and K₂CO₃ (66.9 mg, 0.48 mmol), and the resulting mixture was stirred at 100 °C for 3 hrs under nitrogen atmosphere. The reaction mixture was diluted with brine (10 mL), extracted with ethyl acetate (10 mL × 3) and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-(2-chloro-5-fluoropyrimidin-4-yl)-5-fluoro-1,9-dimethyl-1,2,3,4-tetrahydroacridin-1-ol (**16.1**, 65.0 mg). **LC-MS (ESI):** *m/z* 392.1 [M+H]⁺.

[0240] To a mixture of 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-1,9-dimethyl-1,2,3,4-tetrahydroacridin-1-ol (**16.1**, 70.0 mg, 0.178 mmol) and (3*S*,4*R*)-4-aminotetrahydropyran-3-ol hydrochloride (42 mg, 0.24 mmol) in DMSO (3 mL) were added KF (23.1 mg, 0.40 mmol) and K₂CO₃ (55.1 mg, 0.40 mmol), and the resulting mixture was stirred at 100 °C for 3 hrs. The reaction mixture was filtered and the filtrates were subjected to prep-HPLC to afford 5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-1,9-dimethyl-1,2,3,4-tetrahydroacridin-1-ol (**16**, 20.0 mg, 22%) as a yellow solid. **LC-MS (ESI):** *m/z* 457.1 [M+H]⁺. **¹H NMR** (500 MHz, DMSO-*d*₆) δ 8.62 (s, 1H), 8.50 (d, *J* = 3.6 Hz, 1H), 8.02 (d, *J* = 11.6 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 5.30 (s, 1H), 4.94 (d, *J* = 5.3 Hz, 1H), 3.85 - 3.82 (m, 3H), 3.55 - 3.48 (m, 1H), 3.42 - 3.28 (m, 2H), 3.11 - 3.07 (m, 2H), 3.06 (s, 3H), 2.05 - 1.92 (m, 4H), 1.91 - 1.81 (m, 1H), 1.57 (s, 3H), 1.55 - 1.50 (m, 1H).

Example 10. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol



[0241] To a mixture of 4-chloro-2-fluoroaniline (**17.1**, 500 g, 3.44 mol) and K_2CO_3 (523 g, 3.79 mol) in acetone (5 L) was added 1-bromobut-2-yne (455 g, 3.44 mol), and the resulting mixture was stirred at 70 °C for 16 hrs under nitrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford *N*-(but-2-yn-1-yl)-4-chloro-2-fluoroaniline (**17.2**, 550 g, 81%) as a yellow oil. **LC-MS (ESI) m/z 198.2 $[M+H]^+$.**

[0242] To a mixture of *N*-(but-2-yn-1-yl)-4-chloro-2-fluoroaniline (**17.2**, 550 g, 2.79 mol,) and $NaHCO_3$ (469 g, 5.58 mol) in acetone (5 L) was added iodine (1417 g, 5.58 mol), and the resulting mixture was stirred at room temperature for 3 hrs under nitrogen atmosphere. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (1 L) and extracted with ethyl acetate (4 L $\times$ 3). The organic layers were washed with brine (2 L), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 6-chloro-8-fluoro-3-iodo-4-methylquinoline (**17.3**, 130 g, 14%) as a brown solid. **LC-MS (ESI) m/z 322.5 $[M+H]^+$.**

[0243] To a solution of 6-chloro-8-fluoro-3-iodo-4-methylquinoline (**17.3**, 20.0 g, 62.3 mmol) in CCl₄ (250 mL) were added *N*-chlorosuccinimide (16.6 g, 124 mmol) and benzoyl peroxide (3.01 g, 12.4 mmol). The resulting mixture was stirred at 90 °C for 16 hrs under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and subjected to silica gel column chromatography to afford 6-chloro-4-(chloromethyl)-8-fluoro-3-iodoquinoline (**17.4**, 11.5 g, 46%) as a brown solid. **LC-MS (ESI)** *m/z* 355.9 [M+H]⁺.

[0244] To a solution of ethyl 3-ethoxy-3-oxopropanoate (3.50 mL, 23.0 mmol) in anhydrous DMF (40.0 mL) was added sodium hydride (640 mg, 16.0 mmol, 60% w.t. in mineral oil) slowly at 0 °C. The mixture was stirred at 0 °C for 10 mins followed by addition of 6-chloro-4-(chloromethyl)-8-fluoro-3-iodoquinoline (**17.4**, 3.56 g, 10.0 mmol). The resulting mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL x 3). The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuum to get a residue, which was subjected to silica gel column chromatography to afford diethyl 2-((6-chloro-8-fluoro-3-iodoquinolin-4-yl)methyl)malonate (**17.5**, 4.10 g, 85%) as a yellow oil. **LCMS (ESI)**: *m/z* 480.0 [M+H]⁺.

[0245] To a solution of diethyl 2-((6-chloro-8-fluoro-3-iodoquinolin-4-yl)methyl)malonate (**17.5**, 4.79 g, 10.0 mmol) in anhydrous THF (600 mL) was added *n*-butyllithium (10.0 mL, 22.0 mmol, 2.2 mol/L in hexane) dropwise at -78 °C under nitrogen atmosphere, and the mixture was stirred at -78 °C for 10 mins. The reaction mixture was quenched with sat. NH₄Cl (50.0 mL) and concentrated in vacuum to remove most of tetrahydrofuran. The resulting mixture was filtered, and the filter cake was washed with water and dried in vacuum to give ethyl 8-chloro-6-fluoro-3-oxo-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline-2-carboxylate (**17.6**, 2.38 g, 77%) as a yellow solid. **LCMS (ESI)**: *m/z* 308.0 [M+H]⁺.

[0246] To a suspension of ethyl 8-chloro-6-fluoro-3-oxo-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline-2-carboxylate (**17.6**, 1.33 g, 4.32 mmol) in DMSO/H₂O (15 mL/2 mL) was added *p*-TsOH (294 mg, 2.16 mmol), and the mixture was stirred at 120 °C for 1 hr. The reaction mixture was cooled to room temperature, diluted with water (20 mL) and then extracted with ethyl acetate (60 mL x 2). The combined organic layers were dried over anhy. Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (**17.7**, 449 mg, 44%) as a grey solid. **LCMS (ESI)**: *m/z* 236.0 [M+H]⁺.

[0247] To a solution of 8-chloro-6-fluoro-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (**17.7**, 600 mg, 2.54 mmol) in anhydrous DCM (12 mL) was added methylmagnesium bromide (8.40 mL, 3 M in diethyl ether) quickly at -78 °C under nitrogen atmosphere, and the mixture was stirred at -78 °C for 10 mins. The reaction mixture was quenched with sat. NH₄Cl (5 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhy. Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-3-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**17.8**, 456 mg, 71%) as a yellow solid. **LCMS (ESI)**: *m/z* 252.0 [M+H]⁺.

[0248] To a mixture of 8-chloro-6-fluoro-3-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**17.8**, 278 mg, 1.10 mmol) and bis(pinacolate)diboron (420 mg, 1.65 mmol) in dioxane (20 mL) were added Xphos (105 mg, 0.22 mmol), Pd₂(dba)₃ (100 mg, 0.11 mmol) and KOAc (325 mg, 3.30 mmol). The resulting mixture was stirred at 100 °C for 1 hr under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 6-fluoro-3-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**17.9**, 350 mg, 73%) as a brown oil. **LCMS (ESI)**: *m/z* 344.2 [M+H]⁺.

[0249] To a mixture of 6-fluoro-3-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**17.9**, 350 mg, 1.02 mmol) and 2,4,5-trichloropyrimidine (280 mg, 1.53 mmol) in dioxane (6 mL)/water (0.6 mL) were added Pd(PPh₃)₄ (118 mg, 0.102 mmol) and K₂CO₃ (423 mg, 3.06 mmol). The resulting mixture was stirred at 100 °C for 1 hr under nitrogen atmosphere. The mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-3-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**17.10**, 141 mg, 38%) as a yellow solid. **LCMS (ESI)**: *m/z* 364.0 [M+H]⁺.

[0250] To a mixture of 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-3-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**17.10**, 140 mg, 0.384 mmol) and (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (118 mg, 0.769 mmol) in anhydrous DMSO (4 mL) was added *N,N*-diisopropylethylamine (1.54 mmol, 0.25 mL), and the resulting mixture was stirred at 90 °C for 1.5 hrs. The reaction mixture was filtered and the filtrate was subjected to prep-HPLC to afford 8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3-

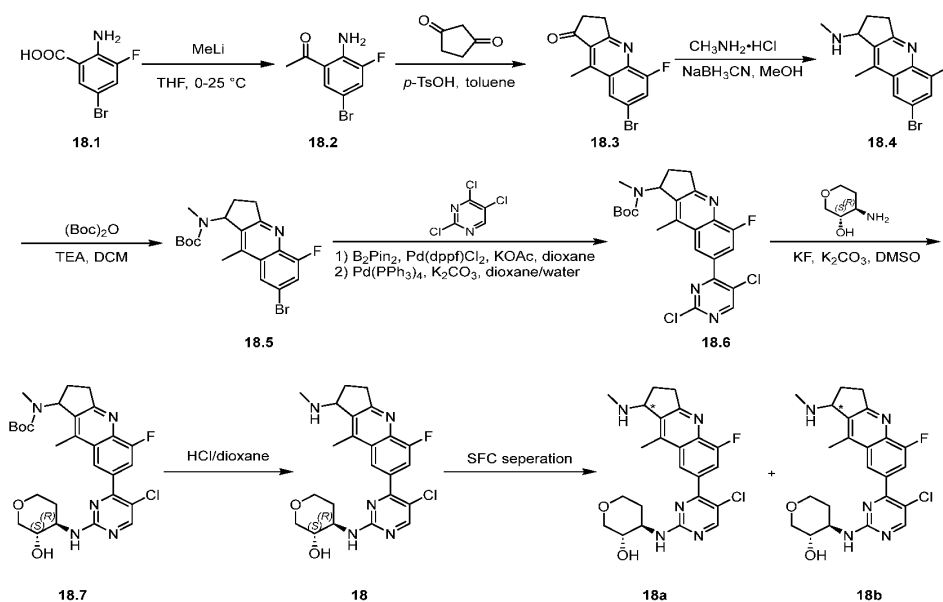
methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**17**, 62.0 mg, 38%) as a white solid, which was further separated by chiral SFC to give:

[0251] Isomer 1: (17a, 100% de); Retention time: 1.035 min; **LCMS (ESI):** *m/z* 445.1 [M+H]⁺; **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.48 (s, 1H), 8.17 (s, 1H), 7.89 (d, *J* = 11.6 Hz, 1H), 7.61 (s, 1H), 5.48 (s, 1H), 4.94 (d, *J* = 5.4 Hz, 1H), 3.88 - 3.75 (m, 4H), 3.55 - 3.44 (m, 1H), 3.40 - 3.36 (m, 1H), 3.23 - 3.12 (m, 1H), 3.05 (t, *J* = 10.4 Hz, 1H), 2.32 - 2.23 (m, 2H), 2.00 - 1.91 (m, 1H), 1.58 (s, 3H), 1.56 - 1.44 (m, 1H).

[0252] Isomer 2: (17b, 100% de); Retention time: 1.768 min; **LCMS (ESI):** *m/z* 445.1 [M+H]⁺; **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.48 (s, 1H), 8.17 (s, 1H), 7.89 (d, *J* = 11.7 Hz, 1H), 7.60 (s, 1H), 5.48 (s, 1H), 4.94 (d, *J* = 5.4 Hz, 1H), 3.91 - 3.77 (m, 4H), 3.53 - 3.46 (m, 1H), 3.40 - 3.35 (m, 1H), 3.24 - 3.12 (m, 1H), 3.10 - 3.00 (m, 1H), 2.34 - 2.20 (m, 2H), 2.01 - 1.88 (m, 1H), 1.58 (s, 3H), 1.55 - 1.45 (m, 1H).

[0253] Analytical method: Instrument: SHIMADZU-20AD-XR; Column: Cellulose SZ, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 50%; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm. **SFC method:** Instrument: GILSON-LC06; Column: Cellulose SZ, 30 * 250 mm, 5 μm; Mobile phase: A for Hex (10 mM NH₃) and B for EtOH; Gradient: B 50%; Flow rate: 40 mL/min; High pressure: 70 bar; Column temperature: 25 °C; Wavelength: 253 nm/230 nm; Cycle time: ~13 min.

Example 11. (3*S*,4*R*)-4-((5-chloro-4-((*S*)-5-fluoro-9-methyl-1-(methylamino)-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-7-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol and (3*S*,4*R*)-4-((5-chloro-4-((*R*)-5-fluoro-9-methyl-1-(methylamino)-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-7-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol



[0254] To a solution of 2-amino-5-bromo-3-fluorobenzoic acid (**18.1**, 5.00 g, 21.3 mmol) in tetrahydrofuran (50 mL) was added methyllithium (53.4 mL, 85.5 mmol 1.6 M in diethyl ether) dropwise at -20 °C under nitrogen atmosphere, and the mixture was stirred at 25 °C for 2 hrs. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL), diluted with water (100 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 1-(2-amino-5-bromo-3-fluorophenyl)ethan-1-one (**18.2**, 6.70 g, 89%) as a yellow solid. **LC-MS (ESI)**: m/z 232.0 $[M+H]^+$.

[0255] A mixture of 1-(2-amino-5-bromo-3-fluorophenyl)ethan-1-one (**18.2**, 2.40 g, 10.3 mmol), cyclopentane-1,3-dione (2.03 g, 20.7 mmol) and *p*-toluenesulfonic acid (0.79 g, 4.13 mmol) in toluene (20 mL) was stirred at 130 °C for 12 hrs. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 7-bromo-5-fluoro-9-methyl-2,3-dihydro-1H-cyclopenta[*b*]quinolin-1-one (**18.3**, 1.10 g, 36%) as a gray solid. **LC-MS (ESI)**: m/z 294.0 $[M+H]^+$.

[0256] A mixture of 7-bromo-5-fluoro-9-methyl-2,3-dihydro-1H-cyclopenta[*b*]quinolin-1-one (**18.3**, 320 mg, 1.09 mmol), methanamine hydrochloride (735 mg, 10.9 mmol) and sodium cyanoborohydride (205 mg, 3.26 mmol) in methanol (10.0 mL) was stirred at 80 °C for 12 hrs. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 7-bromo-5-fluoro-*N*,9-dimethyl-2,3-dihydro-1H-

cyclopenta[*b*]quinolin-1-amine (**18.4**, 280 mg, 83%) as a yellow oil. **LC-MS (ESI)**: *m/z* 309.0 [M+H]⁺.

[0257] To a mixture of 7-bromo-5-fluoro-*N*,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-amine (**18.4**, 260 mg, 0.84 mmol) and triethylamine (0.35 mL, 2.52 mmol) in dichloromethane (3.0 mL) was added *di-tert*-butyl dicarbonate (459 mg, 2.10 mmol) at 25 °C for 12 hrs. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford *tert*-butyl (7-bromo-5-fluoro-9-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-yl)(methyl)carbamate (**18.5**, 100 mg, 29%) as a yellow oil. **LC-MS (ESI)**: *m/z* 409.1 [M+H]⁺.

[0258] A mixture of *tert*-butyl (7-bromo-5-fluoro-9-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-yl)(methyl)carbamate (**18.5**, 90.0 mg, 0.220 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (72.6 mg, 0.286 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (18.0 mg, 0.022 mmol) and potassium acetate (43.2 mg, 0.44 mmol) in dioxane (1.0 mL) was stirred at 90 °C for 4 hrs under nitrogen atmosphere. The reaction mixture was cooled to room temperature. To the mixture were added water (0.2 mL), tetrakis(triphenylphosphine)palladium (25.3 mg, 0.022 mmol), potassium carbonate (60.6 mg, 0.44 mmol) and 2,4,5-trichloropyrimidine (44.2 mg, 0.241 mmol) at room temperature, and the resulting mixture was stirred at 90 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford *tert*-butyl (7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-9-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-yl)(methyl)carbamate (**18.6**, 110 mg, crude) as a yellow oil. **LC-MS (ESI)**: *m/z* 477.1 [M+H]⁺.

[0259] A mixture of *tert*-butyl (7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-9-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-yl)(methyl)carbamate (**18.6**, 110 mg, crude), (3*S*,4*R*)-4-aminotetrahydropyran-3-ol hydrochloride (48.2 mg, 0.31 mmol), potassium fluoride (48.7 mg, 0.84 mmol) and potassium carbonate (57.9 mg, 0.42 mmol) in dimethyl sulfoxide (1.0 mL) was stirred at 120 °C for 1 hr. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give *tert*-butyl (7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-

methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-yl)(methyl)carbamate (**18.7**, 100 mg, crude).

LC-MS (ESI): *m/z* 558.2 [*M*+*H*]⁺.

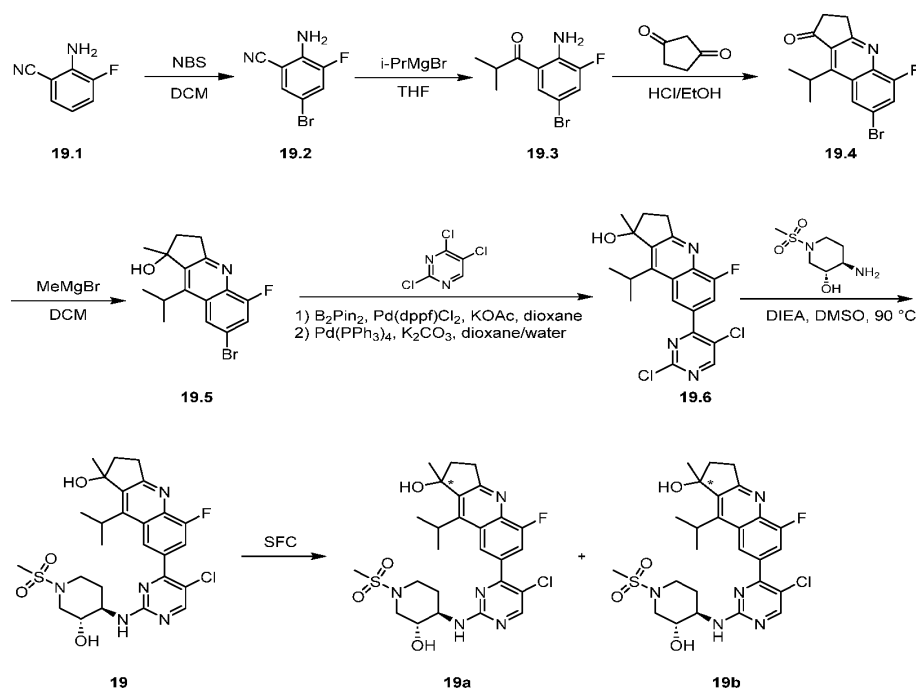
[0260] A mixture of *tert*-butyl (7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-yl)(methyl)carbamate (**18.7**, 100 mg, crude) and hydrochloric acid (1.0 mL, 4 mol/L in dioxane) in ethyl acetate (1 mL) was stirred at 25 °C for 4 hrs. The mixture was concentrated under reduced pressure and neutralized with saturated NaHCO₃ solution to pH 7. The resulting mixture was subjected to prep-HPLC to afford (3*S*,4*R*)-4-((5-chloro-4-(5-fluoro-9-methyl-1-(methylamino)-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-7-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**18**, 43.6 mg) as a white solid, which was further separated by chiral SFC to give:

[0261] **Isomer 1: (18a, 99.7% de); Retention time:** 3.105 min. **LC-MS (ESI):** *m/z* 458.2 [*M*+*H*]⁺; **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.46 (s, 1H), 8.45 - 8.2 (m, 1H), 7.97 - 7.76 (m, 1H), 7.68 - 7.45 (m, 1H), 4.94 (d, *J* = 5.4 Hz, 1H), 4.37 - 4.3 (m, 1H), 3.92 - 3.76 (m, 3H), 3.55 - 3.44 (m, 1H), 3.40 - 3.20 (m, 2H), 3.09 - 3.01 (m, 1H), 3.0 - 2.90 (m, 1H), 2.72 (s, 3H), 2.34 (s, 3H), 2.20 - 2.10 (m, 2H), 2.05 - 1.85 (m, 1H), 1.59 - 1.42 (m, 1H).

[0262] **Isomer 2: (18b, 100% de); Retention time:** 5.633 min; **LC-MS (ESI):** *m/z* 458.2 [*M*+*H*]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.46 (s, 1H), 8.45 - 8.2 (m, 1H), 7.97 - 7.76 (m, 1H), 7.68 - 7.45 (m, 1H), 4.94 (d, *J* = 5.4 Hz, 1H), 4.42 - 4.3 (m, 1H), 3.92 - 3.76 (m, 3H), 3.55 - 3.44 (m, 1H), 3.40 - 3.20 (m, 2H), 3.09 - 3.01 (m, 1H), 3.0 - 2.90 (m, 1H), 2.73 (s, 3H), 2.35 (s, 3H), 2.20 - 2.10 (m, 2H), 2.05 - 1.88 (m, 1H), 1.59 - 1.42 (m, 1H).

[0263] **Analytical method:** Instrument: SHIMADZU-20AD-XR; Column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1%DEA) and B for EtOH; Gradient: B 50%; Flow rate: 1.67mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm. **SFC Method:** Instrument: GILSON-03; Column: CHIRALPAK IH-3, 20 * 250 mm, 5 μm; Mobile phase: A for Hex (0.1% NH₃) and B for EtOH; Gradient: B 50%; Flow rate: 40 mL/min; high pressure: 135 bar; Column temperature: 25 °C; Wavelength: 257 nm/232 nm.

Example 12. (*R*)-7-(5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol and (*S*)-7-(5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol



[0264] To a solution of 2-amino-3-fluorobenzene-1-carbonitrile (**19.1**, 15.0 g, 110 mmol) in dichloromethane (150 mL) was added *N*-bromosuccinimide (21.6 g, 121 mmol) at 25 °C, and the mixture was stirred at 25 °C for 12 hrs. The reaction mixture was quenched with saturated sodium sulfite (200 mL) and extracted with dichloromethane (150 mL × 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 2-amino-5-bromo-3-fluorobenzene-1-carbonitrile (**19.2**, 23.0 g, 97%) as a purple solid. **LC-MS (ESI)**: *m/z* 215.0 [M+H]⁺.

[0265] To a solution of 2-amino-5-bromo-3-fluorobenzene-1-carbonitrile (**19.2**, 5.00 g, 23.3 mmol) in tetrahydrofuran (50.0 mL) was added bromo(prop-2-yl)magnesium (41.5 mL, 116 mmol) dropwise under nitrogen atmosphere at 0 °C, and the mixture was stirred at 25 °C for 3 hrs. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL), diluted with water (100 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 1-(2-amino-5-bromo-3-fluorophenyl)-2-methylpropan-1-one (**19.3**, 4.10 g, 68%) as a yellow solid. **LC-MS (ESI)**: *m/z* 260.0 [M+H]⁺.

[0266] A mixture of 1-(2-amino-5-bromo-3-fluorophenyl)-2-methylpropan-1-one (**19.3**, 4.10 g, 15.8 mmol) and cyclopentane-1,3-dione (1.86 g, 18.9 mmol) in hydrochloride solution

(40 ml, 2 mol/L in ethyl alcohol) was stirred at 90 °C for 12 hrs. The reaction mixture was concentrated under reduced pressure and diluted with water (100 mL). The resulting mixture was adjusted to pH 8 with saturated sodium carbonate solution and extracted with ethyl acetate (100 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentration under reduced pressure. The residue was triturated with petroleum ether: ethyl acetate = 5:1 (20 mL) to give 7-bromo-5-fluoro-9-isopropyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-one (**19.4**, 2.30 g, 45%) as a gray solid. **LC-MS (ESI)**: *m/z* 322.0 [M+H]⁺.

[0267] To a solution of 7-bromo-5-fluoro-9-isopropyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-one (**19.4**, 1.30 g, 4.04 mmol) in dichloromethane (13 mL) was added methylmagnesium bromide (13.5 mL, 40.4 mmol) at -78 °C under nitrogen atmosphere, and the mixture was stirred at -78 °C for 1 hr. The reaction mixture was quenched with saturated ammonium chloride (10 mL), diluted with water (50 mL) and then extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-bromo-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**19.5**, 10 g, 73%) as a yellow solid. **LC-MS (ESI)**: *m/z* 338.1 [M+H]⁺.

[0268] To a mixture of 7-bromo-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**19.5**, 100 mg, 0.30 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (97.6 mg, 0.38 mmol) in dioxane (2 mL) were added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (24.2 mg, 0.030 mmol) and potassium acetate (58.0 mg, 0.59 mmol). The resulting mixture was stirred at 90 °C for 2 hrs under nitrogen atmosphere and then cooled to room temperature. To the mixture were added water (0.4 mL), potassium carbonate (71.7 mg, 0.52 mmol), tetrakis(triphenylphosphine)palladium(0) (30.0 mg, 0.026 mmol) and 2,4,5-trichloropyrimidine (61.9 mg, 0.34 mmol), and the mixture was stirred at 90 °C under nitrogen atmosphere for 2 hrs. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**19.6**, 150 mg, crude) as a yellow oil. **LC-MS (ESI)**: *m/z* 406.1 [M+H]⁺.

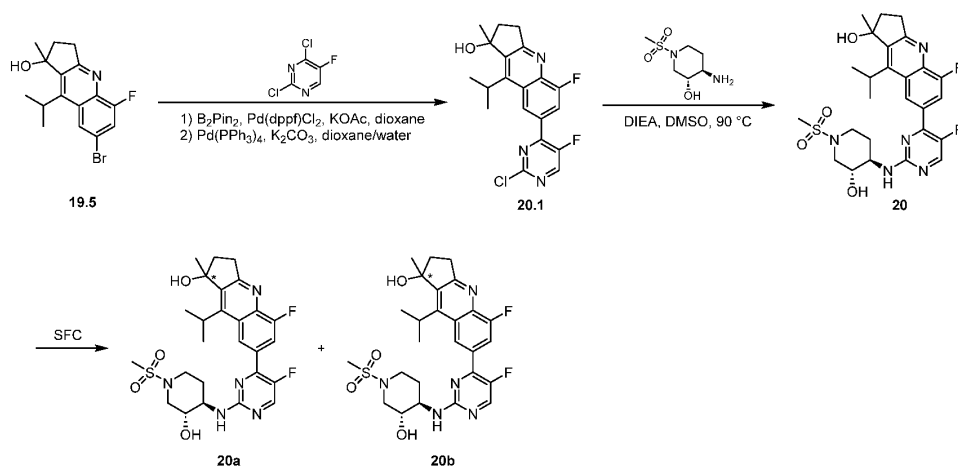
[0269] A mixture of 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**19.6**, 100 mg, crude), (3*R*,4*R*)-4-amino-1-(methylsulfonyl)piperidin-3-ol (72 mg, 0.37 mmol) and *N,N*-diisopropylethylamine (95.4 mg, 0.74 mmol) in anhydrous dimethyl sulfoxide (1 mL) was stirred at 90 °C for 5 hrs. The reaction mixture was filtered and subjected to prep-HPLC to give 7-(5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**19**, 62.3 mg) as a white solid, which was further separated by chiral SFC to give:

[0270] **Isomer 1: (19a, 100% de); Retention time:** 1.371 min. **LC-MS (ESI):** *m/z* 564.2 [M+H]⁺; **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.70 - 8.50 (m, 1H), 8.48 (s, 1H), 7.95 - 7.75 (m, 1H), 7.65 - 7.50 (m, 1H), 5.63 (s, 1H), 5.24 (d, *J* = 4.4 Hz, 1H), 4.56 - 4.45 (m, 1H), 3.90 - 3.75 (m, 1H), 3.69 - 3.56 (m, 2H), 3.54 - 3.45 (m, 1H), 3.10 - 2.95 (m, 2H), 2.90 (s, 3H), 2.88 - 2.75 (m, 1H), 2.70 - 2.60 (m, 1H), 2.3 - 2.17 (m, 2H), 2.15 - 1.97 (m, 1H), 1.61 - 1.46 (m, 10H).

[0271] **Isomer 2: (19b, 99.9% de); Retention time:** 1.870 min; **LC-MS (ESI):** *m/z* 564.2 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.70 - 8.50 (m, 1H), 8.48 (s, 1H), 7.95 - 7.75 (m, 1H), 7.65 - 7.50 (m, 1H), 5.63 (s, 1H), 5.33 - 5.13 (m, 1H), 4.56 - 4.45 (m, 1H), 3.90 - 3.75 (m, 1H), 3.67 - 3.56 (m, 2H), 3.54 - 3.45 (m, 1H), 3.1 - 2.95 (m, 2H), 2.90 (s, 3H), 2.88 - 2.75 (m, 1H), 2.70 - 2.57 (m, 1H), 2.3 - 2.17 (m, 2H), 2.15 - 1.97 (m, 1H), 1.61 - 1.46 (m, 10H).

[0272] **Analytical method:** Instrument: SHIMADZU-20AD-XR; Column: Cellulose SZ, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 50% ; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm. **SFC Method:** Instrument: GILSON-LC06; Column: Cellulose SZ, 30 * 250mm, 5 μm; Mobile phase: A for Hex (10 mM NH₃) and B for EtOH; Gradient: B 50%; Flow rate: 40 mL/min; High pressure: 66 bar; Column temperature: 25 °C; Wavelength: 257 nm/234 nm.

Example 13. (*R*)-5-fluoro-7-(5-fluoro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol and (*S*)-5-fluoro-7-(5-fluoro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol



[0273] To a mixture of 7-bromo-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1H-cyclopenta[b]quinolin-1-ol (**19.5**, 100 mg, 0.30 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (97.6 mg, 0.38 mmol) in dioxane (2 mL) were added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (24.2 mg, 0.030 mmol) and potassium acetate (58.0 mg, 0.59 mmol). The resulting mixture was stirred at 90 °C for 1 hr under nitrogen atmosphere and then cooled to room temperature. To the mixture were added water (0.4 mL), potassium carbonate (71.7 mg, 0.52 mmol), tetrakis(triphenylphosphine)palladium(0) (30.0 mg, 0.026 mmol) and 2,4-dichloro-5-fluoropyrimidine (63.60 mg, 0.38 mmol), and the resulting mixture was stirred at 90 °C under nitrogen atmosphere for 2 hrs. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 7-(2-chloro-5-fluoropyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1H-cyclopenta[b]quinolin-1-ol (**20.1**, 120 mg, crude) as a yellow oil. **LC-MS (ESI):** m/z 390.1 [M+H]⁺.

[0274] A mixture of 7-(2-chloro-5-fluoropyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1H-cyclopenta[b]quinolin-1-ol (**20.1**, 120 mg, crude), (3R,4R)-4-amino-1-(methylsulfonyl)piperidin-3-ol (89.7 mg, 0.46 mmol) and N,N-diisopropylethylamine (0.149 mL, 0.923 mmol) in dimethyl sulfoxide (1 mL) was stirred at 90 °C for 5 hrs. The reaction mixture was filtered and subjected to prep-HPLC to afford 5-fluoro-7-(5-fluoro-2-(((3R,4R)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-9-isopropyl-1-methyl-2,3-dihydro-1H-cyclopenta[b]quinolin-1-ol (**20**, 56.4 mg) as a yellow solid, which was further separated by chiral SFC to give:

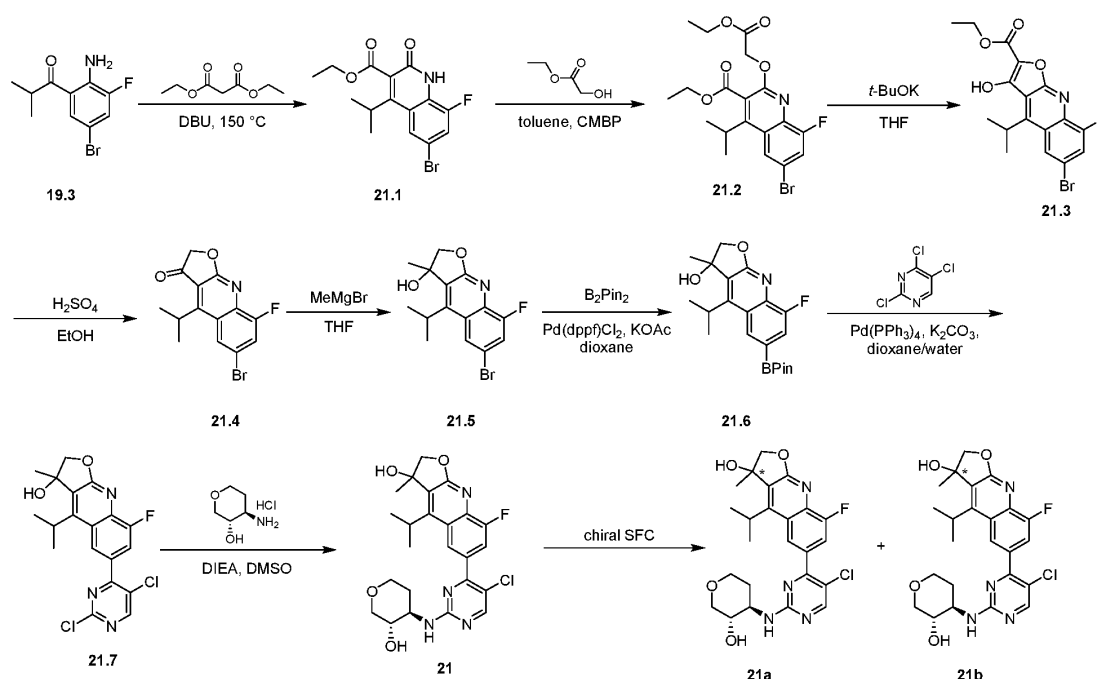
[0275] **Isomer 1: (20a, 100% de); Retention time:** 1.285 min. **LC-MS (ESI):** m/z 548.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 8.91 (s, 1H), 8.52 (d, J = 3.9 Hz, 1H), 8.04 (d, J =

11.8 Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 5.65 (s, 1H), 5.25 (d, $J = 4.5$ Hz, 1H), 4.61 - 4.40 (m, 1H), 3.95 - 3.75 (m, 1H), 3.70 - 3.59 (m, 2H), 3.56 - 3.47 (m, 1H), 3.10 - 2.96 (m, 2H), 2.95 - 2.82 (m, 4H), 2.71 - 2.62 (m, 1H), 2.30 - 2.17 (m, 2H), 2.16 - 2.05 (m, 1H), 1.62 - 1.50 (m, 10H).

[0276] Isomer 2: (20b, 100% de); Retention time: 1.798 min; **LC-MS (ESI):** m/z 548.2 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ 8.90 (s, 1H), 8.52 (d, $J = 3.9$ Hz, 1H), 8.04 (d, $J = 11.8$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 5.64 (s, 1H), 5.24 (d, $J = 4.5$ Hz, 1H), 4.61 - 4.40 (m, 1H), 3.95 - 3.75 (m, 1H), 3.70 - 3.58 (m, 2H), 3.56 - 3.47 (m, 1H), 3.10 - 2.96 (m, 2H), 2.95 - 2.82 (m, 4H), 2.71 - 2.62 (m, 1H), 2.30 - 2.17 (m, 2H), 2.16 - 2.05 (m, 1H), 1.62 - 1.50 (m, 10H).

[0277] Analytical method: Instrument: SHIMADZU-20AD-XR; Column: Cellulose SZ, 4.6 * 50 mm, 3.0 μ m; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 50%; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25°C; Wavelength: 254 nm. **SFC Method:** Instrument: GILSON-LC06; Column: Cellulose SZ, 30 * 250 mm, 5 μ m; Mobile phase: A for Hex (10 mM NH_3) and B for EtOH; Gradient: B 50%; Flow rate: 40 mL/min; High pressure: 112 bar; Column temperature: 25 °C; Wavelength: 254 nm/227 nm.

Example 14. (*R*)-6-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-8-fluoro-4-isopropyl-3-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol and (*S*)-6-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-8-fluoro-4-isopropyl-3-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol



[0278] A mixture of 1-(2-amino-5-bromo-3-fluorophenyl)-2-methylpropan-1-one (**19.3**, 32.0 g, crude), ethyl 3-ethoxy-3-oxopropanoate (56.0 mL, 369 mmol) and DBU (18.4 mL, 123 mmol) was stirred at 150 °C for 3 hrs. The reaction mixture was cooled to room temperature and then triturated with a mixture of 2 N HCl aqueous solution (50 mL), water (100 mL) and petroleum ether (50 mL). The resulting mixture was filtered and the filter cake was washed with PE/EA (3/1, 50 mL). The solid was collected and dried in vacuum to afford ethyl 6-bromo-8-fluoro-2-oxo-4-(prop-2-yl)-1*H*-quinoline-3-carboxylate (**21.1**, 30.0 g) as a yellow solid. **LC-MS (ESI)**: *m/z* 356.3 [*M*+*H*]⁺.

[0279] A mixture of ethyl 6-bromo-8-fluoro-2-oxo-4-(prop-2-yl)-1*H*-quinoline-3-carboxylate (**21.1**, 25.0 g, 70.2 mmol) and ethyl hydroxyacetate (8.77 g, 84.2 mmol) in toluene (250 mL) was added (tributyl-λ⁵-phosphanylidene)acetonitrile (23.7 g, 98.2 mmol), and the mixture was stirred at 100 °C for 4 hrs under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford ethyl 6-bromo-2-[(2-ethoxy-2-oxoethyl)oxy]-8-fluoro-4-(prop-2-yl)quinoline-3-carboxylate (**21.2**, 28.0 g, 90%) as a yellow oil. **LC-MS (ESI)**: *m/z* 442.1 [*M*+*H*]⁺.

[0280] To a solution of ethyl 6-bromo-2-[(2-ethoxy-2-oxoethyl)oxy]-8-fluoro-4-(prop-2-yl)quinoline-3-carboxylate (**21.2**, 1.00 g, 2.26 mmol) in THF (10 mL) was added *t*-BuOK (4.52 mL, 4.52 mmol, 1 mol/L in THF) dropwise at room temperature, and the mixture was stirred at room temperature for 1 hrs. The reaction mixture was quenched with 2 N HCl (3 mL), diluted with water (30 mL) and extracted with ethyl acetate (20 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give ethyl 6-bromo-8-fluoro-3-oxo-4-(prop-2-yl)-2,3-dihydrofuro[2,3-*b*]quinoline-2-carboxylate (**21.3**, 400 mg, crude). **LC-MS (ESI)**: *m/z* 396.1 [*M*+*H*]⁺.

[0281] A solution of ethyl 6-bromo-8-fluoro-3-oxo-4-(prop-2-yl)-2,3-dihydrofuro[2,3-*b*]quinoline-2-carboxylate (**21.3**, 400 mg, crude) in ethanol (3 mL) was added 6 N H₂SO₄ (1 mL) slowly at 0 °C, and the mixture was stirred at 100 °C for 1 hr. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with saturated NaHCO₃ solution (15 mL × 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 6-bromo-8-fluoro-4-(prop-2-yl)-2,3-dihydrofuro[2,3-*b*]quinolin-3-one (**21.4**, 320 mg, two steps yield 44%) as a colorless oil. **LC-MS (ESI)**: *m/z* 324.1 [*M*+*H*]⁺.

[0282] To a solution of 6-bromo-8-fluoro-4-(prop-2-yl)-2,3-dihydrofuro[2,3-*b*]quinolin-3-one (**21.4**, 360 mg, 1.14 mmol) in DCM (6 mL) was added CH₃MgBr (4.93 mL, 3 mol/L in THF) at -60 °C, and the mixture was stirred at -60 °C for 30 mins. The reaction mixture was quenched with 2 N HCl (3 mL) and extracted with DCM (10 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 6-bromo-8-fluoro-3-methyl-4-(prop-2-yl)-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol (**21.5**, 140 mg, 41.7%) as a colorless oil. **LC-MS (ESI)**: *m/z* 340.0 [M+H]⁺.

[0283] To a mixture of 6-bromo-8-fluoro-3-methyl-4-(prop-2-yl)-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol (**21.5**, 140 mg, 0.41 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (156 mg, 0.62 mmol) in dioxane (3 mL) were added Pd(dppf)Cl₂ (30.5 mg, 0.041 mmol) and KOAc (121 mg, 1.23 mmol). The resulting mixture was stirred at 100 °C for 1 hr under nitrogen atmosphere and then cooled to room temperature. To the mixture were added water (1 mL), 2,4,5-trichloropyrimidine (94 µL, 0.82 mmol), K₂CO₃ (171 mg, 1.24 mmol), Pd(PPh₃)₄ (47.7 mg, 0.041 mmol) and PPh₃ (43.35 mg, 0.165 mmol), and the resulting mixture was stirred at 100 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 6-(2,5-dichloropyrimidin-4-yl)-8-fluoro-4-isopropyl-3-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol (**21.7**, 130 mg, two steps yield 77.1%) as a brown oil. **LC-MS (ESI)**: *m/z* 408.1 [M+H]⁺.

[0284] A mixture of 6-(2,5-dichloropyrimidin-4-yl)-8-fluoro-3-methyl-4-(prop-2-yl)-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol (**21.7**, 130 mg, 0.32 mmol), (3*S*,4*R*)-4-aminotetrahydropyran-3-ol hydrochloride (146 mg, 0.95 mmol) and *N,N*-diisopropylethylamine (166 µL, 0.95 mmol) in DMSO (2 mL) was stirred at 110 °C for 2 hrs. The reaction mixture was filtered and subjected to prep-HPLC to give 6-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-8-fluoro-4-isopropyl-3-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol (**21**, 78.3 mg, 50%) as a white solid, which was further separated by chiral SFC to give:

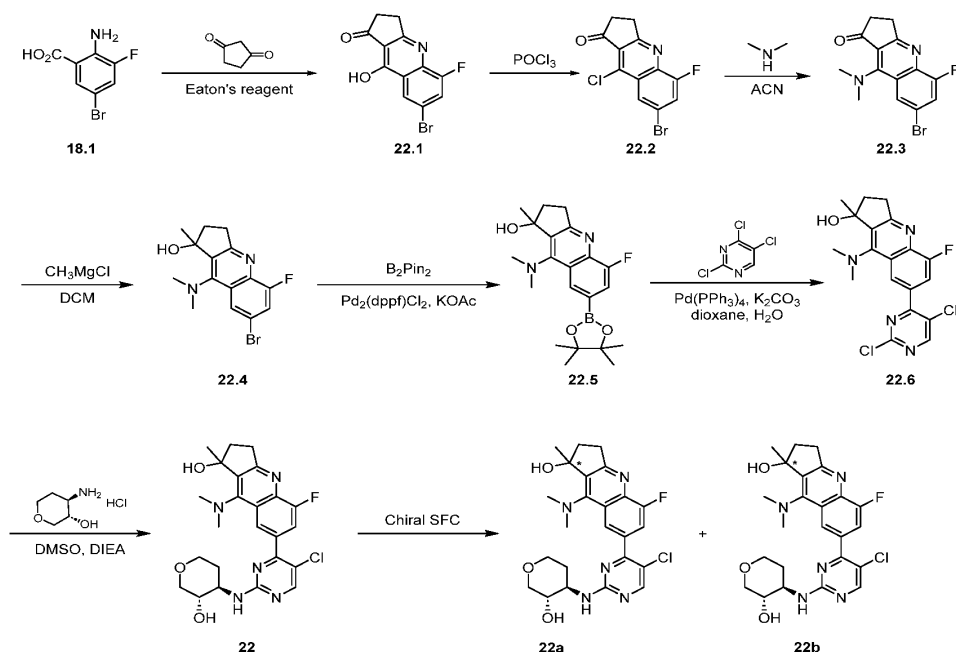
[0285] **Isomer 1: (21a, 100% de); Retention time:** 0.920 min; **LC-MS (ESI)**: *m/z* 489.1 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.58 (s, 1H), 8.45 (s, 1H), 8.02 - 7.72 (m, 1H), 7.54 (d, *J* = 7.0 Hz, 1H), 6.13 (s, 1H), 4.96 (s, 1H), 4.48 (d, *J* = 9.2 Hz, 1H), 4.39 (d, *J* = 9.6 Hz, 1H),

4.23 - 4.14 (m, 1H), 3.92 - 3.76 (m, 3H), 3.55 - 3.46 (m, 1H), 3.29 - 3.25 (m, 1H), 3.02 (t, $J = 10.4$ Hz, 1H), 2.03 - 1.88 (m, 1H), 1.63 (s, 3H), 1.60 - 1.44 (m, 7H).

[0286] Isomer 2: (21b, 100% de); Retention time: 1.359 min; LC-MS (ESI): m/z 489.1 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ 8.57 (s, 1H), 8.45 (s, 1H), 7.99 - 7.72 (m, 1H), 7.53 (d, $J = 7.2$ Hz, 1H), 6.12 (s, 1H), 4.95 (d, $J = 5.3$ Hz, 1H), 4.48 (d, $J = 9.3$ Hz, 1H), 4.40 (d, $J = 9.3$ Hz, 1H), 4.24 - 4.13 (m, 1H), 3.91 - 3.77 (m, 3H), 3.54 - 3.47 (m, 1H), 3.31 - 3.22 (m, 1H), 3.02 (t, $J = 10.8$ Hz, 1H), 2.06 - 1.89 (m, 1H), 1.64 (s, 3H), 1.59 - 1.45 (m, 7H).

[0287] Analytical method: Instrument: SHIMADZU-20AD-XR; Column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm ; Mobile phase: A for Hex (0.1% DEA) and B for IPA; Gradient: B 50%; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm. **SFC Method:** Instrument: GILSON-LC07; Column: CHIRALPAK IK, 30 * 250 mm, 5 μm ; Mobile phase: A for Hex (10 mM NH_3) and B for IPA; Gradient: B 50%; Flow rate: 40 mL/min; High pressure: 121 bar; Column temperature: 25 °C; Wavelength: 202 nm/260 nm; Cycle time: ~15 min.

Example 15. (*R*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-(dimethylamino)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol and (*S*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-(dimethylamino)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol



[0288] A mixture of 2-amino-5-bromo-3-fluorobenzoic acid (**18.1**, 10.0 g, 42.7 mmol) and cyclopentane-1,3-dione (5.03 g, 51.3 mmol) in Eaton's Reagent (50 mL) was stirred at 135 °C for 1.5 hrs. The mixture was cooled to room temperature and diluted with water (100 mL). The resulting mixture was adjusted to pH 7 with NaOH solid slowly at 0 °C and then filtered. The filter cake was collected and subjected to silica gel column chromatography to afford 7-bromo-5-fluoro-9-hydroxy-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-one (**22.1**, 1.50 g, 11.8%) as a brown solid. **LC-MS (ESI)**: *m/z* 296.0 [M+H]⁺.

[0289] A mixture of 7-bromo-5-fluoro-9-hydroxy-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-one (**22.1**, 1.50 g, 5.06 mmol) and POCl₃ (7 mL) was stirred at 60 °C for 16 hrs. The reaction mixture was cooled to room temperature and slowly quenched with water (20 mL). The resulting mixture was extracted with ethyl acetate (30 mL × 3) and the combined organic layers were concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-bromo-9-chloro-5-fluoro-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-one (**22.2**, 540 mg, 33.9%) as a yellow solid. **LC-MS (ESI)**: *m/z* 314.0 [M+H]⁺.

[0290] To a solution of 7-bromo-9-chloro-5-fluoro-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-one (**22.2**, 1.00 g, 3.18 mmol) in acetonitrile (10 mL) was added dimethylamine (7.9 mL, 15.9 mmol, 2 mol/L in THF), and the mixture was stirred 25 °C for 2 hrs. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-bromo-9-(dimethylamino)-5-fluoro-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-one (**22.3**, 710 mg, 69.1%). **LC-MS (ESI)**: *m/z* 323.2 [M+H]⁺.

[0291] To a solution of 7-bromo-9-(dimethylamino)-5-fluoro-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-one (**22.3**, 710 mg, 2.19 mmol) in DCM (7 mL) was added methylmagnesium bromide (3.66 mL, 10.9 mmol, 3 mol/L) quickly at 0 °C, and the mixture was stirred at 0 °C for 30 mins. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 7-bromo-9-(dimethylamino)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**22.4**, 700 mg, 93.9%). **LC-MS (ESI)**: *m/z* 339.1 [M+H]⁺.

[0292] A mixture of 7-bromo-9-(dimethylamino)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**22.4**, 700 mg, 2.06 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.05 g, 4.13 mmol), potassium acetate

(405 mg, 4.13 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (153 mg, 0.206 mmol) in dioxane (10 mL) was stirred at 90 °C for 4 hrs under nitrogen atmosphere. The reaction mixture was cooled to room temperature. To the mixture were added water (4 mL), 2,4,5-trichloropyrimidine (0.46 mL, 4.00 mmol), Pd(PPh₃)₄ (231 mg, 0.20 mmol) and K₂CO₃ (552 mg, 4.00 mmol), and the resulting mixture was stirred at 90 °C for 3 hrs under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 7-(2,5-dichloropyrimidin-4-yl)-9-(dimethylamino)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**22.6**, 170 mg, two steps yield 20.8%) as a yellow solid. **LC-MS (ESI):** *m/z* 407.3 [M+H]⁺.

[0293] A mixture of 7-(2,5-dichloropyrimidin-4-yl)-9-(dimethylamino)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**22.6**, 170 mg, 0.417 mmol), (3*S*,4*R*)-4-aminotetrahydropyran-3-ol hydrogen chloride (96.2 mg, 0.63 mmol) and *N,N*-diisopropylethylamine (162 mg, 1.25 mmol) in DMSO (2 mL) was stirred at 120 °C for 2 hrs. The reaction mixture was filtered and the filtrate was subjected to prep-HPLC to afford 7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-(dimethylamino)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**22**, 72.0 mg, 35.4%) as a white solid, which was further separated by chiral SFC to give:

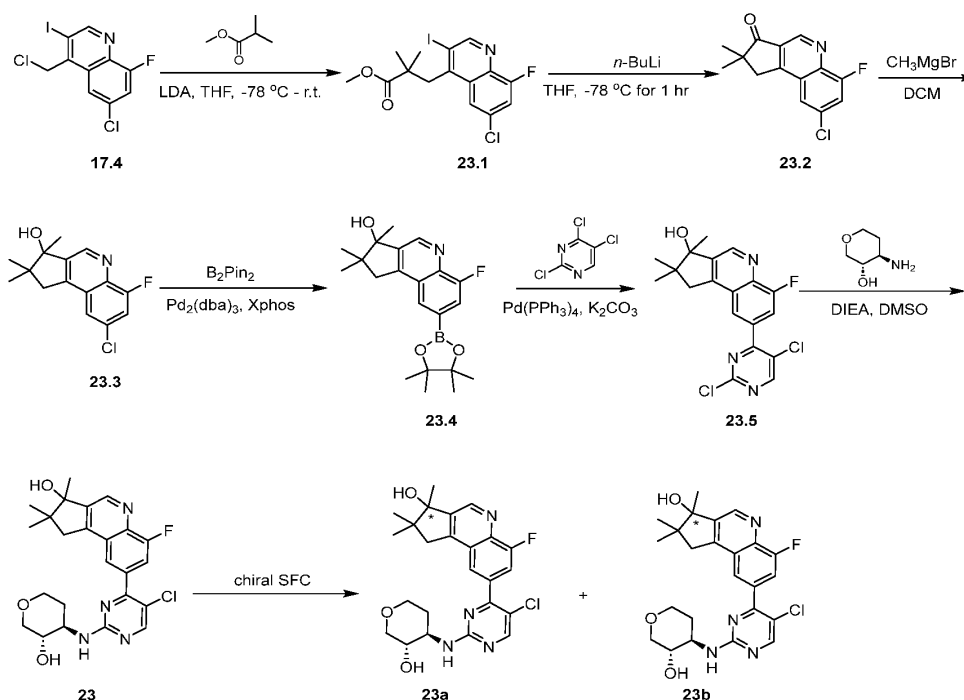
[0294] **Isomer 1: (22a, 100% de); Retention time:** 2.18 min, **LC-MS (ESI):** *m/z* 488.2 [M+H]⁺; **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.58 - 8.30 (m, 2H), 7.84 (s, 1H), 7.57 (s, 1H), 5.41 (s, 1H), 4.97 (d, *J* = 5.5 Hz, 1H), 3.95 - 3.71 (m, 3H), 3.58 - 3.49 (m, 1H), 3.42 - 3.35 (m, 1H), 3.25 - 2.92 (m, 10H), 2.20 (t, *J* = 7.3 Hz, 2H), 1.98 (s, 1H), 1.65 (d, *J* = 1.7 Hz, 3H).

[0295] **Isomer 2: (22b, 100% de); Retention time:** 3.88 min, **LC-MS (ESI):** *m/z* 488.2 [M+H]⁺; **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.55 - 8.35 (m, 2H), 7.84 (s, 1H), 7.58 (s, 1H), 5.42 (s, 1H), 4.97 (d, *J* = 5.3 Hz, 1H), 3.95 - 3.72 (m, 3H), 3.56 - 3.47 (m, 1H), 3.42 - 3.35 (m, 1H), 3.21 - 2.94 (m, 10H), 2.23 - 2.15 (m, 2H), 1.97 (s, 1H), 1.65 (s, 3H).

[0296] **Analytical separation method:** Instrument: SHIMADZU-20AD-XR; Column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1% DEA) and B for IPA; Gradient: B 50% ; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm. **SFC method:** Instrument: GILSON-LC07; Column: CHIRALPAK IK, 30 * 250 mm, 5 μm; Mobile phase: A for Hex (10 mM NH₃) and B for IPA; Gradient: B 50%; Flow rate: 40 mL/min; High pressure: 128 bar; Column temperature: 25 °C; Wavelength: 250 nm/202

nm; Cycle time: ~48 min; Sample preparation: compound was dissolved in ~3 mL for EtOH/DCM; Injection: 2 mL per injection.

Example 16. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2,3-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2,3-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol



[0297] To a solution of methyl isobutyrate (6.28 mL, 54.8 mmol) in THF (120 mL) was added lithium diisopropylamide (29.5 mL, 59.0 mmol, 2 mol/L in THF) dropwise at -78 °C under nitrogen atmosphere. The mixture was stirred at -78 °C for 30 mins followed by addition of a solution of 6-chloro-4-(chloromethyl)-8-fluoro-3-iodoquinoline (**17.4**, 15.0 g, 42.14 mmol) in THF (80 mL) dropwise at the same temperature. The resulting mixture was warmed to room temperature and stirred for 3 hrs under nitrogen atmosphere. The reaction mixture was quenched with saturated NH₄Cl solution (30 mL), diluted with water (200 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford methyl 3-(6-chloro-8-fluoro-3-iodoquinolin-4-yl)-2,2-dimethylpropanoate (**23.1**, 12.0 g, 67.5%) as a yellow solid. **LC-MS (ESI)** *m/z* 422.0 [M+H]⁺.

[0298] To a solution of methyl 3-(6-chloro-8-fluoro-3-iodoquinolin-4-yl)-2,2-dimethylpropanoate (**23.1**, 33.0 g, 78.3 mmol) in THF (200 mL) was added *n*-butyllithium (37.6 mL, 93.9 mmol, 2.5 mol/L in THF) dropwise at -78 °C under nitrogen atmosphere, and the mixture was stirred at -78 °C for 1 hrs. The reaction mixture was quenched with saturated NH₄Cl solution (20 mL), diluted with water (200 mL) and extracted with ethyl acetate (80 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-2,2-dimethyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (**23.2**, 10.3 g, 49.9%) as a pale yellow solid. **LC-MS (ESI)** *m/z* 264.1 [M+H]⁺.

[0299] To a solution of 8-chloro-6-fluoro-2,2-dimethyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (**23.2**, 2.50 g, 9.48 mmol) in dichloromethane (20 mL) was added methylmagnesium bromide (15.8 mL, 47.4 mmol, 3 mol/L in THF) dropwise at -78 °C under nitrogen atmosphere, and the mixture was stirred at room temperature for 1.5 hrs. The reaction mixture was quenched with saturated NH₄Cl solution (8 mL), diluted with water (50 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-2,2,3-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**23.3**, 2.10 g, 79.2%) as a white solid. **LC-MS (ESI)** *m/z* 280.1 [M+H]⁺.

[0300] A mixture of 8-chloro-6-fluoro-2,2,3-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**23.3**, 2.10 g, 7.51 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.86 g, 11.3 mmol), tris(dibenzylideneacetone)dipalladium (1.37 g, 1.50 mmol), potassium acetate (2.21 g, 22.5 mmol) and 2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (716 mg, 1.50 mmol) in dioxane (15 mL) was stirred at 90 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered. The filtrates were concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 6-fluoro-2,2,3-trimethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**23.4**, 2.54 g, 91.1%) as a brown solid. **LC-MS (ESI)**: *m/z* 372.2 [M+H]⁺.

[0301] A mixture of 6-fluoro-2,2,3-trimethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**23.4**, 2.00 g, 5.38 mmol), 2,4,5-trichloropyrimidine (1.58 g, 8.62 mmol), tetrakis(triphenylphosphine)palladium (934 mg, 0.81

mmol) and potassium carbonate (1.49 g, 10.8 mmol) in dioxane/water (10 mL/2.5 mL) was stirred at 90 °C for 1.5 hrs under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-2,2,3-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**23.5**, 1.70 g, 80.4%) as a yellow solid. **LC-MS (ESI):** *m/z* 392.1 [M+H]⁺.

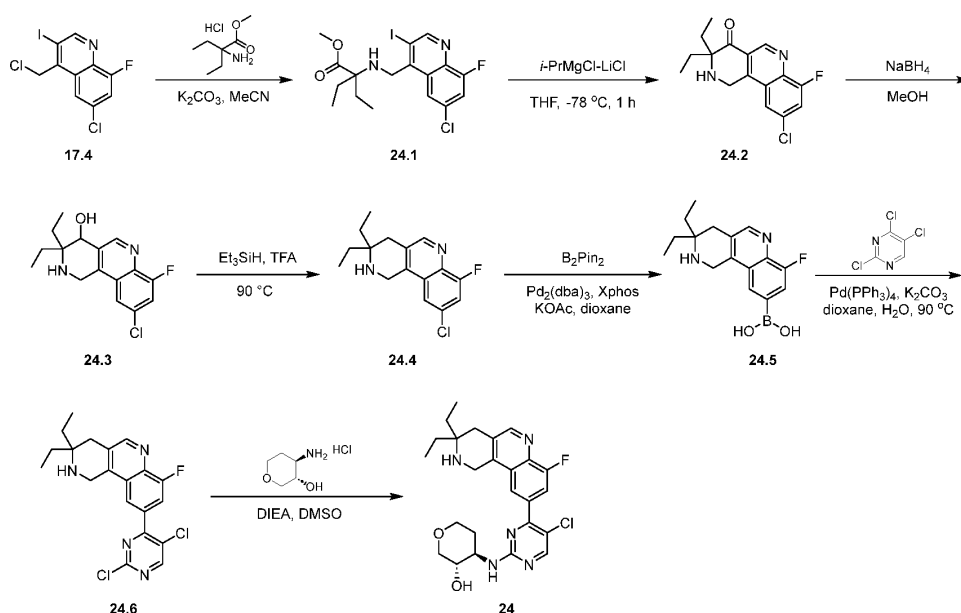
[0302] A mixture of 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-2,2,3-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**23.5**, 1.70 g, 4.33 mmol), (3*S*,4*R*)-4-aminotetrahydropyran-3-ol hydrogen chloride (812 mg, 6.93 mmol) and *N,N*-diisopropylethylamine (2.86 mL, 17.3 mmol) in dimethyl sulfoxide (8 mL) was stirred at 110 °C for 2.5 hrs. The reaction mixture was filtered and the filtrate was subjected to silica gel column chromatography to afford 8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2,3-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**23**, 1.40 g, 68.3%) as a white solid, which was further separated by chiral SFC to give:

[0303] **Isomer 1: (23a, 100% de); Retention time:** 1.387 min. **LCMS (ESI):** *m/z* 473.4 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 8.47 (s, 1H), 8.15 (s, 1H), 7.89 (d, *J* = 11.2 Hz, 1H), 7.58 (s, 1H), 5.18 (s, 1H), 4.93 (d, *J* = 5.4 Hz, 1H), 3.86 - 3.75 (m, 3H), 3.58 - 3.42 (m, 1H), 3.36 - 3.33 (m, 1H), 3.19 - 2.96 (m, 3H), 1.97 - 1.91 (m, 1H), 1.55 - 1.45 (m, 1H), 1.43 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H).

[0304] **Isomer 2: (23b, 100% de); Retention time:** 3.841 min. **LCMS (ESI):** *m/z* 473.4 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 8.47 (s, 1H), 8.15 (s, 1H), 7.88 (d, *J* = 11.9 Hz, 1H), 7.58 (s, 1H), 5.18 (s, 1H), 4.93 (d, *J* = 5.4 Hz, 1H), 3.86 - 3.75 (m, 3H), 3.59 - 3.39 (m, 1H), 3.36 - 3.33 (m, 1H), 3.19 - 2.96 (m, 3H), 1.97 - 1.91 (m, 1H), 1.59 - 1.47 (m, 1H), 1.43 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H).

[0305] **Analytical method:** Column: ChiralPak IH, 100 × 4.6 mm I.D., 5 μm, Mobile phase: A for CO₂ and B for Methanol (0.05% DEA), Gradient: 8 min @B 40%, Flow rate: 2.0 mL/min, Back pressure: 100 bar, Column temperature: 40 °C. **SFC separation method:** SHIMADZU PREP SOLUTION SFC; ChiralPak IH, 150 × 20 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for MeOH + 0.1% NH₄OH; Gradient: B 40 %; Flow rate: 40 mL /min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 15 min.

Example 17. (3*S*,4*R*)-4-((5-chloro-4-(3,3-diethyl-7-fluoro-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol



[0306] A mixture of 6-chloro-4-(chloromethyl)-8-fluoro-3-iodoquinoline (**17.4**, 18.0 g, 50.5 mmol), methyl 2-amino-2-ethylbutanoate (1.35 g, 9.27 mmol), K_2CO_3 (27.9 g, 202 mmol) and KI (0.84 g, 5.05 mmol) in MeCN (200 mL) was stirred at 80°C for 16 hrs. The mixture was cooled to room temperature and then filtered. The filtrate was concentrated under reduced pressure and the residue was diluted with water (100 mL) and extracted with DCM (100 mL $\times$ 2). The combined organic layers were washed with water (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was triturated with PE/EtOAc ($\sim$ 5/1, 50 mL) and filtered. The filtrate was concentrated in vacuum to afford methyl 2-(((6-chloro-8-fluoro-3-iodoquinolin-4-yl)methyl)amino)-2-ethylbutanoate (**24.1**, 16.0 g, 68.1%) as a yellow solid. **LC-MS (ESI)**: m/z 465.0 $[\text{M}+\text{H}]^+$.

[0307] To a solution of lithium magnesium dichloride propan-2-ide (74.5 mL, 96.8 mmol) in THF (200 mL) was added a solution of methyl 2-(((6-chloro-8-fluoro-3-iodoquinolin-4-yl)methyl)amino)-2-ethylbutanoate (**24.1**, 15.0 g, 32.2 mmol) in THF (100 mL) dropwise at -78°C , and the mixture was stirred at -78°C for 1 hr under nitrogen atmosphere. The reaction mixture was quenched with 2 N HCl (40 mL), neutralized with NaHCO_3 (20 mL) and extracted with ethyl acetate (250 mL $\times$ 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and then triturated with PE/EtOAc (5/1) to afford 9-chloro-3,3-diethyl-7-fluoro-1,2,3,4-tetrahydropyrido[4,3-*c*]quinolin-4-one (**24.2**, 5.00 g, 50.5%) as a white solid. **LC-MS (ESI)**: m/z 307.1 $[\text{M}+\text{H}]^+$.

[0308] To a solution of 9-chloro-3,3-diethyl-7-fluoro-1,2,3,4-tetrahydropyrido[4,3-*c*]quinolin-4-one (**24.2**, 1.50 g, 4.89 mmol) in MeOH (20 mL) was added NaBH₄ (0.18 g, 4.89 mmol) at 0 °C, and the mixture was stirred at 0 °C for 10 mins. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 9-chloro-3,3-diethyl-7-fluoro-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-4-ol (**24.3**, 500 mg, 33.1%) as a yellow solid. **LC-MS (ESI)**: *m/z* 309.1[M+H]⁺.

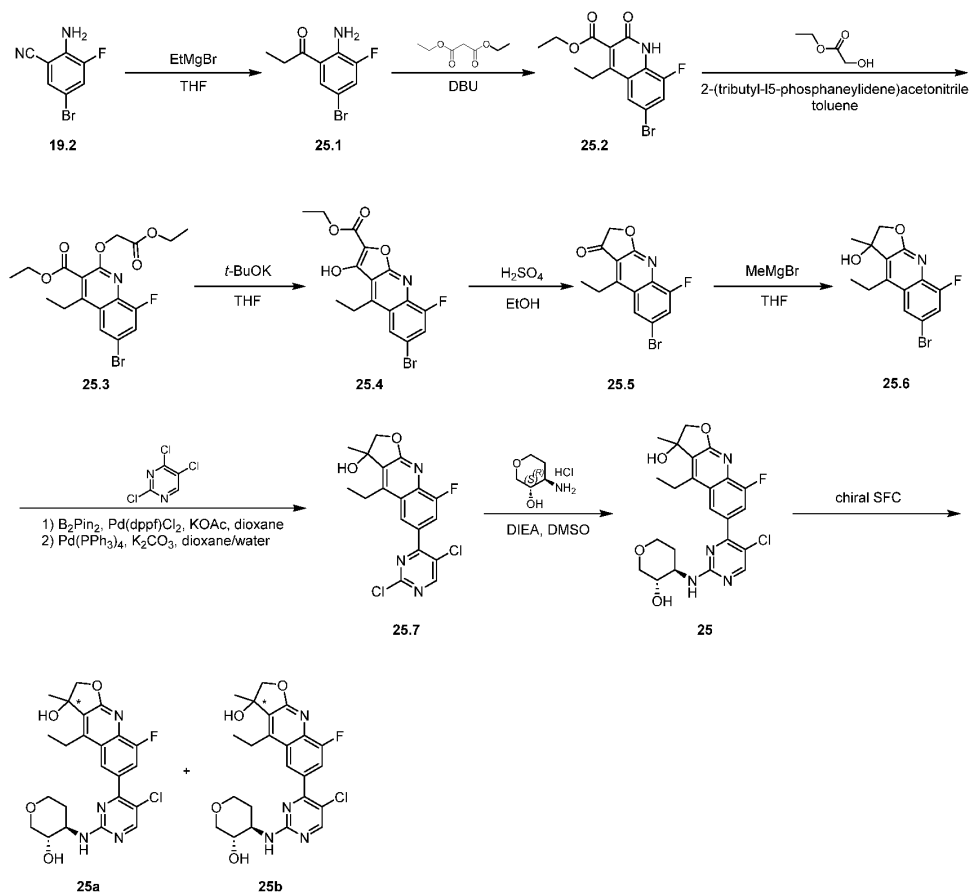
[0309] To a mixture of 9-chloro-3,3-diethyl-7-fluoro-1,2,3,4-tetrahydropyrido[4,3-*c*]quinolin-4-ol (**24.3**, 400 mg, 1.29 mmol) and Et₃SiH (827 μL, 5.18 mmol) was added TFA (793 μL, 10.3 mmol) at 0 °C, and the mixture was stirred at 90 °C for 4 hrs. The reaction mixture was concentrated under reduced pressure, diluted with water (3 mL) and then extracted with petroleum ether (5 mL × 3). The aqueous phase was adjusted to pH 8 with saturated NaHCO₃ solution and extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 9-chloro-3,3-diethyl-7-fluoro-1,2,3,4-tetrahydropyrido[4,3-*c*]quinoline (**24.4**, 370 mg, 97.3%) as a yellow solid. **LC-MS (ESI)**: *m/z* 293.1[M+H]⁺.

[0310] To a mixture of 9-chloro-3,3-diethyl-7-fluoro-1,2,3,4-tetrahydropyrido[4,3-*c*]quinoline (**24.4**, 185 mg, 0.63 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (240 mg, 0.95 mmol) in dioxane (5 mL) were added Pd₂(dba)₃ (28.9 mg, 0.032 mmol), Xphos (30.1 mg, 0.063 mmol) and KOAc (186 mg, 1.90 mmol). The resulting mixture was stirred at 90 °C for 2 hrs under nitrogen atmosphere and then cooled to room temperature. To the mixture were added water (0.6 mL), 2,4,5-trichloropyrimidine (215 μL, 1.87 mmol), K₂CO₃ (259 mg, 1.87 mmol) and Pd(PPh₃)₄ (72.2 mg, 0.062 mmol), and the resulting mixture was stirred at 100 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (5 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 9-(2,5-dichloropyrimidin-4-yl)-3,3-diethyl-7-fluoro-1,2,3,4-tetrahydropyrido[4,3-*c*]quinoline (**24.6**, 250 mg, crude) as a yellow solid. **LC-MS (ESI)**: *m/z* 405.1 [M+H]⁺.

[0311] A mixture of 9-(2,5-dichloropyrimidin-4-yl)-3,3-diethyl-7-fluoro-1,2,3,4-tetrahydropyrido[4,3-*c*]quinoline (**24.6**, 250 mg, crude), (3*S*,4*R*)-4-aminotetrahydropyran-3-ol

hydrochloride (189 mg, 1.23 mmol) and DIEA (305 μ L, 1.85 mmol) in DMSO (1.5 mL) was stirred at 100 °C for 1 hr. The reaction mixture was filtered and subjected to prep-HPLC to afford (3*S*,4*R*)-4-((5-chloro-4-(3,3-diethyl-7-fluoro-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**24**, 64.0 mg, three steps yield 21%) as a white solid. **LC-MS** (ESI) m/z 486.2 $[M+H]^+$. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.74 (s, 1H), 8.47 (s, 1H), 8.14 (s, 1H), 7.85 (d, J = 11.4 Hz, 1H), 7.68 - 7.44 (m, 1H), 5.05 - 4.85 (m, 1H), 4.28 (s, 2H), 3.91 - 3.75 (m, 3H), 3.34 - 3.29 (m, 2H), 3.08 - 3.01 (m, 1H), 2.76 (s, 2H), 2.07 - 1.87 (m, 1H), 1.56 - 1.29 (m, 5H), 0.86 (t, J = 7.4 Hz, 6H).

Example 18. (*R*)-6-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-ethyl-8-fluoro-3-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol and (*S*)-6-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-ethyl-8-fluoro-3-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol



[0312] To a solution of 2-amino-5-bromo-3-fluorobenzene-1-carbonitrile (**19.2**, 10.0 g, 46.5 mmol) in tetrahydrofuran (50 mL) was added ethylmagnesium bromide (232 mL, 232

mmol, 1 mol/L) at -10 °C, and the mixture was stirred at 25 °C for 2 hrs. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL), diluted with water (200 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 1-(2-amino-5-bromo-3-fluorophenyl)propan-1-one (**25.1**, 11.0 g, 96%) as a yellow solid. **LC-MS (ESI)**: m/z 246.0 [M+H]⁺.

[0313] A mixture of 1-(2-amino-5-bromo-3-fluorophenyl)propan-1-one (**25.1**, 9.70 g, 39.4 mmol), ethyl 3-ethoxy-3-oxopropanoate (30 mL, 197 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (6.00 g, 39.4 mmol) was stirred at 120 °C for 12 hrs. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford ethyl 6-bromo-4-ethyl-8-fluoro-2-oxo-1,2-dihydroquinoline-3-carboxylate (**25.2**, 6.30 g, 47 %) as a yellow solid. **LC-MS (ESI)**: m/z 342.0 [M+H]⁺.

[0314] A mixture of ethyl 6-bromo-4-ethyl-8-fluoro-2-oxo-1,2-dihydroquinoline-3-carboxylate (**25.2**, 3.00 g, 8.77 mmol), ethyl 2-hydroxyacetate (1.19 g, 11.4 mmol) and 2-(tributyl-15-phosphaneylidene)acetonitrile (3.17 g, 13.2 mmol) in toluene (30 mL) was stirred at 100 °C for 12 hrs. The mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford ethyl 6-bromo-2-(2-ethoxy-2-oxoethoxy)-4-ethyl-8-fluoroquinoline-3-carboxylate (**25.3**, 2.70 g, 72%) as a yellow oil. **LC-MS (ESI)**: m/z 428.0 [M+H]⁺.

[0315] To a solution of ethyl 6-bromo-2-(2-ethoxy-2-oxoethoxy)-4-ethyl-8-fluoroquinoline-3-carboxylate (**25.3**, 2.6 g, 6.07 mmol) in tetrahydrofuran (260 mL) was added potassium *t*-butoxide (7.9 mL, 7.9 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 mins. The reaction mixture was quenched with hydrochloric acid aqueous solution (3.1 mL, 6.2 mmol, 2 mol/L) at 0 °C. The mixture was diluted with water (400 mL) and extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford ethyl 6-bromo-4-ethyl-8-fluoro-3-hydroxyfuro[2,3-*b*]quinoline-2-carboxylate (**25.4**, 2.60 g, crude) as a yellow solid. **LC-MS (ESI)**: m/z 382.0 [M+H]⁺.

[0316] To a mixture of ethyl 6-bromo-4-ethyl-8-fluoro-3-hydroxyfuro[2,3-*b*]quinoline-2-carboxylate (**25.4**, 2.60 g, crude) and sulfuric acid (7.8 mL, 46.8 mmol) in ethyl alcohol (20 mL, 342 mmol) was stirred at 100 °C for 12 hrs. The reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (100 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 6-bromo-4-ethyl-8-fluorofuro[2,3-*b*]quinolin-3(2*H*)-one (**25.5**, 900 mg) as a yellow solid. **LC-MS (ESI)**: m/z 310.0 $[M+H]^+$.

[0317] To a solution of 6-bromo-4-ethyl-8-fluorofuro[2,3-*b*]quinolin-3(2*H*)-one (**25.5**, 800 mg, 2.58 mmol) in dichloromethane (8 mL) was added methylmagnesium bromide (8.6 mL, 25.8 mmol) at -78 °C, and the mixture was stirred at 0 °C for 1 hr. The reaction mixture was quenched with saturated ammonium chloride solution (10 mL), diluted with water (100 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 6-bromo-4-ethyl-8-fluoro-3-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol (**25.6**, 620 mg, 74%) as a yellow solid. **LC-MS (ESI)**: m/z 326.0 $[M+H]^+$.

[0318] A mixture of 6-bromo-4-ethyl-8-fluoro-3-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol (**25.6**, 300 mg, 0.92 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (467 mg, 1.84 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (75.3 mg, 0.092 mmol) and potassium acetate (181 mg, 1.84 mmol) in dioxane (3 mL) was stirred at 90 °C under nitrogen atmosphere for 3 hrs. The reaction mixture was cooled to room temperature. To the mixture were added water (0.6 mL), potassium carbonate (254 mg, 1.84 mmol), 2,4,5-trichloropyrimidine (506 mg, 2.76 mmol) and tetrakis(triphenylphosphine)palladium(0) (106 mg, 0.092 mmol), and the mixture was stirred at 100 °C under nitrogen atmosphere for 3 hrs. The mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 6-(2,5-dichloropyrimidin-4-yl)-4-ethyl-8-fluoro-3-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol (**25.7**, 350 mg, two steps yield 97%) as a yellow oil. **LC-MS (ESI)**: m/z 394.0 $[M+H]^+$.

[0319] A mixture of 6-(2,5-dichloropyrimidin-4-yl)-4-ethyl-8-fluoro-3-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol (**25.7**, 430 mg, 1.09 mmol), (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (419 mg, 2.73 mmol), potassium fluoride (253 mg, 4.36 mmol) and

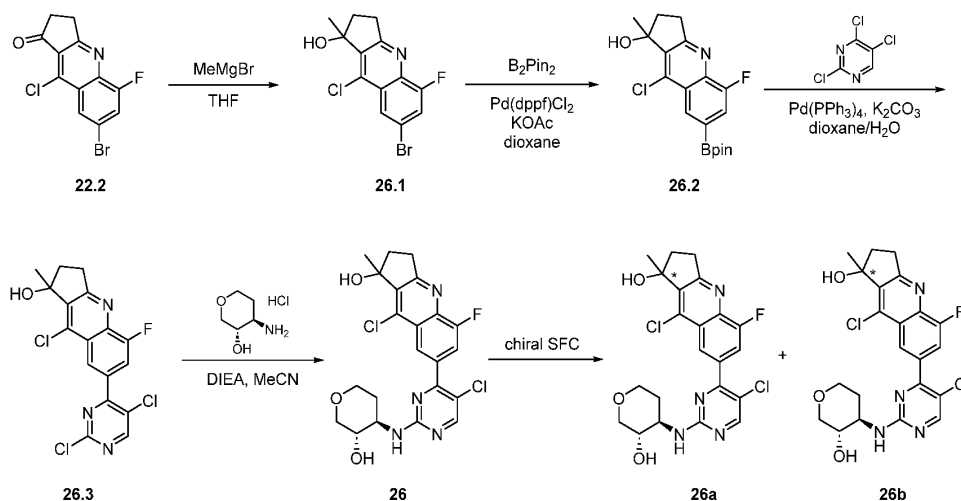
potassium carbonate (452 mg, 3.27 mmol) in dimethyl sulfoxide (4 mL) was stirred at 120 °C for 4 hrs. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 6-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-ethyl-8-fluoro-3-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-3-ol (**25**, 303 mg, 58%) as a yellow solid, which was further separated by chiral SFC to give:

[0320] Isomer 1: (25a, 99.98% de); Retention time: 0.577 min. **LC-MS (ESI):** *m/z* 475.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.45 (s, 1H), 8.41 - 8.2 (m, 1H), 8.01 - 7.72 (m, 1H), 7.66 - 7.46 (m, 1H), 6.05 (s, 1H), 4.94 (d, *J* = 5.4 Hz, 1H), 4.52 - 4.38 (m, 2 H), 3.92 - 3.74 (m, 3H), 3.58 - 3.43 (m, 1H), 3.33 - 3.16 (m, 3 H), 3.10 - 2.97 (m, 1H), 2.06 - 1.85 (m, 1H), 1.68 (s, 3H), 1.57 - 1.46 (m, 1H), 1.35 (t, *J* = 7.5 Hz, 3H).

[0321] Isomer 2: (25b, 99.88% de); Retention time: 0.867 min; **LC-MS (ESI):** *m/z* 475.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.45 (s, 1H), 8.41 - 8.2 (m, 1H), 8.01 - 7.72 (m, 1H), 7.66 - 7.46 (m, 1H), 6.05 (s, 1H), 4.94 (d, *J* = 5.4 Hz, 1H), 4.52 - 4.38 (m, 2 H), 3.92 - 3.74 (m, 3H), 3.58 - 3.43 (m, 1H), 3.33 - 3.16 (m, 3 H), 3.10 - 2.97 (m, 1H), 2.06 - 1.85 (m, 1H), 1.68 (s, 3H), 1.57 - 1.46 (m, 1H), 1.35 (t, *J* = 7.5 Hz, 3H).

[0322] Analytical method: Instrument: Agilent 1260; Column: CHIRALPAK IG-3, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 30% ; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm. **SFC Method:** Instrument: GILSON-LC03; Column: CHIRALPAK IG, 30 * 250 mm, 5 μm; Mobile phase: A for MtBE (10 mMNH₃) and B for MeOH; Gradient: B 30%; Flow rate: 40 mL/min; High pressure: 112 bar; Column temperature: 25 °C; Wavelength: 259 nm/206 nm.

Example 19. (*R*)-9-chloro-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol and (*S*)-9-chloro-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol



[0323] To a solution of 7-bromo-9-chloro-5-fluoro-2,3-dihydro-1H-cyclopenta[1,2-b]quinolin-1-one (**22.2**, 180 mg, 0.57 mmol) in dichloromethane (5 mL) was added CH_3MgBr (0.95 mL, 3 mol/L in THF) at -60°C , and the mixture was stirred at -60°C for 30 mins. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 7-bromo-9-chloro-5-fluoro-1-methyl-2,3-dihydro-1H-cyclopenta[1,2-b]quinolin-1-ol (**26.1**, 130 mg, 68.7%) as a yellow solid. **LC-MS (ESI)**: m/z 330.0 $[\text{M}+\text{H}]^+$.

[0324] A mixture of 7-bromo-9-chloro-5-fluoro-1-methyl-2,3-dihydro-1H-cyclopenta[1,2-b]quinolin-1-ol (**26.1**, 370 mg, 1.12 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (426 mg, 1.68 mmol), Pd(dppf)Cl_2 (83.0 mg, 0.11 mmol) and KOAc (329 mg, 3.36 mmol) in dioxane (7 mL) was stirred at 100°C for 1 hr under nitrogen atmosphere. Then, to the mixture were added water (2 mL), 2,4,5-trichloropyrimidine (256 μL , 2.23 mmol), K_2CO_3 (463 mg, 3.35 mmol), $\text{Pd(PPh}_3)_4$ (129 mg, 0.11 mmol) and PPh_3 (117 mg, 0.45 mmol), and the resulting mixture was stirred at 100°C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (5 mL $\times$ 2). The combined organic layers were washed with brine (10 mL $\times$ 2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 9-chloro-7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-1-methyl-2,3-dihydro-1H-cyclopenta[1,2-b]quinolin-1-ol (**26.3**, 600 mg, crude) as a brown oil. **LC-MS (ESI)**: m/z 398.0 $[\text{M}+\text{H}]^+$.

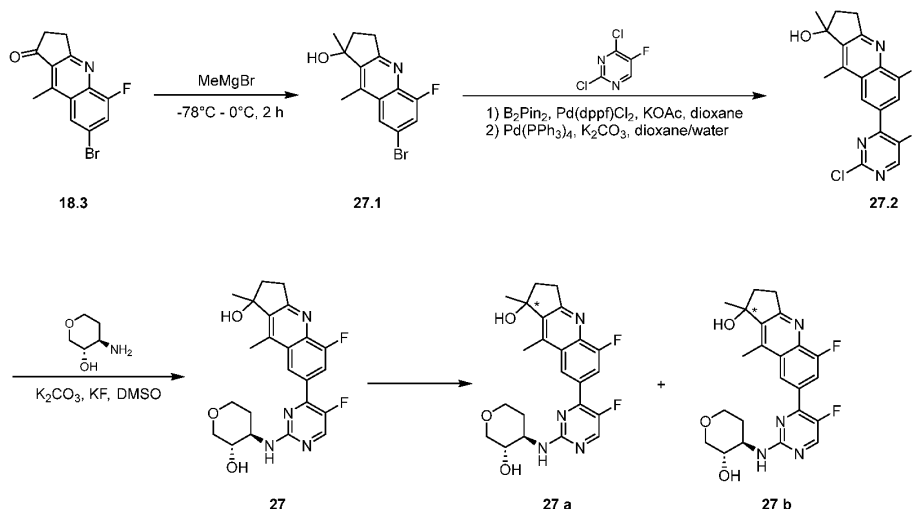
[0325] A mixture of 9-chloro-7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**26.3**, 550 mg, crude), (3*S*,4*R*)-4-aminotetrahydropyran-3-ol hydrochloride (423 mg, 2.76 mmol) and DIEA (698 μ L, 4.14 mmol) in MeCN (7 mL) was stirred at 110 °C for 2 hrs. The reaction mixture was filtered and subjected to prep-HPLC to afford 9-chloro-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**26**, 293 mg) as a white solid, which was separated by chiral SFC to give:

[0326] **Isomer 1: (26a, 100% de);** Retention time: 1.641 min. **LCMS (ESI):** *m/z* 479.2 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.48 (s, 2H), 8.01 (d, *J* = 10.4 Hz, 1H), 7.61 (s, 1H), 5.65 (s, 1H), 4.95 (d, *J* = 5.3 Hz, 1H), 3.86 - 3.77 (m, 3H), 3.55 - 3.49 (m, 1H), 3.31 - 3.28 (m, 1H), 3.22 - 2.99 (m, 3H), 2.34 - 2.19 (m, 2H), 1.99 - 1.85 (m, 1H), 1.63 (s, 3H), 1.56 - 1.45 (m, 1H).

[0327] **Isomer 2: (26b, 100% de);** Retention time: 2.653 min. **LCMS (ESI):** *m/z* 479.2 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.48 (s, 2H), 8.01 (d, *J* = 9.7 Hz, 1H), 7.62 (s, 1H), 5.65 (s, 1H), 4.94 (d, *J* = 5.4 Hz, 1H), 3.90 - 3.76 (m, 3H), 3.54 - 3.48 (m, 1H), 3.31 - 3.27 (m, 1H), 3.23 - 3.00 (m, 3H), 2.34 - 2.18 (m, 2H), 1.99 - 1.84 (m, 1H), 1.63 (s, 3H), 1.57 - 1.43 (m, 1H).

[0328] **Analytical method:** Column: ChiralPak AS, 100 $\times$ 4.6mm I.D., 3 μ m, Mobile phase: A for CO₂ and B for Methanol (0.05% DEA), Gradient: 8 min @B 30%, Flow rate: 2.0 mL/min, Back pressure: 100 bar, Column temperature: 40 °C. **SFC separation method:** Waters Thar 80 preparative SFC; Column: ChiralPak AS, 250 $\times$ 30 mm I.D., 5 μ m; Mobile phase: A for CO₂ and B for MEOH (0.1% 2 mol/L NH₃ in MeOH); Gradient: B 50 %; Flow rate: 60 mL/min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 10 min.

Example 20. (*R*)-5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-1,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol and (*S*)-5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-1,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol



[0329] To a solution of 7-bromo-5-fluoro-9-methyl-2,3-dihydro-1H-cyclopenta[b]quinolin-1-one (**18.3**, 1.50 g, 5.10 mmol) in tetrahydrofuran (15 mL) was added methylmagnesium bromide (17.0 mL, 51.0 mmol) at -78 °C under nitrogen atmosphere, and the mixture was stirred at 0 °C for 1 hr. The reaction mixture was quenched with saturated ammonium chloride solution (10 mL), diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-bromo-5-fluoro-1,9-dimethyl-2,3-dihydro-1H-cyclopenta[b]quinolin-1-ol (**27.1**, 1.40 g, 89%) as a yellow solid. **LC-MS (ESI)**: m/z 310.0 [M+H]⁺.

[0330] A mixture of 7-bromo-5-fluoro-1,9-dimethyl-2,3-dihydro-1H-cyclopenta[b]quinolin-1-ol (**27.1**, 700 mg, 2.25 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (802 mg, 3.16 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloro palladium(II) (185 mg, 0.226 mmol) and potassium acetate (443 mg, 4.51 mmol) in dioxane (7 mL) was stirred at 90 °C under nitrogen atmosphere for 3 hrs. The reaction mixture was cooled to room temperature. To the mixture were added water (1.5 mL), potassium carbonate (623 mg, 4.51 mmol), tetrakis(triphenylphosphine)palladium(0) (261 mg, 0.226 mmol) and 2,4-dichloro-5-fluoropyrimidine (753 mg, 4.51 mmol), and the resulting mixture was stirred at 100 °C under nitrogen atmosphere for 3 hrs. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 7-(2-chloro-5-

fluoropyrimidin-4-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**27.2**, 640 mg, two steps yield 78%) as a yellow solid. **LC-MS (ESI)**: *m/z* 348.1 [M+H]⁺.

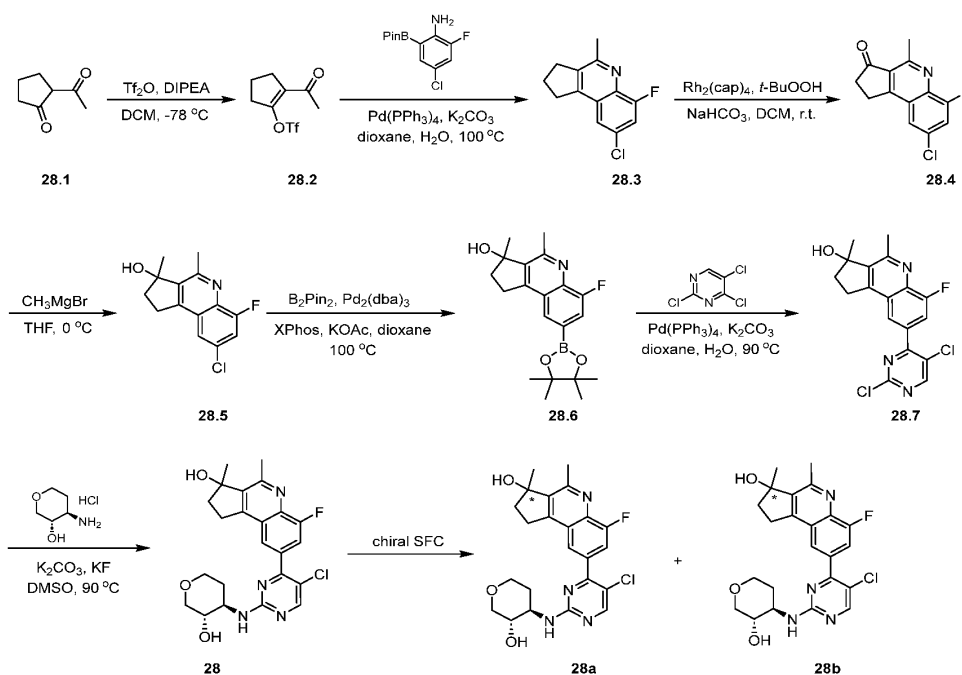
[0331] A mixture of 7-(2-chloro-5-fluoropyrimidin-4-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**27.2**, 640 mg, 1.77 mmol), (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (679 mg, 4.42 mmol), potassium fluoride (411 mg, 7.08 mmol) and potassium carbonate (733 mg, 5.31 mmol) in dimethyl sulfoxide (6 mL) was stirred at 120 °C for 4 hrs. The mixture was quenched with water (50 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-1,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**27**, 473 mg, 61%) as a yellow solid, which was further separated by chiral SFC to give:

[0332] **Isomer 1: (27a, 100% de); Retention time:** 1.300 min. **LCMS (ESI)**: *m/z* 443.2 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.59 (s, 1H), 8.49 (d, *J* = 3.8 Hz, 1H), 8.04 (d, *J* = 11.9 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 5.58 (s, 1H), 4.95 (d, *J* = 5.3 Hz, 1H), 3.87 - 3.79 (m, 3H), 3.59 - 3.48 (m, 1H), 3.39 - 3.34 (m, 1H), 3.09 - 3.00 (m, 3H), 2.85 (s, 3H), 2.28 - 2.16 (m, 2H), 2.06 - 1.98 (m, 1H), 1.57 - 1.46 (m, 4H).

[0333] **Isomer 2: (27b, 100% de); Retention time:** 2.225 min. **LCMS (ESI)**: *m/z* 443.2 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.59 (s, 1H), 8.49 (d, *J* = 3.8 Hz, 1H), 8.05 (d, *J* = 12.1 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 5.58 (s, 1H), 4.95 (d, *J* = 5.4 Hz, 1H), 3.88 - 3.79 (m, 3H), 3.58 - 3.47 (m, 1H), 3.39 - 3.34 (m, 1H), 3.09 - 3.00 (m, 3H), 2.85 (s, 3H), 2.28 - 2.15 (m, 2H), 2.06 - 1.98 (m, 1H), 1.56 - 1.45 (m, 4H).

[0334] **Analytical method:** Column: ChiralPak IH, 100 × 4.6mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 30% B; Flow rate: 2.5 mL/min; Back pressure: 100 bar, Column temperature: 40 °C. **SFC separation method:** Waters Thar 80 preparative SFC; ChiralPak IH, 150 × 20 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for MeOH (0.1% 7 mol/L NH₃ in MeOH); Gradient: B 30 %; Flow rate: 40 mL /min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 8 min.

Example 21. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol



[0335] To a solution of 2-acetylcyclopentan-1-one (**28.1**, 5.00 g, 39.6 mmol) in dichloromethane (100 mL) were added *N,N*-diisopropylethylamine (13.8 mL, 79.3 mmol) and trifluoromethanesulfonyl anhydride (7.3 mL, 43.6 mmol) at -78 °C, and the mixture was stirred at -78 °C for 30 mins. The reaction mixture was poured into water (50 mL) and extracted with dichloromethane (50 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 2-acetylcyclopent-1-en-1-yl trifluoromethanesulfonate (**28.2**, 9.10 g, 89% yield) as a yellow oil. **LC-MS (ESI)**: *m/z* 259.1 [M+H]⁺.

[0336] To a mixture of 2-acetylcyclopent-1-en-1-yl trifluoromethanesulfonate (**28.2**, 9.10 g, 35.2 mmol) and 4-chloro-2-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (9.56 g, 35.2 mmol) in 1,4-dioxane (100 mL) and water (10 mL) were added tetrakis(triphenylphosphine)palladium (4.07 g, 3.52 mmol) and potassium carbonate (14.6 g, 105.6 mmol), and the mixture was stirred at 100 °C for 6 hrs under nitrogen atmosphere. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and then extracted with ethyl acetate (50 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-4-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (**28.3**, 5.42 g, 66% yield) as a yellow solid. **LC-MS (ESI)**: *m/z* 236.1 [M+H]⁺.

[0337] To a mixture of 8-chloro-6-fluoro-4-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (**28.3**, 5.42 g, 23.0 mmol), 2-hydroperoxy-2-methylpropane (27.6 mL, 138 mmol, 5 mol/L) and sodium bicarbonate (3.86 g, 46.0 mmol) in dichloromethane (100 mL) was added dirhodium(II) tetrakis(caprolactam) dirhodium (440 mg, 0.67 mmol). The reaction mixture was stirred at room temperature for 48 hrs followed by addition of 2-hydroperoxy-2-methylpropane (27.6 mL, 138 mmol, 5 mol/L), sodium bicarbonate (3.86 g, 46.0 mmol) and dirhodium(II) tetrakis(caprolactam) dirhodium (250 mg, 0.38 mmol). The resulting mixture was stirred at room temperature for 48 hrs. The reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (50 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-4-methyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (**28.4**, 2.58 g, 45%) as a yellow solid. **LC-MS (ESI):** *m/z* 250.1 [M+H]⁺.

[0338] To a solution of 8-chloro-6-fluoro-4-methyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (**28.4**, 0.96 g, 3.85 mmol) in dichloromethane (50 mL) was added methylmagnesium bromide (6.4 mL, 19.2 mmol, 3 mol/L) quickly at -78 °C under nitrogen atmosphere, and the mixture was warmed to room temperature and stirred for 1 hr. The mixture was poured into saturated aqueous ammonium chloride (20 mL) and extracted with dichloromethane (20 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**28.5**, 0.96 g, 94% yield) as a yellow solid. **LC-MS (ESI):** *m/z* 266.1 [M+H]⁺.

[0339] To a mixture of 8-chloro-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**28.5**, 1.43 g, 5.38 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.05 g, 8.07 mmol) and potassium acetate (1.58 g, 16.15 mmol) in 1,4-dioxane (35 mL) were added 2-(dicyclohexylphosphino)-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (515 mg, 1.08 mmol) and tris(dibenzylideneacetone)dipalladium (494 mg, 0.54 mmol). The reaction mixture was stirred at 100 °C for 2 hrs under nitrogen atmosphere and then cooled to room temperature. To the mixture were added 2,4,5-trichloropyrimidine (2.63 g, 16.14 mmol), water (3.5 mL), tetrakis(triphenylphosphine)palladium (624 mg, 0.54 mmol) and potassium carbonate (1.49 g, 10.8 mmol), and the resulting mixture was stirred at 90 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (50 mL) and extracted

with ethyl acetate (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**28.7**, 1.44 g, two steps yield 71%) as a yellow solid. **LC-MS (ESI):** *m/z* 378.1 [M+H]⁺.

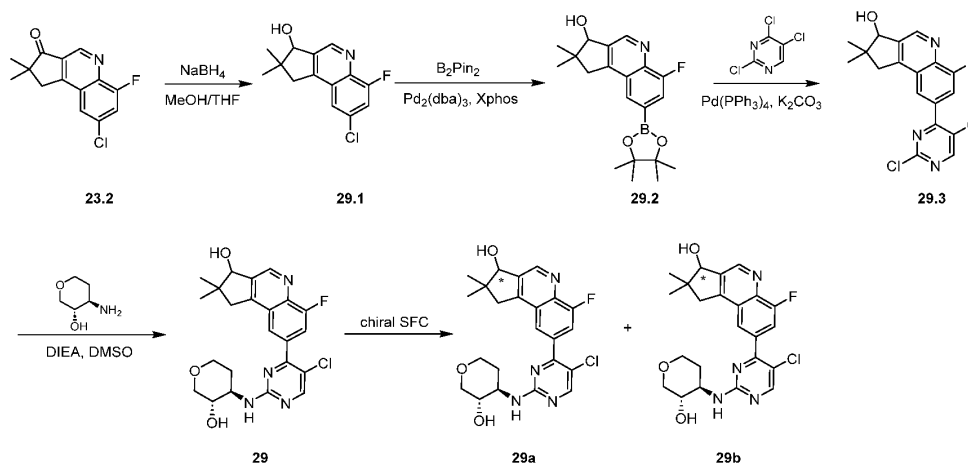
[0340] A mixture of 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**28.7**, 1.44 g, 3.81 mmol), potassium carbonate (1.05 g, 7.62 mmol), potassium fluoride (664 mg, 11.43 mmol) and (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (877 mg, 5.71 mmol) in dimethylsulfoxide (15 mL) was stirred at 90 °C for 2 hrs. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with water (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**28**, 1.02 g, 58% yield) as a yellow solid, which was further separated by chiral SFC to give:

[0341] **Isomer 1: (28a, 100% de); Retention time:** 2.960 min. **LCMS (ESI):** *m/z* 459.1 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.46 (s, 1H), 8.13 (s, 1H), 7.83 (d, *J* = 11.4 Hz, 1H), 7.56 (s, 1H), 5.47 (s, 1H), 4.93 (d, *J* = 5.4 Hz, 1H), 3.89 - 3.76 (m, 3H), 3.54 - 3.45 (m, 1H), 3.36 - 3.32 (m, 1H), 3.27 - 3.25 (m, 1H), 3.09 - 3.03 (m, 2H), 2.81 (s, 3H), 2.37 - 2.21 (m, 2H), 1.94 (s, 1H), 1.55 - 1.45 (m, 4H).

[0342] **Isomer 2: (28b, 99.24% de); Retention time:** 4.170 min. **LCMS (ESI):** *m/z* 459.1 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.46 (s, 1H), 8.13 (s, 1H), 7.83 (d, *J* = 10.8 Hz, 1H), 7.56 (s, 1H), 5.47 (s, 1H), 4.92 (d, *J* = 5.4 Hz, 1H), 3.90 - 3.76 (m, 3H), 3.55 - 3.45 (m, 1H), 3.36 - 3.32 (m, 1H), 3.31 - 3.25 (m, 1H), 3.09 - 3.02 (m, 2H), 2.81 (s, 3H), 2.38 - 2.19 (m, 2H), 1.98 - 1.92 (m, 1H), 1.56 - 1.44 (m, 4H).

[0343] **Analytical method:** Column: ChiralPak AD, 100 × 4.6 mm I.D., 3 μm, Mobile phase: A for CO₂ and B for Methanol (0.05% DEA), Gradient: 8 min @B 50%, Flow rate: 2.0 mL/min, Back pressure: 100 bar, Column temperature: 40 °C. **SFC separation method:** Waters Thar 80 preparative SFC; ChiralPak AD, 250 × 30 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for MeOH (0.1% 7 mol/L NH₃ in MeOH); Gradient: B 50 %; Flow rate: 60mL /min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 20 min.

Example 22. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol



[0344] To a solution of 8-chloro-6-fluoro-2,2-dimethyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (**23.2**, 660 mg, 2.50 mmol) in MeOH (3 mL) and THF (3 mL) was added NaBH₄ (189 mg, 5.00 mmol) slowly, and the mixture was stirred at room temperature for 20 mins. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-2,2-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**29.1**, 634 mg, 95.3%) as a white solid. **LC-MS (ESI):** *m/z* 266.1 [M+H]⁺.

[0345] A mixture of 8-chloro-6-fluoro-2,2-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**29.1**, 2.00 g, 7.53 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.87 g, 11.3 mmol), tris(dibenzylideneacetone)dipalladium (1.38 g, 1.51 mmol), potassium acetate (2.22 g, 22.6 mmol) and 2-dicyclohexylphosphino-2',4',6'-*tri-i*-propyl-1,1'-biphenyl (718 mg, 1.51 mmol) in dioxane (15 mL) was stirred at 90 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 6-fluoro-2,2-dimethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**29.2**, 2.31 g, 85.9%) as a brown solid. **LC-MS (ESI)**: *m/z* 358.2 [M+H]⁺.

[0346] A mixture of 6-fluoro-2,2-dimethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**29.2**, 2.31 g, 6.46 mmol), 2,4,5-

trichloropyrimidine (1.90 g, 10.4 mmol), tetrakis(triphenylphosphine)palladium (1.12 g, 0.97 mmol) and potassium carbonate (1.79 g, 13.0 mmol) in dioxane/water (12 mL/3 mL) was stirred at 90 °C for 1.5 hrs under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-2,2-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**29.3**, 1.82 g, 74.4%) as a yellow solid. **LC-MS (ESI)**: *m/z* 378.1 [M+H]⁺.

[0347] A mixture of 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-2,2-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**29.3**, 1.82 g, 4.81 mmol), (3*S*,4*R*)-4-aminotetrahydropyran-3-ol hydrogen chloride (1.33 g, 8.66 mmol) and *N,N*-diisopropylethylamine (3.18 mL, 19.2 mmol) in dimethyl sulfoxide (12 mL) was stirred at 110 °C for 2.5 hrs. The reaction mixture was filtered and the filtrate was subjected to silica gel column chromatography to afford 8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**29**, 1.46 g, 66.1%) as a white solid, which was further separated by chiral SFC to give:

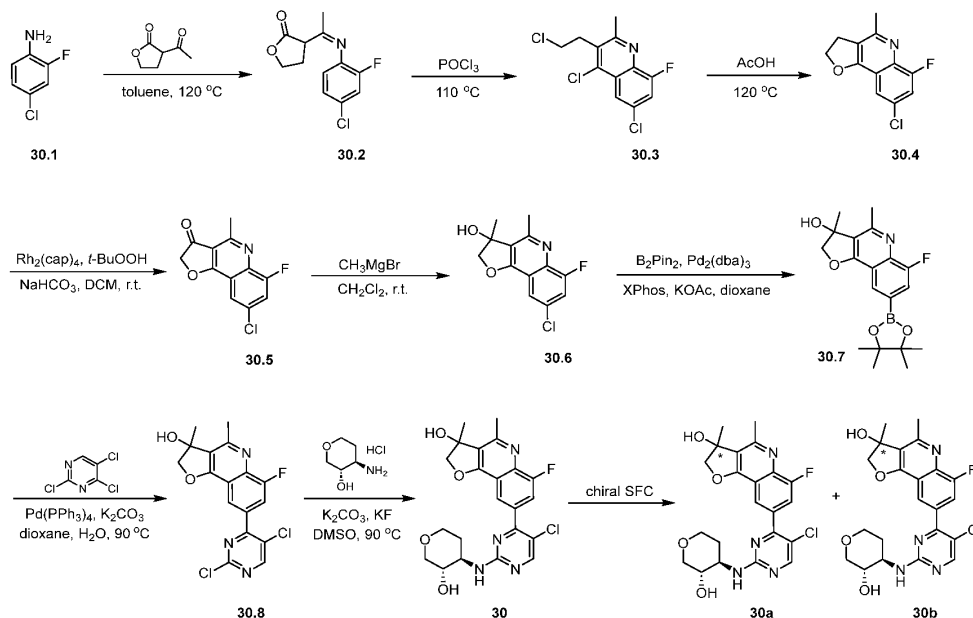
[0348] **Isomer 1: (29a, 100% de); Retention time:** 1.531 min. **LCMS (ESI)**: *m/z* 459.4 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.95 (s, 1H), 8.47 (s, 1H), 8.14 (s, 1H), 7.89 (d, *J* = 11.6 Hz, 1H), 7.59 (s, 1H), 5.61 (d, *J* = 6.4 Hz, 1H), 4.93 (d, *J* = 5.4 Hz, 1H), 4.87 (d, *J* = 6.3 Hz, 1H), 3.85 - 3.77 (m, 3H), 3.55 - 3.48 (m, 1H), 3.38 - 3.31 (m, 1H), 3.18 - 2.93 (m, 3H), 2.01 - 1.95 (m, 1H), 1.57 - 1.43 (m, 1H), 1.21 (s, 3H), 1.01 (s, 3H).

[0349] **Isomer 2: (29b, 100% de); Retention time:** 3.436 min. **LCMS (ESI)**: *m/z* 459.4 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.95 (s, 1H), 8.47 (s, 1H), 8.14 (s, 1H), 7.89 (d, *J* = 11.8 Hz, 1H), 7.59 (s, 1H), 5.61 (d, *J* = 6.3 Hz, 1H), 4.93 (d, *J* = 5.2 Hz, 1H), 4.87 (d, *J* = 6.1 Hz, 1H), 3.85 - 3.76 (m, 3H), 3.51 - 3.33 (m, 2H), 3.18 - 2.95 (m, 3H), 2.01 - 1.95 (m, 1H), 1.57 - 1.43 (m, *J* = 9.2 Hz, 1H), 1.21 (s, 3H), 1.01 (s, 3H).

[0350] **Analytical method:** Column: ChiralPak IH, 100 × 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2 mL/min; Column temperature: 40 °C. **SFC separation method:** Instrument: Waters Thar 80 preparative SFC; Column: ChiralPak IH, 250 × 20 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for MeOH (0.1% 7mol/L NH₃ in MeOH); Gradient: B 50 %; Flow rate: 40 mL /min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 7 min.

Example 23. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydrofuro[3,2-*c*]quinolin-3-ol and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-

3-(hydroxytetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydrofuro[3,2-c]quinolin-3-ol



[0351] To a solution of 4-chloro-2-fluoroaniline (**30.1**, 10.0 g, 68.7 mmol) in toluene (40 mL) was added 3-acetyldihydrofuran-2(3H)-one (17.6 g, 137 mmol), and the mixture was stirred at 120 °C for 24 hrs. The reaction mixture was concentrated under reduced pressure to give (Z)-3-(1-((4-chloro-2-fluorophenyl)imino)ethyl)dihydrofuran-2(3H)-one (**30.2**, 17.6 g, crude) as a yellow solid. **LC-MS (ESI)**: m/z 256.2 $[M+H]^+$.

[0352] A mixture of phosphorus oxychloride (70 mL) and (Z)-3-(1-((4-chloro-2-fluorophenyl)imino)ethyl)dihydrofuran-2(3H)-one (**30.2**, 17.6 g, crude) was stirred at 110 °C for 4 hrs. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water (50 mL). The resulting mixture was adjusted to pH 7 with saturated sodium carbonate solution and then extracted with dichloromethane (50 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 4,6-dichloro-3-(2-chloroethyl)-8-fluoro-2-methylquinoline (**30.3**, 10.8 g) as a yellow solid. **LC-MS (ESI)**: m/z 292.0 $[M+H]^+$.

[0353] A mixture of acetic acid (60 mL) and 4,6-dichloro-3-(2-chloroethyl)-8-fluoro-2-methylquinoline (**30.3**, 7.2 g, 24.6 mmol) was stirred at 120 °C for 5 hrs. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water (50 mL). The resulting mixture was adjusted to pH 7 with saturated sodium carbonate solution and then

extracted with dichloromethane (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-4-methyl-2,3-dihydrofuro[3,2-*c*]quinoline (**30.4**, 2.42 g, 41% yield) as a yellow solid. **LC-MS (ESI)**: *m/z* 238.1 [M+H]⁺.

[0354] To a mixture of 8-chloro-6-fluoro-4-methyl-2,3-dihydrofuro[3,2-*c*]quinoline (**30.4**, 2.42 g, 10.2 mmol), 2-hydroperoxy-2-methylpropane (12 mL, 60.0 mmol, 5 mol/L) and sodium bicarbonate (1.71 g, 20.4 mmol) in dichloromethane (40 mL) and *tert*-butanol (10 mL) was added dirhodium(II) tetrakis(caprolactam) dirhodium (336 mg, 0.51 mmol). The mixture was stirred at room temperature for 24 hrs followed by the addition of 2-hydroperoxy-2-methylpropane (12 mL, 60.0 mmol, 5 mol/L), sodium bicarbonate (1.71 g, 20.4 mmol) and dirhodium(II) tetrakis(caprolactam) dirhodium (336 mg, 0.51 mmol), and the resulting mixture was stirred at room temperature for 24 hrs. The reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (50 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-4-methylfuro[3,2-*c*]quinolin-3(2*H*)-one (**30.5**, 240 mg, 9%) as a yellow solid. **LC-MS (ESI)**: *m/z* 252.1 [M+H]⁺.

[0355] To a solution of 8-chloro-6-fluoro-4-methylfuro[3,2-*c*]quinolin-3(2*H*)-one (**30.5**, 170 mg, 3.85 mmol) in dichloromethane (10 mL) was added methylmagnesium bromide (1.10 mL, 3.30 mmol, 3 mol/L) at room temperature, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into saturated aqueous ammonium chloride (10 mL) and extracted with dichloromethane (10 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-3,4-dimethyl-2,3-dihydrofuro[3,2-*c*]quinolin-3-ol (**30.6**, 170 mg, 93% yield) as a yellow solid. **LC-MS (ESI)**: *m/z* 268.2 [M+H]⁺.

[0356] To a mixture of 8-chloro-6-fluoro-3,4-dimethyl-2,3-dihydrofuro[3,2-*c*]quinolin-3-ol (**30.6**, 210 mg, 0.78 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (297 mg, 1.17 mmol) and potassium acetate (230 mg, 2.34 mmol) in 1,4-dioxane (7 mL) were added 2-(dicyclohexylphosphino)-2',4',6'-*tri-i*-propyl-1,1'-biphenyl (76.0 mg, 0.16 mmol) and tris(dibenzylideneacetone)dipalladium (73.0 mg, 0.08 mmol). The mixture was stirred at 100 °C for 2 hrs under nitrogen atmosphere and then cooled to room temperature. To the mixture were added 2,4,5-trichloropyrimidine (428 mg, 2.34 mmol), water (1 mL),

tetrakis(triphenylphosphine)palladium (92.0 mg, 0.08 mmol) and potassium carbonate (216 mg, 1.56 mmol), and the resulting mixture was stirred at 90 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (10 mL × 2). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydrofuro[3,2-*c*]quinolin-3-ol (**30.8**, 150 mg, two steps yield 51%) as a yellow solid. **LC-MS (ESI)**: *m/z* 380.0 [M+H]⁺.

[0357] A mixture of 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydrofuro[3,2-*c*]quinolin-3-ol (**30.8**, 150 mg, 0.39 mmol), potassium carbonate (108 mg, 0.78 mmol), potassium fluoride (69.0 mg, 1.18 mmol) and (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (91.0 mg, 0.59 mmol) in dimethylsulfoxide (3 mL) was stirred at 90 °C for 2 hrs. The mixture was diluted with water (15 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with water (5 mL × 3), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydrofuro[3,2-*c*]quinolin-3-ol (**30**, 21.8 mg, 12% yield) as a white solid, which was further separated by chiral SFC to give:

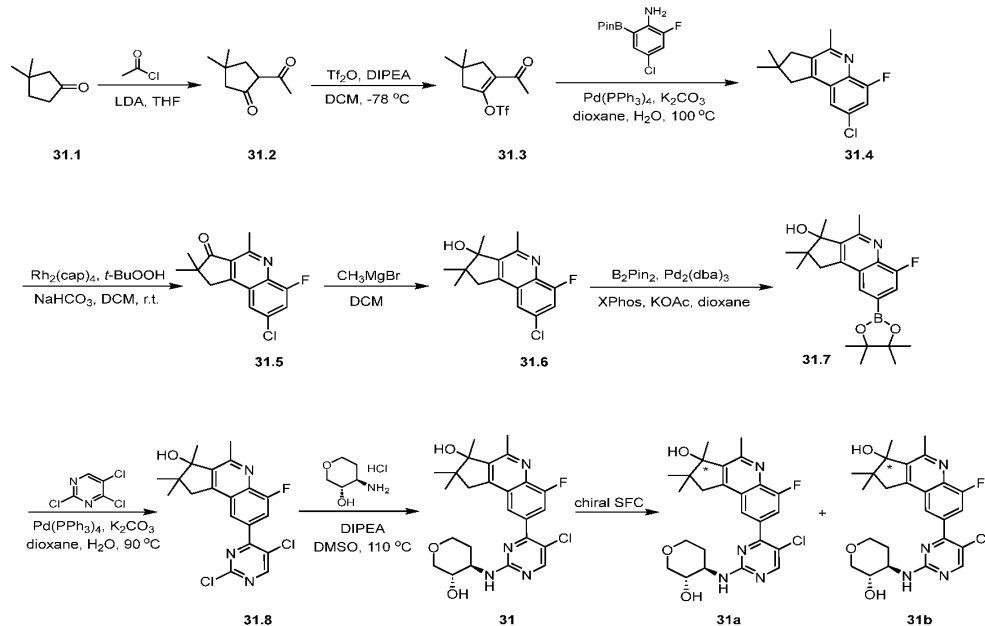
[0358] **Isomer 1: (30a, 100% de); Retention time:** 3.433 min. **LCMS (ESI)**: *m/z* 461.3 [M+H]⁺. **¹H NMR** (400 MHz, CDCl₃) δ 8.29 (s, 1H), 8.04 (s, 1H), 7.76 (dd, *J* = 11.8, 1.7 Hz, 1H), 5.38 (d, *J* = 6.4 Hz, 1H), 4.82 (d, *J* = 10.4 Hz, 1H), 4.61 (d, *J* = 10.3 Hz, 1H), 4.09 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.99 (dd, *J* = 11.5, 3.9 Hz, 1H), 3.92 - 3.83 (m, 1H), 3.66 (d, *J* = 4.7 Hz, 1H), 3.52 - 3.42 (m, 1H), 3.31 (s, 1H), 3.26 - 3.17 (m, 1H), 2.84 (s, 3H), 2.07 - 2.02 (m, 1H), 1.85 (s, 3H), 1.77 - 1.66 (m, 1H).

[0359] **Isomer 2: (30b, 100% de); Retention time:** 4.732 min. **LCMS (ESI)**: *m/z* 461.4 [M+H]⁺. **¹H NMR** (400 MHz, CDCl₃) δ 8.25 (s, 1H), 7.97 (s, 1H), 7.78 (d, *J* = 11.1 Hz, 1H), 5.50 (d, *J* = 6.4 Hz, 1H), 4.80 (d, *J* = 10.3 Hz, 1H), 4.59 (d, *J* = 10.3 Hz, 1H), 4.09 (dd, *J* = 11.2, 4.9 Hz, 1H), 4.01 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.95 - 3.87 (m, 1H), 3.70 - 3.62 (m, 1H), 3.54 - 3.46 (m, 1H), 3.32 - 3.10 (m, 1H), 2.83 (s, 3H), 2.15 - 2.06 (m, 1H), 1.83 (s, 3H), 1.76 - 1.66 (m, 1H).

[0360] **Analytical method:** Column: ChiralPak C-IC, 100 × 4.6 mm I.D., 3 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Column temperature: 40 °C. **SFC separation method:** Instrument: SHIMADZU PREP SOLUTION SFC; Column: ChiralPak C-IC, 250 × 30 mm I.D., 5 μm; Mobile phase: A for CO₂

and B for IPA (0.1% 7 mol/L NH₃ in MeOH); Gradient: B 45 %; Flow rate: 60 mL /min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 16 min.

Example 24. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2,3,4-tetramethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2,3,4-tetramethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol



[0361] To a solution of 3,3-dimethylcyclopentan-1-one (**31.1**, 18.7 g, 166 mmol) in THF (200 mL) at -78 °C was added lithium diisopropylamide (100 mL, 200 mmol, 2 mol/L in THF) dropwise under nitrogen atmosphere, and the mixture was stirred at -78 °C for 30 mins followed by addition of acetyl chloride (14.2 mL, 200 mmol) dropwise. The resulting mixture was stirred at -78 °C for 2.5 hrs. The reaction mixture was quenched with saturated NH₄Cl aqueous solution (15 mL) and diluted with saturated NaCl aqueous solution (300 mL). The aqueous layer was extracted with ethyl acetate (50 mL × 3), and the organic phase was dried over anhydrous Na₂SO₄ and concentrated in vacuum. The residue was subjected to silica gel chromatography to afford 2-acetyl-4,4-dimethylcyclopentan-1-one (**31.2**, 9.10 g, crude) as a yellow oil. **LC-MS (ESI)**: *m/z* 155.1 [*M*+*H*]⁺.

[0362] To a mixture of 2-acetyl-4,4-dimethylcyclopentan-1-one (**31.2**, 9.10 g, crude) and *N,N*-diisopropylethylamine (20.5 mL, 118.0 mmol) in DCM (60 mL) was added trifluoromethanesulfonic anhydride (11.9 mL, 70.8 mmol) dropwise at -78 °C, and the mixture

was stirred at -78 °C for 30 mins. The reaction mixture was concentrated in vacuum and the residue was subjected to silica gel chromatography to afford 2-acetyl-4,4-dimethylcyclopent-1-en-1-yl trifluoromethanesulfonate (**31.3**, 5.20 g) as a yellow oil. **LC-MS (ESI)**: m/z 287.1 [M+H]⁺.

[0363] A mixture of 2-acetyl-4,4-dimethylcyclopent-1-en-1-yl trifluoromethanesulfonate (**31.3**, 5.20 g, 18.1 mmol), 4-chloro-2-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (5.92 g, 21.8 mmol), palladium(0) tetrakis(triphenylphosphane) (3.15 g, 2.72 mmol) and K₂CO₃ (7.53 g, 54.5 mmol) in dioxane (30 mL) and water (6 mL) was stirred at 100 °C under nitrogen atmosphere for 6 hrs. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered. The filtrate was concentrated in vacuum and subjected to silica gel chromatography to afford 8-chloro-6-fluoro-2,2,4-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (**31.4**, 2.75 g, 57.4%) as a white solid. **LC-MS (ESI)**: m/z 264.1 [M+H]⁺.

[0364] To a mixture of 8-chloro-6-fluoro-2,2,4-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (**31.4**, 2.75 g, 10.4 mmol), tetrakis(azepan-2-one) dirhodiane (343 mg, 0.52 mmol) and NaHCO₃ (1.75 g, 20.8 mmol) in DCM (15 mL) was added 2-hydroperoxy-2-methylpropane (20.8 mL, 104.2 mmol, 5 mol/L) slowly. The reaction mixture was stirred at room temperature for 3 days and 2-hydroperoxy-2-methylpropane (41.7 mL, 208.5 mmol, 5 mol/L) was added in portions during the reaction. The reaction mixture was added slowly to the saturated sodium thiosulphate aqueous solution (100 mL) and extracted with DCM (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuum. The residue was subjected to silica gel chromatography to afford 8-chloro-6-fluoro-2,2,4-trimethyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (**31.5**, 380 mg, 13%) as a white solid. **LC-MS (ESI)**: m/z 278.1 [M+H]⁺.

[0365] To a solution of 8-chloro-6-fluoro-2,2,4-trimethyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (**31.5**, 380 mg, 1.37 mmol) in dichloromethane (6 mL) was added methylmagnesium bromide (2.28 mL, 6.84 mmol, 3 mol/L in THF) dropwise at -78 °C under nitrogen atmosphere, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was quenched with saturated NH₄Cl solution (5 mL), diluted with water (50 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-6-fluoro-2,2,3,4-tetramethyl-2,3-dihydro-

1*H*-cyclopenta[*c*]quinolin-3-ol (**31.6**, 360 mg, 89.5%) as a white solid. **LC-MS (ESI)**: *m/z* 294.1 [M+H]⁺.

[0366] A mixture of 8-chloro-6-fluoro-2,2,3,4-tetramethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**31.6**, 360 mg, 1.22 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (467 mg, 1.84 mmol), tris(dibenzylideneacetone)dipalladium (225 mg, 0.25 mmol), potassium acetate (361 mg, 3.67 mmol) and 2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (117 mg, 0.25 mmol) in dioxane (6 mL) was stirred at 90 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 6-fluoro-2,2,3,4-tetramethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**31.7**, 424 mg, 89.8%) as a brown solid. **LC-MS (ESI)**: *m/z* 386.2 [M+H]⁺.

[0367] A mixture of 6-fluoro-2,2,3,4-tetramethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**31.7**, 424 mg, 1.10 mmol), 2,4,5-trichloropyrimidine (323 mg, 1.76 mmol), tetrakis(triphenylphosphine)palladium (190 mg, 0.16 mmol) and potassium carbonate (304 mg, 2.20 mmol) in dioxane/water (6 mL/2 mL) was stirred at 90 °C for 1.5 hrs under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-2,2,3,4-tetramethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**31.8**, 320 mg, 71.6%) as a yellow solid. **LC-MS (ESI)**: *m/z* 406.1 [M+H]⁺.

[0368] A mixture of 8-(2,5-dichloropyrimidin-4-yl)-6-fluoro-2,2,3,4-tetramethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**31.8**, 320 mg, 0.79 mmol), (3*S*,4*R*)-4-aminotetrahydropyran-3-ol hydrogen chloride (242 mg, 1.57 mmol) and *N,N*-diisopropylethylamine (521 μL, 3.15 mmol) in dimethyl sulfoxide (2 mL) was stirred at 110 °C for 2 hrs. The reaction mixture was filtered and the filtrates were subjected to prep-HPLC to afford 8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2,3,4-tetramethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**31**, 247 mg, 64.4%) as a white solid, which was further separated by chiral SFC to give:

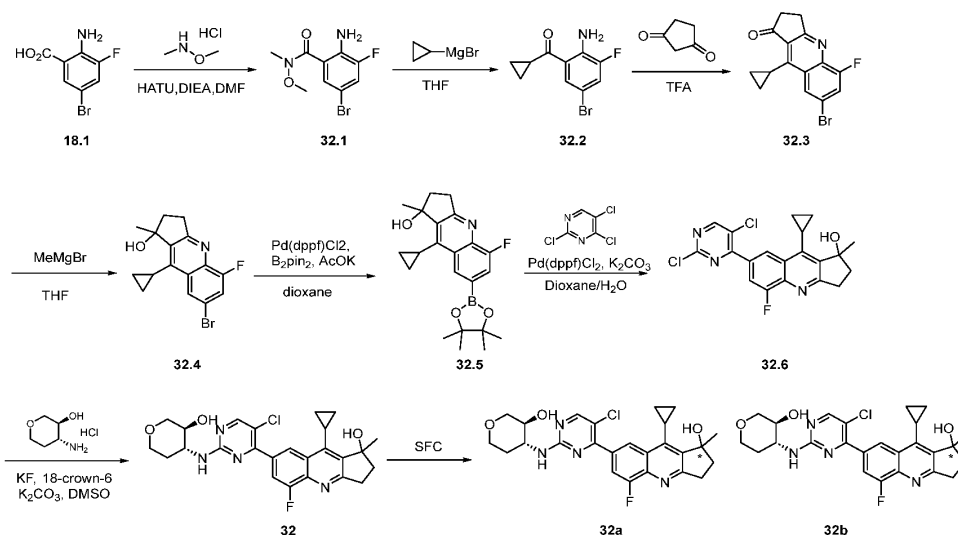
[0369] **Isomer 1**: (**31a**, 100% de); **Retention time**: 1.028 min. **LCMS (ESI)**: *m/z* 487.4 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.46 (s, 1H), 8.10 (s, 1H), 7.83 (d, *J* = 11.7 Hz, 1H), 7.56 (s, 1H), 5.11 (s, 1H), 4.90 (s, 1H), 3.85 - 3.77 (m, 3H), 3.51 - 3.47 (m, 1H), 3.34 - 3.31 (m,

1H), 3.16 - 2.97 (m, 2H), 2.94 - 2.86 (m, 1H), 2.82 (s, 3H), 1.98 - 1.94 (m, 1H), 1.54 - 1.42 (m, 1H), 1.37 (s, 3H), 1.16 (s, 3H), 0.95 (s, 3H).

[0370] Isomer 2: (31b, 100% de); Retention time: 2.189 min. **LCMS (ESI):** m/z 487.4 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ 8.46 (s, 1H), 8.10 (s, 1H), 7.83 (d, $J = 11.7$ Hz, 1H), 7.56 (s, 1H), 5.12 (s, 1H), 4.93 (s, 1H), 3.85 - 3.77 (m, 3H), 3.51 - 3.47 (m, 1H), 3.34 - 3.31 (m, 1H), 3.12 - 3.03 (m, 2H), 2.94 - 2.86 (m, 1H), 2.82 (s, 3H), 1.97 - 1.91 (m, 1H), 1.55 - 1.42 (m, 1H), 1.37 (s, 3H), 1.16 (s, 3H), 0.95 (s, 3H).

[0371] Analytical method: Column: ChiralPak AS, 100×4.6 mm I.D., 3 μ m; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Column temperature: 40 °C. **SFC separation method:** Instrument: Waters Thar 80 preparative SFC; Column: ChiralPak AS, 250×30 mm I.D., 5 μ m; Mobile phase: A for CO₂ and B for MeOH (0.1% 2 mol/L NH₃ in MeOH); Gradient: B 50 %; Flow rate: 60 mL /min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 10 min.

Example 25. (*R*)-9-cyclopropyl-5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol and (*S*)-9-cyclopropyl-5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol



[0372] To a solution of 2-amino-5-bromo-3-fluorobenzoic acid (**18.1**, 8.50 g, 36.3 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (10.6 g, 109 mmol) in DMF (100 mL) were added HATU (16.6 g, 43.6 mmol) and DIEA (28.2 g, 218 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (50 mL) and extracted

with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 2-amino-5-bromo-3-fluoro-*N*-methoxy-*N*-methylbenzamide (**32.1**, 9.00 g, 89.4%) as white solid. **LCMS (ESI):** *m/z* 277.1 & 279.1 [M+H]⁺.

[0373] To a solution 2-amino-5-bromo-3-fluoro-*N*-methoxy-*N*-methylbenzamide (**32.1**, 3.00 g, 10.8 mmol) in anhydrous THF (10 mL) was added bromo(cyclopropyl)magnesium (10.9 mL, 10.8 mmol, 1 mol/L in THF) dropwise at -40 °C, and the mixture was stirred at -40 °C for 5 hrs under nitrogen atmosphere. The reaction mixture was quenched with saturated aqueous NH₄Cl (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford (2-amino-5-bromo-3-fluorophenyl)(cyclopropyl)methanone (**32.2**, 2.20 g, 78.7%) as a yellow solid. **LCMS (ESI):** *m/z* 257.9 & 259.9 [M+H]⁺.

[0374] A mixture of (2-amino-5-bromo-3-fluorophenyl)(cyclopropyl)methanone (**32.2**, 1.50 g, 5.81 mmol) and cyclopentane-1,3-dione (0.68 g, 6.97 mmol) in TFA (15 mL) was stirred at 80 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure and diluted with water (20 mL). The resulting mixture was adjusted to pH 8 with saturated aqueous NaHCO₃ and then extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-bromo-9-cyclopropyl-5-fluoro-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-one (**32.3**, 850 mg, 45.7 %) as a brown solid. **LCMS (ESI):** *m/z* 319.9 & 321.9 [M+H]⁺.

[0375] To a solution of methylmagnesium bromide (3.20 mL, 9.37 mmol, 3 mol/L in Et₂O) in THF (5 mL) was added a solution of 7-bromo-9-cyclopropyl-5-fluoro-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-one (**32.3**, 500 mg, 1.56 mmol) in THF (2 mL) dropwise at 0 °C under nitrogen atmosphere, and the mixture was stirred at 0 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was quenched with saturated aqueous NH₄Cl (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-bromo-9-cyclopropyl-5-fluoro-1-

methyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**32.4**, 280 mg, 53.3%) as brown solid.

LCMS (ESI): m/z 336.1 & 338.1 $[M+H]^+$.

[0376] A mixture of 7-bromo-5-fluoro-3-methyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-3-ol (**32.4**, 250 mg, 0.84 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (284 mg, 1.11 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (61.0 mg, 0.074 mmol) and potassium acetate (219 mg, 2.23 mmol) in dioxane (12 mL) was stirred at 100 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 5-fluoro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**32.5**, 242 mg, 84.9%). **LCMS (ESI):** m/z 384.2 $[M+H]^+$.

[0377] A mixture of 5-fluoro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**32.5**, 250 mg, 0.73 mmol), 2,4,5-trichloropyrimidine (268 mg, 1.46 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (59.8 mg, 0.073 mmol) and K₂CO₃ (303 mg, 2.19 mmol) in dioxane (3 mL) and water (0.5 mL) was stirred at 90 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**32.6**, 250 mg, 94.2%) as a yellow solid. **LCMS (ESI):** m/z 404.2 $[M+H]^+$.

[0378] To a solution of 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-ol (**32.6**, 200 mg, 0.495 mmol) and (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (92.0 mg, 0.594 mmol) in DMSO (3 mL) were added potassium fluoride (87.0 mg, 1.485 mmol), 18-crown-6 (27 mg, 0.10 mmol) and K₂CO₃ (69.0 mg, 0.495 mmol), and the mixture was stirred at 110 °C for 2 hrs. The reaction mixture was filtered and then subjected to prep-HPLC to afford 7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-cyclopropyl-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**32**, 200 mg, 65.5%) as a white solid, which was further separated by chiral SFC to give:

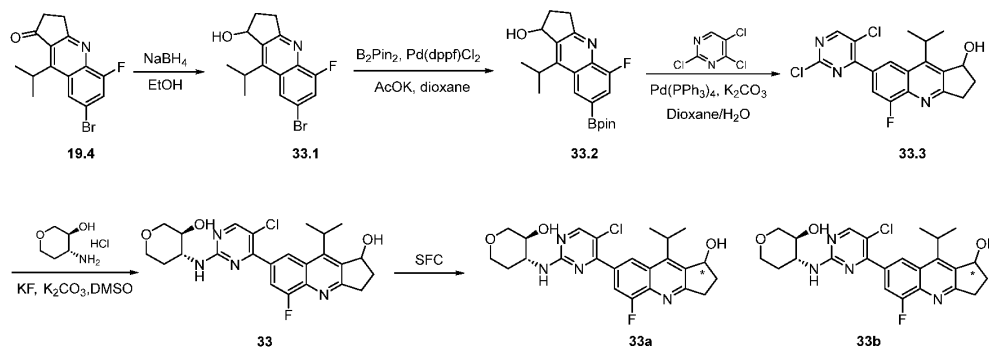
[0379] **Isomer 1:** (**32a**, 100% de); **Retention time:** 3.225 min. **LCMS (ESI):** m/z 485.2 $[M+H]^+$. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.81 (s, 1H), 8.47 (s, 1H), 7.86 (s, 1H), 7.54 (s, 1H), 5.34 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 3.98 - 3.73 (m, 3H), 3.61 - 3.42 (m, 1H), 3.38 - 3.32 (m, 1H), 3.28 - 3.15 (m, 1H), 3.10 - 3.00 (m, 1H), 3.02 - 2.87 (m, 1H), 2.42 - 2.27 (m, 1H), 2.23 -

2.06 (m, 2H), 2.04 - 1.90 (m, 1H), 1.81 (s, 3H), 1.70 - 1.59 (m, 1H), 1.55 - 1.44 (m, 1H), 1.38 - 1.26 (m, 1H), 1.20 - 1.09 (m, 1H), 0.71 - 0.57 (m, 1H).

[0380] Isomer 2: (32b, 98.8% de); Retention time: 4.208 min. **LCMS (ESI):** m/z 485.3 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ 8.79 (s, 1H), 8.47 (s, 1H), 7.85 (s, 1H), 7.55 (s, 1H), 5.34 (s, 1H), 4.94 (d, $J = 5.4$ Hz, 1H), 3.96 - 3.71 (m, 3H), 3.59 - 3.42 (m, 1H), 3.40 - 3.33 (m, 1H), 3.29 - 3.17 (m, 1H), 3.09 - 3.00 (m, 1H), 3.00 - 2.88 (m, 1H), 2.43 - 2.28 (m, 1H), 2.24 - 2.06 (m, 2H), 2.05 - 1.89 (m, 1H), 1.86 - 1.76 (m, 3H), 1.68 - 1.59 (m, 1H), 1.56 - 1.45 (m, 1H), 1.35 - 1.25 (m, 1H), 1.20 - 1.09 (m, 1H), 0.74 - 0.54 (m, 1H).

[0381] Analytical method: Column: ChiralCel OX, 100×4.6 mm I.D., 5 μ m, Mobile phase: A for CO₂ and B for Methanol (0.05% DEA), Gradient: 8 min @B 50%, Flow rate: 1.8 mL/min, Back pressure: 100 bar, Column temperature: 40 °C. **SFC separation method:** Instrument: SHIMADZU PREP SOLUTION SFC; Column: ChiralCel OX, 250×20 mm I.D., 5 μ m; Mobile phase: A for CO₂ and B for MeOH (0.1% 2 mol/L NH₃ in MeOH); Gradient: B 50 %; Flow rate: 35 mL /min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 11 min.

Example 26. (*R*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-isopropyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol and (*S*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-isopropyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol



[0382] To a solution of 7-bromo-5-fluoro-9-isopropyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-one (**19.4**, 300 mg, 0.93 mmol) in ethanol (10 mL) was added NaBH₄ (70.0 mg, 1.86 mmol), and the reaction mixture was stirred at 25 °C for 1 hr. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 7-bromo-5-fluoro-9-isopropyl-2,3-dihydro-1*H*-

cyclopenta[*b*]quinolin-1-ol (**33.1**, 300 mg, crude) as a yellow solid. **LCMS (ESI):** *m/z* 324.0 & 326.0 [M+H]⁺.

[0383] To a mixture of 7-bromo-5-fluoro-9-isopropyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**33.1**, 300 mg, crude), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (282 mg, 1.11 mmol) and potassium acetate (272 mg, 2.78 mmol) in dioxane (10 mL) was added Pd(dppf)Cl₂ (68.0 mg, 0.093 mmol). The resulting mixture was stirred at 100 °C for 2 hrs under nitrogen atmosphere and then cooled to room temperature. To the mixture were added 2,4,5-trichloropyrimidine (198 mg, 1.08 mmol), water (1.5 mL), Pd(PPh₃)₄ (63.0 mg, 0.054 mmol) and K₂CO₃ (223 mg, 1.62 mmol), and the resulting mixture was stirred at 100 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-9-isopropyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**33.3**, 258 mg) as a yellow solid. **LCMS (ESI):** *m/z* 392.0 [M+H]⁺.

[0384] To a solution of 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-9-isopropyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**33.3**, 208 mg, 0.53 mmol) in DMSO (2 mL) were added (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (162 mg, 1.06 mmol), K₂CO₃ (220 mg, 1.59 mmol) and KF (92.0 mg, 1.59 mmol), and the mixture was stirred at 110 °C for 2 hrs. The reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine (20 mL × 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to prep-HPLC to afford 7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-isopropyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**33**, 98.0 mg, 39%) as a white solid, which was further separated by chiral SFC to give:

[0385] **Isomer 1: (33a, 99% de); Retention time:** 1.529 min. **LCMS (ESI):** *m/z* 473.2 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.60 (s, 1H), 8.46 (s, 1H), 7.89 (s, 1H), 7.61 - 7.43 (m, 1H), 5.48 - 5.37 (m, 2H), 4.94 (d, *J* = 5.4 Hz, 1H), 4.01 - 3.77 (m, 4H), 3.58 - 3.46 (m, 1H), 3.40 - 3.35 (m, 1H), 3.29 - 3.24 (m, 1H), 3.09 - 2.89 (m, 2H), 2.44 - 2.30 (m, 1H), 2.09 - 1.89 (m, 2H), 1.61 - 1.47 (m, 7H).

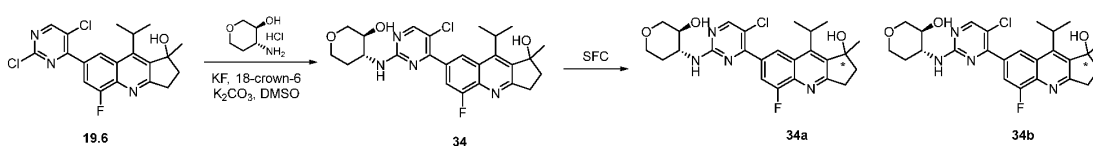
[0386] **Isomer 2: (33b, 99% de); Retention time:** 1.987 min. **LCMS (ESI):** *m/z* 473.2 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.60 (s, 1H), 8.46 (s, 1H), 7.91 (s, 1H), 7.62 - 7.46

(m, 1H), 5.47 - 5.39 (m, 2H), 4.94 (d, $J = 5.4$ Hz, 1H), 3.99 - 3.77 (m, 4H), 3.56 - 3.45 (m, 1H), 3.39 - 3.36 (m, 1H), 3.28 - 3.23 (m, 1H), 3.09 - 2.91 (m, 2H), 2.44 - 2.30 (m, 1H), 2.10 - 1.90 (m, 2H), 1.60 - 1.47 (m, 7H).

[0387] Analytical method: Column: ChiralPak IH, 100×4.6 mm I.D., $5 \mu\text{m}$; Mobile phase: A for CO_2 and B for methanol (0.05% DEA); Gradient: 8 min @ 30% B; Flow rate: 2.5 mL/min; Column temperature: 40°C .

[0388] SFC separation method: Instrument: Waters Thar 80 preparative SFC; Column: ChiralPak IH, 250×20 mm I.D., $5 \mu\text{m}$; Mobile phase: A for CO_2 and B for MeOH (0.1% 2 mol/L NH_3 in MeOH); Gradient: B 25 %; Flow rate: 40 mL /min; Back pressure: 100 bar; Column temperature: 35°C ; Wavelength: 220 nm; Cycle-time: 10 min.

Example 27. (*R*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol and (*S*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol



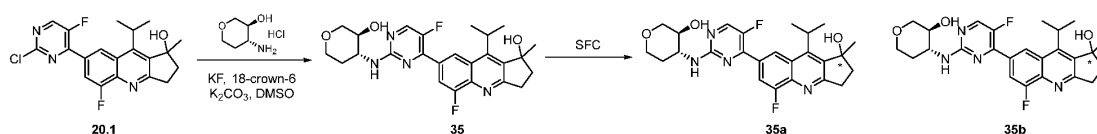
[0389] To a solution of 7-(2,5-dichloropyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**19.6**, 370 mg, 0.91 mmol) in DMSO (6 mL) were added (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (128 mg, 1.09 mmol), K_2CO_3 (126 mg, 0.91 mmol), KF (159 mg, 2.73 mmol) and 18-crown-6 (48.0 mg, 0.18 mmol), and the mixture was stirred at 110°C for 1 hr. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (20 mL $\times$ 2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to prep-HPLC to afford 7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**34**, 180 mg, 41%) as a white solid, which was further separated by chiral SFC to give:

[0390] Isomer 1: (34a, 100% de); Retention time: 2.895 min. **LCMS (ESI):** m/z 487.3 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{DMSO}-d_6$) δ 8.72 - 8.51 (m, 1H), 8.47 (s, 1H), 7.98 - 7.74 (m, 1H), 7.54 (d, $J = 7.6$ Hz, 1H), 5.62 (s, 1H), 4.94 (d, $J = 5.4$ Hz, 1H), 4.59 - 4.42 (m, 1H), 3.91 - 3.80 (m, 3H), 3.57 - 3.46 (m, 1H), 3.31 - 3.25 (m, 1H), 3.11 - 2.96 (m, 3H), 2.26 - 2.20 (m, 2H), 2.04 - 1.90 (m, 1H), 1.63 - 1.44 (m, 10H).

[0391] Isomer 2: (34b, 100% de); Retention time: 3.825 min. **LCMS (ESI):** m/z 487.3 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ 8.72 - 8.50 (m, 1H), 8.47 (s, 1H), 7.99 - 7.74 (m, 1H), 7.54 (d, J = 7.1 Hz, 1H), 5.62 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 4.55 - 4.46 (m, 1H), 3.93 - 3.75 (m, 3H), 3.56 - 3.44 (m, 1H), 3.30 - 3.26 (m, 1H), 3.09 - 2.93 (m, 3H), 2.27 - 2.15 (m, 2H), 2.03 - 1.87 (m, 1H), 1.59 - 1.45 (m, 10H).

[0392] Analytical method: Column: ChiralCel OX, 100 $\times$ 4.6 mm I.D., 5 μ m, Mobile phase: A for CO₂ and B for Methanol (0.05% DEA), Gradient: 8 min @B 40%, Flow rate: 2.0 mL/min, Back pressure: 100 bar, Column temperature: 35 $^{\circ}$ C. **SFC separation method:** SHIMADZU PREP SOLUTION SFC; Column: ChiralCel OX, 250 $\times$ 20 mm I.D., 5 μ m; Mobile phase: A for CO₂ and B for MeOH (0.1% 2 mol/L NH₃ in MeOH); Gradient: B 40 %; Flow rate: 40 mL/min; Back pressure: 100 bar; Column temperature: 35 $^{\circ}$ C; Wavelength: 220 nm; Cycle-time: 10 min.

Example 28. (*R*)-5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol and (*S*)-5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol



[0393] To a solution of 7-(2-chloro-5-fluoropyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**20.1**, 190 mg, 0.487 mmol) in DMSO (6 mL) were added (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (90.0 mg, 0.585 mmol), potassium carbonate (67.4 mg, 0.487 mmol), 18-crown-6 (25.8 mg, 0.097 mmol) and potassium fluoride (85.0 mg, 1.46 mmol), and the mixture was stirred at 110 $^{\circ}$ C for 1 hr under nitrogen atmosphere. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were washed with brine (40 mL $\times$ 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to prep-HPLC to afford 5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**35**, 90.0 mg, 39%) as a white solid, which was further separated by chiral SFC to give:

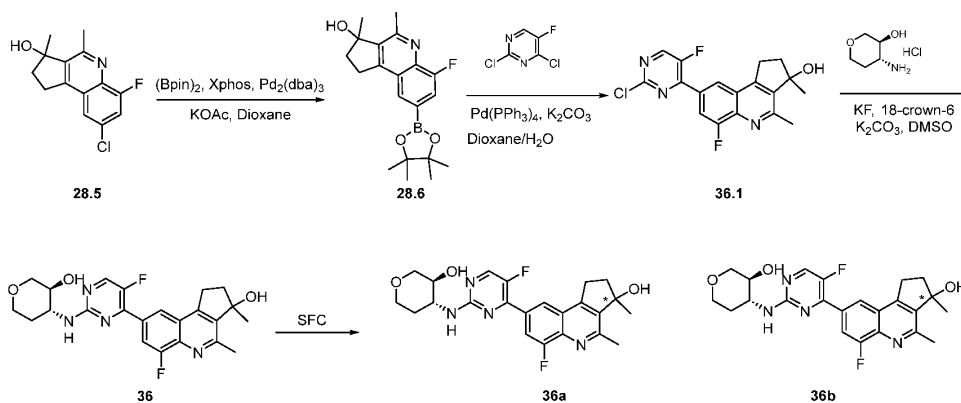
[0394] Isomer 1: (35a, 100% de); Retention time: 1.991 min. **LC-MS (ESI):** m/z 471.3 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ 8.93 (s, 1H), 8.51 (d, J = 4.1 Hz, 1H), 8.04 (d, J =

11.8 Hz, 1H), 7.28 (d, $J = 7.9$ Hz, 1H), 5.64 (s, 1H), 4.96 (d, $J = 5.1$ Hz, 1H), 4.63 - 4.41 (m, 1H), 4.00 - 3.76 (m, 3H), 3.59 - 3.50 (m, 1H), 3.43 - 3.39 (m, 1H), 3.12 - 2.96 (m, 3H), 2.29 - 2.18 (m, 2H), 2.08 - 1.99 (m, 1H), 1.65 - 1.45 (m, 10H).

[0395] Isomer 2: (35b, 98.5% de); Retention time: 2.435 min. **LC-MS (ESI):** m/z 471.3 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ 8.93 (s, 1H), 8.51 (d, $J = 3.9$ Hz, 1H), 8.04 (d, $J = 11.7$ Hz, 1H), 7.28 (d, $J = 7.8$ Hz, 1H), 5.64 (s, 1H), 4.96 (d, $J = 5.2$ Hz, 1H), 4.63 - 4.37 (m, 1H), 3.99 - 3.79 (m, 3H), 3.59 - 3.50 (m, 1H), 3.44 - 3.39 (m, 1H), 3.10 - 2.97 (m, 3H), 2.28 - 2.17 (m, 2H), 2.07 - 1.98 (m, 1H), 1.63 - 1.45 (m, 10H).

[0396] Analytical method: Column: ChiralPak IB 100×4.6 mm I.D., 3 μ m, Mobile phase: A for CO₂ and B for Methanol (0.05% DEA), Gradient: 8 min @B 30%, Flow rate: 2.0 mL/min, Back pressure: 100 bar, Column temperature: 40 °C. **SFC separation method:** Instrument: SHIMADZU PREP SOLUTION SFC; Column: ChiralPak IB, 250×30 mm I.D., 5 μ m; Mobile phase: A for CO₂ and B for MeOH (0.1% 2 mol/L NH₃ in MeOH); Gradient: B 30%; Flow rate: 60 mL/min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 9 min.

Example 29. (*R*)-6-fluoro-8-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol and (*S*)-6-fluoro-8-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol



[0397] To a solution of 8-chloro-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**28.5**, 2.10 g, 7.9 mmol) in dioxane (60 mL) were added 4,4,4',5,5,5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.61 g, 10.3 mmol), Xphos (0.75 g, 1.58 mmol), Pd₂(dba)₃ (1.45 g, 1.58 mmol) and potassium acetate (2.33 g, 23.7 mmol). The resulting mixture was stirred at 100 °C for 2 hrs under nitrogen atmosphere and then cooled to

room temperature. To the mixture were added 2,4-dichloro-5-fluoropyrimidine (2.36 g, 14.1 mmol), Pd(PPh₃)₄ (1.36 g, 1.18 mmol), potassium carbonate (2.17 g, 15.7 mmol) and water (12 mL), and the resulting mixture was stirred at 90 °C under nitrogen atmosphere for 12 hrs. The mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (90 mL x 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-(2-chloro-5-fluoropyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**36.1**, 2.42 g, two steps yield 84.6%) as a yellow oil. **LC-MS (ESI):** *m/z* 362.1 [M+H]⁺.

[0398] To a solution of 8-(2-chloro-5-fluoropyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**36.1**, 2.40 g, 6.63 mmol) in dimethylsulfoxide (20 mL) were added 18-crown-6 (0.35 g, 1.33 mmol), (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (1.22 g, 7.96 mmol), potassium carbonate (0.92 g, 6.63 mmol) and potassium fluoride (1.16 g, 19.9 mmol), and the mixture was stirred at 110 °C under nitrogen atmosphere for 3 hrs. The mixture was cooled to room temperature, diluted with water (60 mL) and extracted with ethyl acetate (60 mL x 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 6-fluoro-8-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**36**, 1.30 g, crude) as a white solid, which was further separated by chiral SFC to give:

[0399] **Isomer 1: (36a, 100% de); Retention time:** 1.405 min. **LCMS (ESI):** *m/z* 443.2 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.50 (d, *J* = 3.7 Hz, 1H), 8.34 (s, 1H), 8.06 (d, *J* = 12.4 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 5.48 (s, 1H), 4.94 (s, 1H), 3.90 - 3.77 (m, 3H), 3.54 - 3.48 (m, 1H), 3.40 - 3.32 (m, 2H), 3.14 - 3.05 (m, 2H), 2.82 (s, 3H), 2.39 - 2.20 (m, 2H), 2.04 - 1.99 (m, 1H), 1.58 - 1.43 (m, 4H).

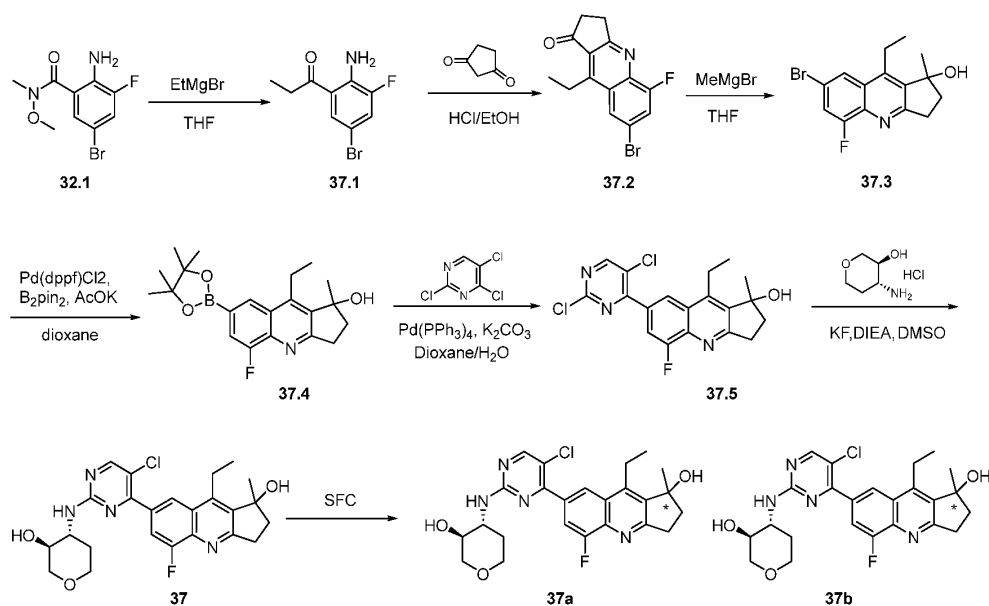
[0400] **Isomer 2: (36b, 100% de); Retention time:** 3.793 min. **LCMS (ESI):** *m/z* 443.2 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.50 (d, *J* = 3.8 Hz, 1H), 8.34 (s, 1H), 8.06 (d, *J* = 12.0 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 5.49 (s, 1H), 4.93 (d, *J* = 4.7 Hz, 1H), 3.90 - 3.78 (m, 3H), 3.54 - 3.48 (m, 1H), 3.44 - 3.33 (m, 2H), 3.16 - 3.03 (m, 2H), 2.82 (s, 3H), 2.38 - 2.21 (m, 2H), 2.04 - 1.98 (m, 1H), 1.57 - 1.43 (m, 4H).

[0401] **Analytical method:** Column: ChiralPak IH, 100 × 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 30% B; Flow rate: 2.5

mL/min; Column temperature: 40 °C. **SFC separation method:** SHIMADZU PREP

SOLUTION SFC; Column: ChiralPak IH, 250 × 20 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for MeOH (0.1% 7 mol/L NH₃ in MeOH); Gradient: B 40 %; Flow rate: 40 mL /min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 8 min.

Example 30. (*R*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-ethyl-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol and (*S*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-ethyl-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol



[0402] To a solution of 2-amino-5-bromo-3-fluoro-*N*-methoxy-*N*-methylbenzamide (**32.1**, 2.00 g, 7.20 mmol) in THF (30 mL) was added ethylmagnesium bromide (3.6 mL, 7.20 mmol, 2 mol/L in THF) at -40 °C, and the mixture was stirred at -40 °C for 5 hrs under nitrogen atmosphere. The reaction mixture was quenched with aqueous NH₄Cl solution (20 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 1-(2-amino-5-bromo-3-fluorophenyl)propan-1-one (**37.1**, 1.60 g, 90%) as a yellow solid. **LCMS (ESI):** *m/z* 246.0 & 248.0 [M+H]⁺.

[0403] To a mixture of 1-(2-amino-5-bromo-3-fluorophenyl)propan-1-one (**37.1**, 1.60 g, 6.50 mmol) and cyclopentane-1,3-dione (770 mg, 7.80 mmol) in ethanol (25 mL) was added conc. HCl (5 mL), and the resulting mixture was stirred at 100 °C for 15 hrs. The reaction

mixture was adjusted to pH 8 with saturated NaHCO₃ aqueous solution at room temperature and then extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-bromo-9-ethyl-5-fluoro-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-one (**37.2**, 1.50 g, 75%) as a brown solid. **LCMS (ESI):** *m/z* 308.0 & 310.0 [M+H]⁺.

[0404] To a solution of methylmagnesium bromide (7.80 mL, 23.4 mmol) in THF (30 mL) was added a solution of 7-bromo-9-ethyl-5-fluoro-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinolin-1-one (**37.2**, 1.20 g, 3.90 mmol) in THF (8 mL) and DCM (8 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was quenched with saturated NH₄Cl aqueous solution (30 mL) and extracted with ethyl acetate (40 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-bromo-9-ethyl-5-fluoro-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-one (**37.3**, 1.20 g, 66%) as a yellow solid. **LCMS (ESI):** *m/z* 324.0 & 326.0 [M+H]⁺.

[0405] To a mixture of 7-bromo-9-ethyl-5-fluoro-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-one (**37.3**, 350 mg, 1.08 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (548 mg, 2.16 mmol) and potassium acetate (317 mg, 3.24 mmol) in dioxane (10 mL) was added Pd(dppf)Cl₂ (79 mg, 0.108 mmol). The resulting mixture was stirred at 100 °C for 5 hrs under nitrogen atmosphere and then cooled to room temperature. To the mixture were added 2,4,5-trichloropyrimidine (369 mg, 2.16 mmol), Pd(PPh₃)₄ (124 mg, 0.108 mmol), water (2.5 mL) and K₂CO₃ (450 mg, 3.24 mmol), and the resulting mixture was stirred at 100 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 7-(2,5-dichloropyrimidin-4-yl)-9-ethyl-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**37.5**, 349 mg, two steps yield 82.5%) as a yellow solid. **LCMS (ESI):** *m/z* 392.1 [M+H]⁺.

[0406] To a solution 7-(2,5-dichloropyrimidin-4-yl)-9-ethyl-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**37.5**, 300 mg, 0.76 mmol) in DMSO (5 mL) were added (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (176 mg, 1.17 mmol), *N,N*-

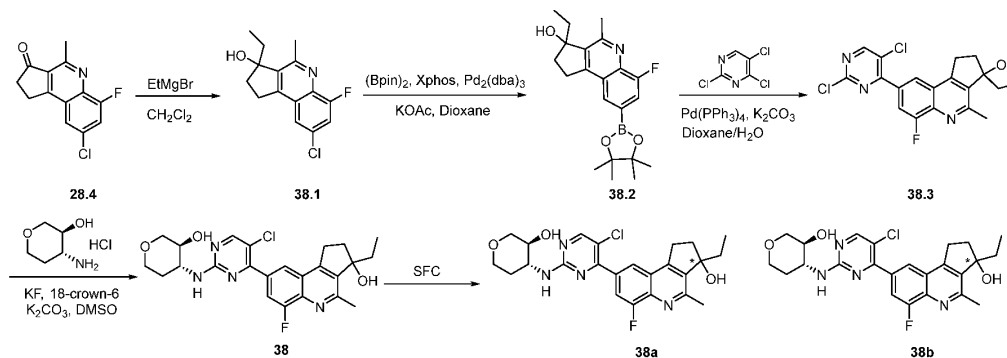
diisopropylethylamine (395 mg, 3.04 mmol) and KF (44 mg, 0.76 mmol), and the mixture was stirred at 110 °C for 15 hrs. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to prep-HPLC to afford 7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-ethyl-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**37**, 100 mg, 27%) as a white solid, which was further separated by chiral SFC to give:

[0407] Isomer 1: (37a, 100% de); Retention time: 1.496 min. **LCMS (ESI):** *m/z* 473.1 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.47 (s, 1H), 8.37 (s, 1H), 7.83 (s, 1H), 7.56 (s, 1H), 5.56 (s, 1H), 4.95 (s, 1H), 3.86 - 3.78 (m, 3H), 3.53 - 3.33 (m, 4H), 3.08 - 2.99 (m, 3H), 2.27 - 2.19 (m, 2H), 2.05 - 1.90 (m, 1H), 1.57 - 1.46 (m, 4H), 1.34 (t, *J* = 7.4 Hz, 3H).

[0408] Isomer 2: (37b, 100% de); Retention time: 2.334 min. **LCMS (ESI):** *m/z* 473.1 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.47 (s, 1H), 8.37 (s, 1H), 7.83 (s, 1H), 7.56 (s, 1H), 5.56 (s, 1H), 4.94 (d, *J* = 5.3 Hz, 1H), 3.86 - 3.79 (m, 3H), 3.53 - 3.33 (m, 4H), 3.08 - 2.99 (m, 3H), 2.27 - 2.19 (m, 2H), 2.05 - 1.90 (m, 1H), 1.57 - 1.46 (m, 4H), 1.34 (t, *J* = 7.4 Hz, 3H).

[0409] Analytical method: Column: ChiralPak IH, 100 × 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 30% B; Flow rate: 2.5 mL/min; Column temperature: 40 °C. **SFC separation method:** Instrument: SHIMADZU PREP SOLUTION SFC; Column: ChiralPak IH, 250 × 20 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for EtOH (0.1% 7 mol/L NH₃ in MeOH); Gradient: B 30 %; Flow rate: 40 mL/min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 8 min.

Example 31. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-3-ethyl-6-fluoro-4-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-3-ethyl-6-fluoro-4-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol

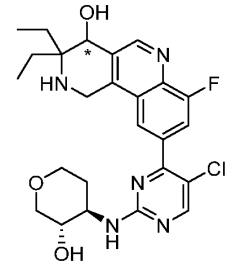
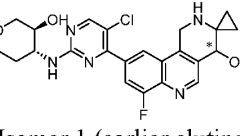
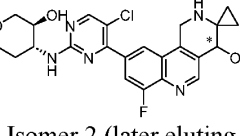
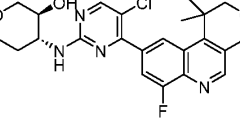


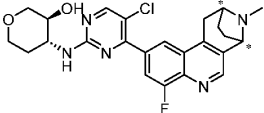
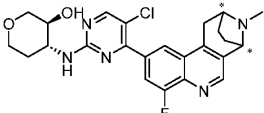
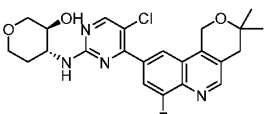
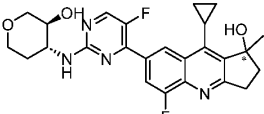
[0410] To a solution of 8-chloro-6-fluoro-4-methyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (**28.4**, 500 mg, 2.00 mmol) in dichloromethane (10 mL) was added ethylmagnesium bromide (3.0 mL, 10.0 mmol, 3.4 mol/L) at 0 °C, and the mixture was stirred at 0 °C for 2 hrs under nitrogen atmosphere. The reaction mixture was quenched with water (90 mL) and extracted with dichloromethane (80 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-chloro-3-ethyl-6-fluoro-4-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**38.1**, 500 mg, 89%) as a yellow solid. **LC-MS (ESI)**: *m/z* 280.1 [M+H]⁺.

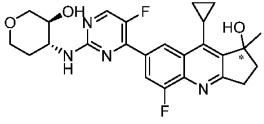
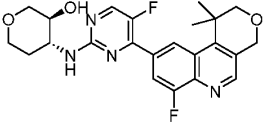
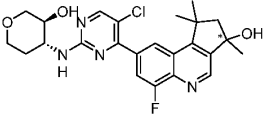
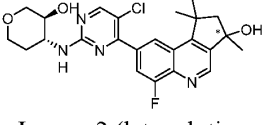
[0411] To a solution of 8-chloro-3-ethyl-6-fluoro-4-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**38.1**, 450 mg, 1.61 mmol) in dioxane (18 mL) were added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (572 mg, 2.25 mmol), Xphos (153 mg, 0.322 mmol), Pd₂(dba)₃ (295 mg, 0.322 mmol) and potassium acetate (474 mg, 4.83 mmol). The resulting mixture was stirred at 100 °C for 3 hrs under nitrogen atmosphere and then cooled to room temperature. To the mixture were added 2,4,5-trichloropyrimidine (525 mg, 2.86 mmol), Pd(PPh₃)₄ (275 mg, 0.238 mmol), potassium carbonate (439 mg, 3.18 mmol) and water (3 mL), and the resulting mixture was stirred at 90 °C for 12 hrs under nitrogen atmosphere. The reaction mixture was diluted with water (60 mL) and extracted with ethyl acetate (50 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-(2,5-dichloropyrimidin-4-yl)-3-ethyl-6-fluoro-4-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**38.3**, 471 mg, two steps yield 74.6%) as a yellow oil. **LC-MS (ESI)**: *m/z* 392.1 [M+H]⁺.

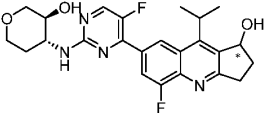
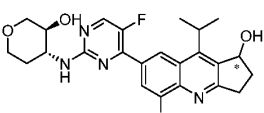
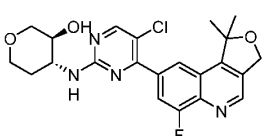
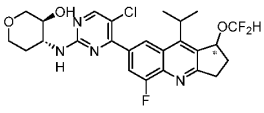
[0412] To a solution of 8-(2,5-dichloropyrimidin-4-yl)-3-ethyl-6-fluoro-4-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**38.3**, 400 mg, 1.02 mmol) in dimethyl sulfoxide (8 mL) were added 18-crown-6 (54.0 mg, 0.204 mmol), (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol hydrochloride (188 mg, 1.22 mmol), potassium carbonate (141 mg, 1.02 mmol) and potassium fluoride (178 mg, 3.06 mmol), and the mixture was stirred at 110 °C for 3 hrs under nitrogen atmosphere. The reaction mixture was cooled to room temperature, diluted with water (30 mL) and then extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford 8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-

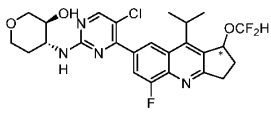
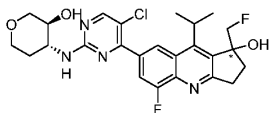
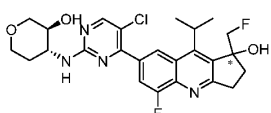
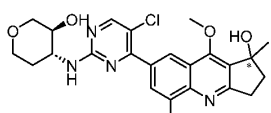
7		LC-MS (ESI): m/z 500.4 [M+H] ⁺ ; ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.70 (s, 1H), 8.44 (s, 1H), 8.19 - 8.09 (m, 1H), 7.88 - 7.77 (m, 1H), 7.62 - 7.46 (m, 1H), 4.91 (d, <i>J</i> = 5.3 Hz, 1H), 4.27 (s, 2H), 3.93 - 3.63 (m, 6H), 3.58 - 3.36 (m, 4H), 3.01 (t, <i>J</i> = 10.6 Hz, 1H), 2.80 (s, 2H), 1.99 - 1.84 (m, 1H), 1.56 - 1.41 (m, 5H).
8		LC-MS (ESI): m/z 464.1 [M+H] ⁺ ; ¹H NMR (400 MHz, CD ₃ OD- <i>d</i> ₄) δ 8.74 (s, 1H), 8.43 (s, 1H), 8.38 (s, 1H), 8.25 (s, 1H), 7.94 (d, <i>J</i> = 11.2 Hz, 1H), 4.72 (s, 2H), 4.02 - 3.84 (m, 3H), 3.63 - 3.59 (m, 1H), 3.49 - 3.45 (m, 1H), 3.23 - 3.16 (m, 1H), 3.08 (s, 2H), 2.09 (d, <i>J</i> = 13.2 Hz, 1H), 1.68 - 1.55 (m, 1H).
9		LC-MS (ESI): m/z 536.2 [M+H] ⁺ ; ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.83 (s, 1H), 8.48 (s, 1H), 8.33 - 8.06 (m, 1H), 8.04 - 7.82 (m, 1H), 7.78 - 7.36 (m, 1H), 5.00 (s, 2H), 4.94 (d, <i>J</i> = 5.4 Hz, 1H), 3.92 - 3.74 (m, 3H), 3.59 - 3.44 (m, 1H), 3.39 - 3.34 (m, 1H), 3.15 - 2.97 (m, 6H), 2.09 - 1.82 (m, 1H), 1.54 - 1.45 (m, 7H).
10		LC-MS (ESI): m/z 475.2 [M+H] ⁺ ; ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.79 (s, 1H), 8.49 (s, 1H), 8.22 - 8.07 (m, 1H), 7.98 - 7.81 (m, 1H), 7.65 - 7.47 (m, 1H), 4.93 (d, <i>J</i> = 5.7 Hz, 1H), 4.37 - 3.97 (m, 2H), 3.88 - 3.77 (m, 3H), 3.55 - 3.46 (m, 1H), 3.41 - 3.35 (m, 1H), 3.29 - 3.26 (m, 1H), 3.09 - 3.02 (m, 1H), 2.92 - 2.77 (m, 1H), 2.10 - 1.83 (m, 1H), 1.57 - 1.47 (m, 1H), 1.10 (s, 6H).
11		LC-MS (ESI): m/z 500.2 [M+H] ⁺ ; ¹H NMR (400 MHz, CDCl ₃) δ 9.53 (s, 1H), 8.39 (s, 1H), 8.23 (s, 1H), 7.96 (dd, <i>J</i> = 10.9, 1.9 Hz, 1H), 5.39 (d, <i>J</i> = 6.0 Hz, 1H), 4.64 (s, 2H), 4.09 - 3.99 (m, 2H), 3.88 (s, 1H), 3.65 (dt, <i>J</i> = 9.3, 4.8 Hz, 1H), 3.52 - 3.45 (m, 1H), 3.20 (d, <i>J</i> = 10.5 Hz, 1H), 2.09 (d, <i>J</i> = 13.2 Hz, 1H), 1.90 - 1.85 (m, 2H), 1.80 - 1.65 (m, 4H), 1.01 - 0.91 (m, 6H).
12a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 502.2 [M+H] ⁺ ; ¹H NMR (400 MHz, CDCl ₃) δ 8.98 (s, 1H), 8.35 (s, 1H), 8.01 (s, 1H), 7.86 (d, <i>J</i> = 10.8 Hz, 1H), 5.54 (s, 1H), 4.70 - 4.56 (m, 1H), 4.52 (s, 1H), 4.29 (d, <i>J</i> = 18.0 Hz, 1H), 4.13 - 3.83 (m, 3H), 3.67 - 3.56 (m, 1H), 3.46 (t, <i>J</i> = 11.4 Hz, 1H), 3.21 (t, <i>J</i> = 10.5 Hz, 1H), 2.14 - 1.86 (m, 2H), 1.77 - 1.60 (m, 2H), 1.48 - 1.21 (m, 3H), 1.04 (s, 3H), 0.96 (s, 3H). de: 100%; Retention time: 3.476 min; column: OD-3, 0.46 cm I.D.* 5 cm L; mobile phase: CO ₂ : EtOH = 70 : 30; flow rate: 2.5 mL/min; column temperature: 25 °C; wavelength: 254 nm.

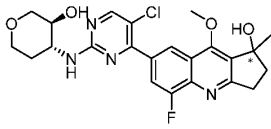
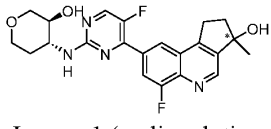
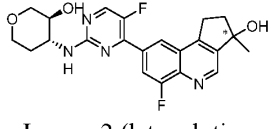
12b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 502.2 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.33 (s, 1H), 7.97 (s, 1H), 7.81 (d, J = 10.8 Hz, 1H), 5.54 (s, 1H), 4.71 - 4.55 (m, 1H), 4.50 (s, 1H), 4.27 (d, J = 17.9 Hz, 1H), 4.12 - 3.83 (m, 3H), 3.67 - 3.58 (m, 1H), 3.48 (t, J = 11.5 Hz, 1H), 3.20 (t, J = 10.5 Hz, 1H), 2.07 (d, J = 12.9 Hz, 1H), 1.99 - 1.84 (m, 1H), 1.76 - 1.60 (m, 2H), 1.45 - 1.22 (m, 3H), 1.03 (s, 3H), 0.95 (s, 3H). de: 99%; Retention time: 4.119 min; column: OD-3, 0.46 cm I.D.* 5 cm L; mobile phase: CO_2 : EtOH = 70 : 30; flow rate: 2.5 mL/min; column temperature: 25 °C; wavelength: 254 nm.
39a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 472.3 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.92 (s, 1H), 8.48 (s, 1H), 8.23 (s, 1H), 7.89 (d, J = 10.5 Hz, 1H), 7.58 (s, 1H), 5.59 (d, J = 6.6 Hz, 1H), 4.93 (d, J = 5.4 Hz, 1H), 4.43 - 4.32 (m, 1H), 4.25 (d, J = 6.6 Hz, 1H), 4.21 - 4.11 (m, 1H), 3.91 - 3.73 (m, 3H), 3.56 - 3.44 (m, 1H), 3.38 - 3.32 (m, 2H), 3.09 - 3.02 (m, 1H), 2.04 - 1.88 (m, 1H), 1.58 - 1.42 (m, 1H), 0.81 - 0.71 (m, 1H), 0.65 - 0.48 (m, 3H). de: 100%; Retention time: 2.127 min. instrument: Shimadzu-UC; column: ChiralPak AY, 100 × 4.6 mm I.D., 5 μm, Mobile phase: A for CO_2 and B for isopropanol (0.05% DEA), Gradient: 8 min @B 50%, Flow rate: 1.8 mL/min, Back pressure: 100 bar, Column temperature: 40 °C.
39b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 472.3 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.92 (s, 1H), 8.48 (s, 1H), 8.23 (s, 1H), 7.89 (d, J = 10.5 Hz, 1H), 7.58 (s, 1H), 5.59 (d, J = 6.6 Hz, 1H), 4.93 (d, J = 5.4 Hz, 1H), 4.41 - 4.31 (m, 1H), 4.26 (d, J = 6.3 Hz, 1H), 4.23 - 4.13 (m, 1H), 3.92 - 3.76 (m, 3H), 3.57 - 3.45 (m, 1H), 3.39 - 3.33 (m, 2H), 3.11 - 3.00 (m, 1H), 2.04 - 1.89 (m, 1H), 1.59 - 1.41 (m, 1H), 0.83 - 0.71 (m, 1H), 0.65 - 0.51 (m, 3H). de: 100%; Retention time: 4.960 min. instrument: Shimadzu-UC; column: ChiralPak AY, 100 × 4.6 mm I.D., 5 μm, Mobile phase: A for CO_2 and B for isopropanol (0.05% DEA), Gradient: 8 min @B 50%, Flow rate: 1.8 mL/min, Back pressure: 100 bar, Column temperature: 40 °C.
40		LCMS (ESI): m/z 459.2 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.73 (s, 1H), 8.68 - 8.54 (m, 1H), 8.49 (s, 1H), 8.00 - 7.75 (m, 1H), 7.57 (d, J = 7.9 Hz, 1H), 4.97 (s, 2H), 4.95 (d, J = 5.4 Hz, 1H), 3.94 - 3.77 (m, 3H), 3.67 (s, 2H), 3.60 - 3.49 (m, 1H), 3.33 - 3.30 (m, 1H), 3.07 - 3.00 (m, 1H), 2.01 - 1.93 (m, 1H), 1.66 - 1.45 (m, 7H).

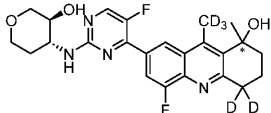
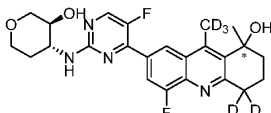
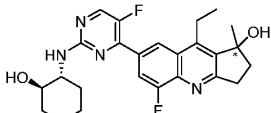
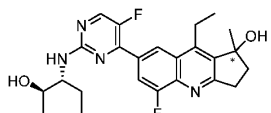
41a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 470.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.47 (s, 1H), 8.19 (s, 1H), 7.86 (d, J = 11.3 Hz, 1H), 7.57 (s, 1H), 4.92 (d, J = 5.4 Hz, 1H), 4.13 (d, J = 5.7 Hz, 1H), 3.85 - 3.78 (m, 3H), 3.59 - 3.36 (m, 4H), 3.08 - 3.01 (m, 1H), 2.85 - 2.76 (m, 1H), 2.33 - 2.13 (m, 5H), 2.02 - 1.89 (m, 1H), 1.80 - 1.73 (m, 1H), 1.60 - 1.43 (m, 2H). de: 100%; Retention time: 2.670 min. instrument: Shimadzu-UC; column: ChiralCel OJ, 100 $\times$ 4.6 mm I.D., 3 μm, Mobile phase: A for CO₂ and B for methanol (0.05% DEA), Gradient: 8 min @B 20%, Flow rate: 2.5 mL/min, Back pressure: 100 bar, Column temperature: 40 $^{\circ}$C.
41b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 470.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.48 (s, 1H), 8.20 (s, 1H), 7.86 (d, J = 11.2 Hz, 1H), 7.58 (s, 1H), 4.93 (d, J = 5.4 Hz, 1H), 4.14 (d, J = 5.9 Hz, 1H), 3.90 - 3.75 (m, 3H), 3.58 - 3.36 (m, 4H), 3.12 - 3.02 (m, 1H), 2.87 - 2.79 (m, 1H), 2.30 - 2.13 (m, 5H), 2.02 - 1.89 (m, 1H), 1.81 - 1.73 (m, 1H), 1.61 - 1.43 (m, 2H). de: 96.91%; Retention time: 3.496 min. instrument: Shimadzu-UC; column: ChiralCel OJ, 100 $\times$ 4.6 mm I.D., 3 μm, Mobile phase: A for CO₂ and B for methanol (0.05% DEA), Gradient: 8 min @B 20%, Flow rate: 2.5 mL/min, Back pressure: 100 bar, Column temperature: 40 $^{\circ}$C.
42		LCMS (ESI): m/z 459.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.47 (s, 1H), 8.07 (s, 1H), 7.87 (d, J = 10.7 Hz, 1H), 7.57 (s, 1H), 5.17 (s, 2H), 4.92 (s, 1H), 3.86 - 3.77 (m, 3H), 3.53 - 3.35 (m, 2H), 3.11 - 2.99 (m, 1H), 2.89 (s, 2H), 1.99 - 1.92 (m, 1H), 1.54 - 1.47 (m, 1H), 1.28 (s, 6H).
43a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 469.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.50 (d, J = 3.9 Hz, 1H), 8.05 (d, J = 11.6 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 5.35 (s, 1H), 4.95 (d, J = 4.0 Hz, 1H), 3.95 - 3.77 (m, 3H), 3.61 - 3.47 (m, 1H), 3.42 - 3.34 (m, 1H), 3.26 - 3.20 (m, 1H), 3.12 - 3.04 (m, 1H), 3.01 - 2.89 (m, 1H), 2.44 - 2.35 (m, 1H), 2.24 - 2.08 (m, 2H), 2.08 - 1.95 (m, 1H), 1.81 (s, 3H), 1.69 - 1.58 (m, 1H), 1.57 - 1.44 (m, 1H), 1.38 - 1.27 (m, 1H), 1.25 - 1.11 (m, 1H), 0.73 - 0.58 (m, 1H). de: 100%; Retention time: 2.738 min. instrument: Shimadzu-UC; column: ChiralCel OX, 100 $\times$ 4.6 mm I.D., 5 μm, Mobile phase: A for CO₂ and B for methanol (0.05% DEA), Gradient: 8 min @B 50%, Flow rate: 1.8 mL/min, Back pressure: 100 bar, Column temperature: 40 $^{\circ}$C.

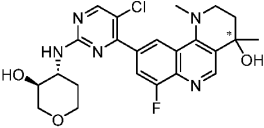
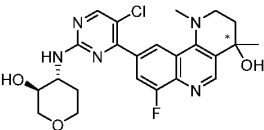
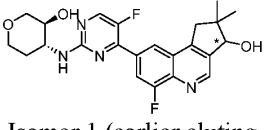
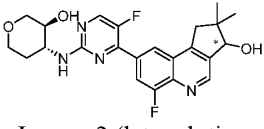
43b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 469.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.50 (d, $J = 3.9$ Hz, 1H), 8.05 (d, $J = 11.9$ Hz, 1H), 7.27 (d, $J = 7.9$ Hz, 1H), 5.35 (s, 1H), 4.95 (d, $J = 5.4$ Hz, 1H), 3.94 - 3.77 (m, 3H), 3.58 - 3.48 (m, 1H), 3.42 - 3.34 (m, 1H), 3.28 - 3.16 (m, 1H), 3.11 - 3.04 (m, 1H), 3.00 - 2.90 (m, 1H), 2.45 - 2.34 (m, 1H), 2.24 - 2.09 (m, 2H), 2.07 - 1.95 (m, 1H), 1.81 (s, 3H), 1.69 - 1.60 (m, 1H), 1.57 - 1.45 (m, 1H), 1.39 - 1.27 (m, 1H), 1.26 - 1.13 (m, 1H), 0.73 - 0.61 (m, 1H). de: 99.48%; Retention time: 3.750 min. instrument: Shimadzu-UC; column: ChiralCel OX, 100×4.6 mm I.D., 5 μm, Mobile phase: A for CO₂ and B for methanol (0.05% DEA), Gradient: 8 min @B 50%, Flow rate: 1.8 mL/min, Back pressure: 100 bar, Column temperature: 40 °C.
44		LCMS (ESI): m/z 443.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.73 (s, 1H), 8.53 (d, $J = 3.9$ Hz, 1H), 8.07 (d, $J = 11.7$ Hz, 1H), 7.32 (d, $J = 7.9$ Hz, 1H), 4.96 (s, 3H), 3.97 - 3.77 (m, 3H), 3.68 (s, 2H), 3.61 - 3.45 (m, 1H), 3.42 - 3.35 (m, 1H), 3.11 - 3.02 (m, 1H), 2.06 - 2.00 (m, 1H), 1.62 - 1.46 (m, 7H).
45a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 473.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.60 - 8.38 (m, 2H), 7.94 (s, 1H), 7.57 (s, 1H), 5.38 (s, 1H), 4.94 (d, $J = 5.4$ Hz, 1H), 3.96 - 3.72 (m, 3H), 3.62 - 3.42 (m, 1H), 3.36 - 3.32 (m, 1H), 3.07 - 3.00 (m, 1H), 2.30 - 2.16 (m, 2H), 1.97 (s, 1H), 1.64 (s, 3H), 1.62 (s, 3H), 1.57 (s, 3H), 1.55 - 1.46 (m, 1H). de: 100%; Retention time: 2.405 min. instrument: Shimadzu-UC; column: ChiralPak IC, 100×4.6 mm I.D., 3 μm, Mobile phase: A for CO₂ and B for methanol (0.05% DEA), Gradient: 8 min @B 50%, Flow rate: 2.0 mL/min, Back pressure: 100 bar, Column temperature: 40 °C.
45b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 473.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.65 - 8.38 (m, 2H), 7.93 (s, 1H), 7.57 (s, 1H), 5.38 (s, 1H), 4.94 (d, $J = 5.4$ Hz, 1H), 3.92 - 3.75 (m, 3H), 3.60 - 3.44 (m, 1H), 3.36 - 3.32 (m, 1H), 3.07 - 2.99 (m, 1H), 2.31 - 2.16 (m, 2H), 1.97 (s, 1H), 1.64 (s, 3H), 1.62 (s, 3H), 1.57 (s, 3H), 1.55 - 1.45 (m, 1H). de: 100%; Retention time: 4.492 min. instrument: Shimadzu-UC; column: ChiralPak IC, 100×4.6 mm I.D., 3 μm, Mobile phase: A for CO₂ and B for methanol (0.05% DEA), Gradient: 8 min @B 50%, Flow rate: 2.0 mL/min, Back pressure: 100 bar, Column temperature: 40 °C.

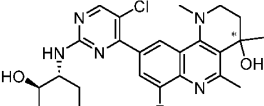
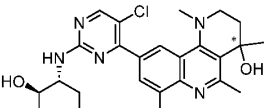
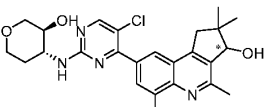
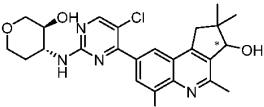
46a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 457.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.50 (d, $J = 3.9$ Hz, 1H), 8.05 (d, $J = 12.3$ Hz, 1H), 7.27 (d, $J = 7.8$ Hz, 1H), 5.43 (d, $J = 1.7$ Hz, 2H), 4.96 (d, $J = 5.4$ Hz, 1H), 4.01 - 3.77 (m, 4H), 3.55 - 3.48 (m, 1H), 3.28 - 3.23 (m, 2H), 3.10 - 2.91 (m, 2H), 2.42 - 2.33 (m, 1H), 2.07 - 1.99 (m, 2H), 1.60 - 1.48 (m, 7H). de: 100%; Retention time: 1.908 min. instrument: Shimadzu-UC; column: ChiralPak AD, 100×4.6 mm I.D., 3 μm, Mobile phase: A for CO₂ and B for methanol (0.05% DEA), Gradient: 8 min @B 40%, Flow rate: 2.2 mL/min, Back pressure: 100 bar, Column temperature: 40 °C.
46b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 457.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.50 (d, $J = 3.9$ Hz, 1H), 8.05 (d, $J = 11.7$ Hz, 1H), 7.28 (d, $J = 7.8$ Hz, 1H), 5.43 (s, 2H), 4.95 (d, $J = 5.3$ Hz, 1H), 4.02 - 3.79 (m, 4H), 3.55 - 3.48 (m, 1H), 3.29 - 3.21 (m, 2H), 3.11 - 2.91 (m, 2H), 2.42 - 2.33 (m, 1H), 2.07 - 1.98 (m, 2H), 1.63 - 1.46 (m, 7H). de: 100%; Retention time: 3.030 min. instrument: Shimadzu-UC; column: ChiralPak AD, 100×4.6 mm I.D., 3 μm, Mobile phase: A for CO₂ and B for methanol (0.05% DEA), Gradient: 8 min @B 40%, Flow rate: 2.2 mL/min, Back pressure: 100 bar, Column temperature: 40 °C.
47		LCMS (ESI): m/z 445.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.49 (s, 1H), 8.33 (s, 1H), 7.96 (s, 1H), 7.58 (s, 1H), 5.25 (s, 2H), 4.94 (d, $J = 5.4$ Hz, 1H), 3.86 - 3.78 (m, 3H), 3.54 - 3.48 (m, 1H), 3.36 - 3.33 (m, 1H), 3.07 - 2.99 (m, 1H), 1.99 - 1.86 (m, 1H), 1.72 (s, 6H), 1.60 - 1.43 (m, 1H).
48a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 523.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.47 (s, 1H), 7.98 (s, 1H), 7.55 (s, 1H), 6.97 (t, $J = 75.5$ Hz, 1H), 6.09 (d, $J = 5.0$ Hz, 1H), 4.94 (d, $J = 5.4$ Hz, 1H), 3.87 - 3.78 (m, 4H), 3.55 - 3.47 (m, 1H), 3.35 - 3.32 (m, 2H), 3.14 - 2.98 (m, 2H), 2.45 - 2.30 (m, 2H), 2.01 - 1.95 (m, 1H), 1.58 - 1.49 (m, 7H). de: 100%; Retention time: 1.526 min. instrument: Shimadzu-UC; column: ChiralPak IB, 100×4.6 mm I.D., 5 μm, Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.

48b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 523.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.64 (s, 1H), 8.47 (s, 1H), 7.98 (s, 1H), 7.57 (d, J = 6.9 Hz, 1H), 6.97 (t, J = 75.5 Hz, 1H), 6.09 (d, J = 5.0 Hz, 1H), 4.95 (d, J = 5.0 Hz, 1H), 3.87 - 3.78 (m, 4H), 3.54 - 3.48 (m, 1H), 3.35 - 3.32 (m, 2H), 3.15 - 2.98 (m, 2H), 2.48 - 2.42 (m, 1H), 2.39 - 2.31 (m, 1H), 2.01 - 1.94 (m, 1H), 1.61 - 1.47 (m, 7H). de: 100%; Retention time: 2.501 min. instrument: Shimadzu-UC; column: ChiralPak IB, 100 × 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.
49a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 505.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.81 - 8.52 (m, 1H), 8.47 (s, 1H), 8.04 - 7.72 (m, 1H), 7.55 (d, J = 7.4 Hz, 1H), 6.10 (s, 1H), 4.94 (d, J = 5.3 Hz, 1H), 4.65 - 4.55 (m, 1H), 4.52 - 4.35 (m, 2H), 3.97 - 3.75 (m, 3H), 3.59 - 3.44 (m, 1H), 3.32 - 3.25 (m, 1H), 3.13 - 2.97 (m, 3H), 2.50 - 2.46 (m, 1H), 2.22 - 2.09 (m, 1H), 2.04 - 1.90 (m, 1H), 1.64 - 1.45 (m, 7H). de: 100%; Retention time: 2.180 min. instrument: Shimadzu-UC; column: ChiralPak IB, 100 × 4.6 mm I.D., 3 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 30% B; Flow rate: 2.5 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.
49b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 505.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.76 - 8.51 (m, 1H), 8.47 (s, 1H), 8.05 - 7.74 (m, 1H), 7.55 (d, J = 7.2 Hz, 1H), 6.10 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 4.66 - 4.54 (m, 1H), 4.53 - 4.37 (m, 2H), 3.94 - 3.75 (m, 3H), 3.60 - 3.43 (m, 1H), 3.32 - 3.25 (m, 1H), 3.15 - 2.94 (m, 3H), 2.50 - 2.45 (m, 1H), 2.23 - 2.08 (m, 1H), 2.05 - 1.88 (m, 1H), 1.60 - 1.45 (m, 7H). de: 99.2%; Retention time: 4.278 min. instrument: Shimadzu-UC; column: ChiralPak IB, 100 × 4.6 mm I.D., 3 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 30% B; Flow rate: 2.5 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.
50a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 475.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.47 (s, 1H), 8.38 (s, 1H), 7.88 (s, 1H), 7.56 (s, 1H), 5.53 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 4.17 (s, 3H), 3.86 - 3.76 (m, 3H), 3.56 - 3.46 (m, 1H), 3.34 - 3.17 (m, 2H), 3.08 - 2.97 (m, 2H), 2.22 - 2.15 (m, 2H), 2.02 - 1.87 (m, 1H), 1.69 (s, 3H), 1.57 - 1.44 (m, 1H). de: 100%; Retention time: 3.012 min. instrument: Shimadzu-UC; column: ChiralPak IC, 100 × 4.6 mm I.D., 3 μm; Mobile phase: A for CO₂ and B for isopropanol (0.05% DEA); Gradient: 8 min @ 50% B; Flow rate: 1.8 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.

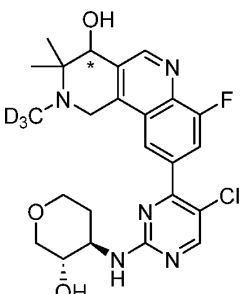
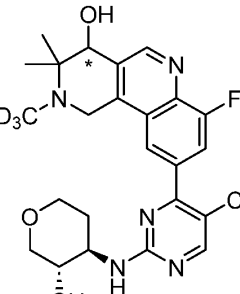
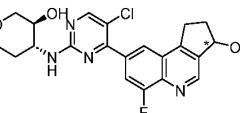
50b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 475.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.39 (s, 1H), 7.90 (s, 1H), 7.56 (s, 1H), 5.53 (s, 1H), 4.94 (d, $J = 5.4$ Hz, 1H), 4.17 (s, 3H), 3.89 - 3.77 (m, 3H), 3.56 - 3.46 (m, 1H), 3.34 - 3.17 (m, 2H), 3.08 - 2.97 (m, 2H), 2.22 - 2.15 (m, 2H), 2.02 - 1.87 (m, 1H), 1.69 (s, 3H), 1.58 - 1.45 (m, 1H). de: 100%; Retention time: 4.492 min. instrument: Shimadzu-UC; column: ChiralPak IC, 100×4.6 mm I.D., 3 μm; Mobile phase: A for CO₂ and B for isopropanol (0.05% DEA); Gradient: 8 min @ 50% B; Flow rate: 1.8 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.
51a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 429.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.52 (d, $J = 3.6$ Hz, 1H), 8.38 (s, 1H), 8.11 (d, $J = 12.1$ Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 1H), 5.48 (s, 1H), 4.94 (d, $J = 5.4$ Hz, 1H), 3.88 - 3.79 (m, 3H), 3.63 - 3.48 (m, 1H), 3.43 - 3.35 (m, 2H), 3.27 - 3.19 (m, 1H), 3.12 - 3.03 (m, 1H), 2.35 - 2.20 (m, 2H), 2.15 - 1.96 (m, 1H), 1.59 (s, 3H), 1.56 - 1.47 (m, 1H). de: 100%; Retention time: 1.427 min. instrument: Shimadzu-UC; column: ChiralPak AS, 100×4.6 mm I.D., 3 μm; Mobile phase: A for CO₂ and B for isopropanol (0.05% DEA); Gradient: 8 min @ 30% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.
51b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 429.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.52 (d, $J = 3.7$ Hz, 1H), 8.39 (s, 1H), 8.11 (d, $J = 12.5$ Hz, 1H), 7.33 (d, $J = 7.7$ Hz, 1H), 5.48 (s, 1H), 4.94 (d, $J = 5.4$ Hz, 1H), 3.88 - 3.79 (m, 3H), 3.63 - 3.48 (m, 1H), 3.43 - 3.34 (m, 2H), 3.27 - 3.19 (m, 1H), 3.12 - 3.02 (m, 1H), 2.34 - 2.22 (m, 2H), 2.15 - 1.96 (m, 1H), 1.59 (s, 3H), 1.56 - 1.47 (m, 1H). de: 99.9%; Retention time: 4.607 min. instrument: Shimadzu-UC; column: ChiralPak AS, 100×4.6 mm I.D., 3 μm; Mobile phase: A for CO₂ and B for isopropanol (0.05% DEA); Gradient: 8 min @ 30% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.

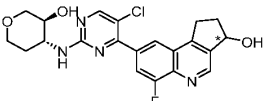
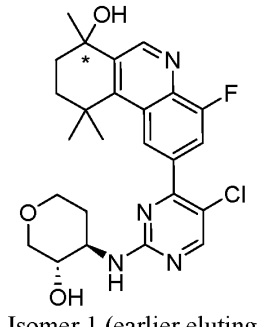
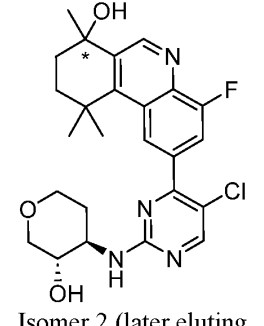
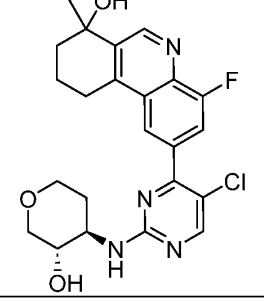
52a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 462.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.61 (s, 1H), 8.49 (d, J = 3.7 Hz, 1H), 8.02 (d, J = 11.6 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 5.28 (s, 1H), 4.94 (d, J = 5.3 Hz, 1H), 3.87 - 3.79 (m, 3H), 3.55 - 3.48 (m, 1H), 3.09 - 2.96 (m, 3H), 2.07 - 1.75 (m, 4H), 1.61 - 1.43 (m, 4H). de: 100%; Retention time: 3.324 min. instrument: Shimadzu-UC; column: ChiralPak C-IC, 100 × 4.6 mm I.D., 3 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.
52b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 462.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.61 (s, 1H), 8.49 (d, J = 3.8 Hz, 1H), 8.02 (d, J = 11.9 Hz, 1H), 7.28 (d, J = 7.3 Hz, 1H), 5.30 (s, 1H), 4.94 (d, J = 5.3 Hz, 1H), 3.87 - 3.79 (m, 3H), 3.57 - 3.50 (m, 1H), 3.12 - 2.97 (m, 3H), 2.07 - 1.75 (m, 4H), 1.59 - 1.48 (m, 4H). de: 100%; Retention time: 5.683 min. instrument: Shimadzu-UC; column: ChiralPak C-IC, 100 × 4.6 mm I.D., 3 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.
53a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 457.5 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.61 (s, 1H), 8.51 (d, J = 3.8 Hz, 1H), 8.03 (d, J = 12.0 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 5.57 (s, 1H), 4.95 (d, J = 5.4 Hz, 1H), 3.99 - 3.63 (m, 3H), 3.59 - 3.51 (m, 1H), 3.47 - 3.34 (m, 3H), 3.12 - 3.00 (m, 3H), 2.27 - 2.14 (m, 2H), 2.10 - 2.02 (m, 1H), 1.57 - 1.48 (m, 4H), 1.36 (t, J = 7.5 Hz, 3H). de: 100%; Retention time: 2.584 min. instrument: Shimadzu-UC; column: ChiralPak IH, 100 × 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 20% B; Flow rate: 2.5 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.
53b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 457.5 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.62 (s, 1H), 8.51 (d, J = 3.8 Hz, 1H), 8.03 (d, J = 12.0 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 5.57 (s, 1H), 4.95 (d, J = 5.4 Hz, 1H), 3.99 - 3.63 (m, 3H), 3.59 - 3.51 (m, 1H), 3.47 - 3.34 (m, 3H), 3.12 - 3.00 (m, 3H), 2.27 - 2.14 (m, 2H), 2.10 - 2.02 (m, 1H), 1.57 - 1.48 (m, 4H), 1.36 (t, J = 7.5 Hz, 3H). de: 100%; Retention time: 3.246 min. instrument: Shimadzu-UC; column: ChiralPak IH, 100 × 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 20% B; Flow rate: 2.5 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.

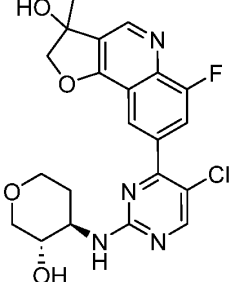
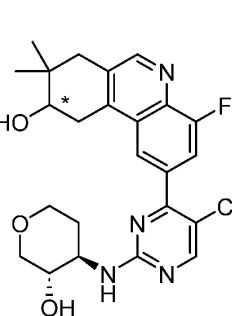
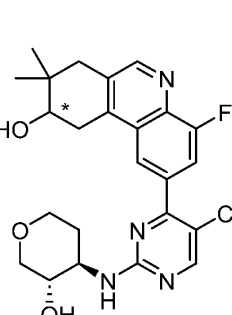
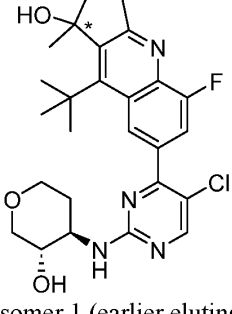
54a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 474.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.45 (s, 1H), 8.39 (s, 1H), 7.81 (s, 1H), 7.52 (s, 1H), 5.32 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 3.92 - 3.77 (m, 3H), 3.56 - 3.41 (m, 2H), 3.30 - 3.25 (m, 5H), 3.08 - 3.00 (m, 1H), 2.02 - 1.88 (m, 3H), 1.60 - 1.45 (m, 4H). de: 100%; Retention time: 1.707 min. instrument: Shimadzu-UC; column: ChiralPak IH, 100 $\times$ 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 $^{\circ}$C.
54b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 474.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.45 (s, 1H), 8.39 (s, 1H), 7.81 (s, 1H), 7.52 (s, 1H), 5.32 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 3.92 - 3.77 (m, 3H), 3.56 - 3.41 (m, 2H), 3.30 - 3.25 (m, 5H), 3.08-3.00 (m, 1H), 2.02 - 1.88 (m, 3H), 1.60 - 1.45 (m, 4H). de: 99.3%; Retention time: 2.21 min. instrument: Shimadzu-UC; column: ChiralPak IH, 100 $\times$ 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 $^{\circ}$C.
55a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 443.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.51 (d, J = 3.7 Hz, 1H), 8.34 (s, 1H), 8.11 (d, J = 12.3 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 5.62 (d, J = 6.4 Hz, 1H), 4.93 (d, J = 5.4 Hz, 1H), 4.87 (d, J = 6.3 Hz, 1H), 3.87 - 3.79 (m, 3H), 3.56 - 3.48 (m, 1H), 3.45 - 3.34 (m, 1H), 3.23 - 2.92 (m, 3H), 2.05 - 1.96 (m, 1H), 1.57 - 1.45 (m, 1H), 1.22 (s, 3H), 1.02 (s, 3H). de: 100%; Retention time: 1.188 min. instrument: Shimadzu-UC; column: ChiralPak IH, 100 $\times$ 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 $^{\circ}$C.
55b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 443.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.51 (d, J = 3.7 Hz, 1H), 8.34 (s, 1H), 8.11 (d, J = 12.2 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 5.63 (d, J = 6.4 Hz, 1H), 4.94 (d, J = 5.4 Hz, 1H), 4.87 (d, J = 6.3 Hz, 1H), 3.87 - 3.79 (m, 3H), 3.60 - 3.43 (m, 1H), 3.45 - 3.34 (m, 1H), 3.24 - 2.90 (m, 3H), 2.05 - 1.96 (m, 1H), 1.57 - 1.45 (m, 1H), 1.22 (s, 3H), 1.02 (s, 3H). de: 98.7%; Retention time: 1.612 min. instrument: Shimadzu-UC; column: ChiralPak IH, 100 $\times$ 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 $^{\circ}$C.

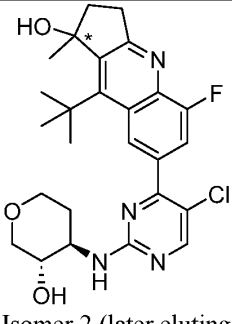
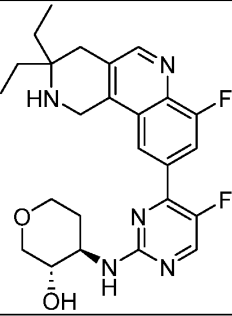
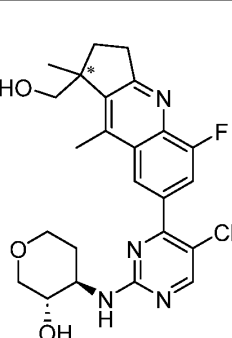
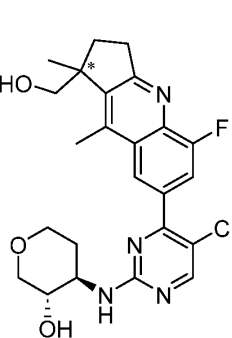
56a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 488.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.43 (s, 1H), 8.26 (s, 1H), 7.74 (d, J = 10.0 Hz, 1H), 7.49 (s, 1H), 5.14 (s, 2H), 3.85 - 3.76 (m, 3H), 3.49 - 3.32 (m, 4H), 3.18 (s, 3H), 3.08 - 3.00 (m, 1H), 2.85 (s, 3H), 2.09 - 1.89 (m, 3H), 1.61 - 1.45 (m, 4H). de: 100%; Retention time: 2.96 min. instrument: Shimadzu-UC; column: ChiralPak IH, 100 × 4.6 mm I.D., 5 μm; Mobile phase: A for <i>n</i>-hexane (0.05% DEA) and B for ethanol; Gradient: 10min @ 20% B; Flow rate: 1.5 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.
56b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 488.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.43 (s, 1H), 8.26 (s, 1H), 7.74 (d, J = 10.0 Hz, 1H), 7.49 (s, 1H), 5.14 (s, 2H), 3.85 - 3.76 (m, 3H), 3.49 - 3.33 (m, 4H), 3.18 (s, 3H), 3.08 - 3.00 (m, 1H), 2.85 (s, 3H), 2.09 - 1.89 (m, 3H), 1.61 - 1.45 (m, 4H). de: 98.9%; Retention time: 5.052 min. instrument: Shimadzu-UC; column: ChiralPak IH, 100 × 4.6 mm I.D., 5 μm; Mobile phase: A for <i>n</i>-hexane (0.05% DEA) and B for ethanol; Gradient: 10min @ 20% B; Flow rate: 1.5 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.
57a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 473.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.46 (s, 1H), 8.11 (s, 1H), 7.86 (d, J = 11.9 Hz, 1H), 7.56 (s, 1H), 5.35 (s, 1H), 4.72 (s, 1H), 3.86 - 3.74 (m, 3H), 3.55 - 3.47 (m, 1H), 3.38 - 3.31 (m, 2H), 3.18 - 2.94 (m, 3H), 2.75 (s, 3H), 2.00 - 1.94 (m, 1H), 1.56 - 1.43 (m, 1H), 1.18 (s, 3H), 1.07 (s, 3H). de: 100%; Retention time: 1.235 min. instrument: Shimadzu-UC; column: ChiralPak IH, 100 × 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.
57b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 473.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.46 (s, 1H), 8.10 (s, 1H), 7.86 (d, J = 11.9 Hz, 1H), 7.57 (s, 1H), 5.35 (s, 1H), 4.72 (s, 1H), 3.86 - 3.74 (m, 3H), 3.55 - 3.47 (m, 1H), 3.38 - 3.31 (m, 2H), 3.18 - 2.94 (m, 3H), 2.75 (s, 3H), 2.00 - 1.94 (m, 1H), 1.56 - 1.43 (m, 1H), 1.18 (s, 3H), 1.07 (s, 3H). de: 100%; Retention time: 3.977 min. instrument: Shimadzu-UC; column: ChiralPak IH, 100 × 4.6 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for methanol (0.05% DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Back pressure: 100 bar, Column temperature: 40 °C.

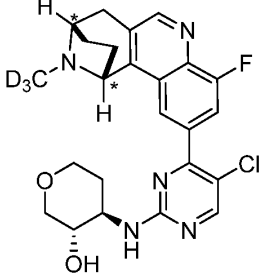
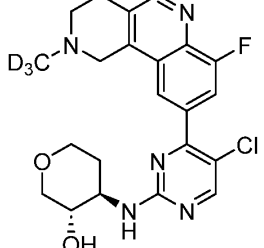
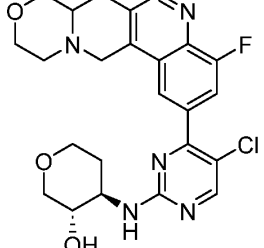
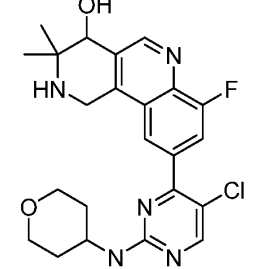
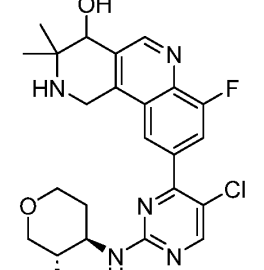
58		LCMS (ESI): m/z 495.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.94 (s, 1H), 8.55 (s, 1H), 8.48 (s, 2H), 8.04 (s, 1H), 7.58 (s, 1H), 4.93 (d, J = 5.4 Hz, 1H), 4.90 (s, 2H), 3.92 - 3.77 (m, 3H), 3.54 - 3.41 (m, 4H), 3.36 - 3.33 (m, 1H), 3.04 (t, J = 10.4 Hz, 1H), 2.02 - 1.88 (m, 1H), 1.58 - 1.43 (m, 1H).
59		LCMS (ESI): m/z 459.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.47 (s, 1H), 8.29 (s, 1H), 7.92 (s, 1H), 7.56 (s, 1H), 5.21 (s, 2H), 4.94 (d, J = 5.4 Hz, 1H), 3.86 - 3.79 (m, 3H), 3.56 - 3.48 (m, 1H), 3.40 - 3.33 (m, 1H), 3.04 (t, J = 10.5 Hz, 1H), 2.62 (s, 3H), 2.02 - 1.96 (m, 1H), 1.71 (s, 6H), 1.55 - 1.47 (m, 1H).
60		LCMS (ESI): m/z 474.4 $[M+H]^+$. 1H NMR (400 MHz, CDCl ₃) δ 8.74 (s, 1H), 8.28 (s, 1H), 8.22 (s, 1H), 7.75 (d, J = 10.9 Hz, 1H), 5.47 (s, 1H), 4.73 - 4.48 (m, 2H), 4.13 (s, 2H), 4.09 - 4.02 (m, 1H), 4.01 - 3.94 (m, 1H), 3.93 - 3.83 (m, 1H), 3.76 - 3.57 (m, 1H), 3.56 - 3.40 (m, 1H), 3.32 - 3.11 (m, 1H), 2.18 - 2.00 (m, 2H), 1.42 (s, 6H).
61		LCMS (ESI): m/z 456.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.78 (s, 1H), 8.47 (s, 1H), 8.20 - 8.18 (m, 1H), 7.86 (d, J_{HF} = 10.4 Hz, 1H), 7.65 - 7.51 (m, 1H), 4.59 - 4.51 (m, 1H), 4.09 - 4.01 (m, 1H), 3.91 - 3.71 (m, 4H), 3.42 - 3.24 (m, 4H), 3.09 - 2.97 (m, 2H), 2.13 - 2.02 (m, 2H), 1.99 - 1.88 (m, 2H), 1.70 - 1.57 (m, 1H), 1.55 - 1.42 (m, 1H).
62		LCMS (ESI): m/z 505.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.47 (s, 2H), 7.91 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 5.06 (s, 1H), 4.94 (d, J = 5.3 Hz, 1H), 3.86 - 3.79 (m, 3H), 3.53 - 3.48 (m, 1H), 3.39 - 3.36 (m, 1H), 3.10-3.02 (m, 3H), 2.22 - 1.89 (m, 9H), 1.67 (s, 3H), 1.56 - 1.48 (m, 1H).
66		LC-MS (ESI): m/z 438.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.69 (s, 1H), 8.27 (s, 1H), 7.96 (s, 1H), 7.75 (d, J = 10.4 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 4.97 (d, J = 5.2 Hz, 1H), 4.30 (s, 2H), 3.83 - 3.78 (m, 3H), 3.52 - 3.37 (m, 3H), 3.05 (t, J = 10.4 Hz, 1H), 2.74 (s, 2H), 2.23 (s, 3H), 2.01 - 1.98 (m, 1H), 1.53 - 1.43 (m, 1H), 1.13 (s, 6H).

67a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 491.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.05 (s, 1H), 8.48 (s, 1H), 8.15 (s, 1H), 7.89 (s, 1H), 7.58 (s, 1H), 5.80 (d, <i>J</i> = 7.6 Hz, 1H), 4.93 (d, <i>J</i> = 5.2 Hz, 1H), 4.43 (d, <i>J</i> = 7.6 Hz, 1H), 4.16 (d, <i>J</i> = 18.4 Hz, 1H), 3.95 - 3.80 (m, 4H), 3.51 - 3.42 (m, 1H), 3.37 - 3.33 (m, 1H), 3.05 (t, <i>J</i> = 10.4 Hz, 1H), 1.97 - 1.96 (m, 1H), 1.55 - 1.48 (m, 1H), 1.20 (s, 3H), 0.81 (s, 3H). de: 100%; Retention time: 1.426 min; instrument: Shimadzu E-UC 01; column: CHIRALPAK IH 5um 4.6 * 100 mm; mobile phase: A: CO₂, B: MeOH (0.05% DEA v/v); gradient: B 40%; flow rate: 2.00 mL/min; high pressure: 100 bar; column temperature: 40 °C; wavelength: 254 nm.
67b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 491.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.05 (s, 1H), 8.48 (s, 1H), 8.16 (s, 1H), 7.89 (d, <i>J</i> = 8.4 Hz, 1H), 7.59 (s, 1H), 5.80 (d, <i>J</i> = 7.6 Hz, 1H), 4.93 (d, <i>J</i> = 5.6 Hz, 1H), 4.43 (d, <i>J</i> = 7.2 Hz, 1H), 4.18 (d, <i>J</i> = 18.4 Hz, 1H), 3.93 - 3.80 (m, 4H), 3.51 - 3.50 (m, 1H), 3.37 - 3.33 (m, 1H), 3.05 (t, <i>J</i> = 10.4 Hz, 1H), 1.99 - 1.93 (m, 1H), 1.55 - 1.50 (m, 1H), 1.20 (s, 3H), 0.81 (s, 3H). de: 99.2%; Retention time: 4.686 min; instrument: Shimadzu E-UC 01; column: CHIRALPAK IH 5um 4.6 * 100 mm; mobile phase: A: CO₂, B: MeOH (0.05% DEA v/v); gradient: B 40%; flow rate: 2.00 mL/min; high pressure: 100 bar; column temperature: 40 °C; wavelength: 254 nm.
71a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 431.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.99 (s, 1H), 8.47 (s, 1H), 8.16 (s, 1H), 7.89 (d, <i>J</i> = 11.6 Hz, 1H), 7.61 (s, 1H), 5.64 (d, <i>J</i> = 6.1 Hz, 1H), 5.40 (q, <i>J</i> = 6.2 Hz, 1H), 4.94 (d, <i>J</i> = 5.4 Hz, 1H), 3.88 - 3.73 (m, 4H), 3.53 - 3.45 (m, 1H), 3.43 - 3.37 (m, 1H), 3.19 - 3.07 (m, 1H), 3.03 (t, <i>J</i> = 10.4 Hz, 1H), 2.62 - 2.53 (m, 1H), 2.03 - 1.88 (m, 2H), 1.56 - 1.42 (m, 1H). de: 100%; Retention time: 0.974 min; Instrument: SHIMADZU-20AD-XR; Column: Cellulose SB, 4.6 * 50 mm, 3.0 um; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 50%; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm.

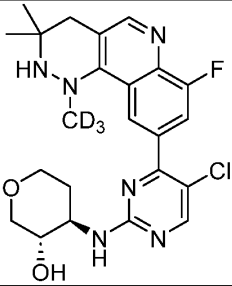
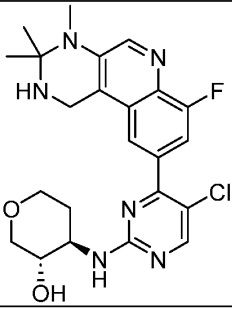
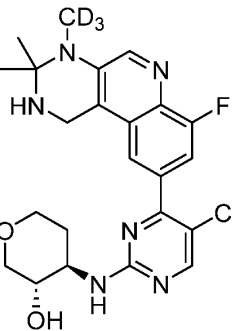
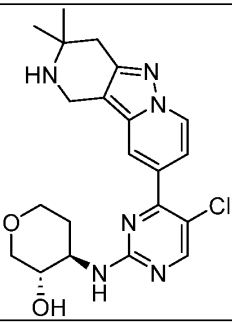
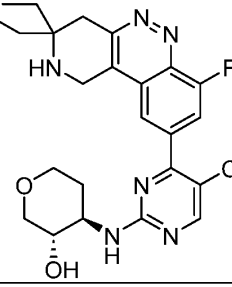
71b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 431.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.99 (s, 1H), 8.47 (s, 1H), 8.17 (s, 1H), 7.89 (d, <i>J</i> = 11.6 Hz, 1H), 7.61 (s, 1H), 5.64 (d, <i>J</i> = 6.1 Hz, 1H), 5.40 (q, <i>J</i> = 6.1 Hz, 1H), 4.94 (d, <i>J</i> = 5.4 Hz, 1H), 3.89 – 3.75 (m, 4H), 3.54 – 3.45 (m, 1H), 3.45 – 3.35 (m, 1H), 3.20 – 3.08 (m, 1H), 3.04 (t, <i>J</i> = 10.4 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.05 – 1.89 (m, 2H), 1.57 – 1.43 (m, 1H). de: 100%; Retention time: 1.221 min; instrument: SHIMADZU-20AD-XR; Column: Cellulose SB, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 50%; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm.
72a	 Isomer 1 (earlier eluting isomer)	LCMS (ESI): m/z 487.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.15 (s, 1H), 8.78 – 8.59 (m, 1H), 8.47 (s, 1H), 7.98 – 7.78 (m, 1H), 7.57 (d, <i>J</i> = 8.1 Hz, 1H), 5.37 (s, 1H), 4.95 (d, <i>J</i> = 5.4 Hz, 1H), 3.91 – 3.78 (m, 3H), 3.56 – 3.47 (m, 1H), 3.31 – 3.26 (m, 1H), 3.06 – 2.98 (m, 1H), 2.04 – 1.94 (m, 2H), 1.89 – 1.79 (m, 3H), 1.61 (d, <i>J</i> = 7.4 Hz, 6H), 1.57 (s, 3H), 1.54 – 1.46 (m, 1H). de: 100%; Retention time: 1.363 min; instrument: UPCC (Waters); Column: EnantioPak® Y3 4.6 * 150 mm, 5 μm; Mobile phase: MeOH [0.2% NH₃ (7 M in MeOH)]; Flow rate: 3 mL/min; Column temperature: 40 °C; Wavelength: 214 nm.
72b	 Isomer 2 (later eluting isomer)	LCMS (ESI): m/z 487.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.15 (s, 1H), 8.80 – 8.59 (m, 1H), 8.47 (s, 1H), 8.00 – 7.78 (m, 1H), 7.56 (d, <i>J</i> = 8.1 Hz, 1H), 5.37 (s, 1H), 4.95 (d, <i>J</i> = 5.4 Hz, 1H), 3.90 – 3.77 (m, 3H), 3.56 – 3.46 (m, 1H), 3.31 – 3.24 (m, 1H), 3.07 – 2.97 (m, 1H), 2.04 – 1.95 (m, 2H), 1.90 – 1.79 (m, 3H), 1.62 (d, <i>J</i> = 5.1 Hz, 6H), 1.57 (s, 3H), 1.54 – 1.46 (m, 1H). de: 98.76%; Retention time: 2.236 min; instrument: UPCC (Waters); Column: EnantioPak® Y3 4.6 * 150 mm, 5 μm; Mobile phase: MeOH [0.2% NH₃ (7 M in MeOH)]; Flow rate: 3 mL/min; Column temperature: 40 °C; Wavelength: 214 nm.
77		LC-MS (ESI): m/z 459.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.16 (s, 1H), 8.47 (s, 1H), 8.30 (s, 1H), 7.87 (d, <i>J</i> = 10.5 Hz, 1H), 7.59 (s, 1H), 5.36 (s, 1H), 4.94 (d, <i>J</i> = 5.4 Hz, 1H), 3.87 – 3.77 (m, 3H), 3.54 – 3.46 (m, 1H), 3.22 – 3.00 (m, 4H), 2.08 – 2.01 (m, 1H), 1.97 – 1.85 (m, 4H), 1.55 (s, 3H), 1.53 – 1.43 (m, 1H).

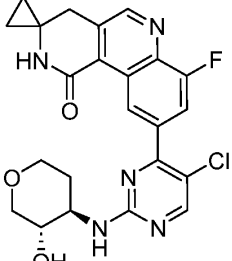
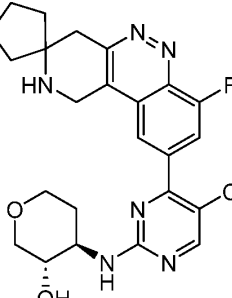
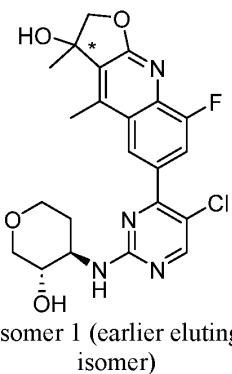
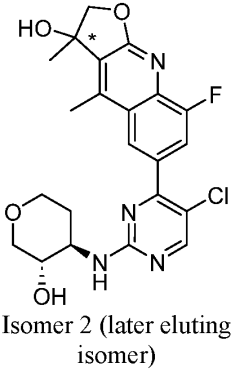
79		LC-MS (ESI): m/z 447.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.91 (s, 1H), 8.47 (s, 1H), 8.28 (s, 1H), 7.95 (dd, <i>J</i> = 12.1, 1.3 Hz, 1H), 7.61 (s, 1H), 5.94 (s, 1H), 4.95 (d, <i>J</i> = 5.4 Hz, 1H), 4.70 (q, <i>J</i> = 10.0 Hz, 2H), 3.89 - 3.76 (m, 3H), 3.53 - 3.45 (m, 1H), 3.30 (d, <i>J</i> = 7.0 Hz, 1H), 3.05 (t, <i>J</i> = 10.4 Hz, 1H), 2.02 - 1.87 (m, 1H), 1.72 (s, 3H), 1.56 - 1.48 (m, 1H).
87a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 473.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.76 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 7.88 (d, <i>J</i> = 10.9 Hz, 1H), 7.62 (s, 1H), 5.02 (d, <i>J</i> = 4.5 Hz, 1H), 4.97 (d, <i>J</i> = 5.4 Hz, 1H), 3.92 - 3.79 (m, 3H), 3.76 (dd, <i>J</i> = 10.0, 5.2 Hz, 1H), 3.58 - 3.46 (m, 1H), 3.41 - 3.36 (m, 2H), 3.11 - 2.99 (m, 2H), 2.89 (d, <i>J</i> = 16.9 Hz, 1H), 2.73 - 2.65 (m, 1H), 2.08 - 1.93 (m, 1H), 1.59 - 1.43 (m, 1H), 0.98 (s, 6H). de: 100%; Retention time: 1.258 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IF-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 10%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
87b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 473.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.75 (s, 1H), 8.50 (s, 1H), 8.29 (s, 1H), 7.88 (d, <i>J</i> = 11.5 Hz, 1H), 7.61 (s, 1H), 5.02 (d, <i>J</i> = 4.5 Hz, 1H), 4.96 (d, <i>J</i> = 5.4 Hz, 1H), 3.94 - 3.79 (m, 3H), 3.79 - 3.70 (m, 1H), 3.63 - 3.48 (m, 1H), 3.41 - 3.36 (m, 2H), 3.15 - 2.98 (m, 2H), 2.89 (d, <i>J</i> = 16.9 Hz, 1H), 2.68 (d, <i>J</i> = 16.9 Hz, 1H), 2.07 - 1.93 (m, 1H), 1.64 - 1.42 (m, 1H), 0.98 (s, 6H). de: 100%; Retention time: 1.721 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IF-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 10%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
91a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 501.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.81 (s, 1H), 8.47 (s, 1H), 7.88 (s, 1H), 7.54 (d, <i>J</i> = 8.1 Hz, 1H), 5.69 (s, 1H), 4.97 (d, <i>J</i> = 5.2 Hz, 1H), 3.94 - 3.78 (m, 3H), 3.58 - 3.46 (m, 1H), 3.32 - 3.27 (m, 1H), 3.18 - 2.96 (m, 3H), 2.21 - 2.10 (m, 1H), 2.05 - 1.95 (m, 2H), 1.82 (s, 9H), 1.77 (s, 3H), 1.64 - 1.48 (m, 1H). de: 100%; Retention time: 2.092 min; instrument: UPCC (Waters); column: EnantioPak® Y1 4.6 * 150 mm, 5 μm; mobile phase: EtOH [1% NH₃ (7 M in MeOH)]; flow rate: 3 mL/min; column temperature: 40 °C; wavelength: 214 nm.

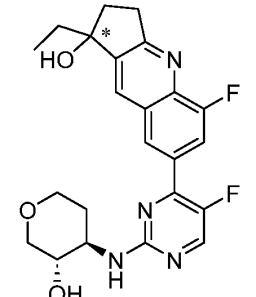
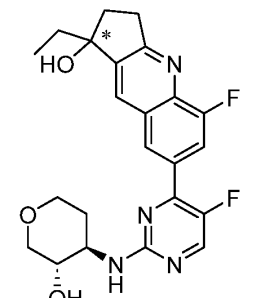
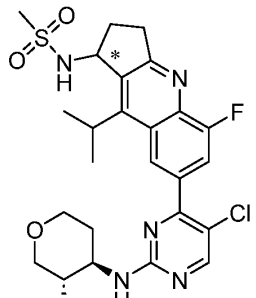
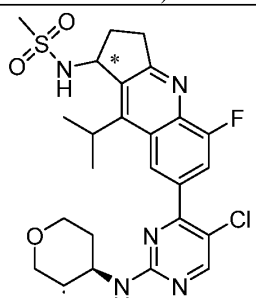
91b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 501.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.81 (s, 1H), 8.47 (s, 1H), 7.88 (s, 1H), 7.54 (d, <i>J</i> = 8.1 Hz, 1H), 5.69 (s, 1H), 4.97 (d, <i>J</i> = 5.2 Hz, 1H), 3.93 - 3.76 (m, 3H), 3.56 - 3.46 (m, 1H), 3.32 - 3.28 (m, 1H), 3.18 - 2.96 (m, 3H), 2.23 - 2.11 (m, 1H), 2.05 - 1.95 (m, 2H), 1.82 (s, 9H), 1.77 (s, 3H), 1.63 - 1.46 (m, 1H). de: 98.82%. Retention time: 2.446 min; instrument: UPCC (Waters); column: EnantioPak® Y1 4.6 * 150 mm, 5μm; mobile phase: EtOH [1% NH₃ (7 M in MeOH)]; flow rate: 3 mL/min; column temperature: 40 °C; wavelength: 214 nm.
92		LC-MS (ESI): m/z 470.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.74 (s, 1H), 8.51 (d, <i>J</i> = 3.8 Hz, 1H), 8.36 (s, 1H), 8.18 - 8.13 (m, 1H), 8.05 (d, <i>J</i> = 11.9 Hz, 1H), 7.32 (d, <i>J</i> = 7.8 Hz, 1H), 4.30 (s, 2H), 3.87 - 3.78 (m, 3H), 3.38 - 3.33 (m, 2H), 3.08 (t, <i>J</i> = 10.4 Hz, 1H), 2.76 (s, 2H), 2.07 - 1.91 (m, 1H), 1.60 - 1.26 (m, 5H), 0.87 (t, <i>J</i> = 7.5 Hz, 6H).
93a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 473.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.46 (s, 1H), 8.42 - 8.24 (m, 1H), 7.96 - 7.71 (m, 1H), 7.67 - 7.45 (m, 1H), 4.96 (d, <i>J</i> = 5.4 Hz, 1H), 4.92 (t, <i>J</i> = 5.5 Hz, 1H), 3.92 - 3.76 (m, 3H), 3.71 (dd, <i>J</i> = 10.8, 5.4 Hz, 1H), 3.58 (dd, <i>J</i> = 10.9, 5.6 Hz, 1H), 3.54 - 3.47 (m, 1H), 3.34 - 3.30 (m, 1H), 3.14 - 2.97 (m, 3H), 2.71 (s, 3H), 2.36 - 2.25 (m, 1H), 2.06 - 1.87 (m, 1H), 1.86 - 1.74 (m, 1H), 1.59 - 1.44 (m, 1H), 1.40 (s, 3H). de: 100%; Retention time: 1.197 min; instrument: SHIMADZU-20AD-XR; Column: Cellulose SZ, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 50% Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm.
93b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 473.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.46 (s, 1H), 8.43 - 8.24 (m, 1H), 7.91 - 7.73 (m, 1H), 7.70 - 7.45 (m, 1H), 5.20 - 4.66 (m, 2H), 3.88 - 3.77 (m, 3H), 3.71 (d, <i>J</i> = 10.8 Hz, 1H), 3.58 (d, <i>J</i> = 10.9 Hz, 1H), 3.54 - 3.47 (m, 1H), 3.32 - 3.28 (m, 1H), 3.14 - 2.97 (m, 3H), 2.71 (s, 3H), 2.35 - 2.25 (m, 1H), 2.05 - 1.88 (m, 1H), 1.87 - 1.74 (m, 1H), 1.60 - 1.44 (m, 1H), 1.40 (s, 3H). de: 100%; Retention time: 3.118 min; instrument: SHIMADZU-20AD-XR; Column: Cellulose SZ, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 50% Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm.

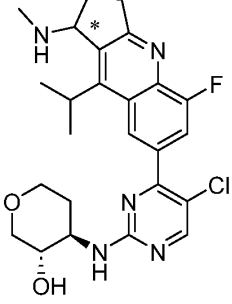
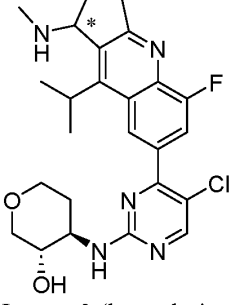
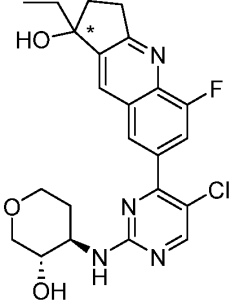
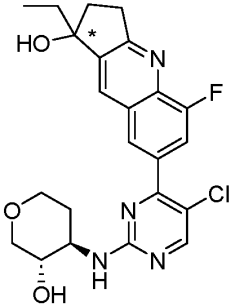
94	 Single enantiomer at *, but absolute configuration unassigned	LC-MS (ESI): m/z 473.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.73 (s, 1H), 8.47 (s, 1H), 8.39 - 8.21 (m, 1H), 7.95 - 7.73 (m, 1H), 7.69 - 7.45 (m, 1H), 5.08 - 4.81 (m, 1H), 4.66 (d, <i>J</i> = 6.4 Hz, 1H), 3.90 - 3.75 (m, 3H), 3.57 - 3.50 (m, 2H), 3.28 - 3.25 (m, 2H), 3.04 (t, <i>J</i> = 10.5 Hz, 1H), 2.64 - 2.53 (m, 1H), 2.39 - 2.24 (m, 1H), 2.22 - 2.10 (m, 1H), 2.09 - 1.84 (m, 1H), 1.73 (t, <i>J</i> = 10.5 Hz, 1H), 1.61 - 1.43 (m, 2H).
95		LC-MS (ESI): m/z 447.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.79 (s, 1H), 8.46 (s, 1H), 8.25 - 8.02 (m, 1H), 7.92 - 7.79 (m, 1H), 7.61 - 7.49 (m, 1H), 5.06 - 4.96 (m, 1H), 3.96 (s, 1H), 3.84 - 3.78 (m, 3H), 3.37 - 3.28 (m, 2H), 3.09 - 2.93 (m, 4H), 2.73 (t, <i>J</i> = 6.1 Hz, 2H), 2.02 - 1.87 (m, 1H), 1.58 - 1.44 (m, 1H).
96		LC-MS (ESI): m/z 486.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.92 (s, 1H), 8.51 (s, 1H), 8.12 (s, 1H), 7.95 (d, <i>J</i> = 10.0 Hz, 1H), 7.61 (s, 1H), 5.41 - 5.00 (m, 1H), 4.89 - 4.56 (m, 1H), 4.25 (d, <i>J</i> = 10.1 Hz, 1H), 4.12 (d, <i>J</i> = 11.8 Hz, 1H), 3.94 - 3.77 (m, 5H), 3.72 - 3.56 (m, 3H), 3.38 - 3.25 (m, 4H), 3.05 (t, <i>J</i> = 10.6 Hz, 2H), 2.05 - 1.87 (m, 1H), 1.57 - 1.41 (m, 1H).
97		LC-MS (ESI): m/z 458.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.01 (s, 1H), 8.49 (s, 1H), 8.20 (s, 1H), 7.87 (d, <i>J</i> = 11.7 Hz, 1H), 7.77 - 7.48 (m, 1H), 5.69 (s, 1H), 4.39 (s, 1H), 4.27 (q, <i>J</i> = 18.8 Hz, 2H), 4.00 - 3.91 (m, 1H), 3.90 - 3.81 (m, 2H), 3.35 - 3.30 (m, 2H), 1.93 - 1.71 (m, 2H), 1.61 - 1.43 (m, 2H), 1.12 (s, 3H), 0.99 (s, 3H).
98		LC-MS (ESI): m/z 476.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.01 (s, 1H), 8.52 (s, 1H), 8.19 (s, 1H), 7.99 - 7.81 (m, 2H), 5.66 (d, <i>J</i> = 5.5 Hz, 1H), 4.65 - 4.44 (m, 1H), 4.42 - 4.36 (m, 1H), 4.34 - 4.20 (m, 3H), 4.07 - 3.92 (m, 1H), 3.88 - 3.76 (m, 1H), 3.50 - 3.44 (m, 2H), 2.17 - 1.89 (m, 1H), 1.70 - 1.53 (m, 1H), 1.11 (s, 3H), 0.98 (s, 3H).

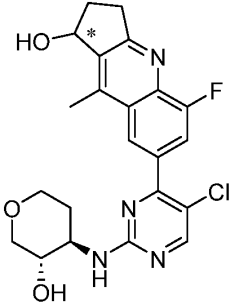
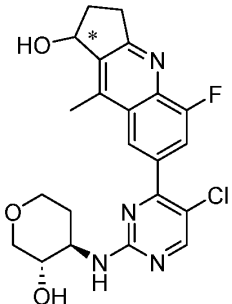
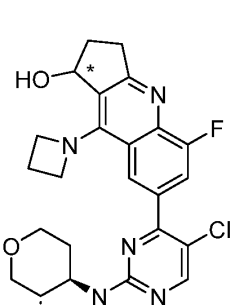
99		LC-MS (ESI): m/z 504.2 [M+H] ⁺ ; ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.94 (s, 1H), 8.52 (s, 1H), 8.23 - 8.15 (m, 1H), 8.02 - 7.80 (m, 2H), 5.37 (s, 1H), 4.69 - 4.45 (m, 1H), 4.42 (s, 1H), 4.33 - 4.19 (m, 2H), 4.11 (d, <i>J</i> = 18.9 Hz, 1H), 4.06 - 3.95 (m, 1H), 3.87 - 3.79 (m, 1H), 3.51 - 3.44 (m, 2H), 2.12 - 1.93 (m, 1H), 1.68 - 1.56 (m, 1H), 1.54 - 1.43 (m, 1H), 1.41 - 1.17 (m, 3H), 0.97 - 0.77 (m, 6H).
100		LC-MS (ESI): m/z 487.2 [M+H] ⁺ ; ¹H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.70 - 8.48 (m, 1H), 8.46 (s, 1H), 7.99 - 7.70 (m, 1H), 7.53 (s, 1H), 4.94 (s, 2H), 3.93 - 3.75 (m, 3H), 3.70 - 3.55 (m, 3H), 3.54 - 3.47 (m, 1H), 3.46 - 3.43 (m, 1H), 3.28 - 3.21 (m, 2H), 3.07 - 2.94 (m, 2H), 2.31 - 2.22 (m, 1H), 2.20 - 2.10 (m, 1H), 2.03 - 1.89 (m, 1H), 1.57 (d, <i>J</i> = 7.2 Hz, 3H), 1.54 - 1.44 (m, 4H).
101		LC-MS (ESI): m/z 459.2 [M+H] ⁺ ; ¹H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.36 (s, 1H), 8.32 (s, 1H), 7.98 (s, 1H), 7.55 (d, <i>J</i> = 12.8 Hz, 1H), 4.29 (s, 2H), 4.04 - 3.87 (m, 3H), 3.68 - 3.44 (m, 2H), 3.21 (t, <i>J</i> = 10.4 Hz, 1H), 2.15 - 2.10 (m, 1H), 1.68 - 1.58 (m, 1H), 1.42 (s, 6H).
102		LC-MS (ESI): m/z 487.1 [M+H] ⁺ ; ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.48 (s, 1H), 8.96 (s, 1H), 8.48 (s, 1H), 8.45 (s, 1H), 7.75 - 7.35 (m, 2H), 4.94 (d, <i>J</i> = 4.4 Hz, 1H), 3.88 - 3.76 (m, 3H), 3.60 - 3.39 (m, 1H), 3.36 - 3.30 (m, 1H), 3.13 (s, 3H), 3.05 - 2.97 (m, 1H), 1.96 - 1.95 (m, 1H), 1.55 - 1.43 (m, 7H).
103		LC-MS (ESI): m/z 488.1 [M+H] ⁺ ; ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.46 (s, 1H), 8.41 (s, 1H), 8.13 (s, 1H), 7.53 (s, 2H), 5.55 (s, 1H), 4.94 (s, 1H), 3.85 - 3.76 (m, 3H), 3.51 - 3.40 (m, 4H), 3.38 - 3.30 (m, 1H), 3.04 - 2.97 (m, 1H), 2.93 (s, 3H), 2.10 - 1.88 (m, 1H), 1.55 - 1.42 (m, 1H), 1.31 (s, 6H).

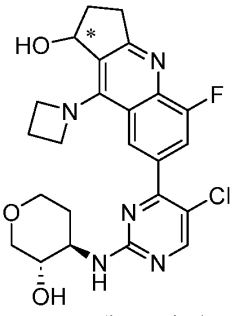
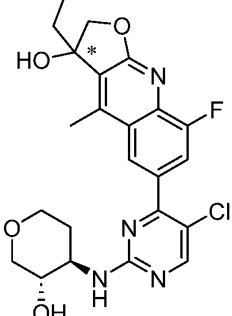
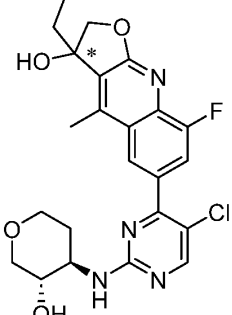
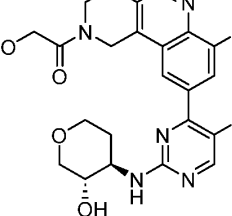
104		LC-MS (ESI): m/z 476.1 [M+H] ⁺ ; ¹H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.40 (s, 1H), 8.34 (s, 1H), 8.30 (s, 1H), 7.85 (d, <i>J</i> = 12.0 Hz, 1H), 4.03 - 3.86 (m, 3H), 3.65 - 3.57 (m, 1H), 3.51 - 3.43 (m, 1H), 3.27 - 3.16 (m, 1H), 2.75 (s, 2H), 2.15 - 2.08 (m, 1H), 1.68 - 1.58 (m, 1H), 1.20 (s, 6H).
105		LC-MS (ESI): m/z 473.0 [M+H] ⁺ ; ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.69 (s, 1H), 8.45 (s, 1H), 7.91 (s, 1H), 7.56 (s, 1H), 7.47 (s, 1H), 4.96 (s, 1H), 4.16 (s, 2H), 4.08 (s, 1H), 3.90 - 3.78 (m, 3H), 3.52 - 3.47 (m, 2H), 3.05 - 2.95 (m, 4H), 1.99 - 1.90 (m, 1H), 1.55 - 1.47 (m, 1H), 1.35 (s, 6H).
106		LC-MS (ESI): m/z 476.1 [M+H] ⁺ ; ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.69 (s, 1H), 8.45 (s, 1H), 7.93 (s, 1H), 7.70 - 7.31 (m, 2H), 4.93 (d, <i>J</i> = 5.2 Hz, 1H), 4.16 (s, 2H), 3.85 - 3.78 (m, 3H), 3.58 - 3.47 (m, 1H), 3.33 - 3.30 (m, 1H), 3.07 - 3.02 (m, 1H), 3.00 - 2.91 (m, 1H), 2.01 - 1.89 (m, 1H), 1.52 - 1.45 (m, 1H), 1.35 (s, 6H).
107		LC-MS (ESI): m/z 429.2 [M+H] ⁺ ; ¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.68 (d, <i>J</i> = 7.3 Hz, 1H), 8.43 (s, 1H), 8.26 (s, 1H), 7.51 (d, <i>J</i> = 6.9 Hz, 1H), 7.16 (d, <i>J</i> = 7.2, 1.9 Hz, 1H), 4.10 (s, 2H), 3.84 - 3.80 (m, 3H), 3.49 (td, <i>J</i> = 9.4, 4.8 Hz, 3H), 3.35 - 3.30 (m, 1H), 3.04 (t, <i>J</i> = 10.4 Hz, 1H), 2.76 (s, 2H), 1.94 (d, <i>J</i> = 13.2 Hz, 1H), 1.49 (qd, <i>J</i> = 11.9, 4.5 Hz, 1H), 1.23 (s, 6H).
108		LC-MS (ESI): m/z 487.2 [M+H] ⁺ ; ¹H NMR (400 MHz, CD ₃ CN- <i>d</i> ₃) δ 8.44 (s, 1H), 8.24 (s, 1H), 7.90 (br d, <i>J</i> = 11.6 Hz, 1H), 6.09 (br d, <i>J</i> = 7.6 Hz, 1H), 4.40 (s, 2H), 4.00 - 3.85 (m, 3H), 3.59 (br s, 1H), 3.45 (d, <i>J</i> = 2.2 Hz, 1H), 3.22 (s, 2H), 3.19 - 3.10 (m, 1H), 2.11 - 2.05 (m, 1H), 1.69 - 1.45 (m, 5H), 0.96 (t, <i>J</i> = 7.4 Hz, 6H).

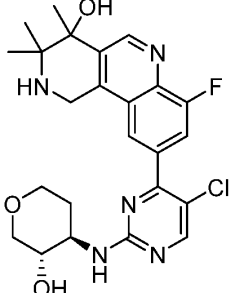
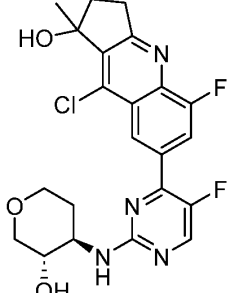
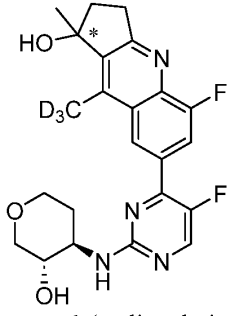
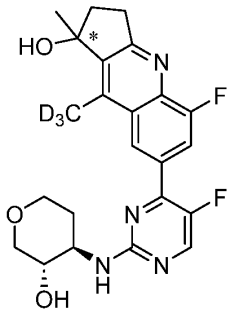
109		LC-MS (ESI): m/z 470.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.73 - 9.48 (m, 1H), 9.04 (s, 1H), 8.72 (s, 1H), 8.48 (s, 1H), 7.92 (br d, <i>J</i> = 11.0 Hz, 1H), 7.67 - 7.47 (m, 1H), 4.94 (br d, <i>J</i> = 4.6 Hz, 1H), 3.91 - 3.75 (m, 3H), 3.55 - 3.44 (m, 1H), 3.38 - 3.33 (m, 1H), 3.16 (s, 2H), 3.04 (t, <i>J</i> = 10.4 Hz, 1H), 2.05 - 1.88 (m, 1H), 1.56 - 1.43 (m, 1H), 0.88 - 0.72 (m, 4H).
110		LC-MS (ESI): m/z 485.1 [M+H]⁺; ¹H NMR (400 MHz, CD₃CN-<i>d</i>₃) δ 8.39 (s, 1H), 8.19 (s, 1H), 7.86 (br d, <i>J</i> = 11.5 Hz, 1H), 6.10 (br d, <i>J</i> = 7.6 Hz, 1H), 4.42 (s, 2H), 3.98 - 3.81 (m, 3H), 3.55 (dt, <i>J</i> = 4.9, 9.5 Hz, 1H), 3.47 - 3.36 (m, 1H), 3.34 - 3.24 (m, 2H), 3.13 (t, <i>J</i> = 10.4 Hz, 1H), 2.05 (td, <i>J</i> = 2.2, 13.3 Hz, 1H), 1.84 - 1.66 (m, 6H), 1.65 - 1.54 (m, 3H).
111a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 461.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.45 (s, 1H), 8.39 - 8.14 (m, 1H), 7.97 - 7.72 (m, 1H), 7.64 - 7.39 (m, 1H), 6.05 (s, 1H), 4.97 (s, 1H), 4.48 (d, <i>J</i> = 9.4 Hz, 1H), 4.40 (d, <i>J</i> = 9.4 Hz, 1H), 3.89 - 3.75 (m, 3H), 3.54 - 3.46 (m, 1H), 3.32 - 3.29 (m, 1H), 3.05 (t, <i>J</i> = 10.4 Hz, 1H), 2.77 (s, 3H), 2.06 - 1.85 (m, 1H), 1.65 (s, 3H), 1.57 - 1.40 (m, 1H). de: 100%; Retention time: 1.442 min; instrument: Agilent-1260; Column: Lux 3u Cellulose-2, 4.6 * 50 mm, 3.0 um; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 50%; Flow rate: 1.0 mL/min High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 220 nm.
111b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 461.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.45 (s, 1H), 8.41 - 8.20 (m, 1H), 7.97 - 7.74 (m, 1H), 7.65 - 7.41 (m, 1H), 6.06 (s, 1H), 4.96 (s, 1H), 4.48 (d, <i>J</i> = 9.3 Hz, 1H), 4.40 (d, <i>J</i> = 9.4 Hz, 1H), 3.89 - 3.75 (m, 3H), 3.54 - 3.47 (m, 1H), 3.32 - 3.27 (m, 1H), 3.05 (t, <i>J</i> = 10.3 Hz, 1H), 2.77 (s, 3H), 2.08 - 1.80 (m, 1H), 1.65 (s, 3H), 1.57 - 1.40 (m, 1H). de: 98%; Retention time: 1.853 min; instrument: Agilent-1260; Column: Lux 3u Cellulose-2, 4.6 * 50 mm, 3.0 um; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 50%; Flow rate: 1.0 mL/min High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 220 nm.

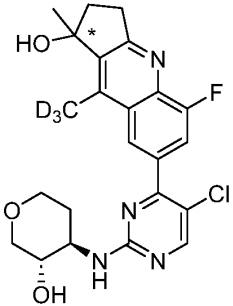
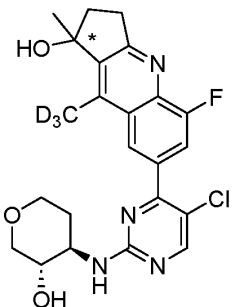
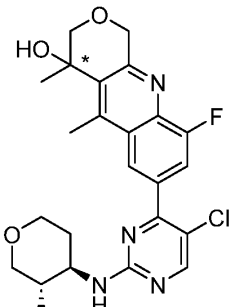
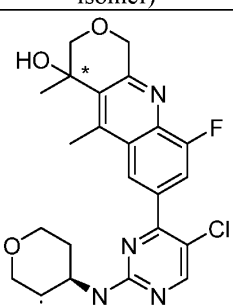
112a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 443.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.55 - 8.44 (m, 2H), 8.37 (s, 1H), 8.07 (d, <i>J</i> = 12.0 Hz, 1H), 7.27 (d, <i>J</i> = 7.9 Hz, 1H), 5.33 (s, 1H), 4.93 (s, 1H), 3.92 - 3.77 (m, 3H), 3.58 - 3.46 (m, 1H), 3.45 - 3.35 (m, 1H), 3.25 - 3.00 (m, 3H), 2.35 - 2.23 (m, 1H), 2.19 - 2.08 (m, 1H), 2.05 - 1.96 (m, 1H), 1.94 - 1.75 (m, 2H), 1.59 - 1.42 (m, 1H), 0.93 (t, <i>J</i> = 7.4 Hz, 3H). de: 99.9%; Retention time: 0.724 min; instrument: EnantioPak® Y4, 4.6 * 150 mm, 5.0 μm; mobile phase: CO₂/MeOH [0.2% NH₃ (7 M in MeOH)] = 50/50; flow rate: 3 mL/min; column temperature: 40 °C; wavelength: 214 nm.
112b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 550.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.55 - 8.44 (m, 2H), 8.37 (s, 1H), 8.08 (d, <i>J</i> = 12.0 Hz, 1H), 7.28 (d, <i>J</i> = 7.9 Hz, 1H), 5.34 (s, 1H), 4.93 (s, 1H), 3.94 - 3.75 (m, 3H), 3.56 - 3.46 (m, 1H), 3.45 - 3.35 (m, 1H), 3.24 - 3.00 (m, 3H), 2.35 - 2.23 (m, 1H), 2.19 - 2.08 (m, 1H), 2.05 - 1.95 (m, 1H), 1.94 - 1.73 (m, 2H), 1.57 - 1.42 (m, 1H), 0.93 (t, <i>J</i> = 7.4 Hz, 3H). de: 99.7%; Retention time: 1.691 min; instrument: EnantioPak® Y4, 4.6 * 150 mm, 5.0 μm; mobile phase: CO₂/MeOH [0.2% NH₃ (7 M in MeOH)] = 50/50; flow rate: 3 mL/min; column temperature: 40 °C; wavelength: 214 nm.
113a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 550.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.75 - 8.40 (m, 2H), 8.07 - 7.80 (m, 1H), 7.70 (d, <i>J</i> = 9.2 Hz, 1H), 7.62 - 7.50 (m, 1H), 5.31 - 5.21 (m, 1H), 5.03 - 4.90 (m, 1H), 3.98 - 3.76 (m, 5H), 3.58 - 3.44 (m, 1H), 3.08 (s, 3H), 3.06 - 2.96 (m, 3H), 2.26 - 2.16 (m, 1H), 2.06 - 1.86 (m, 1H), 1.62 - 1.46 (m, 8H). de: 100%; Retention time: 1.846 min; instrument: EnantioPak® Y4, 4.6 * 150 mm, 5.0 μm; mobile phase: EtOH [1% NH₃ (7 M in MeOH)]; flow rate: 3 mL/min; column temperature: 40 °C; wavelength: 214 nm.
113b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 550.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.75 - 8.38 (m, 2H), 8.07 - 7.80 (m, 1H), 7.70 (d, <i>J</i> = 9.2 Hz, 1H), 7.63 - 7.50 (m, 1H), 5.31 - 5.21 (m, 1H), 4.95 (d, <i>J</i> = 5.4 Hz, 1H), 3.98 - 3.74 (m, 5H), 3.58 - 3.44 (m, 1H), 3.08 (s, 3H), 3.07 - 2.95 (m, 3H), 2.28 - 2.16 (m, 1H), 2.05 - 1.87 (m, 1H), 1.64 - 1.48 (m, 8H). de: 100%; Retention time: 2.581 min; instrument: EnantioPak® Y4, 4.6 * 150 mm, 5.0 μm; mobile phase: EtOH [1% NH₃ (7 M in MeOH)]; flow rate: 3 mL/min; column temperature: 40 °C; wavelength: 214 nm.

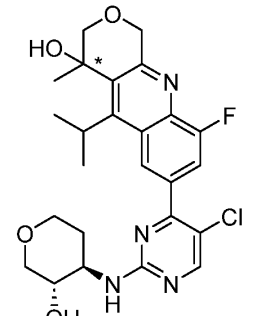
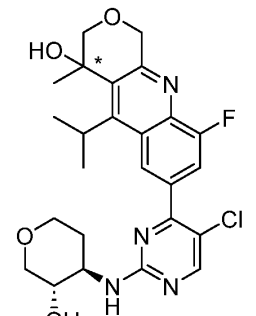
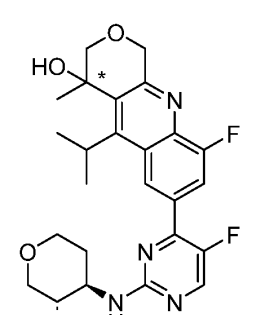
114a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 486.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.70 - 8.40 (m, 2H), 8.02 - 7.75 (m, 1H), 7.66 - 7.5 (s, 1H), 4.98 (d, <i>J</i> = 5.4 Hz, 1H), 4.45 (d, <i>J</i> = 6.2 Hz, 1H), 3.95 - 3.79 (m, 4H), 3.60 - 3.45 (m, 1H), 3.35 - 3.2 (m, 1H), 3.10 - 2.94 (m, 2H), 2.38 (s, 3H), 2.27 - 2.1 (m, 2H), 2.07 - 1.9 (m, 1H), 1.65 - 1.45 (m, 8H). de: 100%; Retention time: 2.154 min; instrument: CHIRALPAK IH-3, 4.6 * 50 mm, 3.0 um mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
114b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 486.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.70 - 8.4 (m, 2H), 8.02 - 7.75 (m, 1H), 7.66 - 7.5 (s, 1H), 4.98 (d, <i>J</i> = 5.4 Hz, 1H), 4.45 (d, <i>J</i> = 6.2 Hz, 1H), 3.95 - 3.79 (m, 4H), 3.60 - 3.45 (m, 1H), 3.35 - 3.2 (m, 1H), 3.10 - 2.94 (m, 2H), 2.38 (s, 3H), 2.27 - 2.1 (m, 2H), 2.08 - 1.87 (m, 1H), 1.65 - 1.45 (m, 8H). de: 97.1%; Retention time: 2.606 min; instrument: CHIRALPAK IH-3, 4.6 * 50 mm, 3.0 um mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
115a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 459.2 [M+H]⁺; ¹H NMR δ 8.47 (s, 1H), 8.33 (s, 1H), 8.27 (s, 1H), 7.83 (d, <i>J</i> = 11.7 Hz, 1H), 7.56 (s, 1H), 5.34 (s, 1H), 4.93 (d, <i>J</i> = 5.4 Hz, 1H), 3.92 - 3.73 (m, 3H), 3.55 - 3.43 (m, 1H), 3.40 - 3.30 (m, 1H), 3.23 - 3.13 (m, 1H), 3.13 - 2.97 (m, 2H), 2.35 - 2.22 (m, 1H), 2.18 - 2.07 (m, 1H), 2.02 - 1.72 (m, 3H), 1.57 - 1.41 (m, 1H), 0.93 (t, <i>J</i> = 7.3 Hz, 3H). de: 100%; Retention time: 0.922 min; instrument: CHIRALPAK IH-3, 4.6 * 50 mm, 3.0 um mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
115b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 459.2 [M+H]⁺; ¹H NMR δ 8.47 (s, 1H), 8.33 (s, 1H), 8.27 (s, 1H), 7.83 (d, <i>J</i> = 11.7 Hz, 1H), 7.56 (s, 1H), 5.34 (s, 1H), 4.94 (d, <i>J</i> = 5.4 Hz, 1H), 3.92 - 3.75 (m, 3H), 3.56 - 3.43 (m, 1H), 3.40 - 3.30 (m, 1H), 3.23 - 3.13 (m, 1H), 3.13 - 2.97 (m, 2H), 2.35 - 2.22 (m, 1H), 2.18 - 2.07 (m, 1H), 2.02 - 1.72 (m, 3H), 1.57 - 1.41 (m, 1H), 0.93 (t, <i>J</i> = 7.3 Hz, 3H). de: 100%; Retention time: 1.255 min; instrument: CHIRALPAK IH-3, 4.6 * 50 mm, 3.0 um mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.

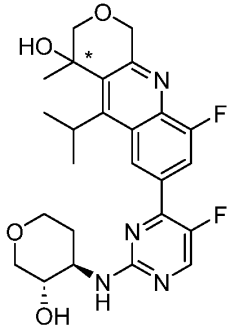
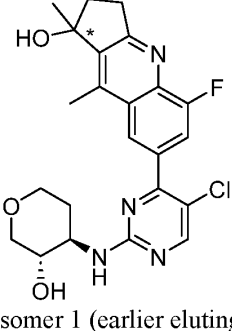
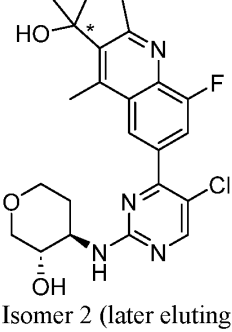
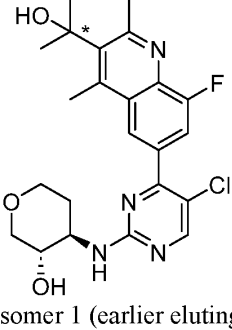
116a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 445.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.47 (s, 1H), 8.45 - 8.28 (m, 1H), 7.80 - 7.95 (m, 1H), 7.65 - 7.50 (m, 1H), 5.47 - 5.42 (m, 1H), 5.40 - 5.33 (m, 1H), 4.94 (d, <i>J</i> = 5.4 Hz, 1H), 3.92 - 3.75 (m, 3H), 3.58 - 3.44 (m, 1H), 3.33 - 3.20 (m, 1H), 3.12 - 2.88 (m, 3H), 2.74 (s, 3H), 2.48 - 2.37 (m, 1H), 2.1 - 1.86 (m, 2H), 1.60 - 1.42 (m, 1H). de: 99.9%; Retention time: 1.631 min; instrument: CHIRALPAK IH-3, 4.6 * 50 mm, 3.0 um mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
116b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 445.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.47 (s, 1H), 8.45 - 8.28 (m, 1H), 7.80 - 7.95 (m, 1H), 7.65 - 7.50 (m, 1H), 5.47 - 5.42 (m, 1H), 5.40 - 5.33 (m, 1H), 4.94 (d, <i>J</i> = 5.4 Hz, 1H), 3.92 - 3.75 (m, 3H), 3.58 - 3.44 (m, 1H), 3.33 - 3.20 (m, 1H), 3.12 - 2.88 (m, 3H), 2.74 (s, 3H), 2.48 - 2.37 (m, 1H), 2.1 - 1.86 (m, 2H), 1.60 - 1.42 (m, 1H). de: 99.9%; Retention time: 3.374 min; instrument: CHIRALPAK IH-3, 4.6 * 50 mm, 3.0 um mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
117a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 486.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.63 - 8.31 (m, 2H), 7.93 (s, 1H), 7.53 - 7.47 (m, 1H), 5.36 (t, <i>J</i> = 6.0 Hz, 1H), 5.25 (s, 1H), 5.09 - 4.88 (m, 3H), 4.75 (s, 2H), 3.97 - 3.75 (m, 3H), 3.61 - 3.45 (m, 1H), 3.42 - 3.35 (m, 1H), 3.21 - 3.12 (m, 1H), 3.04 (t, <i>J</i> = 10.4 Hz, 1H), 2.91 - 2.77 (m, 1H), 2.49 - 2.41 (m, 2H), 2.28 - 2.21 (m, 1H), 2.05 - 1.87 (m, 2H), 1.52 (d, <i>J</i> = 11.8 Hz, 1H). de: 96.89 %; Retention time: 2.33 min; instrument: SHIMADZU-20AD-XR; Column: Cellulose SZ, 4.6 * 50 mm, 3.0 um; Mobile; phase: A for MTBE (0.1% DEA) and B for EtOH; Gradient: B 30% ; Flow rate: 1.97 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm.

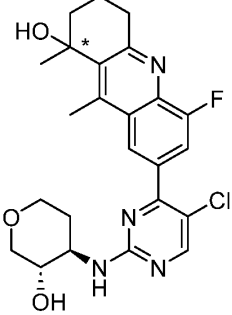
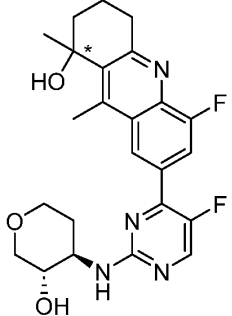
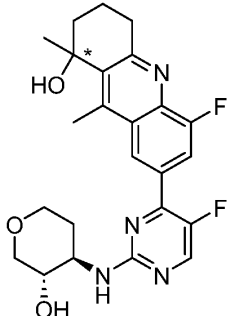
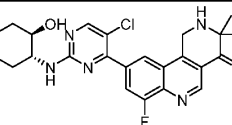
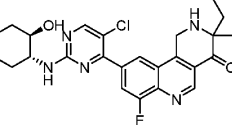
117b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 486.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.61 - 8.36 (m, 2H), 7.93 (s, 1H), 7.55 (d, <i>J</i> = 8.1 Hz, 1H), 5.59 - 5.33 (m, 2H), 5.22 - 4.86 (m, 3H), 4.85 - 4.61 (m, 2H), 3.99 - 3.73 (m, 3H), 3.60 - 3.46 (m, 1H), 3.42 - 3.35 (m, 1H), 3.21 - 3.12 (m, 1H), 3.14 - 2.88 (m, 2H), 2.49 - 2.41 (m, 2H), 2.39 - 2.20 (m, 1H), 2.07 - 1.86 (m, 2H), 1.52 (d, <i>J</i> = 13.2 Hz, 1H). de: 98.35 %; Retention time: 2.581 min; instrument: SHIMADZU-20AD-XR; Column: Cellulose SZ, 4.6 * 50 mm, 3.0 μm; Mobile; phase: A for MTBE (0.1% DEA) and B for EtOH; Gradient: B 30% ; Flow rate: 1.97 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm.
119a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 475.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.46 (s, 1H), 8.33 (s, 1H), 7.87 (s, 1H), 7.52 (s, 1H), 6.04 (s, 1H), 4.93 (s, 1H), 4.62 (s, 1H), 4.35 (d, <i>J</i> = 9.6 Hz, 1H), 3.90 - 3.79 (m, 3H), 3.52 (s, 1H), 3.42 - 3.35 (m, 1H), 3.06 (dd, <i>J</i> = 11.1, 9.7 Hz, 1H), 2.76 (s, 3H), 2.04 - 1.88 (m, 3H), 1.57 - 1.48 (m, 1H), 0.82 (t, <i>J</i> = 7.4 Hz, 3H). de: 100%; Retention time: 2.91 min; instrument: SHIMADZU-20AD-XR, Column: Cellulose SZ, 4.6 * 50 mm, 3.0 μm, Mobile phase: A for Hex (0.1% DEA) and B for EtOH, Gradient: B 20% , Flow rate: 1.67 mL/min, High pressure: 110 bar, Column temperature: 25 °C, Wavelength: 254 nm.
119b	 Isomer 2 (earlier eluting isomer)	LC-MS (ESI): m/z 475.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.46 (s, 1H), 8.32 (s, 1H), 7.87 (s, 1H), 7.52 (s, 1H), 6.04 (s, 1H), 4.93 (d, <i>J</i> = 5.4 Hz, 1H), 4.61 (d, <i>J</i> = 9.6 Hz, 1H), 4.35 (d, <i>J</i> = 9.6 Hz, 1H), 3.91 - 3.77 (m, 3H), 3.51 (s, 1H), 3.39 - 3.33 (m, 1H), 3.06 (t, <i>J</i> = 10.4 Hz, 1H), 2.76 (s, 3H), 2.04 - 1.93 (m, 3H), 1.59 - 1.46 (m, 1H), 0.82 (t, <i>J</i> = 7.4 Hz, 3H). de: 100%; Retention time: 3.66 min; instrument: SHIMADZU-20AD-XR, Column: Cellulose SZ, 4.6 * 50 mm, 3.0 μm, Mobile phase: A for Hex (0.1% DEA) and B for EtOH, Gradient: B 20% , Flow rate: 1.67 mL/min, High pressure: 110 bar, Column temperature: 25 °C, Wavelength: 254 nm.
120		LC-MS (ESI): m/z 488.1 [M+H]⁺; ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.85 (s, 1H), 8.49 (s, 1H), 8.3 - 8.1 (m, 1H), 8.05 - 7.8 (m, 1H), 7.75 - 7.43 (m, 1H), 5.2 - 5.0 (m, 2H), 4.30 - 4.25 (m, 2H), 4.0 - 3.4 (m, 7H), 3.40 - 3.30 (m, 1H), 3.11 - 2.96 (m, 4H), 2.17 - 1.85 (m, 1H), 1.58 - 1.41 (m, 1H).

123		LC-MS (ESI): m/z 488.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.22 (s, 1H), 8.50 (s, 1H), 8.16 (s, 1H), 7.89 (d, <i>J</i> = 11.9 Hz, 1H), 7.61 (s, 1H), 5.38 (s, 1H), 4.96 (s, 1H), 4.35 (s, 2H), 3.96 - 3.78 (m, 4H), 3.57 - 3.47 (m, 1H), 3.42 - 3.35 (m, 1H), 3.07 (t, <i>J</i> = 10.6 Hz, 1H), 1.97 (s, 1H), 1.57 - 1.53 (m, 4H), 1.17 (s, 3H), 1.08 (s, 3H).
124		LC-MS (ESI): m/z 463.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.79 (s, 1H), 8.54 (d, <i>J</i> = 3.7 Hz, 1H), 8.21 (d, <i>J</i> = 11.7 Hz, 1H), 7.36 (d, <i>J</i> = 7.8 Hz, 1H), 5.67 (s, 1H), 4.96 (s, 1H), 3.93 - 3.79 (m, 3H), 3.67 - 3.50 (m, 1H), 3.45 - 3.37 (m, 1H), 3.26 - 3.04 (m, 3H), 2.36 - 2.21 (m, 2H), 2.07 - 1.99 (m, 1H), 1.66 (s, 3H), 1.61 - 1.46 (m, 1H).
125a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 446.3 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.60 (s, 1H), 8.50 (d, <i>J</i> = 3.7 Hz, 1H), 8.06 (d, <i>J</i> = 11.8 Hz, 1H), 7.29 (d, <i>J</i> = 7.8 Hz, 1H), 5.58 (s, 1H), 4.95 (s, 1H), 3.90 - 3.77 (m, 3H), 3.58 - 3.50 (m, 1H), 3.42 - 3.36 (m, 1H), 3.13 - 2.96 (m, 3H), 2.28 - 2.16 (m, 2H), 2.02 (d, <i>J</i> = 13.1 Hz, 1H), 1.56 - 1.46 (m, 4H). de: 100%; Retention time: 1.32 min; instrument: SHIMADZU-20AD-XR; Column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1% DEA) and B for IPA; Gradient: B 50% ; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm.
125b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 446.3 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.60 (s, 1H), 8.50 (d, <i>J</i> = 3.7 Hz, 1H), 8.06 (d, <i>J</i> = 11.8 Hz, 1H), 7.29 (d, <i>J</i> = 7.8 Hz, 1H), 5.57 (s, 1H), 4.94 (s, 1H), 3.88 - 3.81 (m, 3H), 3.54 (s, 1H), 3.43 - 3.37 (m, 1H), 3.16 - 2.95 (m, 3H), 2.28 - 2.16 (m, 2H), 2.03 (s, 1H), 1.57 - 1.45 (m, 4H). de: 100%; Retention time: 2.36 min; instrument: SHIMADZU-20AD-XR; Column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1% DEA) and B for IPA; Gradient: B 50% ; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm.

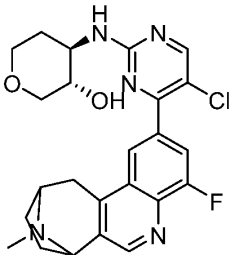
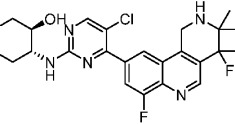
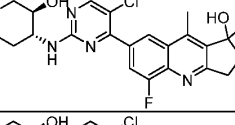
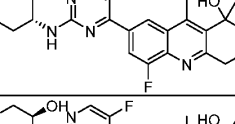
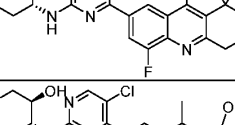
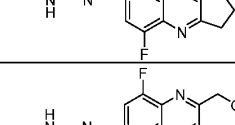
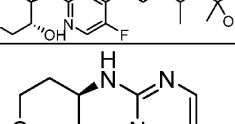
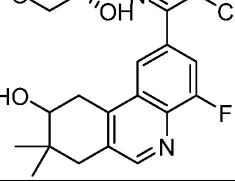
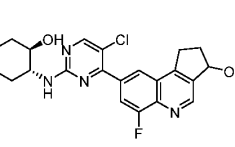
126a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 462.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.46 (s, 1H), 8.45 - 8.24 (m, 1H), 7.97 - 7.77 (m, 1H), 7.69 - 7.48 (m, 1H), 5.56 (s, 1H), 4.94 (s, 1H), 3.89 - 3.77 (m, 3H), 3.53 - 3.40 (m, 2H), 3.10 - 2.99 (m, 3H), 2.30 - 2.14 (m, 2H), 2.07 - 1.84 (m, 1H), 1.56 - 1.47 (m, 4H). de: 100%; Retention time: 1.44 min; instrument: SHIMADZU-20AD-XR; Column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 50%; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm.
126b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 462.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.46 (s, 1H), 8.43 - 8.24 (m, 1H), 7.91 - 7.78 (m, 1H), 7.69 - 7.40 (m, 1H), 5.56 (s, 1H), 4.94 (d, J = 5.3 Hz, 1H), 3.90 - 3.75 (m, 3H), 3.55 - 3.46 (m, 1H), 3.39 - 3.36 (m, 1H), 3.10 - 2.96 (m, 3H), 2.29 - 2.15 (m, 2H), 2.07 - 1.87 (m, 1H), 1.60 - 1.42 (m, 4H). de: 100%; Retention time: 2.37 min; instrument: SHIMADZU-20AD-XR; Column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; Mobile phase: A for Hex (0.1% DEA) and B for EtOH; Gradient: B 50%; Flow rate: 1.67 mL/min; High pressure: 110 bar; Column temperature: 25 °C; Wavelength: 254 nm.
127a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 475.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.47 (s, 1H), 8.41 (s, 1H), 7.88 (s, 1H), 7.57 (s, 1H), 5.52 (s, 1H), 4.96 - 4.88 (m, 3H), 3.90 - 3.76 (m, 3H), 3.78 - 3.68 (m, 2H), 3.55 - 3.45 (m, 1H), 3.37 - 3.33 (m, 1H), 3.09 - 3.02 (m, 1H), 3.01 (s, 3H), 2.00 - 1.90 (m, 1H), 1.62 (s, 3H), 1.57 - 1.45 (m, 1H). de: 100 %; Retention time: 1.083 min; instrument: Agilent-1260; column: CHIRALPAK IE-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for MtBE : Hex = 1:1 (0.1% DEA) and B for MeOH; gradient: B 30%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
127b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 475.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-d₆) δ 8.47 (s, 1H), 8.40 (s, 1H), 7.87 (s, 1H), 7.57 (s, 1H), 5.52 (s, 1H), 5.01 - 4.85 (m, 3H), 3.89 - 3.78 (m, 3H), 3.78 - 3.69 (m, 2H), 3.55 - 3.47 (m, 1H), 3.37 - 3.33 (m, 1H), 3.05 (t, J = 10.4 Hz, 1H), 3.01 (s, 3H), 2.03 - 1.89 (m, 1H), 1.62 (s, 3H), 1.56 - 1.45 (m, 1H). de: 99 %; Retention time: 2.136 min; instrument: Agilent-1260; column: CHIRALPAK IE-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for MtBE : Hex = 1:1 (0.1% DEA) and B for MeOH; gradient: B 30%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.

128a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 503.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.71 (s, 1H), 8.47 (s, 1H), 8.01 - 7.76 (m, 1H), 7.56 (s, 1H), 5.58 (s, 1H), 4.94 (d, <i>J</i> = 5.4 Hz, 1H), 4.91 (s, 2H), 4.85 - 4.79 (m, 1H), 3.92 - 3.78 (m, 3H), 3.75 - 3.68 (m, 2H), 3.55 - 3.46 (m, 1H), 3.36 - 3.27 (m, 1H), 3.03 (t, <i>J</i> = 10.6 Hz, 1H), 2.02 - 1.90 (m, 1H), 1.65 (s, 3H), 1.60 - 1.54 (m, 6H), 1.53 - 1.47 (m, 1H). de: 100 %; Retention time: 0.698 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
128b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 503.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.66 (d, <i>J</i> = 47.0 Hz, 1H), 8.47 (s, 1H), 7.88 (d, <i>J</i> = 48.7 Hz, 1H), 7.56 (s, 1H), 5.57 (s, 1H), 4.94 (d, <i>J</i> = 4.0 Hz, 1H), 4.91 (s, 2H), 4.86 - 4.77 (m, 1H), 3.91 - 3.78 (m, 3H), 3.75 - 3.68 (m, 2H), 3.56 - 3.46 (m, 1H), 3.36 - 3.27 (m, 1H), 3.03 (t, <i>J</i> = 10.5 Hz, 1H), 2.03 - 1.89 (m, 1H), 1.64 (s, 3H), 1.60 - 1.45 (m, 7H). de: 100 %; Retention time: 1.092 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
129a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 487.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.00 (s, 1H), 8.51 (d, <i>J</i> = 3.9 Hz, 1H), 8.06 (d, <i>J</i> = 11.5 Hz, 1H), 7.28 (d, <i>J</i> = 7.9 Hz, 1H), 5.59 (s, 1H), 4.95 (d, <i>J</i> = 5.4 Hz, 1H), 4.92 (s, 2H), 4.87 - 4.78 (m, 1H), 3.93 - 3.80 (m, 3H), 3.76 - 3.66 (m, 2H), 3.58 - 3.48 (m, 1H), 3.30 - 3.27 (m, 1H), 3.07 (t, <i>J</i> = 10.4 Hz, 1H), 2.06 - 1.98 (m, 1H), 1.65 (s, 3H), 1.62 (d, <i>J</i> = 7.1 Hz, 3H), 1.57 (d, <i>J</i> = 7.5 Hz, 3H), 1.55 - 1.47 (m, 1H). de: 100 %; Retention time: 0.980 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 30%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.

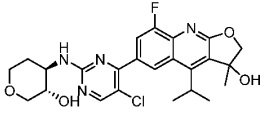
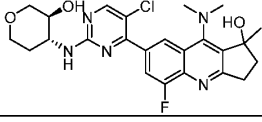
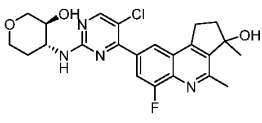
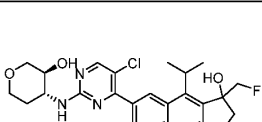
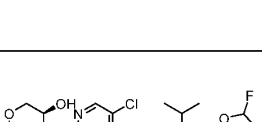
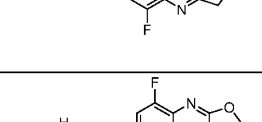
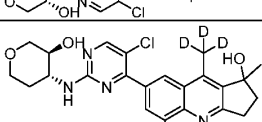
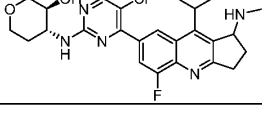
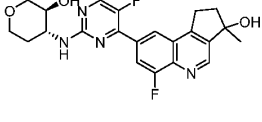
129b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 487.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.99 (s, 1H), 8.51 (d, <i>J</i> = 3.9 Hz, 1H), 8.05 (d, <i>J</i> = 11.6 Hz, 1H), 7.28 (d, <i>J</i> = 7.9 Hz, 1H), 5.58 (s, 1H), 4.98 - 4.88 (m, 3H), 4.87 - 4.79 (m, 1H), 3.93 - 3.80 (m, 3H), 3.78 - 3.68 (m, 2H), 3.53 - 3.50 (m, 1H), 3.30 - 3.25 (m, 1H), 3.06 (t, <i>J</i> = 10.4 Hz, 1H), 2.07 - 1.99 (m, 1H), 1.65 (s, 3H), 1.63 - 1.47 (m, 7H). de: 100 %; Retention time: 1.312 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 30%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
130a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 459.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.46 (s, 1H), 8.37 (s, 1H), 7.85 (s, 1H), 7.56 (s, 1H), 5.56 (s, 1H), 4.93 (d, <i>J</i> = 4.0 Hz, 1H), 3.81 - 3.77 (m, 3H), 3.56-3.46 (m, 1H), 3.40 - 3.35 (m, 1H), 3.10 - 2.96 (m, 3H), 2.83 (s, 3H), 2.29 - 2.15 (m, 2H), 2.00 - 1.89 (m, 1H), 1.57 - 1.43 (m, 4H). de: 99 %; Retention time: 1.457 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
130b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 459.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.46 (s, 1H), 8.39 (d, <i>J</i> = 15.8 Hz, 1H), 7.84 (d, <i>J</i> = 11.3 Hz, 1H), 7.56 (s, 1H), 5.56 (s, 1H), 4.93 (s, 1H), 3.93 - 3.76 (m, 3H), 3.55 - 3.45 (m, 1H), 3.40 - 3.35 (m, 1H), 3.11 - 2.94 (m, 3H), 2.83 (s, 3H), 2.30 - 2.14 (m, 2H), 2.05 - 1.90 (m, 1H), 1.57 - 1.44 (m, 4H). de: 99 %; Retention time: 2.491 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
131a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 473.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.46 (s, 1H), 8.39 (s, 1H), 7.82 (s, 1H), 7.56 (s, 1H), 5.27 (s, 1H), 4.93 (s, 1H), 3.90 - 3.77 (m, 3H), 3.55 - 3.45 (m, 1H), 3.37 - 3.35 (m, 1H), 3.16 - 2.99 (m, 6H), 2.08 - 1.79 (m, 5H), 1.57 (s, 3H), 1.54 - 1.44 (m, 1H). de: 100 %; Retention time: 0.746 min; instrument: SHIMADZU-20AD-XR; column: Cellulose SZ, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.

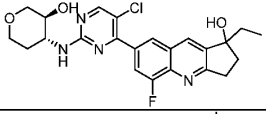
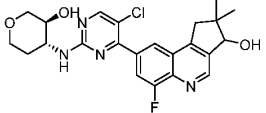
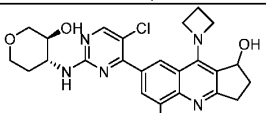
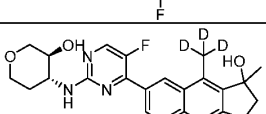
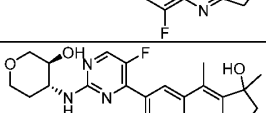
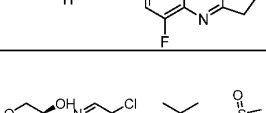
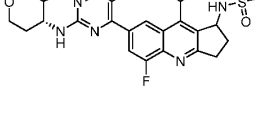
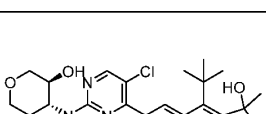
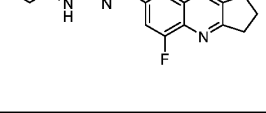
131b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 473.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.38 (s, 1H), 7.82 (s, 1H), 7.55 (s, 1H), 5.27 (s, 1H), 4.93 (d, $J = 5.5$ Hz, 1H), 3.84 - 3.77 (m, 3H), 3.55 - 3.45 (m, 1H), 3.40 - 3.35 (m, 1H), 3.14 - 2.98 (m, 6H), 2.04 - 1.92 (m, 5H), 1.57 (s, 3H), 1.53 - 1.41 (m, 1H). de: 100 %; Retention time: 0.989 min; instrument: SHIMADZU-20AD-XR; column: Cellulose SZ, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
132a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 457.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.49 (d, $J = 3.8$ Hz, 1H), 8.02 (d, $J = 11.7$ Hz, 1H), 7.28 (d, $J = 7.7$ Hz, 1H), 5.29 (s, 1H), 4.94 (s, 1H), 3.89 - 3.78 (m, 3H), 3.54 - 3.49 (m, 1H), 3.41 - 3.36 (m, 1H), 3.15 - 3.03 (m, 6H), 2.00 - 1.92 (m, 4H), 1.90 - 1.82 (m, 1H), 1.57 (s, 3H), 1.55 - 1.45 (m, 1H). de: 100 %; Retention time: 0.850 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
132b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 457.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.49 (d, $J = 3.8$ Hz, 1H), 8.02 (d, $J = 11.8$ Hz, 1H), 7.28 (d, $J = 7.7$ Hz, 1H), 5.29 (s, 1H), 4.93 (dd, $J = 5.4, 1.2$ Hz, 1H), 3.89 - 3.77 (m, 3H), 3.58-3.49 (m, 1H), 3.43 - 3.33 (m, 1H), 3.16 - 2.99 (m, 6H), 2.07 - 1.91 (m, 4H), 1.91 - 1.81 (m, 1H), 1.57 (s, 3H), 1.53 - 1.47 (m, 1H). de: 100 %; Retention time: 2.367 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
133		LC-MS (ESI): m/z 472.0 $[M+H]^+$.
134		LC-MS (ESI): m/z 500.2 $[M+H]^+$.

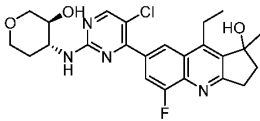
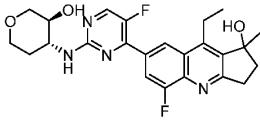
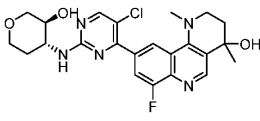
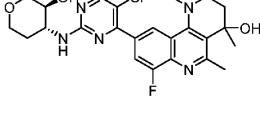
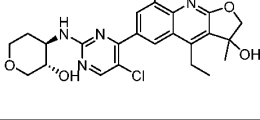
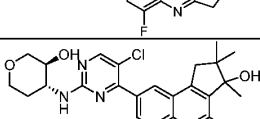
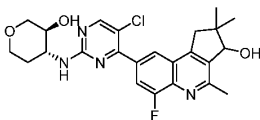
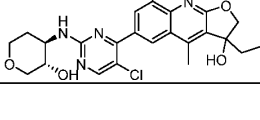
135a	Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 502.2 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.35 (s, 1H), 8.01 (s, 1H), 7.86 (d, J = 10.8 Hz, 1H), 5.54 (s, 1H), 4.70 - 4.56 (m, 1H), 4.52 (s, 1H), 4.29 (d, J = 18.0 Hz, 1H), 4.13 - 3.83 (m, 3H), 3.67 - 3.56 (m, 1H), 3.46 (t, J = 11.4 Hz, 1H), 3.21 (t, J = 10.5 Hz, 1H), 2.14 - 1.86 (m, 2H), 1.77 - 1.60 (m, 2H), 1.48 - 1.21 (m, 3H), 1.04 (s, 3H), 0.96 (s, 3H). de: 100%; Retention time: 3.476 min; column: OD-3, 0.46 cm I.D.* 5 cm L; mobile phase: CO_2 : EtOH = 70 : 30; flow rate: 2.5 mL/min; column temperature: 25 °C; wavelength: 254 nm.
135b	Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 502.2 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.33 (s, 1H), 7.97 (s, 1H), 7.81 (d, J = 10.8 Hz, 1H), 5.54 (s, 1H), 4.71 - 4.55 (m, 1H), 4.50 (s, 1H), 4.27 (d, J = 17.9 Hz, 1H), 4.12 - 3.83 (m, 3H), 3.67 - 3.58 (m, 1H), 3.48 (t, J = 11.5 Hz, 1H), 3.20 (t, J = 10.5 Hz, 1H), 2.07 (d, J = 12.9 Hz, 1H), 1.99 - 1.84 (m, 1H), 1.76 - 1.60 (m, 2H), 1.45 - 1.22 (m, 3H), 1.03 (s, 3H), 0.95 (s, 3H). de: 99%; Retention time: 4.119 min; column: OD-3, 0.46 cm I.D.* 5 cm L; mobile phase: CO_2 : EtOH = 70 : 30; flow rate: 2.5 mL/min; column temperature: 25 °C; wavelength: 254 nm.
137		LC-MS (ESI): m/z 472.3 $[M+H]^+$.
138		LC-MS (ESI): m/z 500.4 $[M+H]^+$.
139		LC-MS (ESI): m/z 464.1 $[M+H]^+$.
140		LC-MS (ESI): m/z 536.2 $[M+H]^+$.
141		LC-MS (ESI): m/z 475.2 $[M+H]^+$.

144		LC-MS (ESI): m/z 470.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.73 (s, 1H), 8.47 (s, 1H), 8.20 (s, 1H), 7.85 (d, J = 12 Hz, 1H), 7.57 (s, 1H), 4.93 (s, 1H), 4.15 (d, J = 5.5 Hz, 1H), 3.88 - 3.76 (m, 3H), 3.64 - 3.56 (m, 1H), 3.54 - 3.47 (m, 1H), 3.45 - 3.36 (m, 2H), 3.05 (t, J = 10.3 Hz, 1H), 2.88 - 2.76 (m, 1H), 2.33 - 2.17 (m, 5H), 2.02 - 1.88 (m, 1H), 1.77 (t, J = 10.3 Hz, 1H), 1.66 - 1.43 (m, 2H).
145		LC-MS (ESI): m/z 494.0 $[M+H]^+$.
146		LC-MS (ESI): m/z 459.2 $[M+H]^+$.
147		LC-MS (ESI): m/z 473.2 $[M+H]^+$.
148		LC-MS (ESI): m/z 457.1 $[M+H]^+$.
149		LC-MS (ESI): m/z 445.1 $[M+H]^+$.
150		LC-MS (ESI): m/z 475.2 $[M+H]^+$.
151		LC-MS (ESI): m/z 473.3 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 8.75 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 7.88 (d, J = 11.5 Hz, 1H), 7.61 (s, 1H), 5.02 (d, J = 4.4 Hz, 1H), 4.97 (d, J = 5.3 Hz, 1H), 3.84 (dd, J = 11.0, 5.1 Hz, 3H), 3.76 (d, J = 5.0 Hz, 1H), 3.52 (s, 2H), 3.13 - 2.93 (m, 3H), 2.89 (d, J = 16.9 Hz, 1H), 2.69 (d, J = 16.8 Hz, 1H), 1.97 (s, 1H), 1.52 (d, J = 7.7 Hz, 1H), 0.98 (s, 6H).
152		LC-MS (ESI): m/z 431.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 9.00 (s, 1H), 8.48 (s, 1H), 8.21 - 8.15 (m, 1H), 7.90 (d, J = 11.8 Hz, 1H), 7.59 (s, 1H), 5.64 (d, J = 6.1 Hz, 1H), 5.41 (q, J = 6.1 Hz, 1H), 4.94 (d, J = 5.4 Hz, 1H), 3.89 - 3.77 (m, 4H), 3.54 - 3.46 (m, 1H), 3.44 - 3.35 (m, 1H), 3.20 - 3.10 (m, 1H), 3.05 (t, J = 10.4 Hz, 1H), 2.63 - 2.54 (m, 1H), 2.06 - 1.90 (m, 2H), 1.57 - 1.43 (m, 1H).

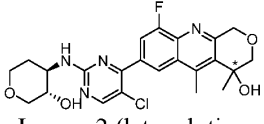
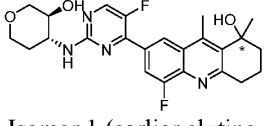
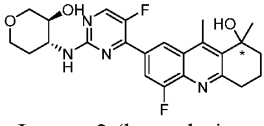
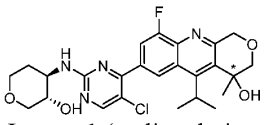
153		LC-MS (ESI): m/z 445.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.48 (s, 1H), 8.17 (s, 1H), 7.89 (d, J = 11.6 Hz, 1H), 7.61 (s, 1H), 5.48 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 3.89 - 3.76 (m, 3H), 3.54 - 3.44 (m, 1H), 3.38 - 3.35 (m, 1H), 3.24 - 3.12 (m, 1H), 3.04 (t, J = 10.4 Hz, 1H), 2.50 - 2.48 (m, 1H), 2.35 - 2.21 (m, 2H), 2.01 - 1.89 (m, 1H), 1.58 (s, 3H), 1.50 (q, J = 10.8, 10.2 Hz, 1H).
154		LC-MS (ESI): m/z 458.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 8.47 (s, 1H), 8.45 - 8.24 (m, 1H), 7.97 - 7.76 (m, 1H), 7.68 - 7.46 (m, 1H), 5.05 - 4.84 (m, 1H), 4.51 - 4.40 (m, 1H), 3.92 - 3.76 (m, 3H), 3.58 - 2.90 (m, 5H), 2.74 (s, 3H), 2.39 (s, 3H), 2.20 - 2.10 (m, 2H), 2.06 - 1.85 (m, 1H), 1.59 - 1.42 (m, 1H).
155		LC-MS (ESI): m/z 487.2 $[M+H]^+$.
156		LC-MS (ESI): m/z 479.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 8.69 - 8.37 (m, 2H), 8.18 - 7.89 (m, 1H), 7.81 - 7.45 (m, 1H), 3.90 - 3.71 (m, 3H), 3.56 - 3.42 (m, 1H), 3.38 - 3.29 (m, 1H), 3.22 - 2.97 (m, 3H), 2.35 - 2.19 (m, 2H), 2.06 - 1.87 (m, 1H), 1.63 (s, 3H), 1.57 - 1.42 (m, 1H).
157		LC-MS (ESI): m/z 564.2 $[M+H]^+$.
158		LC-MS (ESI): m/z 503.2 $[M+H]^+$.
159		LC-MS (ESI): m/z 487.2 $[M+H]^+$.
160		LC-MS (ESI): m/z 548.2 $[M+H]^+$.
161		LC-MS (ESI): m/z 473.3 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.48 (s, 2H), 7.96 (s, 1H), 7.59 (s, 1H), 5.40 (s, 1H), 4.95 (d, J = 5.4 Hz, 1H), 3.83 (dd, J = 11.2, 5.3 Hz, 3H), 3.51 (s, 1H), 3.32 - 3.31 (m, 1H), 3.03 (t, J = 10.3 Hz, 1H), 2.24 (q, J = 13.4 Hz, 2H), 1.96 (s, 1H), 1.63 (d, J = 6.0 Hz, 6H), 1.54 (d, J = 25.5 Hz, 4H).
162		LC-MS (ESI): m/z 473.2 $[M+H]^+$.

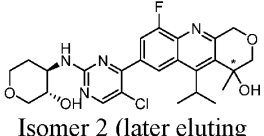
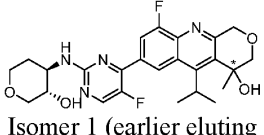
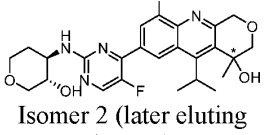
163		LC-MS (ESI): m/z 489.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 8.77 - 8.38 (m, 2H), 8.06 - 7.71 (m, 1H), 7.56 (d, J = 7.1 Hz, 1H), 6.15 (s, 1H), 4.97 (d, J = 5.8 Hz, 1H), 4.50 (d, J = 9.2 Hz, 1H), 4.42 (d, J = 9.0 Hz, 1H), 4.27 - 4.15 (m, 1H), 4.00 - 3.76 (m, 3H), 3.62 - 3.48 (m, 1H), 3.34 - 3.25 (m, 1H), 3.05 (t, J = 10.2 Hz, 1H), 2.06 - 1.89 (m, 1H), 1.66 (s, 3H), 1.63 - 1.42 (m, 7H).
164		LC-MS (ESI): m/z 488.2 $[M+H]^+$.
165		LC-MS (ESI): m/z 459.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.46 (s, 1H), 8.13 (s, 1H), 7.84 (d, J = 12.1 Hz, 1H), 7.57 (s, 1H), 5.48 (s, 1H), 4.93 (s, 1H), 3.89 - 3.76 (m, 3H), 3.53 - 3.46 (m, 1H), 3.27 (d, J = 3.3 Hz, 1H), 3.07 (dt, J = 18.4, 5.9 Hz, 2H), 2.81 (s, 3H), 2.54 (s, 1H), 2.37 - 2.19 (m, 2H), 2.03 - 1.86 (m, 1H), 1.52 (s, 3H), 1.46 (dd, J = 9.0, 5.8 Hz, 1H).
166		LC-MS (ESI): m/z 505.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.76 - 8.52 (m, 1H), 8.47 (s, 1H), 8.06 - 7.73 (m, 1H), 7.55 (d, J = 7.5 Hz, 1H), 6.10 (s, 1H), 4.95 (d, J = 5.3 Hz, 1H), 4.64 - 4.54 (m, 1H), 4.51 - 4.38 (m, 2H), 3.95 - 3.75 (m, 3H), 3.56 - 3.46 (m, 1H), 3.32 - 3.27 (m, 1H), 3.12 - 2.98 (m, 3H), 2.49 - 2.45 (m, 1H), 2.25 - 2.08 (m, 1H), 2.04 - 1.88 (m, 1H), 1.61 - 1.44 (m, 7H).
167		LC-MS (ESI): m/z 523.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.64 (s, 1H), 8.47 (s, 1H), 7.98 (s, 1H), 7.55 (s, 1H), 6.96 (t, J = 75.5 Hz, 1H), 6.09 (d, J = 5.0 Hz, 1H), 4.94 (d, J = 5.4 Hz, 1H), 3.87 - 3.78 (m, 4H), 3.55 - 3.47 (m, 1H), 3.35 - 3.32 (m, 2H), 3.14 - 2.98 (m, 2H), 2.45 - 2.30 (m, 2H), 2.01 - 1.95 (m, 1H), 1.58 - 1.49 (m, 7H).
168		LC-MS (ESI): m/z 461.1 $[M+H]^+$.
169		LC-MS (ESI): m/z 462.2 $[M+H]^+$.
170		LC-MS (ESI): m/z 486.2 $[M+H]^+$.
171		LC-MS (ESI): m/z 429.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.51 (d, J = 3.7 Hz, 1H), 8.37 (s, 1H), 8.10 (d, J = 12.2 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 5.49 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 3.87 - 3.78 (m, 3H), 3.56 - 3.47 (m, 1H), 3.41 - 3.35 (m, 2H), 3.25 - 3.15 (m, 1H), 3.07 (t, J = 10.4 Hz, 1H), 2.36 - 2.20 (m, 2H), 2.06 - 1.94 (m, 1H), 1.57 (s, 3H), 1.54 - 1.43 (m, 1H).

172		LC-MS (ESI): m/z 459.2 $[M+H]^+$.
173		LC-MS (ESI): m/z 459.2 $[M+H]^+$.
174		LC-MS (ESI): m/z 486.4 $[M+H]^+$.
175		LC-MS (ESI): m/z 446.0 $[M+H]^+$.
176		LC-MS (ESI): m/z 443.2 $[M+H]^+$.
177		LC-MS (ESI): m/z 550.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.75 - 8.40 (m, 2H), 8.07 - 7.80 (m, 1H), 7.70 (d, J = 9.2 Hz, 1H), 7.62 - 7.50 (m, 1H), 5.31 - 5.21 (m, 1H), 5.03 - 4.90 (m, 1H), 3.98 - 3.76 (m, 5H), 3.58 - 3.44 (m, 1H), 3.08 (s, 3H), 3.06 - 2.96 (m, 3H), 2.26 - 2.16 (m, 1H), 2.06 - 1.86 (m, 1H), 1.62 - 1.46 (m, 8H).
178		LC-MS (ESI): m/z 501.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.76 (d, J = 57.0 Hz, 1H), 8.48 (s, 1H), 7.86 (d, J = 51.0 Hz, 1H), 7.59 (t, J = 12.9 Hz, 1H), 5.72 (s, 1H), 5.00 (s, 1H), 3.86 (dd, J = 10.8, 5.1 Hz, 3H), 3.54 (d, J = 4.0 Hz, 1H), 3.35 - 3.28 (m, 1H), 3.20 - 2.92 (m, 3H), 2.17 (dd, J = 11.3, 7.2 Hz, 1H), 2.02 (dd, J = 20.2, 11.9 Hz, 2H), 1.83 (s, 9H), 1.78 (s, 3H), 1.57 (t, J = 18.3 Hz, 1H).
179		LC-MS (ESI): m/z 486.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.15 (s, 1H), 8.68 (d, J = 45.3 Hz, 1H), 8.47 (s, 1H), 7.88 (d, J = 43.1 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 5.37 (s, 1H), 4.95 (d, J = 5.3 Hz, 1H), 3.90 - 3.77 (m, 3H), 3.55 - 3.46 (m, 1H), 3.31 - 3.24 (m, 1H), 3.02 (t, J = 10.3 Hz, 1H), 2.05 - 1.95 (m, 2H), 1.90 - 1.78 (m, 3H), 1.61 (d, J = 6.4 Hz, 6H), 1.58 - 1.49 (m, 4H).
181		LC-MS (ESI): m/z 443.2 $[M+H]^+$.

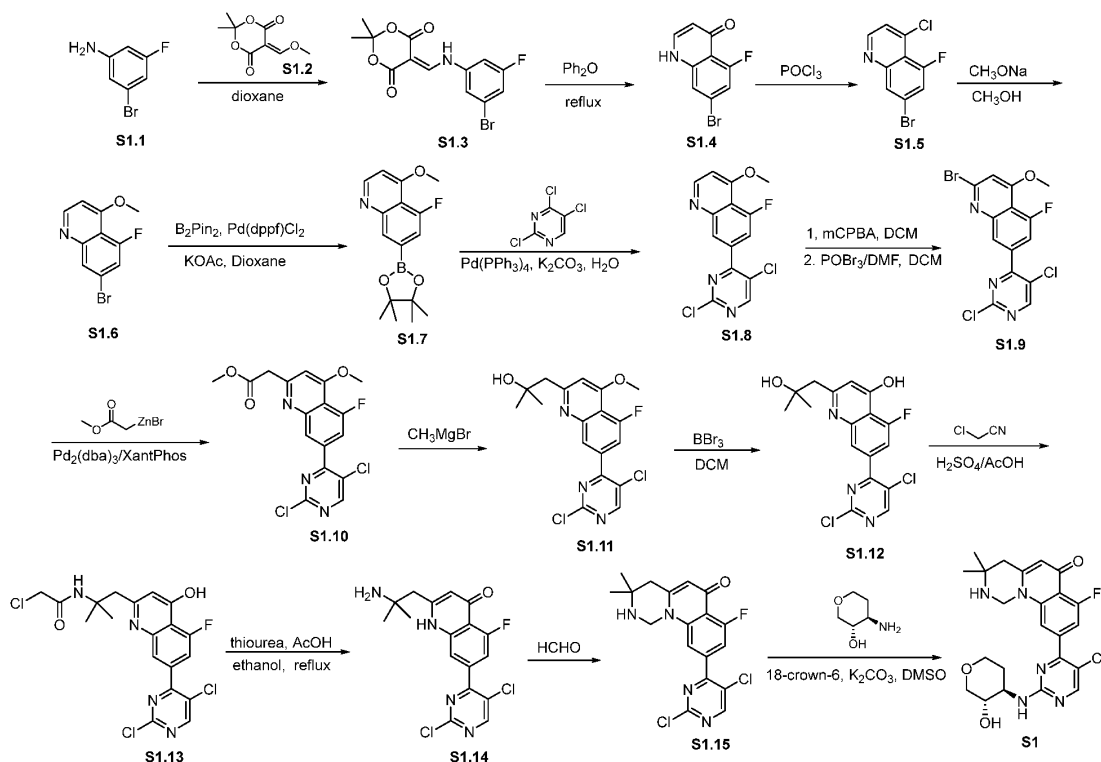
182		LC-MS (ESI): m/z 473.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.47 (s, 1H), 8.37 (s, 1H), 7.83 (s, 1H), 7.56 (s, 1H), 5.56 (s, 1H), 4.94 (d, J = 5.3 Hz, 1H), 3.86 - 3.79 (m, 3H), 3.53 - 3.33 (m, 4H), 3.08 - 2.99 (m, 3H), 2.27 - 2.19 (m, 2H), 2.05 - 1.90 (m, 1H), 1.57 - 1.46 (m, 4H), 1.34 (t, J = 7.4 Hz, 3H).
183		LC-MS (ESI): m/z 457.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.61 (s, 1H), 8.51 (d, J = 3.8 Hz, 1H), 8.03 (d, J = 12.0 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 5.57 (s, 1H), 4.95 (d, J = 5.4 Hz, 1H), 3.90 - 3.63 (m, 3H), 3.59 - 3.51 (m, 1H), 3.47 - 3.34 (m, 3H), 3.12 - 3.00 (m, 3H), 2.27 - 2.14 (m, 2H), 2.10 - 1.96 (m, 1H), 1.57 - 1.48 (m, 4H), 1.36 (t, J = 7.5 Hz, 3H).
184		LC-MS (ESI): m/z 474.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.78 (s, 1H), 8.45 (s, 1H), 8.39 (s, 1H), 7.81 (s, 1H), 7.52 (s, 1H), 5.32 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 3.92 - 3.77 (m, 3H), 3.51 (s, 3H), 3.48 - 3.36 (m, 1H), 3.30 - 3.25 (m, 3H), 3.08 - 3.00 (m, 1H), 2.02 - 1.88 (m, 3H), 1.60 - 1.45 (m, 4H).
185		LC-MS (ESI): m/z 488.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.43 (s, 1H), 8.26 (s, 1H), 7.76 (s, 1H), 7.49 (s, 1H), 5.14 (s, 1H), 4.93 (d, J = 5.4 Hz, 1H), 3.85 - 3.76 (m, 3H), 3.49 - 3.32 (m, 4H), 3.18 (s, 3H), 3.08 - 3.00 (m, 1H), 2.85 (s, 3H), 2.09 - 1.89 (m, 3H), 1.61 - 1.45 (m, 4H).
186		LC-MS (ESI): m/z 475.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.45 (s, 1H), 8.41 - 8.2 (m, 1H), 8.01 - 7.72 (m, 1H), 7.66 - 7.46 (m, 1H), 6.05 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 4.52 - 4.38 (m, 2H), 3.92 - 3.74 (m, 3H), 3.58 - 3.43 (m, 1H), 3.33 - 3.16 (m, 3H), 3.10 - 2.97 (m, 1H), 2.06 - 1.85 (m, 1H), 1.68 (s, 3H), 1.57 - 1.46 (m, 1H), 1.35 (t, J = 7.5 Hz, 3H).
187		LC-MS (ESI): m/z 473.2 $[M+H]^+$.
188		LC-MS (ESI): m/z 487.2 $[M+H]^+$.
189		LC-MS (ESI): m/z 473.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.48 (s, 1H), 8.12 (s, 1H), 7.88 (d, J = 12.1 Hz, 1H), 7.59 (s, 1H), 5.35 (d, J = 7.4 Hz, 1H), 4.96 (s, 1H), 4.74 (d, J = 7.1 Hz, 1H), 3.83 (dd, J = 10.7, 4.9 Hz, 3H), 3.50 (s, 2H), 3.18 - 2.96 (m, 3H), 2.76 (s, 3H), 1.97 (d, J = 11.9 Hz, 1H), 1.59 - 1.47 (m, 1H), 1.19 (s, 3H), 1.08 (s, 3H).
190		LC-MS (ESI): m/z 475.3 $[M+H]^+$.

191		LC-MS (ESI): m/z 473.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.46 (s, 1H), 8.13 (s, 1H), 7.84 (d, J = 10.4 Hz, 1H), 7.56 (s, 1H), 5.42 (s, 1H), 4.92 (d, J = 5.1 Hz, 1H), 3.90 - 3.70 (m, 3H), 3.52 - 3.48 (m, 1H), 3.31 - 3.23 (m, 2H), 3.11 - 2.98 (m, 2H), 2.79 (s, 3H), 2.52 - 2.44 (m, 1H), 2.19 - 2.07 (m, 1H), 2.01 - 1.76 (m, 3H), 1.56 - 1.42 (m, 1H), 0.81 (t, J = 7.4 Hz, 3H).
192		LC-MS (ESI): m/z 456.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.19 (s, 1H), 8.98 (s, 1H), 8.71 (s, 1H), 8.49 (s, 1H), 7.91 (d, J = 11.2 Hz, 1H), 7.61 (s, 1H), 4.93 (d, J = 5.2 Hz, 1H), 3.97 - 3.85 (m, 3H), 3.49 - 3.51 (m, 1H), 3.30 - 3.32 (m, 1H), 2.95 - 3.05 (t, J = 9.6 Hz, 1H), 3.02 (s, 2H), 1.94 - 1.97 (m, 1H), 1.46 - 1.51 (m, 1H), 1.23 (s, 6H).
193a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 473.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.46 (s, 1H), 8.39 (s, 1H), 7.82 (s, 1H), 7.56 (s, 1H), 5.27 (s, 1H), 4.93 (s, 1H), 3.90 - 3.77 (m, 3H), 3.55 - 3.45 (m, 1H), 3.37 - 3.35 (m, 1H), 3.16 - 2.99 (m, 6H), 2.08 - 1.79 (m, 5H), 1.57 (s, 3H), 1.54 - 1.44 (m, 1H). de: 100 %; Retention time: 0.746 min; instrument: SHIMADZU-20AD-XR; column: Cellulose SZ, 4.6 * 50 mm, 3.0 μ m; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 $^{\circ}$ C; wavelength: 254 nm.
193b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 473.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.46 (s, 1H), 8.38 (s, 1H), 7.82 (s, 1H), 7.55 (s, 1H), 5.27 (s, 1H), 4.93 (d, J = 5.5 Hz, 1H), 3.84 - 3.77 (m, 3H), 3.55 - 3.45 (m, 1H), 3.40 - 3.35 (m, 1H), 3.14 - 2.98 (m, 6H), 2.04 - 1.92 (m, 5H), 1.57 (s, 3H), 1.53 - 1.41 (m, 1H). de: 100 %; Retention time: 0.989 min; instrument: SHIMADZU-20AD-XR; column: Cellulose SZ, 4.6 * 50 mm, 3.0 μ m; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 $^{\circ}$ C; wavelength: 254 nm.
195a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 475.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.47 (s, 1H), 8.41 (s, 1H), 7.88 (s, 1H), 7.57 (s, 1H), 5.52 (s, 1H), 4.96 - 4.88 (m, 3H), 3.90 - 3.76 (m, 3H), 3.78 - 3.68 (m, 2H), 3.55 - 3.45 (m, 1H), 3.37 - 3.33 (m, 1H), 3.09 - 3.02 (m, 1H), 3.01 (s, 3H), 2.00 - 1.90 (m, 1H), 1.62 (s, 3H), 1.57 - 1.45 (m, 1H). de: 100 %; Retention time: 1.083 min; instrument: Agilent-1260; column: CHIRALPAK IE-3, 4.6 * 50 mm, 3.0 μ m; mobile phase: A for MtBE : Hex = 1:1 (0.1% DEA) and B for MeOH; gradient: B 30%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 $^{\circ}$ C; wavelength: 254 nm.

195b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 475.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.47 (s, 1H), 8.40 (s, 1H), 7.87 (s, 1H), 7.57 (s, 1H), 5.52 (s, 1H), 5.01 - 4.85 (m, 3H), 3.89 - 3.78 (m, 3H), 3.78 - 3.69 (m, 2H), 3.55 - 3.47 (m, 1H), 3.37 - 3.33 (m, 1H), 3.05 (t, <i>J</i> = 10.4 Hz, 1H), 3.01 (s, 3H), 2.03 - 1.89 (m, 1H), 1.62 (s, 3H), 1.56 - 1.45 (m, 1H). de: 99 %; Retention time: 2.136 min; instrument: Agilent-1260; column: CHIRALPAK IE-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for MtBE : Hex = 1:1 (0.1% DEA) and B for MeOH; gradient: B 30%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
197a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 457.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.62 (s, 1H), 8.49 (d, <i>J</i> = 3.8 Hz, 1H), 8.02 (d, <i>J</i> = 11.7 Hz, 1H), 7.28 (d, <i>J</i> = 7.7 Hz, 1H), 5.29 (s, 1H), 4.94 (s, 1H), 3.89 - 3.78 (m, 3H), 3.54 - 3.49 (m, 1H), 3.41 - 3.36 (m, 1H), 3.15 - 3.03 (m, 6H), 2.00 - 1.92 (m, 4H), 1.90 - 1.82 (m, 1H), 1.57 (s, 3H), 1.55 - 1.45 (m, 1H). de: 100 %; Retention time: 0.850 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
197b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 457.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.62 (s, 1H), 8.49 (d, <i>J</i> = 3.8 Hz, 1H), 8.02 (d, <i>J</i> = 11.8 Hz, 1H), 7.28 (d, <i>J</i> = 7.7 Hz, 1H), 5.29 (s, 1H), 4.93 (dd, <i>J</i> = 5.4, 1.2 Hz, 1H), 3.89 - 3.77 (m, 3H), 3.58-3.49 (m, 1H), 3.43 - 3.33 (m, 1H), 3.16 - 2.99 (m, 6H), 2.07 - 1.91 (m, 4H), 1.91 - 1.81 (m, 1H), 1.57 (s, 3H), 1.53 - 1.47 (m, 1H). de: 100 %; Retention time: 2.367 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
199a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 503.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.71 (s, 1H), 8.47 (s, 1H), 8.01 - 7.76 (m, 1H), 7.56 (s, 1H), 5.58 (s, 1H), 4.94 (d, <i>J</i> = 5.4 Hz, 1H), 4.91 (s, 2H), 4.85 - 4.79 (m, 1H), 3.92 - 3.78 (m, 3H), 3.75 - 3.68 (m, 2H), 3.55 - 3.46 (m, 1H), 3.36 - 3.27 (m, 1H), 3.03 (t, <i>J</i> = 10.6 Hz, 1H), 2.02 - 1.90 (m, 1H), 1.65 (s, 3H), 1.60 - 1.54 (m, 6H), 1.53 - 1.47 (m, 1H). de: 100 %; Retention time: 0.698 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.

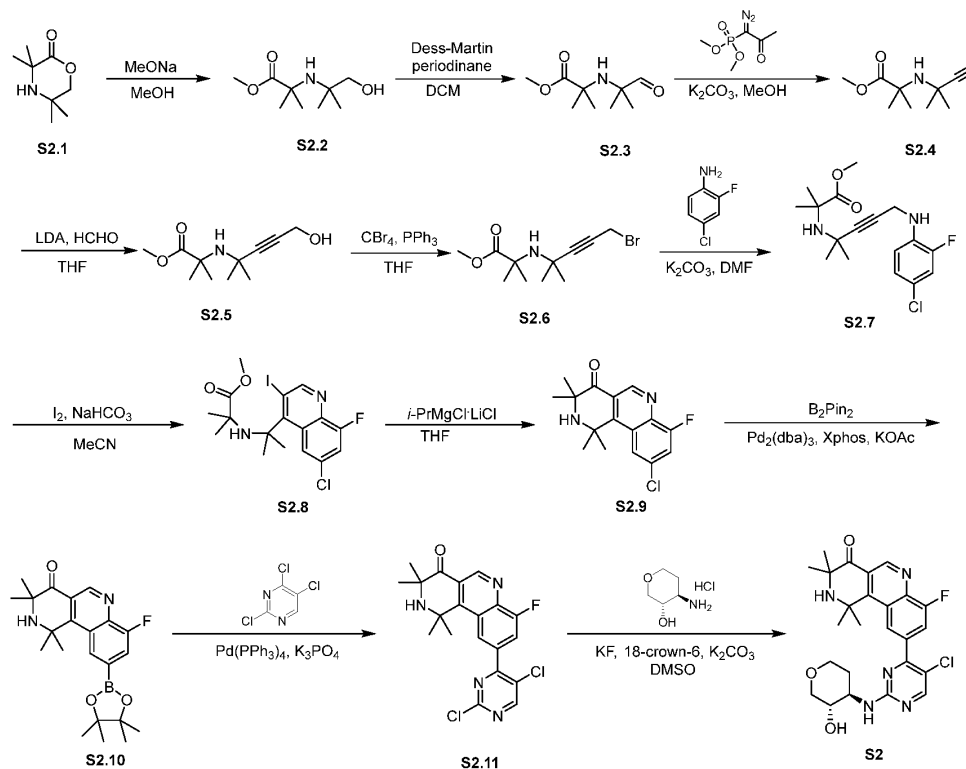
199b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 503.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.66 (d, <i>J</i> = 47.0 Hz, 1H), 8.47 (s, 1H), 7.88 (d, <i>J</i> = 48.7 Hz, 1H), 7.56 (s, 1H), 5.57 (s, 1H), 4.94 (d, <i>J</i> = 4.0 Hz, 1H), 4.91 (s, 2H), 4.86 - 4.77 (m, 1H), 3.91 - 3.78 (m, 3H), 3.75 - 3.68 (m, 2H), 3.56 - 3.46 (m, 1H), 3.36 - 3.27 (m, 1H), 3.03 (t, <i>J</i> = 10.5 Hz, 1H), 2.03 - 1.89 (m, 1H), 1.64 (s, 3H), 1.60 - 1.45 (m, 7H). de: 100 %; Retention time: 1.092 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 50%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
201a	 Isomer 1 (earlier eluting isomer)	LC-MS (ESI): m/z 487.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.00 (s, 1H), 8.51 (d, <i>J</i> = 3.9 Hz, 1H), 8.06 (d, <i>J</i> = 11.5 Hz, 1H), 7.28 (d, <i>J</i> = 7.9 Hz, 1H), 5.59 (s, 1H), 4.95 (d, <i>J</i> = 5.4 Hz, 1H), 4.92 (s, 2H), 4.87 - 4.78 (m, 1H), 3.93 - 3.80 (m, 3H), 3.76 - 3.66 (m, 2H), 3.58 - 3.48 (m, 1H), 3.30 - 3.27 (m, 1H), 3.07 (t, <i>J</i> = 10.4 Hz, 1H), 2.06 - 1.98 (m, 1H), 1.65 (s, 3H), 1.62 (d, <i>J</i> = 7.1 Hz, 3H), 1.57 (d, <i>J</i> = 7.5 Hz, 3H), 1.55 - 1.47 (m, 1H). de: 100 %; Retention time: 0.980 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 30%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.
201b	 Isomer 2 (later eluting isomer)	LC-MS (ESI): m/z 487.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.99 (s, 1H), 8.51 (d, <i>J</i> = 3.9 Hz, 1H), 8.05 (d, <i>J</i> = 11.6 Hz, 1H), 7.28 (d, <i>J</i> = 7.9 Hz, 1H), 5.58 (s, 1H), 4.98 - 4.88 (m, 3H), 4.87 - 4.79 (m, 1H), 3.93 - 3.80 (m, 3H), 3.78 - 3.68 (m, 2H), 3.53 - 3.50 (m, 1H), 3.30 - 3.25 (m, 1H), 3.06 (t, <i>J</i> = 10.4 Hz, 1H), 2.07 - 1.99 (m, 1H), 1.65 (s, 3H), 1.63 - 1.47 (m, 7H). de: 100 %; Retention time: 1.312 min; instrument: SHIMADZU-20AD-XR; column: CHIRALPAK IK-3, 4.6 * 50 mm, 3.0 μm; mobile phase: A for Hex (0.1% DEA) and B for EtOH; gradient: B 30%; flow rate: 1.67 mL/min; high pressure: 110 bar; column temperature: 25 °C; wavelength: 254 nm.

Example S1. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,3-dimethyl-1,2,3,4-tetrahydro-6*H*-pyrimido[1,6-*a*]quinolin-6-one (**S1**)



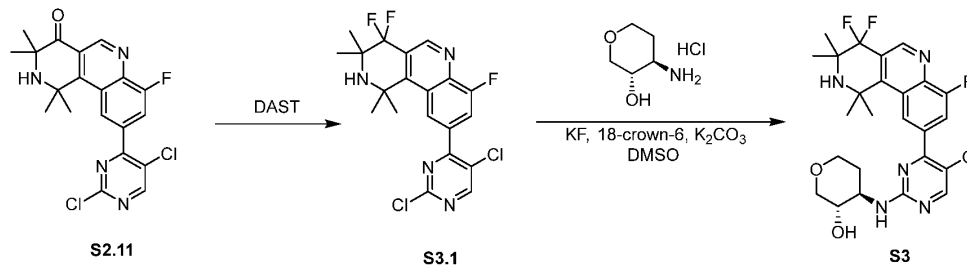
[0417] Starting from reagents **S1.1** and **S1.2**, pyridone derivative **S1.4** is obtained via cyclization of **S1.3**. The pyridone moiety is converted into **S1.6** of methoxy substitution via **S1.5** of chloro substitution. **S1.6** is converted into boronic acid ester **S1.7**, which is coupled with the trichlorosubstituted pyrimidine to give **S1.8**. **S1.8** is brominated via the *m*-CPBA/ POBr_3 procedure. **S1.9** is coupled to give **S1.10**, which is converted into tertiary alcohol **S1.11**. After demethylation of **S1.11** to give **S1.12**, the tertiary alcohol is converted into corresponding tertiary amine **S1.14** via intermediate **S1.13**. Condensation with formaldehyde gives **S1.15**, which is converted into **S1** by substitution with the cyclic amine.

Example S2. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-1,1,3,3-tetramethyl-2,3-dihydrobenzo[*c*][2,6]naphthyridin-4(1*H*)-one (**S2**)



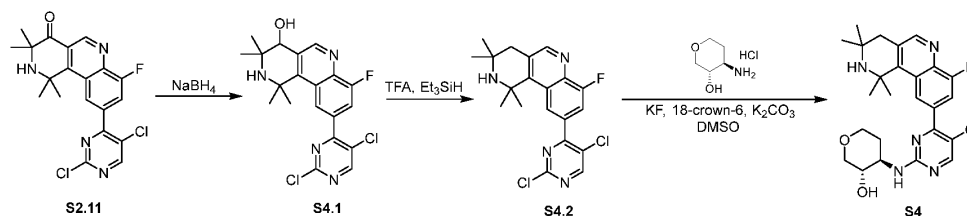
[0418] Intermediate **S2.2** is made by ring-opening esterification of **S2.1**. Oxidation of the hydroxy group in **S2.2** gives the aldehyde **S2.3**, which is converted into the alkyne **S2.4** by reacting with (1-diazo-2-oxopropyl)phosphonate. The primary alcohol **S2.5** is synthesized by reacting **S2.4** with formaldehyde under basic conditions. Subsequent functional transformation leads to corresponding brominated intermediate **S2.6**, which is linked with the disubstituted aniline to give **S2.7**. Intermediate **S2.7** serves as the cyclization precursor to the substituted quinoline **S2.8**, in turn serves as the precursor for cyclization to give the tricyclic **S2.9**. Coupling with trichlorinated pyrimidine is carried out via the boronic ester intermediate **S2.10** to give intermediate **S2.11**, which is substituted to give the terminal product **S2**.

Example S3. (3*S*,4*R*)-4-((5-chloro-4-(4,4,7-trifluoro-1,1,3,3-tetramethyl-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S3**)



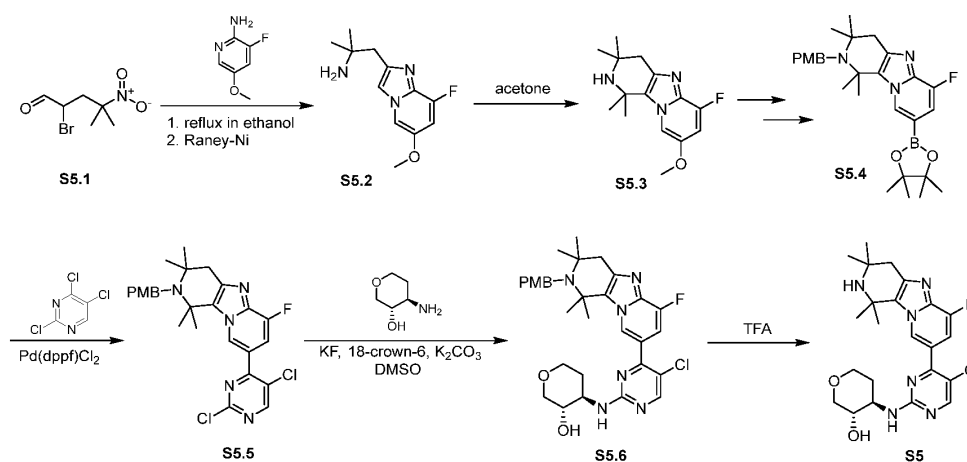
[0419] Intermediate **S2.11** is fluorinated with diethylaminosulfur trifluoride (DAST) to give intermediate **S3.1**, which upon substitution leads to **S3**.

Example S4. (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-1,1,3,3-tetramethyl-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S4**)



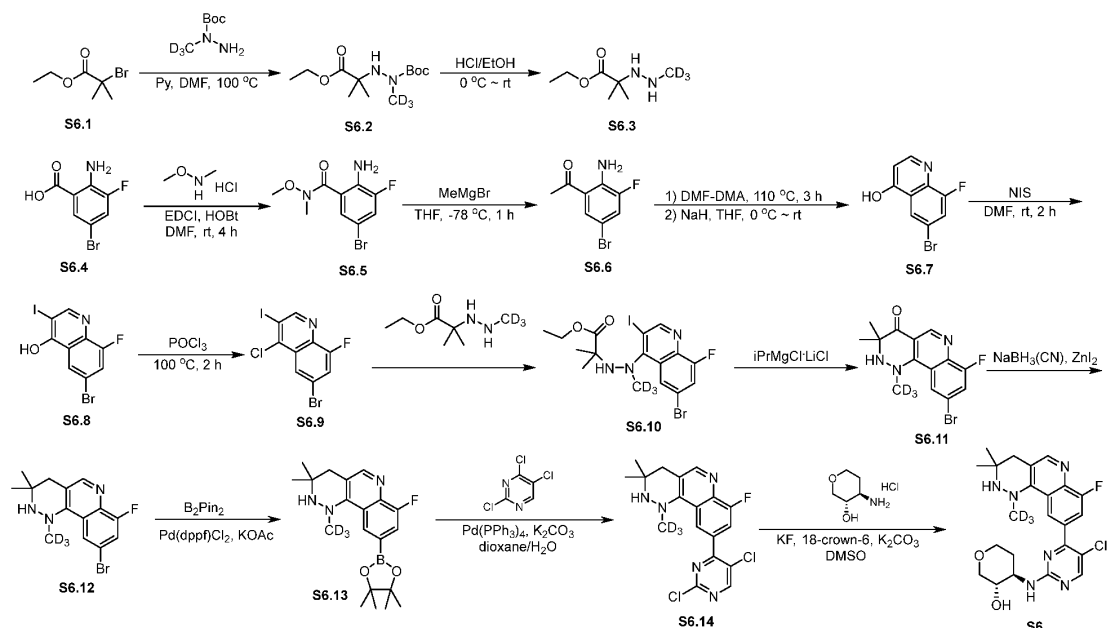
[0420] Reduction of the carbonyl of **S2.11** gives intermediate **S4.2** by two steps. **S4.2** is substituted to give the terminal product **S4**.

Example S5. (3*S*,4*R*)-4-((5-chloro-4-(6-fluoro-1,1,3,3-tetramethyl-1,2,3,4-tetrahydroimidazo[1,2-*a*:5,4-*c'*]dipyridin-8-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S5**)



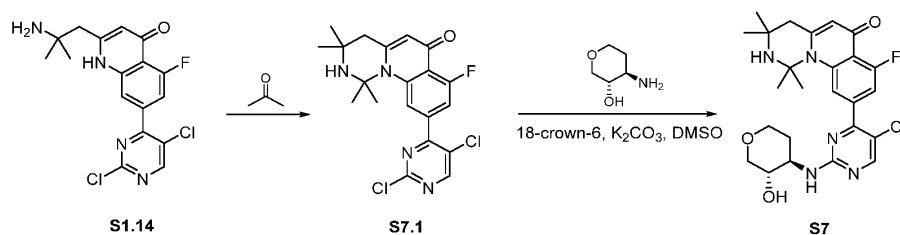
[0421] S5 is synthesized starting from S5.1 according to the synthetic route below, and the first two steps can refer to WO 2003044017 and *Monatshefte fuer Chemie* (2012), 143 (11), 1507-1517.

Example S6. (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-3,3-dimethyl-1-(methyl-*d*₃)-1,2,3,4-tetrahydropyridazino[4,3-*c*]quinolin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (S6)



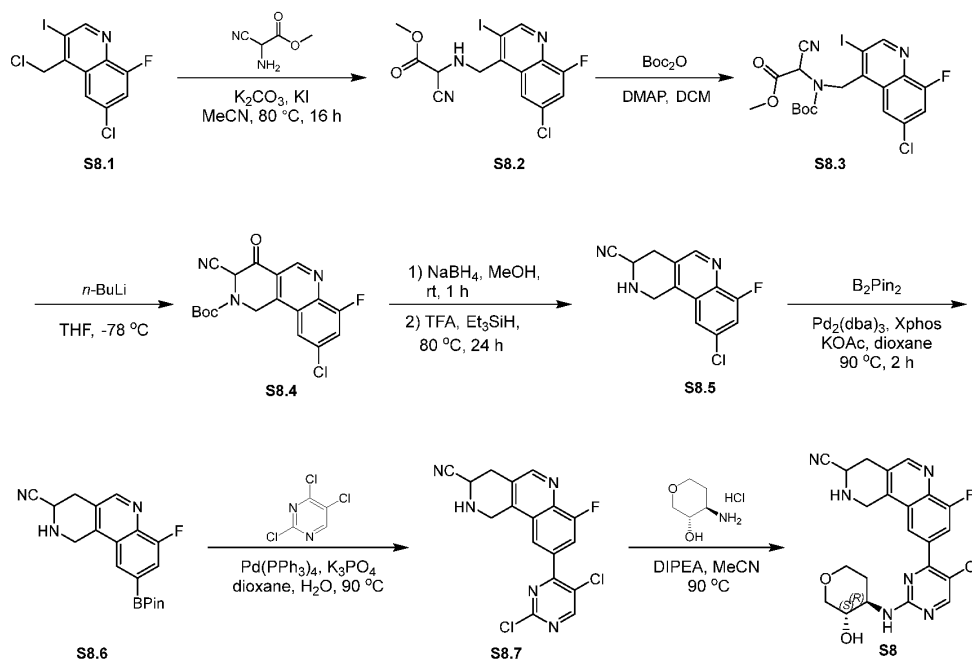
[0422] Starting from S6.4, intermediate S6.6 is made by converting the carboxylic acid into methyl ketone via Weinreb amide S6.5. Cyclization of S6.6 leads to S6.7, which is iodinated to give S6.8, which in turn is converted into S6.9. Substitution with S6.3 (made from S6.1 via S6.2) leads to intermediate S6.10, which upon treated with $\text{iPrMgCl} \cdot \text{LiCl}$ leads to the tricyclic S6.11. Reduction of S6.11 leads to intermediate S6.12, which is converted into corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine leads S6.

Example S7. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-1,1,3,3-tetramethyl-1,2,3,4-tetrahydro-6*H*-pyrimido[1,6-*a*]quinolin-6-one (S7)



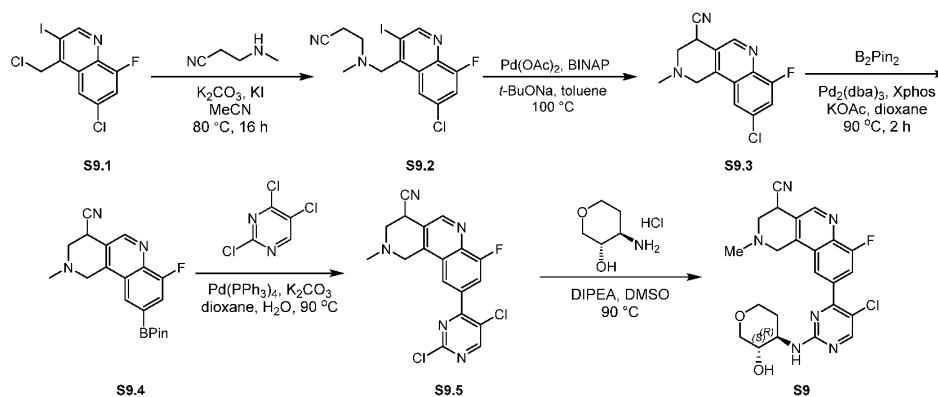
[0423] S7 is made similarly from intermediate S1.14 in the synthesis of S1, using acetone as the condensation partner.

Example S8. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridine-3-carbonitrile (S8)



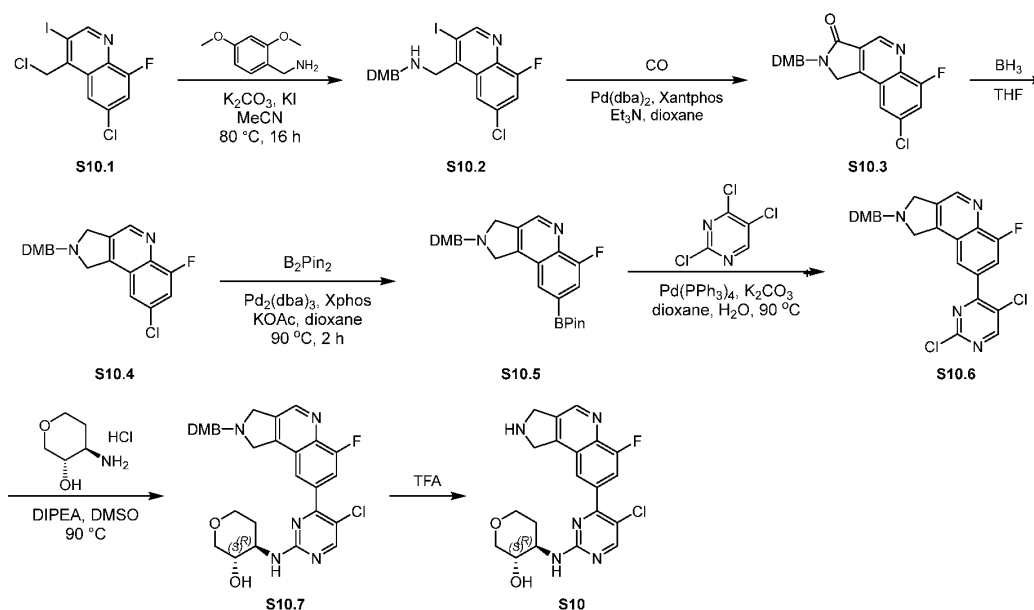
[0424] Starting from S8.1, reacting with amine yields S8.2. Boc protection of the amino group results in S8.3. Subsequently, lithium-halogen exchange with $n-BuLi$ and cyclization lead to S8.4. Reduction of S8.4 gives S8.5, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to S8.

Example S9. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-2-methyl-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridine-4-carbonitrile (S9)



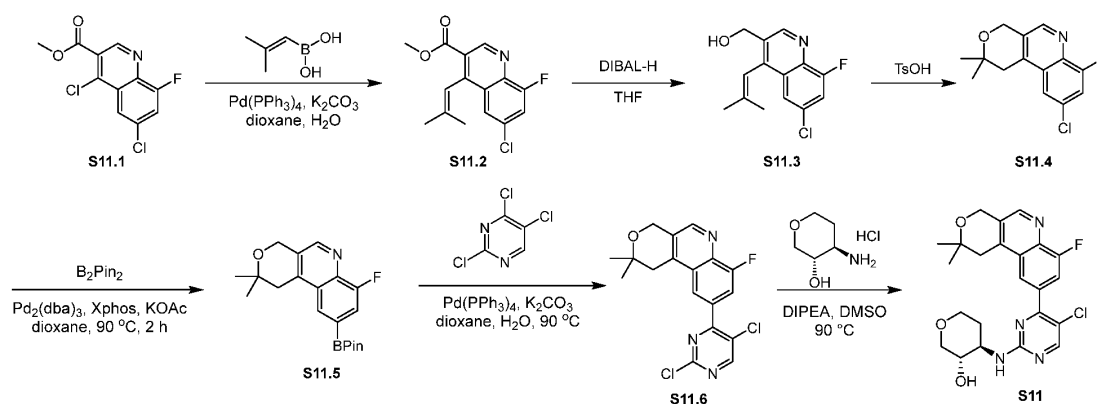
[0425] Starting from **S9.1**, reacting with amine yields **S9.2**. Buckwald coupling results in **S9.3**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to **S9**.

Example S10. (3*S*,4*R*)-4-((5-chloro-4-(6-fluoro-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-8-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S10**)



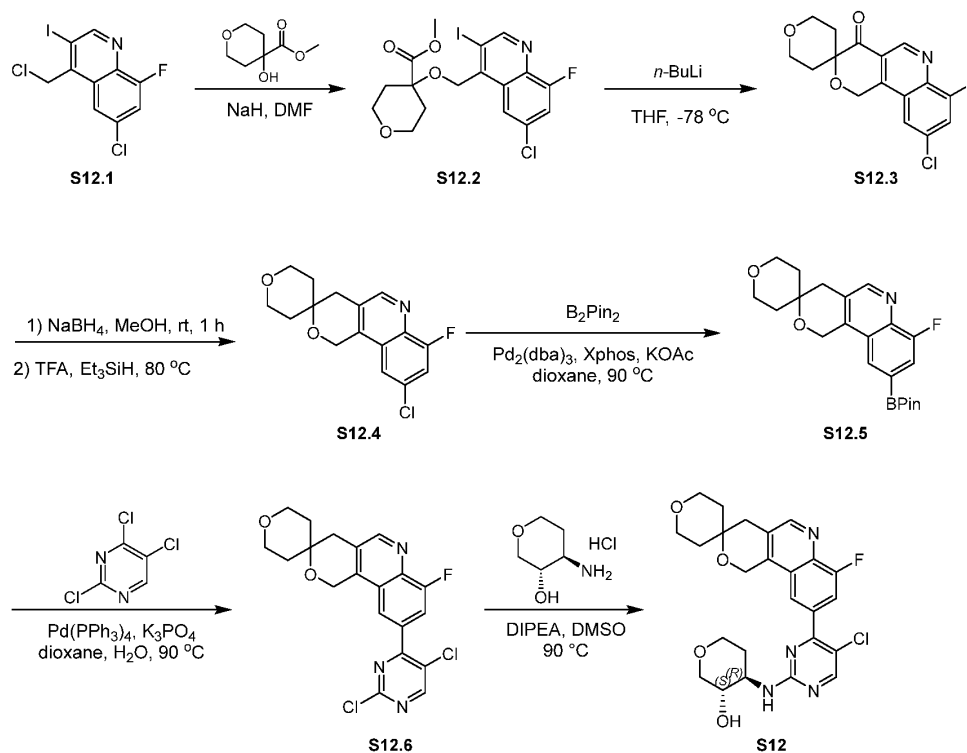
[0426] Starting from **S10.1**, the reaction with amine yields **S10.2**, followed by palladium-catalyzed carbonylation to obtain **S10.3**. Reduction of **S10.3** results in **S10.4**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to **S10.7**. Deprotection of **S10.7** yields **S10**.

Example S11. (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-2,2-dimethyl-1,4-dihydro-2*H*-pyrano[3,4-*c*]quinolin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S11**)



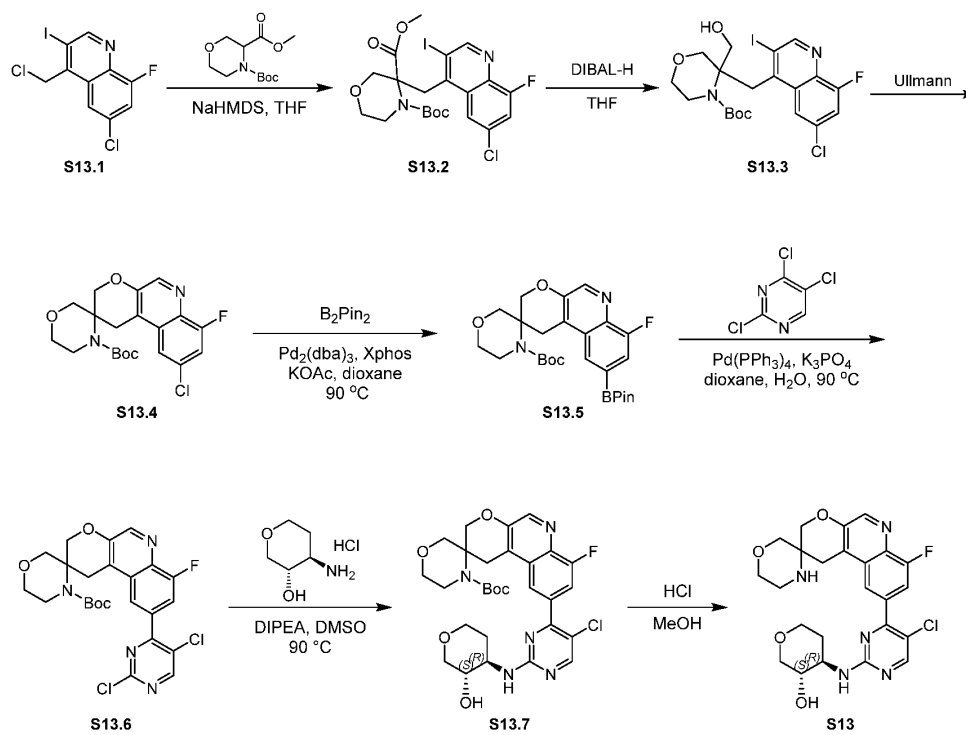
[0427] Starting from **S11.1**, Suzuki reaction with isopropenylboronic acid yields **S11.2**. Ester group reduction results in **S11.3**, and cyclization under acid catalysis gives **S11.4**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to **S11**.

Example S12. (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-2,2-dimethyl-1,4-dihydro-2*H*-pyrano[3,4-*c*]quinolin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S12**)



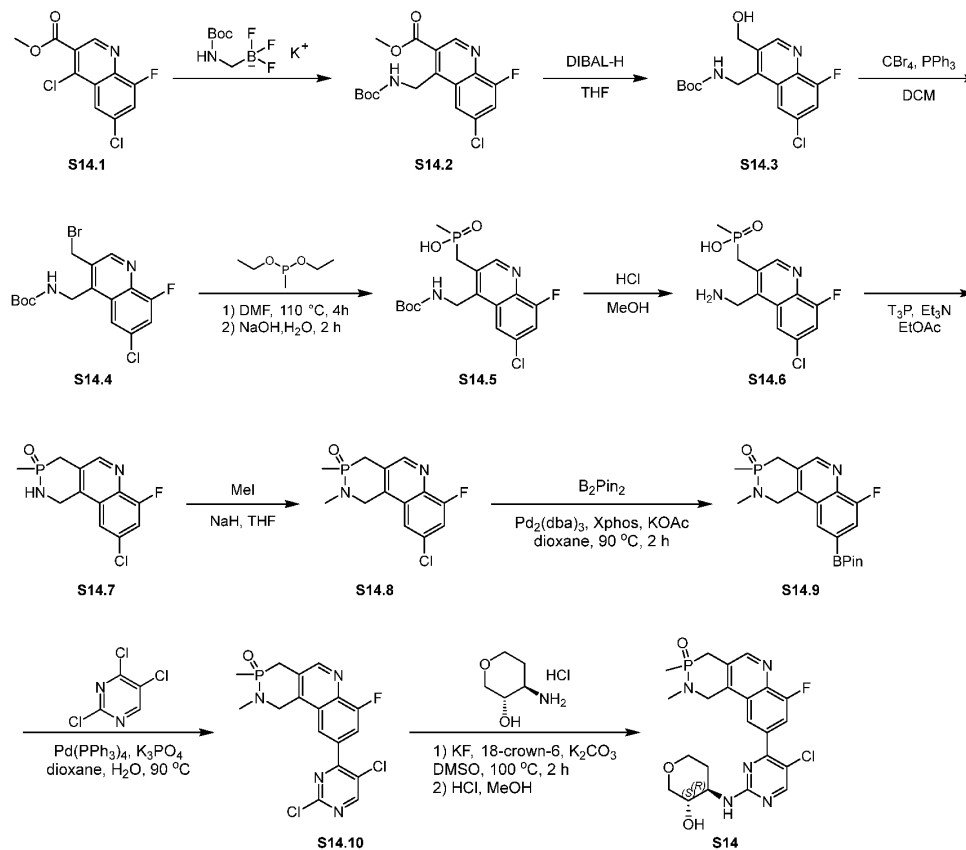
[0428] Starting from **S12.1**, reaction with alcohol yields **S12.2**, followed by lithium-halogen exchange with *n*-BuLi and cyclization to obtain **S12.3**. Reduction of the carbonyl group results in **S12.4**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to **S12**.

Example S13. (3*S*,4*R*)-4-((5-chloro-4-(7'-fluoro-1'*H*,3'*H*-spiro[morpholine-3,2'-pyrano[2,3-*c*]quinolin]-9'-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S13**)



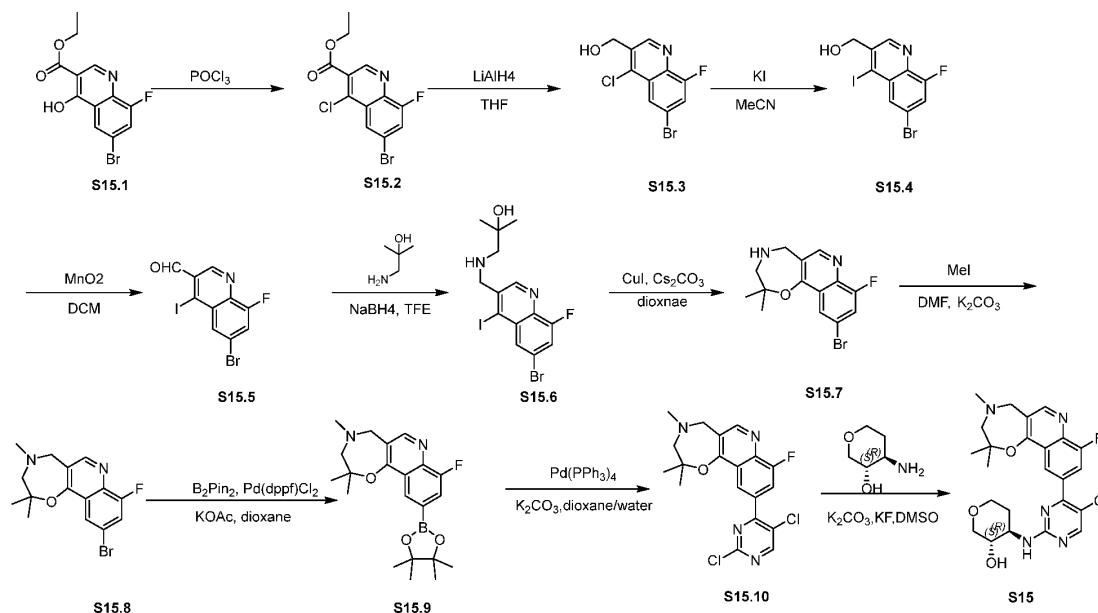
[0429] Starting from intermediate **S13.1**, nucleophilic substitution yields **S13.2**, followed by reduction of the ester group to obtain **S13.3**. Ullmann coupling results in cyclized product **S13.4**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to the formation of **S13.7** followed by deprotection of Boc to obtain **S13**.

Example S14. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-2,3-dimethyl-1,2,4-trihydro-[1,2]azaphosphinino[4,5-*c*]quinoline 3-oxide (**S14**)



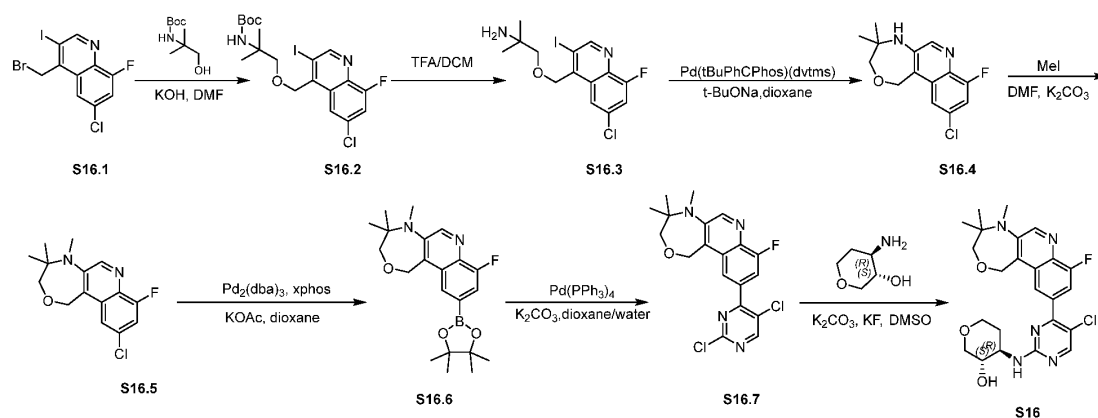
[0430] Starting from **S14.1**, Suzuki coupling yields **S14.2**, followed by reduction of the ester group to obtain **S14.3**. Subsequent Appel reaction results in **S14.4**, which reacts with methyldiethoxyphosphine to yield the phosphinic acid product **S14.5**. De-protection of Boc leads to **S14.6**, followed by condensation to obtain **S14.7**. methylation of **S14.7** results in **S14.8**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to **S14**.

Example S15. (3*S*,4*R*)-4-((5-chloro-4-(8-fluoro-2,2,4-trimethyl-2,3,4,5-tetrahydro-[1,4]oxazepino[6,7-*c*]quinolin-10-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S15**)



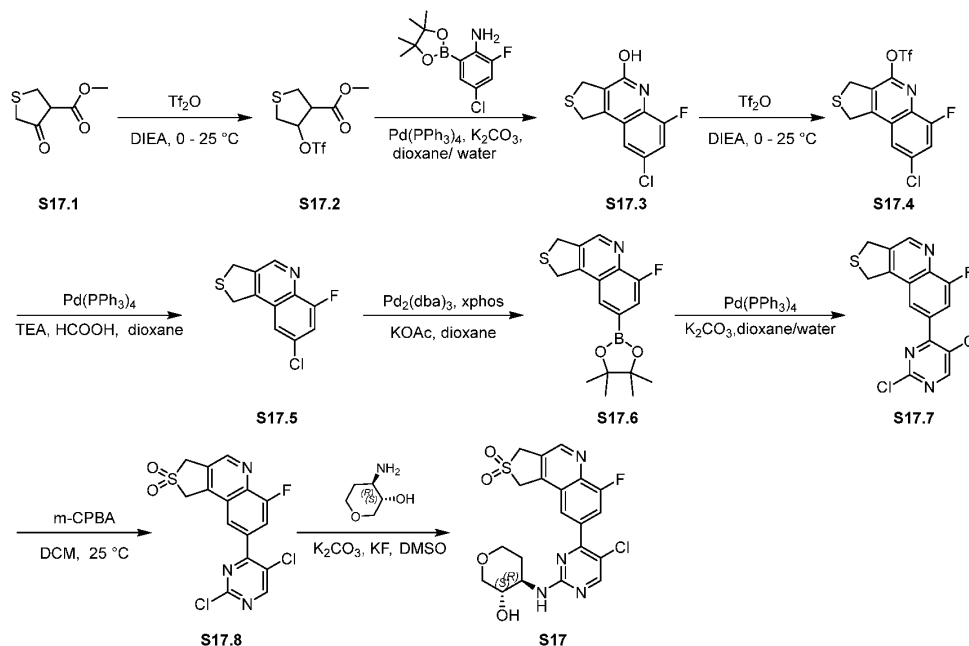
[0431] Starting from **S15.1**, reaction with POCl₃ leads to **S15.2**. The ester group of **S15.2** is reduced to give **S15.3**, which can react with potassium iodide to give **S15.4**. Oxidation of **S15.4** results in **S15.5**. Reductive amination of **S15.5** gives **S15.6**. Cyclization of **S15.6** leads to **S15.7**, which is methylated to give **S15.8**. Coupling with trichlorinated pyrimidine is carried out via the boronic ester intermediate **S15.9** to give intermediate **S15.10**, which is substituted to give the terminal product **S15**.

Example S16. (3*S*,4*R*)-4-((5-chloro-4-(8-fluoro-4,4,5-trimethyl-1,3,4,5-tetrahydro-[1,4]oxazepino[5,6-*c*]quinolin-10-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S16**)



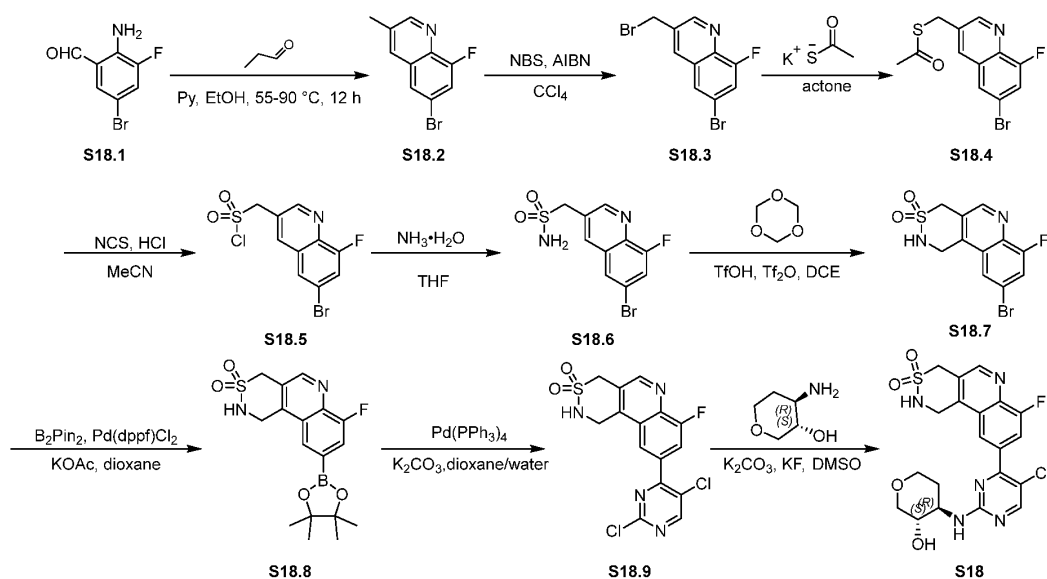
[0432] Starting from intermediate **S16.1**, **S16.4** is obtained via cyclization of **S16.3**. Methylation of **S16.4** results in **S16.5**. Coupling with trichlorinated pyrimidine is carried out via the boronic ester intermediate **S16.6** to give intermediate **S16.7**, which is substituted to give the terminal product **S16**.

Example S17. 8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-1,3-dihydrothieno[3,4-*c*]quinoline 2,2-dioxide (**S17**)



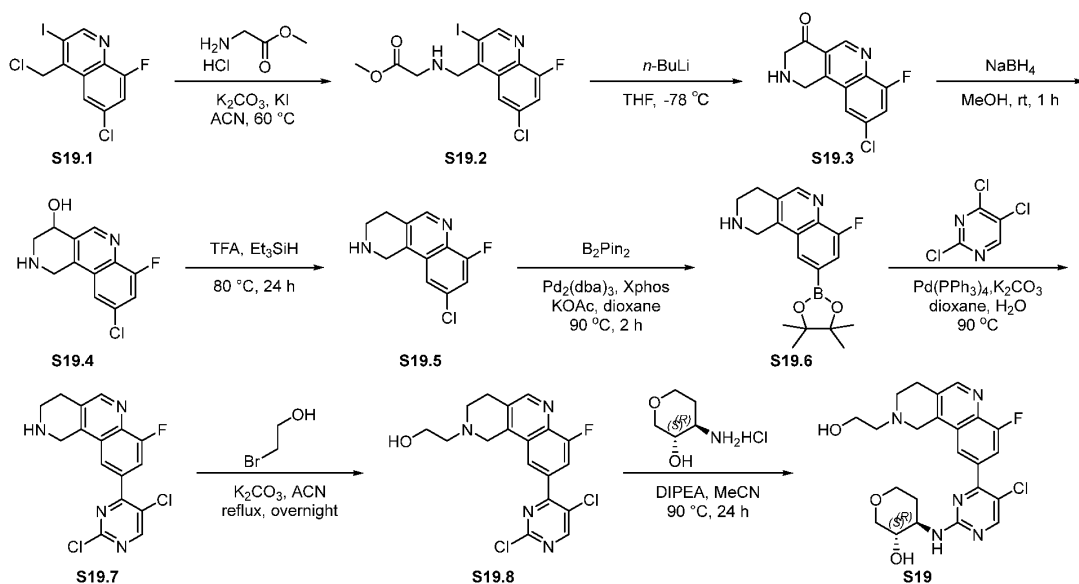
[0433] Starting from **S17.1**, quinoline derivative **S17.3** is obtained via coupling of **S17.2** with 4-chloro-2-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline. The quinoline moiety is converted into **S17.5** via the reduction of **S17.4**. Coupling with trichlorinated pyrimidine is carried out via the boronic ester intermediate **S17.6** to give intermediate **S17.7**, which is oxidated with *m*-CPBA to give **S17.8**. **S17.8** is substituted to give the terminal product **S17**.

Example S18. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-1,4-dihydro-2*H*-[1,2]thiazino[5,4-*c*]quinoline 3,3-dioxide (**S18**)



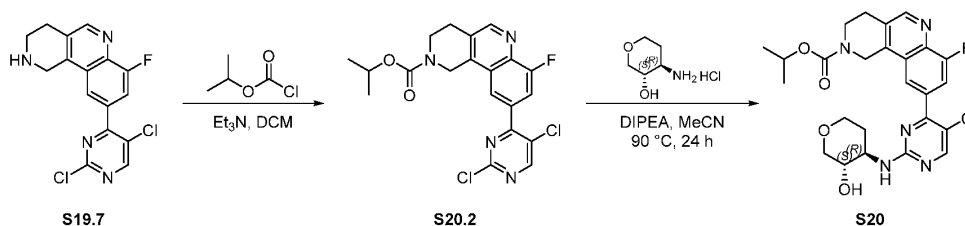
[0434] Starting from **S18.1**, quinoline derivative **S18.2** is obtained via cyclization of **S18.1**. **S18.2** is brominated to give **S18.3**, which is substituted with potassium thioacetate to give **S18.4**. The oxidation of **S18.4** gives **S18.5** via NCS. **S18.6** is obtained via **S18.5** reacts with ammonium hydroxide. Cyclization of **S18.6** leads to **S18.7**. Coupling with trichlorinated pyrimidine is carried out via the boronic ester intermediate **S18.8** to give intermediate **S18.9**, which is substituted to give the terminal product **S18**.

Example S19. (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-2-(2-hydroxyethyl)-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S19**)



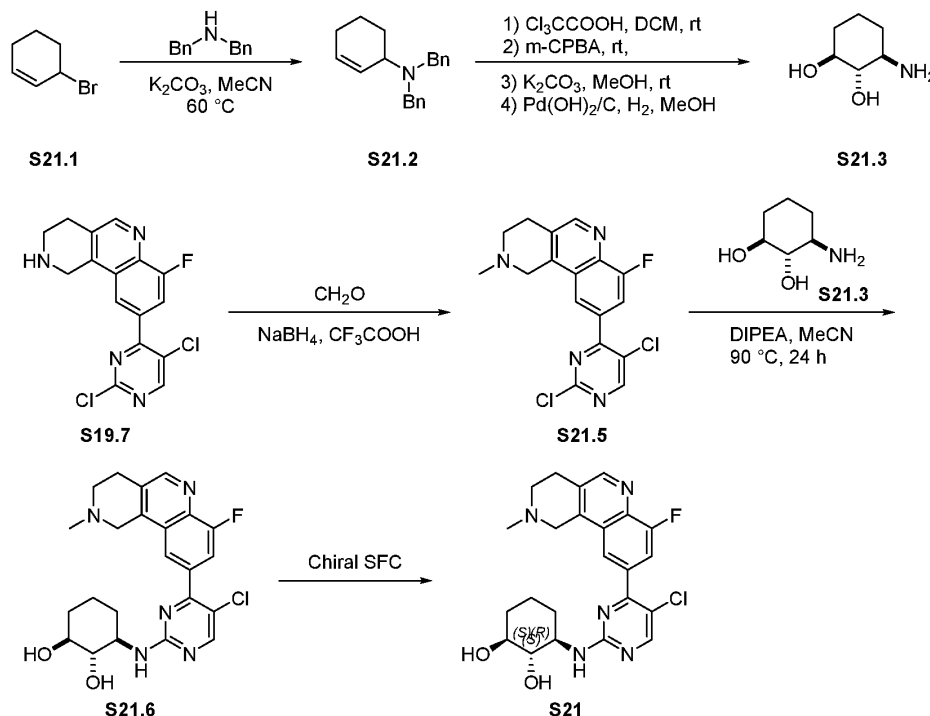
[0435] Starting from intermediate **S19.1**, reaction with amine yields **S19.2**, followed by lithium-halogen exchange with *n*-BuLi and cyclization to obtain **S19.3**. Reduction of the carbonyl group in two steps lead to **S19.5**, which is converted into the corresponding boronic acid pinacol ester. Suzuki coupling yields **S19.7** from **S19.6**. Reaction with bromoethanol produces **S19.8**, and substitution with the cyclic amine leads to **S19**.

Example S20. Isopropyl 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,4-dihydrobenzo[*c*][2,6]naphthyridine-2(1*H*)-carboxylate (**S20**)



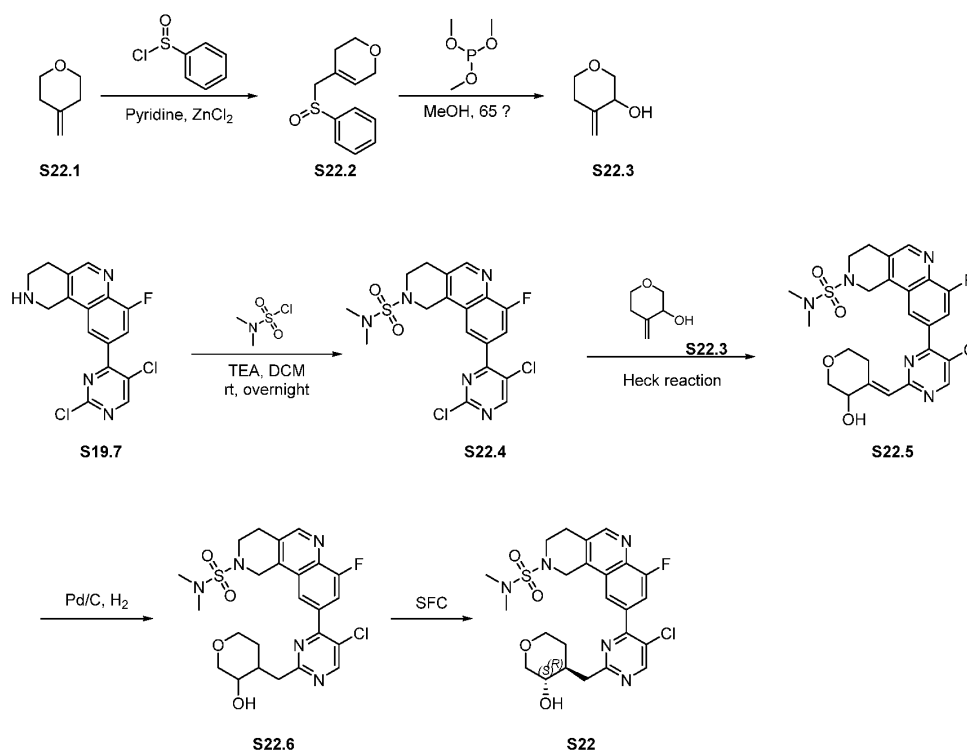
[0436] Starting from intermediate **S19.7**, reaction with isopropyl chloroformate yields **S20.2**, and substitution with the cyclic amine leads to **S20**.

Example S21. (1*S*,2*S*,3*R*)-3-((5-chloro-4-(7-fluoro-2-methyl-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)cyclohexane-1,2-diol (**S21**)



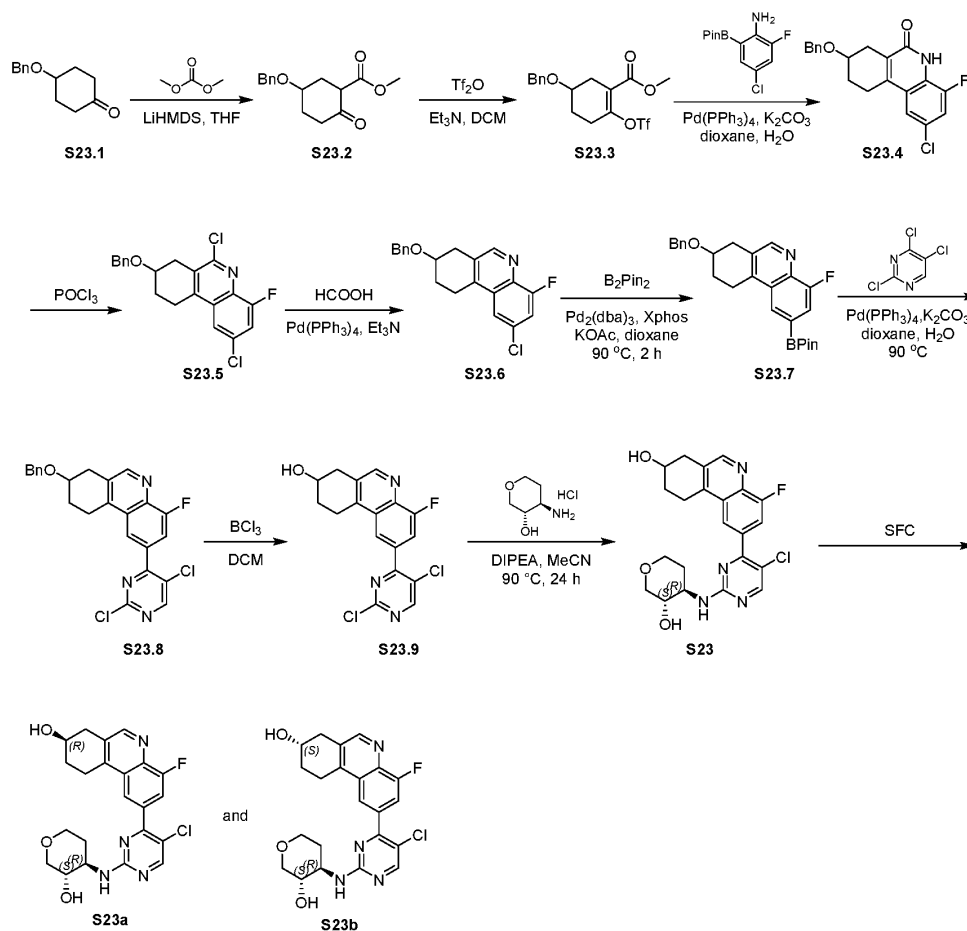
[0437] Intermediate **S21.3** is synthesized following the reference (*Organic Letters*, **2009**, 11, 1333 - 1336). Starting from intermediate **S19.7**, reductive amination yields **S21.5**, and then substitution with **S21.3** leads to **S21.6**, which is separated by chiral SFC to obtain **S21**.

Example S22. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)methyl)pyrimidin-4-yl)-7-fluoro-*N,N*-dimethyl-3,4-dihydrobenzo[*c*][2,6]naphthyridine-2(1*H*)-sulfonamide (**S22**)



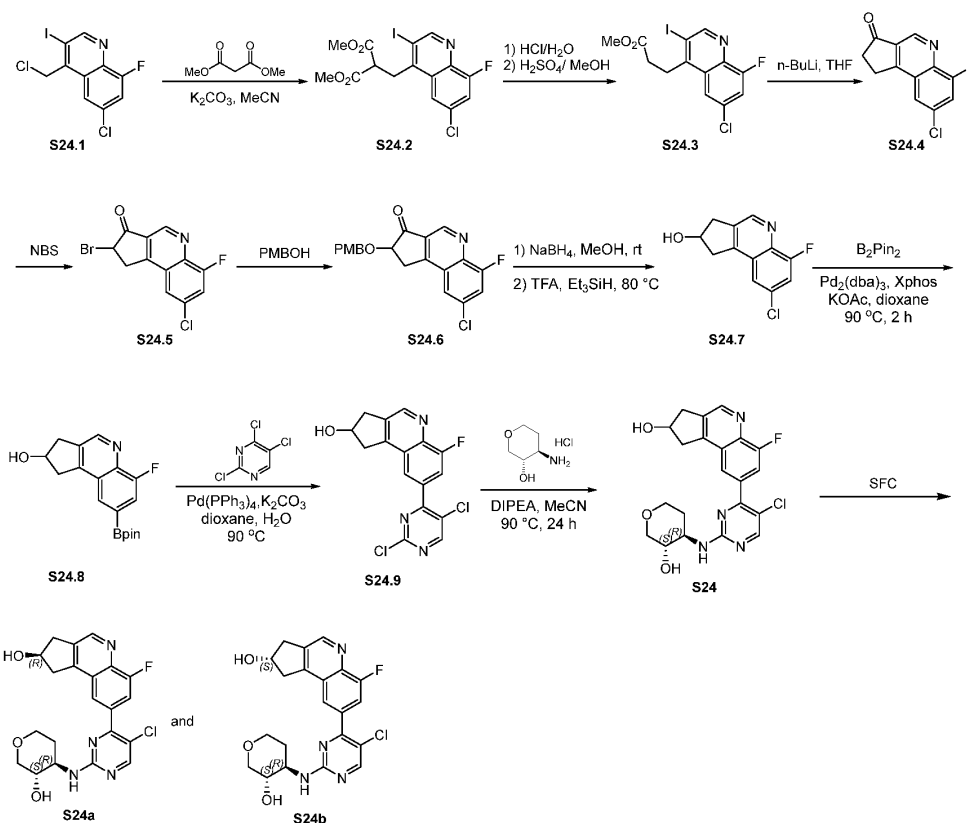
[0438] Intermediate **S22.3** is synthesized following the reference (doi.org/10.1007/BF00962409). Intermediate **S19.7** reacts with dimethylaminosulfonyl chloride to yield **S22.4**. Subsequent Heck reaction with **S22.3** leads to **S22.5**, and the olefin is reduced to obtain **S22.6**, which is separated by chiral SFC to obtain **S22**.

Example S23. (*R*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,8,9,10-tetrahydrophenanthridin-8-ol (**S23a**) and (*S*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,8,9,10-tetrahydrophenanthridin-8-ol (**S23b**)



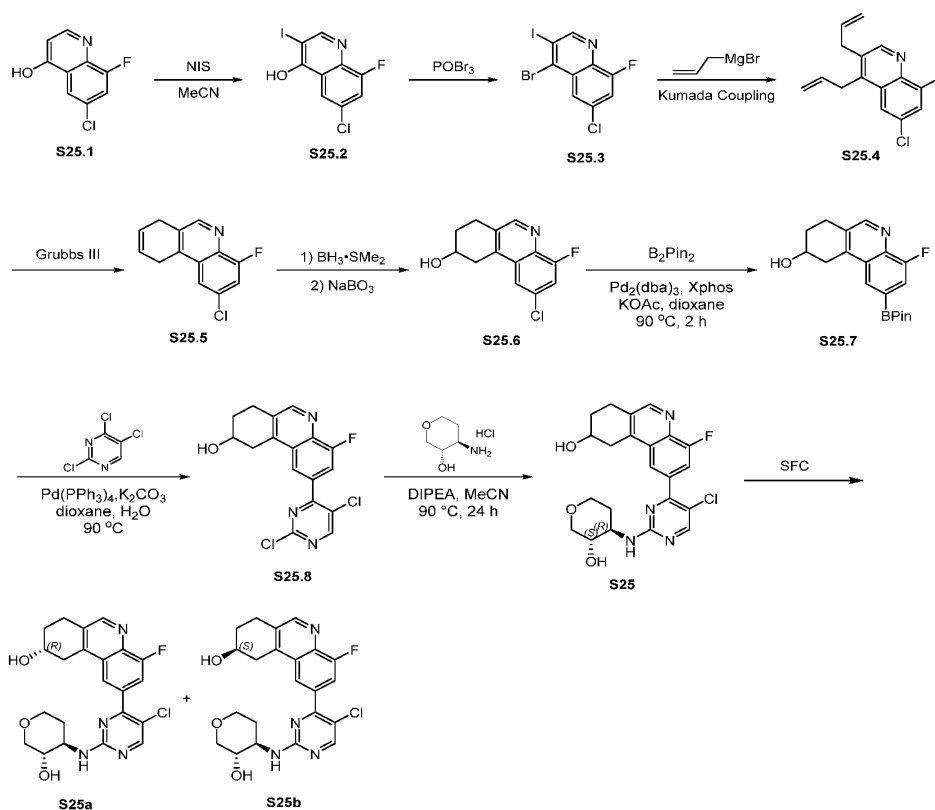
[0439] Starting material **S23.1**, through carbonylation, yields **S23.2**. Reaction with TiF_2O produces **S23.3**, followed by Suzuki coupling to obtain the cyclized product quinolinone **S23.4**. Chlorination and dechlorination of quinolinone **S23.4** lead to **S23.6**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling yields **S23.8**, and de-Bn results in **S23.9**. Substitution with the cyclic amine produces **S23a** and **S23b**.

Example S24. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-2-ol (**S24a**) and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-2-ol (**S24b**)



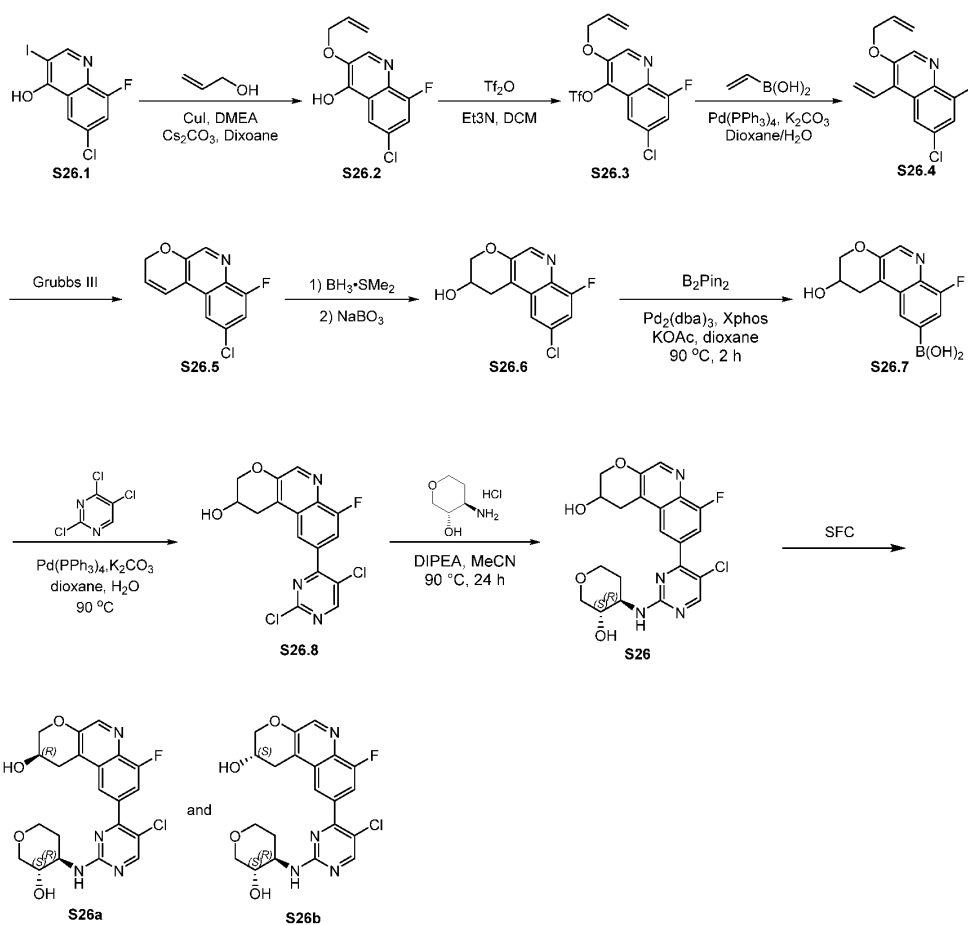
[0440] Starting from intermediate **S24.1**, the reaction with dimethyl malonate yields **S24.2**. Acid hydrolysis and esterification result in the formation of **S24.3**, which is then subjected to lithium-halogen exchange with $n\text{-BuLi}$ and cyclization, leading to the production of **S24.4**. The bromination of the carbonyl α -position yields **S24.5**, which is then subjected to nucleophilic substitution with PMBOH to obtain **S24.6**. Reduction of the carbonyl group, along with de-PMB, results in **S24.7**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to **S24a** and **S24b**.

Example S25. (*R*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,8,9,10-tetrahydrophenanthridin-9-ol (**S25a**) and (*S*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,8,9,10-tetrahydrophenanthridin-9-ol (**S25b**)



[0441] Starting from intermediate **S25.1**, iodination and bromination yield **S25.3**. **S25.3** undergoes Kumada coupling to form **S25.4**, and the Grubbs reaction is used for cyclization to produce **S25.5**. The olefin is then subjected to Brown hydroboration/oxidation to obtain the hydroxy derivative **S25.6**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to the formation of **S25a** and **S25b**.

Example S26. (*R*)-9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-2,3-dihydro-1*H*-pyrano[2,3-*c*]quinolin-2-ol (**S26a**) and (*S*)-9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-2,3-dihydro-1*H*-pyrano[2,3-*c*]quinolin-2-ol (**S26b**)

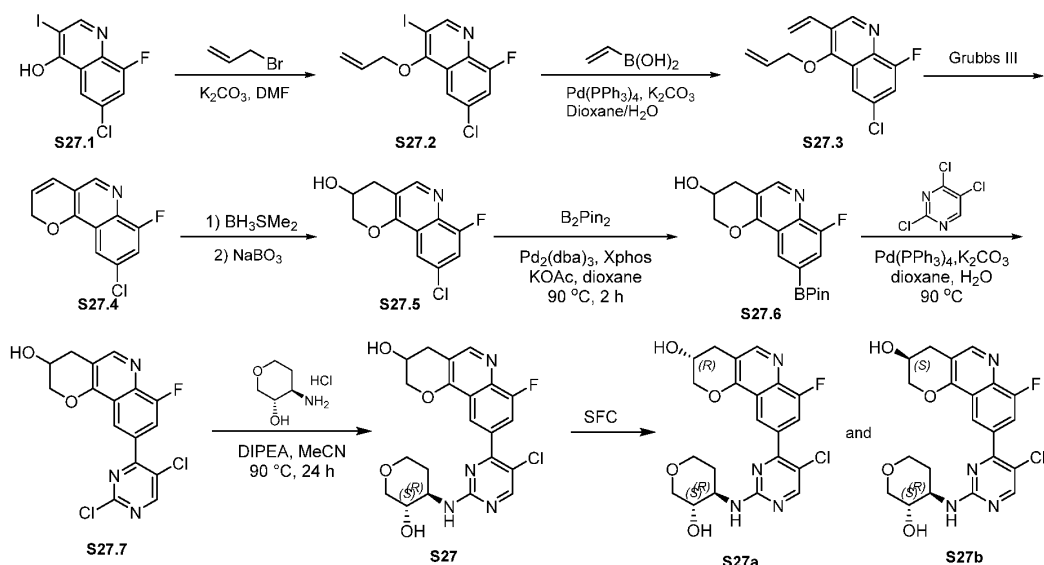


[0442] Starting from intermediate **S26.1**, the Ullmann coupling produces **S26.2**, which then reacts with TiF_2O to form **S26.3**. This is followed by Suzuki coupling with ethenylboronic acid to obtain **S26.4**, and cyclization through Grubbs reaction resulting in **S26.5**. The olefin is subsequently subjected to Brown hydroboration/oxidation to yield the hydroxy derivative **S26.6**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to the formation of both **S26a** and **S26b**.

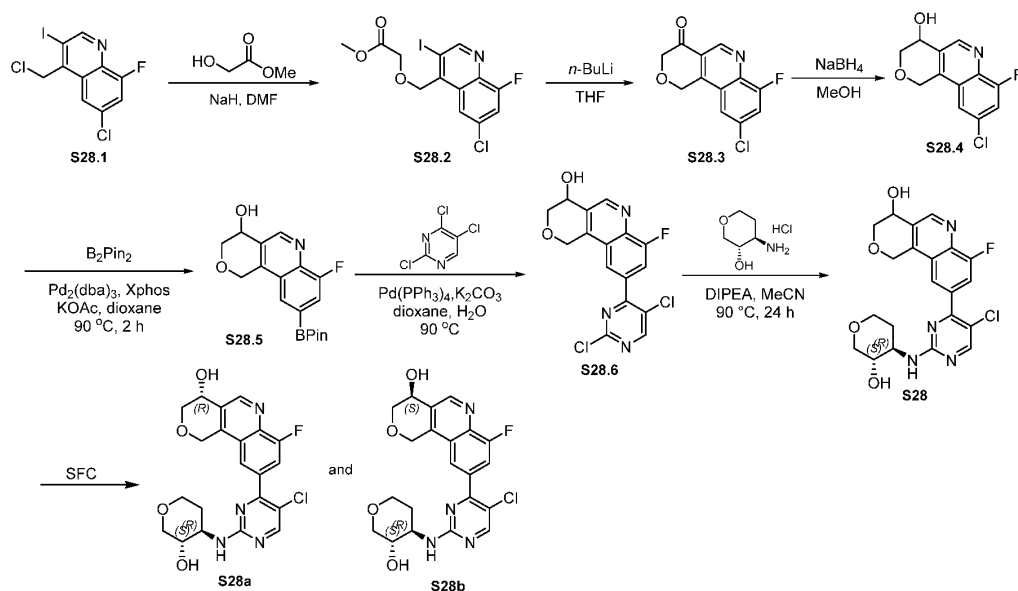
Example S27. (*R*)-9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinolin-3-ol (**S27a**) and (*S*)-9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinolin-3-ol (**S27b**)

[0443] Starting from intermediate **S27.1**, the reaction with allyl bromide yields **S27.2**. Subsequent Suzuki coupling with vinylboronic acid gives rise to **S27.3**. The Grubbs reaction is then employed for cyclization, resulting in the formation of **S27.4**. The olefin is subsequently

converted into a hydroxyl group through Brown hydroboration/oxidation, leading to the generation of **S27.5**, which is further transformed into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine result in the formation of both **S27a** and **S27b**.

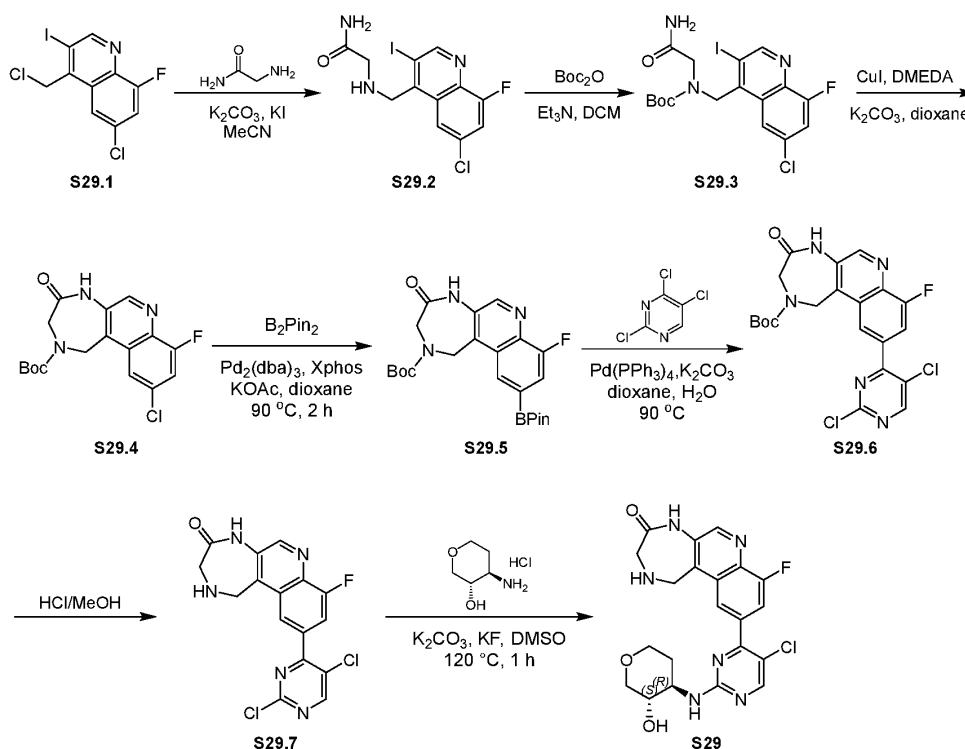


Example S28. (*R*)-9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,4-dihydro-1*H*-pyrano[4,3-*c*]quinolin-4-ol (**S28a**) and (*S*)-9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-3,4-dihydro-1*H*-pyrano[4,3-*c*]quinolin-4-ol (**S28b**)



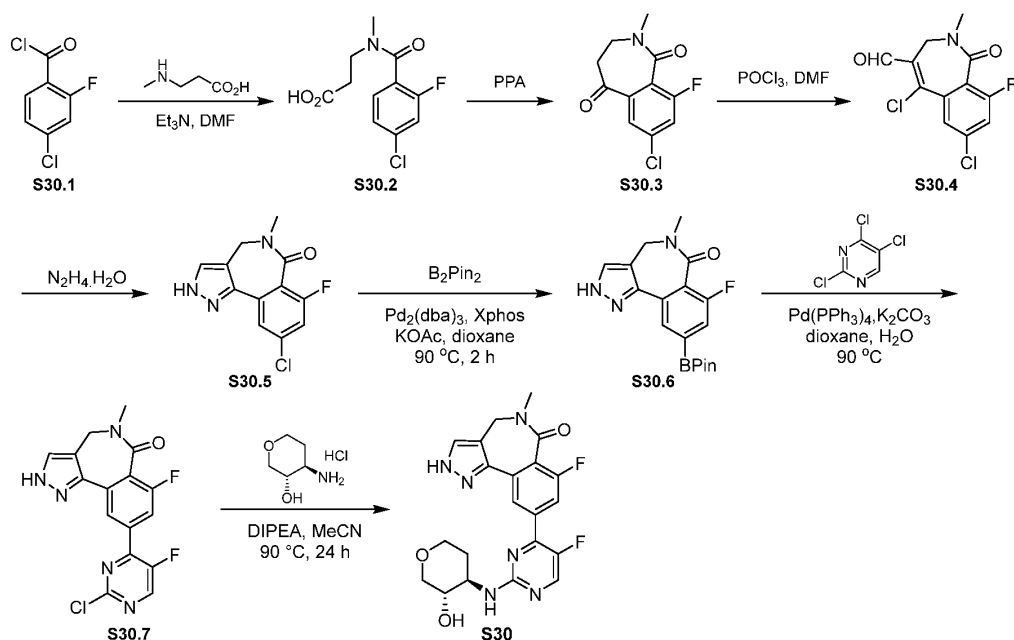
[0444] Starting from intermediate **S28.1**, the reaction with glycolic acid methyl ester yields **S28.2**. Lithium-halogen exchange with *n*-BuLi and cyclization results in **S28.3**. Reduction of the carbonyl group leads to **S28.4**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to **S28a** and **S28b**.

Example S29. 10-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-8-fluoro-1,2,3,5-tetrahydro-4*H*-[1,4]diazepino[5,6-*c*]quinolin-4-one (**S29**)



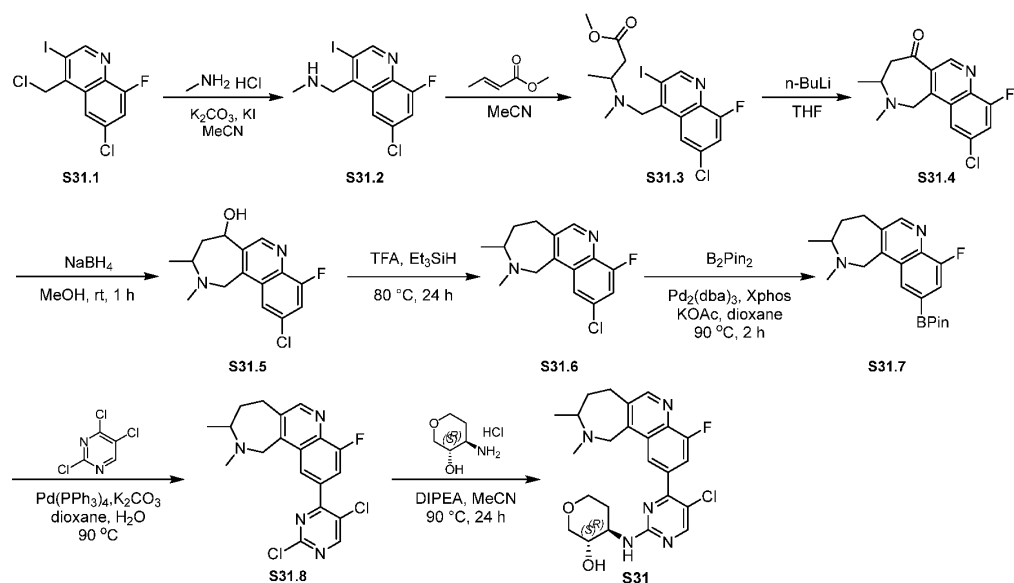
[0445] Starting from intermediate **S29.1**, reaction with Glycinamide yields **S29.2**. Boc protection of the amine results in **S29.3**. Ullmann coupling of **S29.3** leads to **S29.4**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling produces **S29.6**, followed by de-Boc protection to yield **S29.7** and substitution with the cyclic amine and oxidation leading to **S29**.

Example S30. 7-fluoro-9-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-methyl-4,5-dihydrobenzo[*c*]pyrazolo[3,4-*e*]azepin-6(2*H*)-one (**S30**)



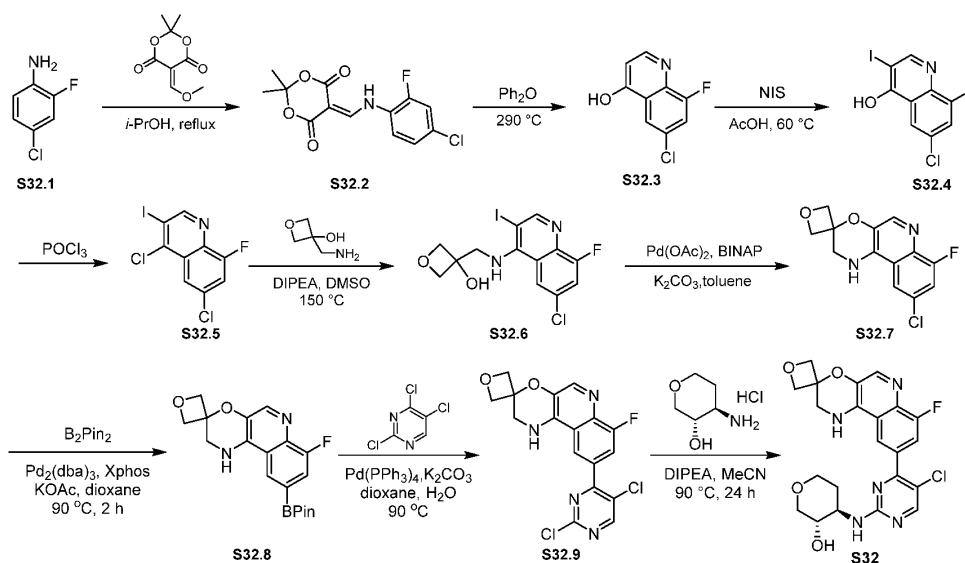
[0446] Starting from intermediate **S30.1**, reaction with methyl aminopropanoate yields **S30.2**. The Friedel-Crafts acylation reaction results in cyclization to obtain **S30.3**. Vilsmeier-Haack reaction and chlorination lead to **S30.4**. Cyclization with hydrazine yields **S30.5**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to **S30**.

Example S31. (3*S*,4*R*)-4-((5-chloro-4-(8-fluoro-2,3-dimethyl-2,3,4,5-tetrahydro-1*H*-azepino[4,3-*c*]quinolin-10-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S31**)



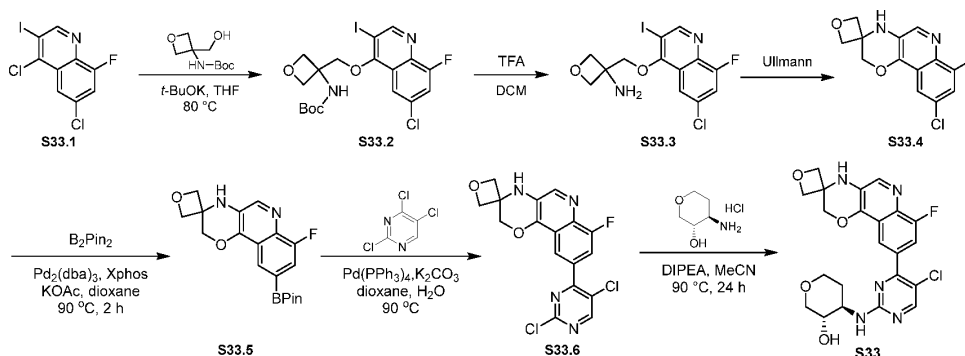
[0447] Starting from intermediate **S31.1**, reaction with methylamine yields **S31.2**. The Michael addition reaction leads to **S31.3**, followed by lithium-halogen exchange with *n*-BuLi and cyclization to obtain **S31.4**. Reduction of the carbonyl group results in **S31.6**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to **S31**.

Example S32. (3*S*,4*R*)-4-((5-chloro-4-(7'-fluoro-1',2'-dihydrospiro[oxetane-3,3']-[1,4]oxazino[2,3-*c*]quinolin]-9'-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S32**)



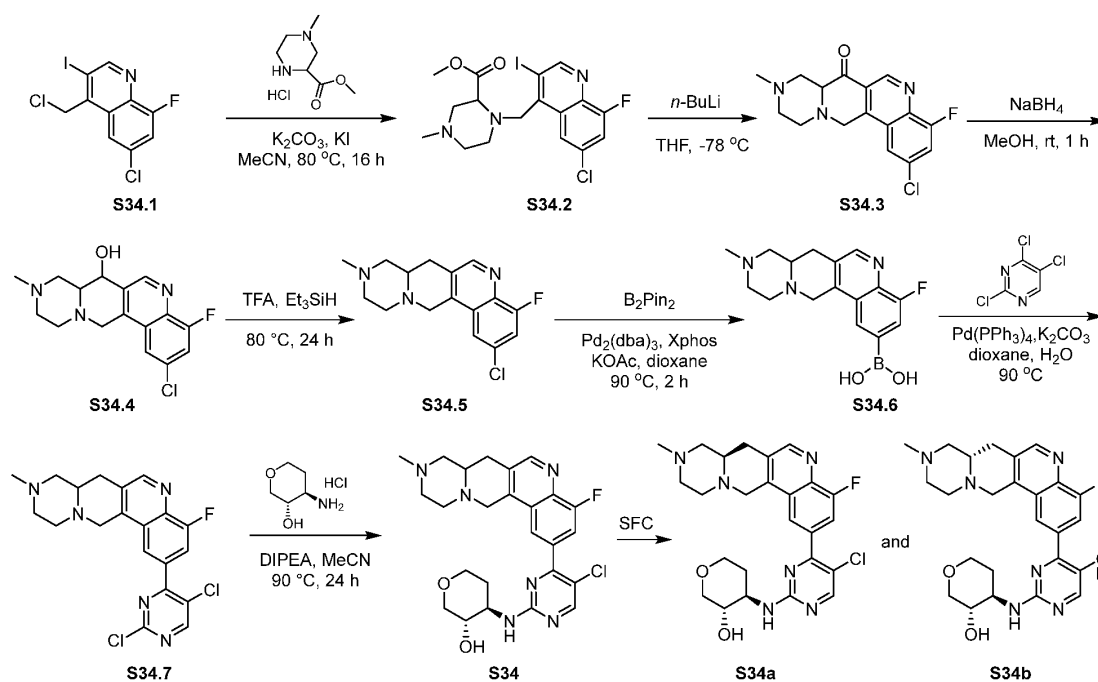
[0448] Starting from intermediate **S32.1**, the first four steps can refer to WO2019229765, leading to **S32.5**. Nucleophilic substitution yields **S32.6**, and Buchwald coupling cyclizes to synthesize **S32.7**, which is converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to **S32**.

Example S33. (3*S*,4*R*)-4-((5-chloro-4-(7'-fluoro-2'*H*,4'*H*-spiro[oxetane-3,3']-[1,4]oxazino[3,2-*c*]quinolin]-9'-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S33**)



[0449] Starting from intermediate **S33.1** (from **S32**), the reaction with an alcohol in the presence of *tert*-butylpotassium results in nucleophilic substitution, yielding **S33.2**. De-Boc with trifluoroacetic acid leads to the formation of **S33.3**. Ullmann coupling is employed for cyclization to synthesize **S33.4**, which is further converted into the corresponding boronic acid pinacol ester. Subsequent Suzuki coupling and substitution with the cyclic amine lead to the formation of **S33**.

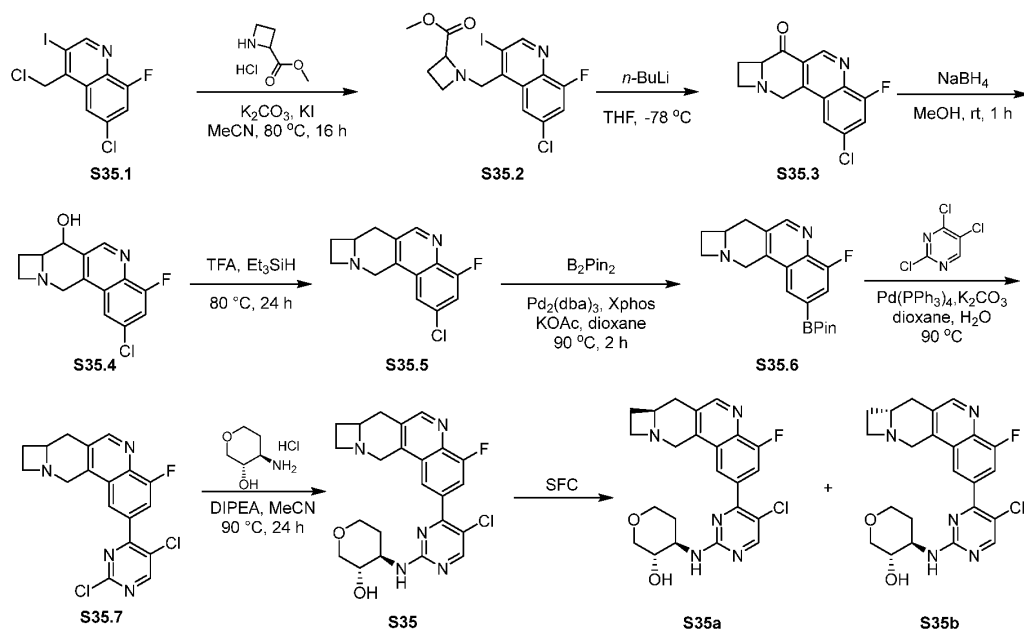
Example S34. (3*S*,4*R*)-4-((5-chloro-4-((*R*)-4-fluoro-9-methyl-7,7*a*,8,10,11,13-hexahydro-9*H*-benzo[*h*]pyrazino[1,2-*b*][2,6]naphthyridin-2-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S34a**) and (3*S*,4*R*)-4-((5-chloro-4-((*S*)-4-fluoro-9-methyl-7,7*a*,8,10,11,13-hexahydro-9*H*-benzo[*h*]pyrazino[1,2-*b*][2,6]naphthyridin-2-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S34b**)



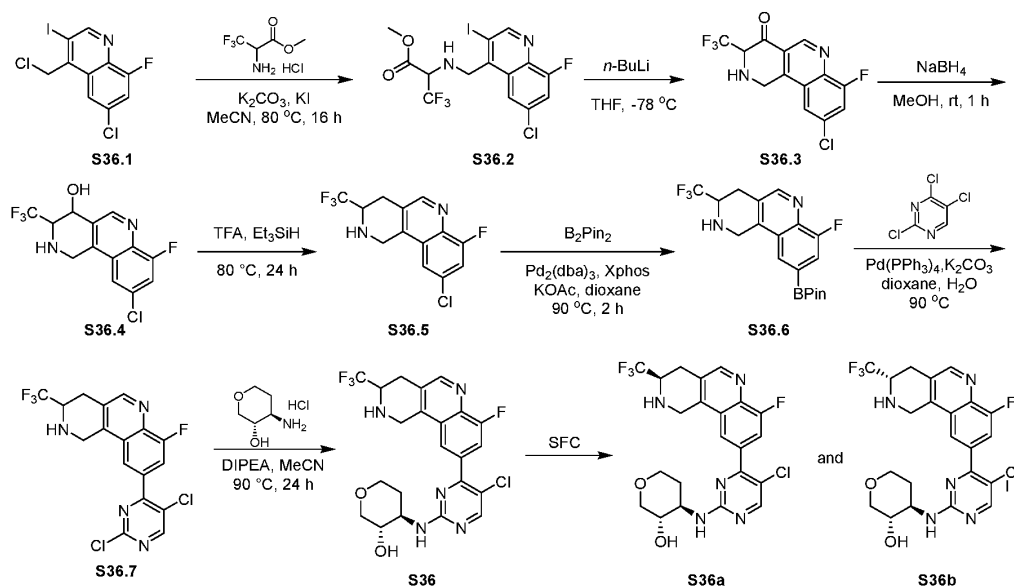
[0450] Intermediate **S34.2** is synthesized through a substitution reaction from the starting material **S34.1**, followed by a lithium-halogen exchange initiated by *n*-butyllithium to induce nucleophilic substitution cyclization. **S34.5** is obtained via a two-step reduction reaction from **S34.3**, which is subsequently transformed into **S34** through similar boronation, Suzuki cross-coupling, and substitution reactions.

Example S35. (3*S*,4*R*)-4-((5-chloro-4-((*R*)-4-fluoro-7,7*a*,8,11-tetrahydro-9*H*-azeto[1,2-*b*]benzo[*h*][2,6]naphthyridin-2-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S35a**) and

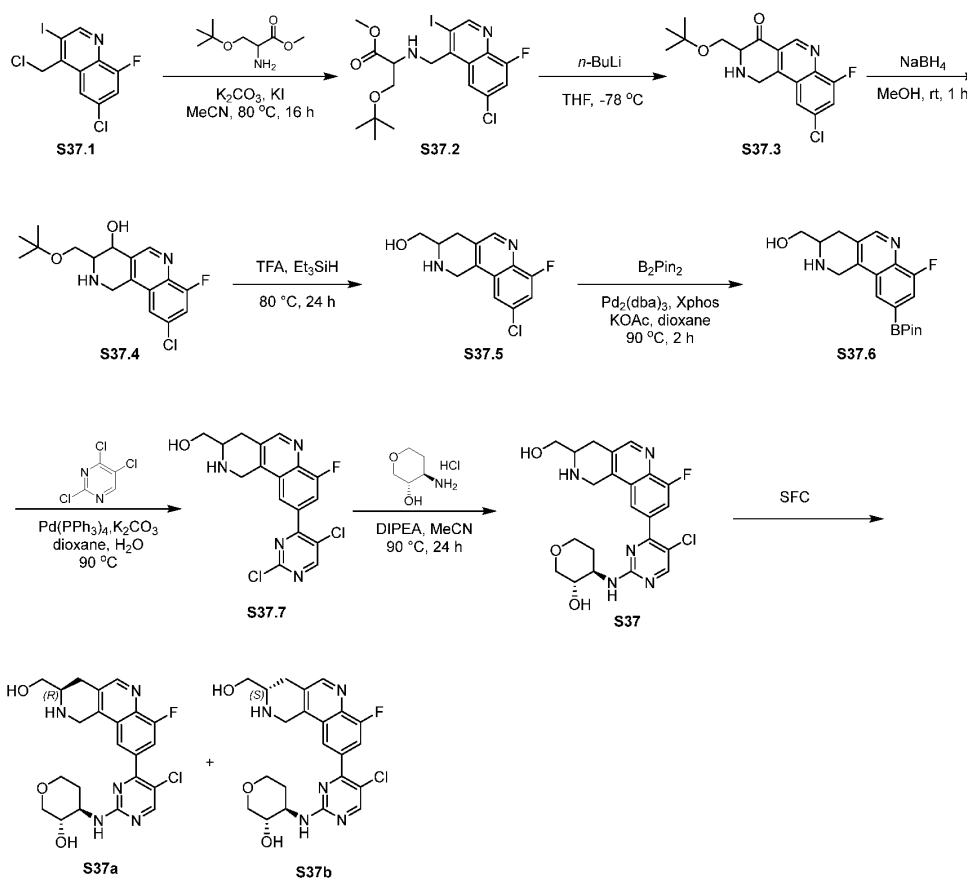
(3*S*,4*R*)-4-((5-chloro-4-((*S*)-4-fluoro-7,7a,8,11-tetrahydro-9*H*-azeto[1,2-*b*]benzo[*h*][2,6]naphthyridin-2-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S35b**)



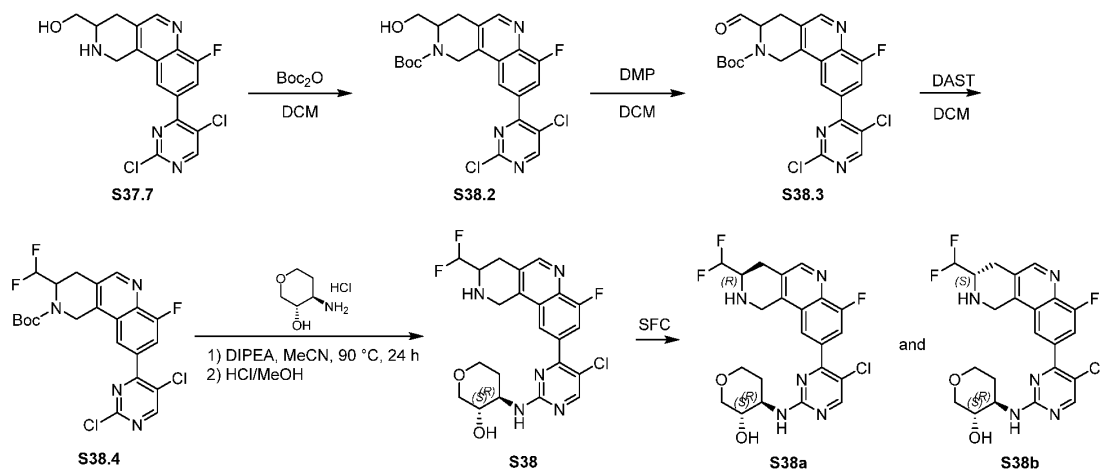
Example S36. (3*S*,4*R*)-4-((5-chloro-4-((*R*)-7-fluoro-3-(trifluoromethyl)-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S36a**) and (3*S*,4*R*)-4-((5-chloro-4-((*S*)-7-fluoro-3-(trifluoromethyl)-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S36b**)



Example S37. (3*S*,4*R*)-4-((5-chloro-4-((*R*)-7-fluoro-3-(hydroxymethyl)-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol
(**S37a**) and (3*S*,4*R*)-4-((5-chloro-4-((*S*)-7-fluoro-3-(hydroxymethyl)-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol
(**S37b**)

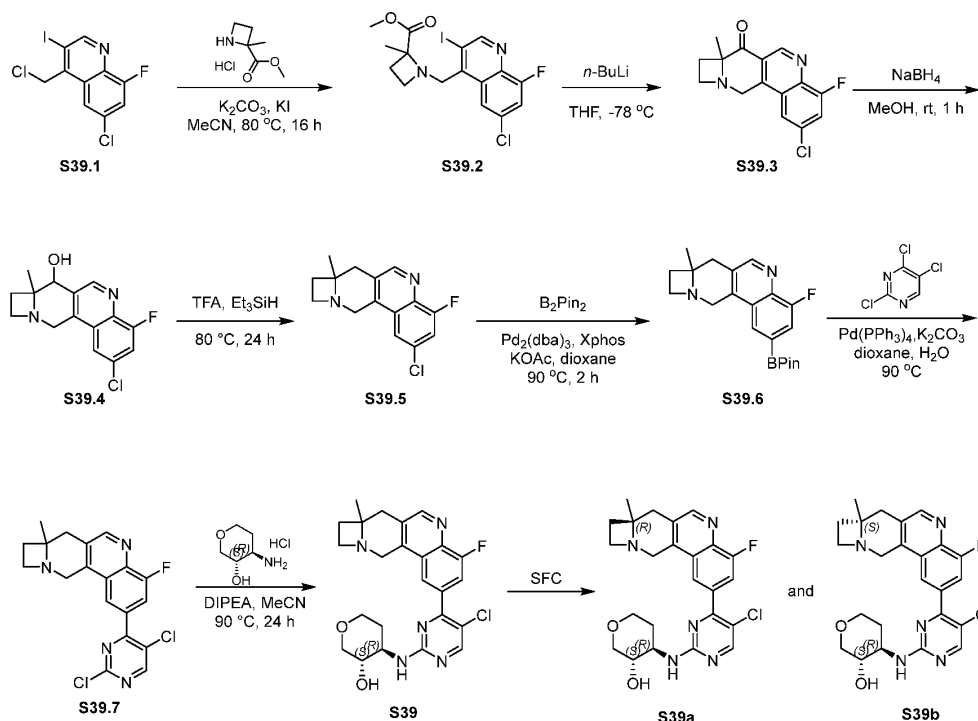


Example S38. (3*S*,4*R*)-4-((5-chloro-4-((*R*)-3-(difluoromethyl)-7-fluoro-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol
(**S38a**) and (3*S*,4*R*)-4-((5-chloro-4-((*S*)-3-(difluoromethyl)-7-fluoro-1,2,3,4-tetrahydrobenzo[*c*][2,6]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol
(**S38b**)

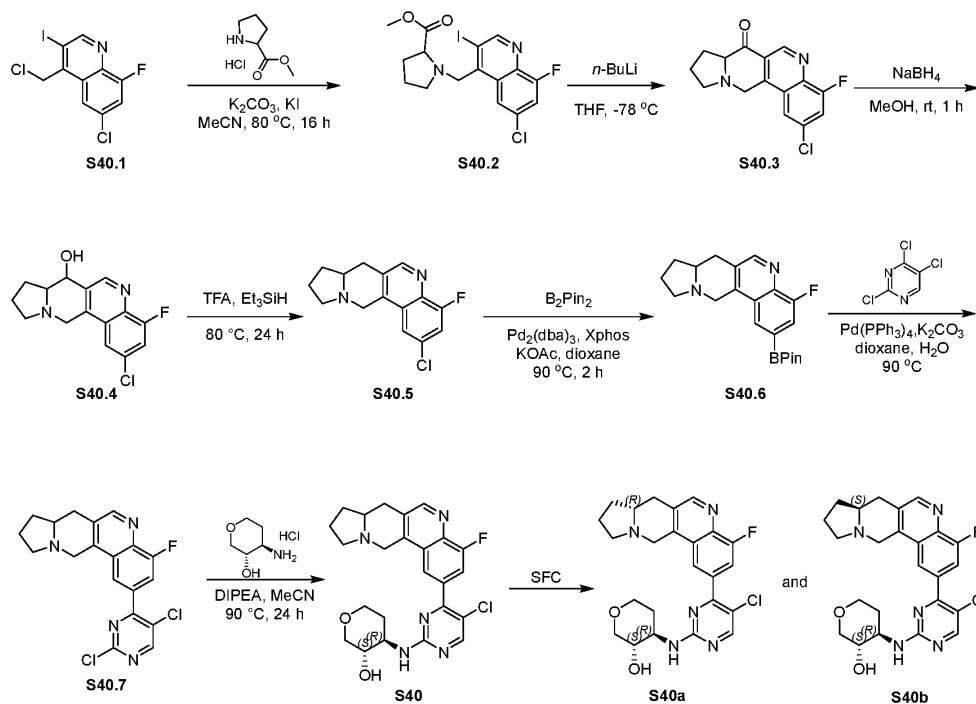


[0451] Starting from intermediate **S37.7**, Boc protection yields **S38.2**. Oxidation of the hydroxyl group with DMP results in aldehyde **S38.3**. After fluorination with DAST , **S38.4** is obtained. Substitution with the cyclic amine leads to **S38**.

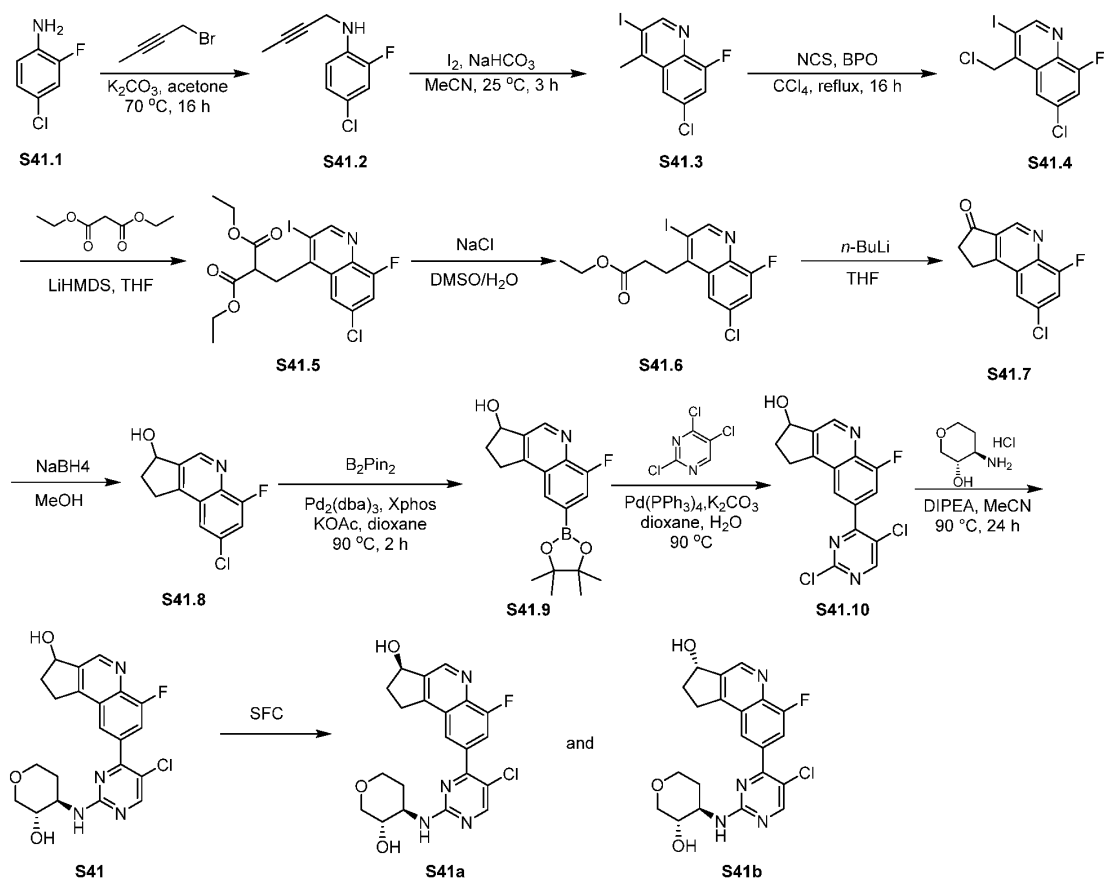
Example S39. (3*S*,4*R*)-4-((5-chloro-4-((*R*)-4-fluoro-7*a*-methyl-7,7*a*,8,11-tetrahydro-9*H*-azeto[1,2-*b*]benzo[*h*][2,6]naphthyridin-2-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S39a**) and (3*S*,4*R*)-4-((5-chloro-4-((*S*)-4-fluoro-7*a*-methyl-7,7*a*,8,11-tetrahydro-9*H*-azeto[1,2-*b*]benzo[*h*][2,6]naphthyridin-2-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S39b**)



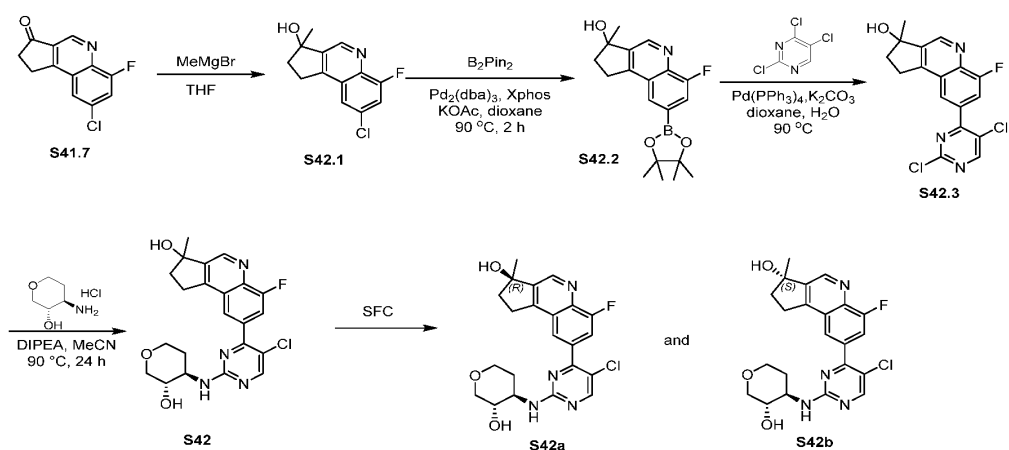
Example S40. (3*S*,4*R*)-4-((5-chloro-4-((*R*)-4-fluoro-7,7*a*,8,9,10,12-hexahydrobenzo[*h*]pyrrolo[1,2-*b*][2,6]naphthyridin-2-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S40a**) and (3*S*,4*R*)-4-((5-chloro-4-((*S*)-4-fluoro-7,7*a*,8,9,10,12-hexahydrobenzo[*h*]pyrrolo[1,2-*b*][2,6]naphthyridin-2-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S40b**)



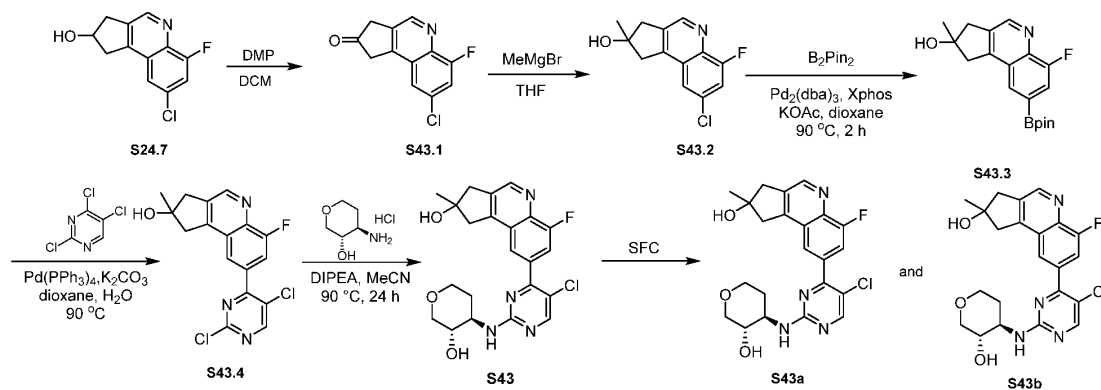
Example S41. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**S41a**) and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**S41b**)



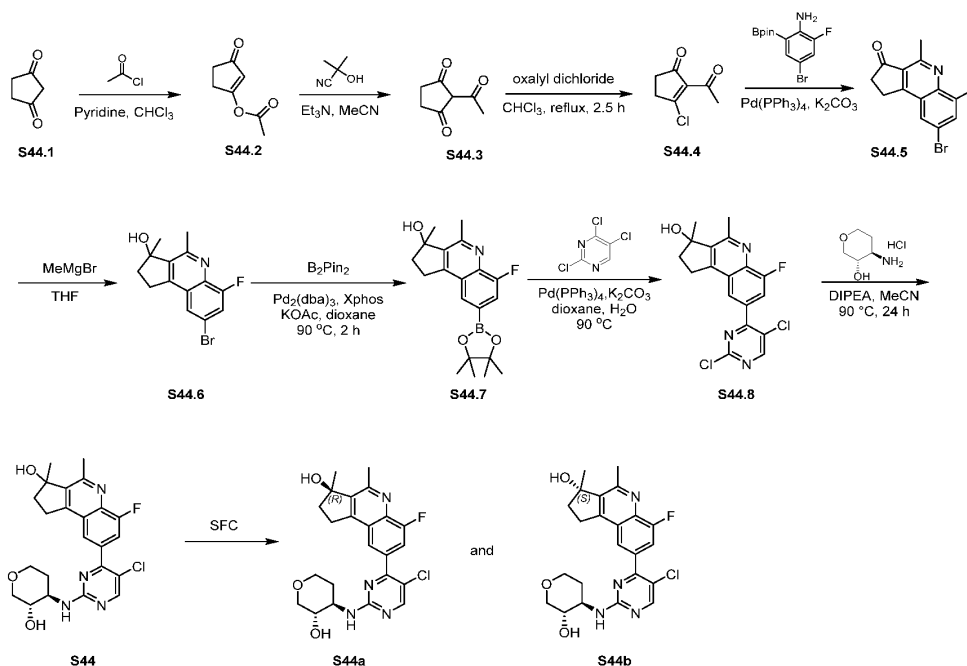
Example S42. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (S42a) and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (S42b)



Example S43. (5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-2-ol (**S43a**) and 8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2-methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-2-ol (**S43b**)

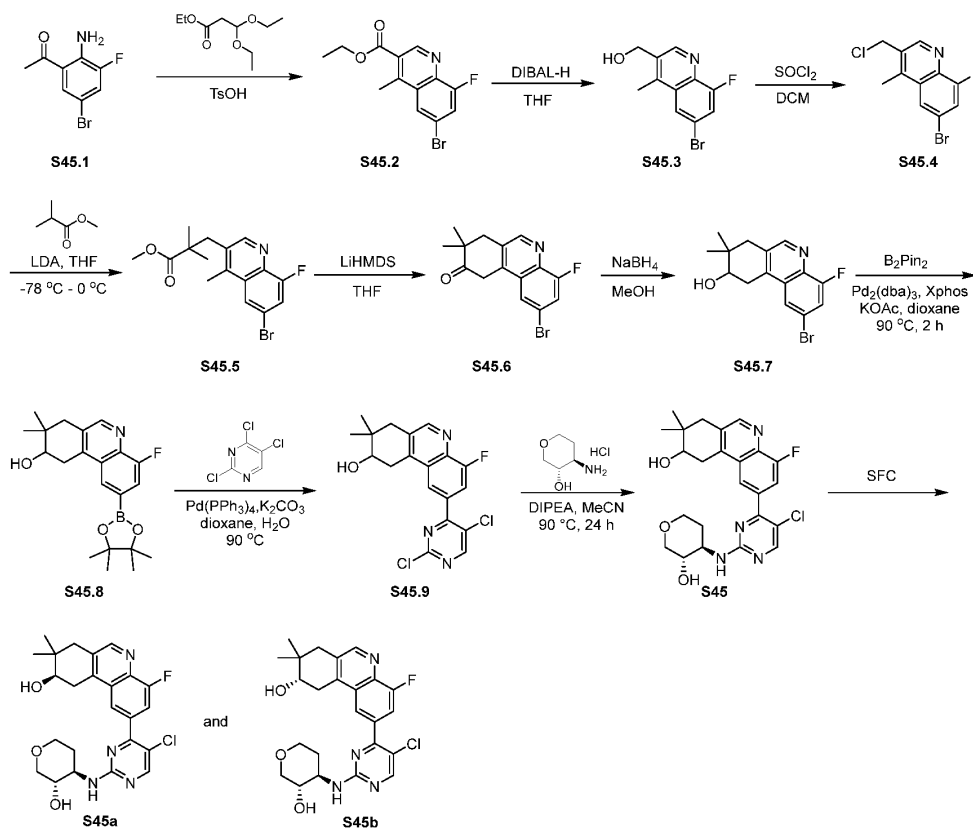


Example S44. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**S44a**) and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-3,4-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**S44b**)

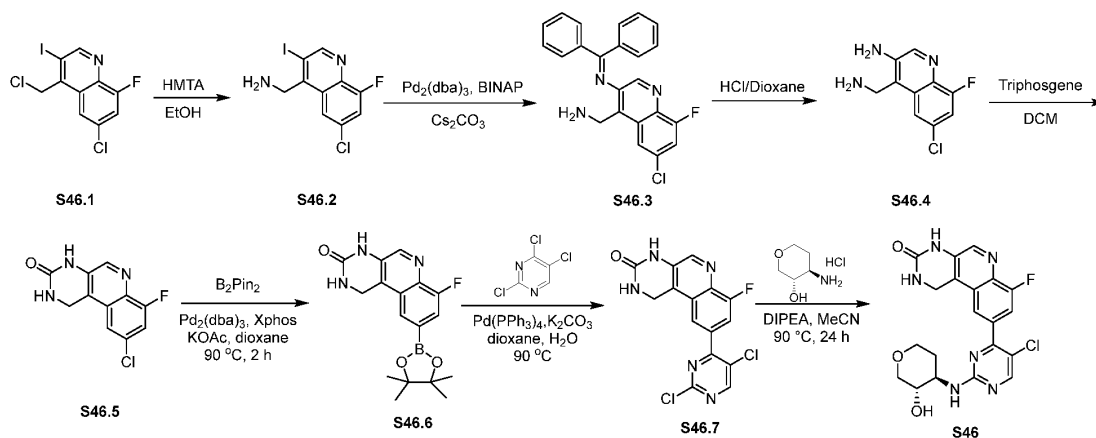


Example S40. (*R*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-8,8-dimethyl-7,8,9,10-tetrahydrophenanthridin-9-ol (**S45a**)

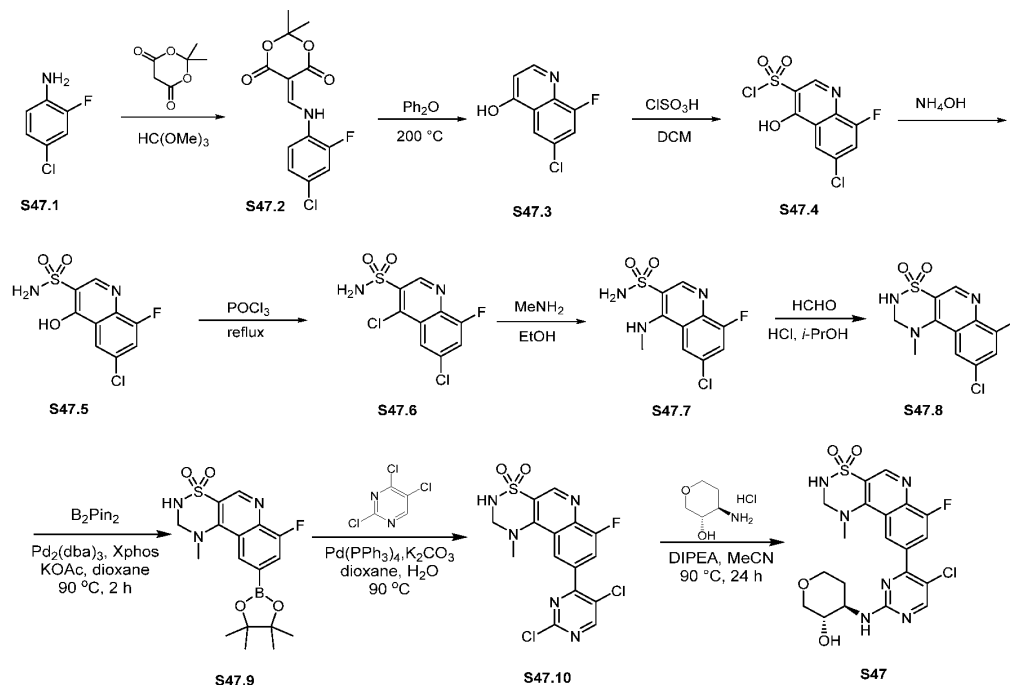
and (*S*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-8,8-dimethyl-7,8,9,10-tetrahydropyranthridin-9-ol (**S45b**)



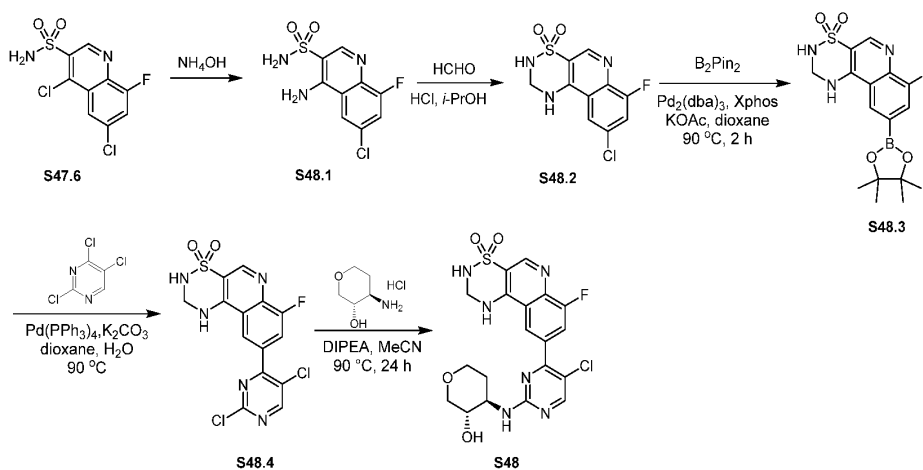
Example S46. (5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-1,4-dihydropyrimido[4,5-*c*]quinolin-3(2*H*)-one (**S46**)



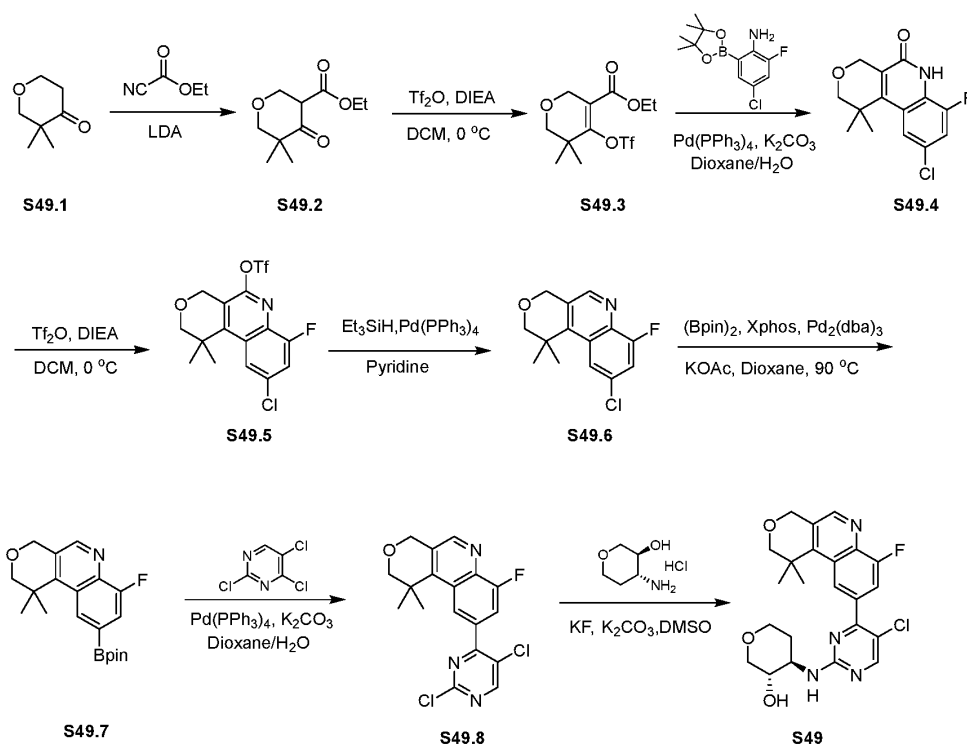
Example S47. (5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-1-methyl-2,3-dihydro-1*H*-[1,2,4]thiadiazino[6,5-*c*]quinoline 4,4-dioxide (**S47**)



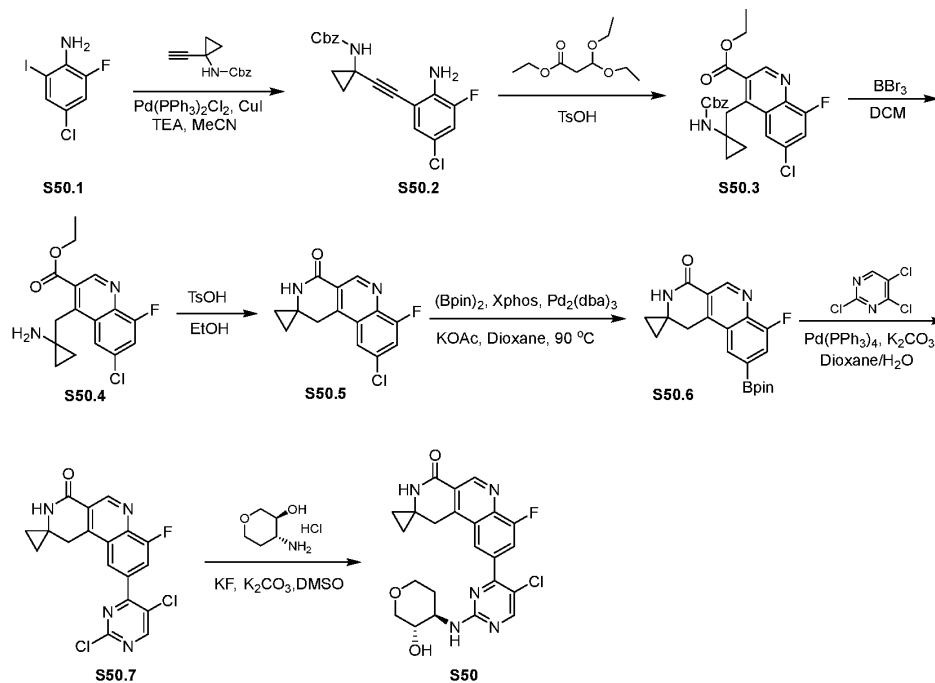
Example S48. (5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-2,3-dihydro-1*H*-[1,2,4]thiadiazino[6,5-*c*]quinoline 4,4-dioxide (**S48**)



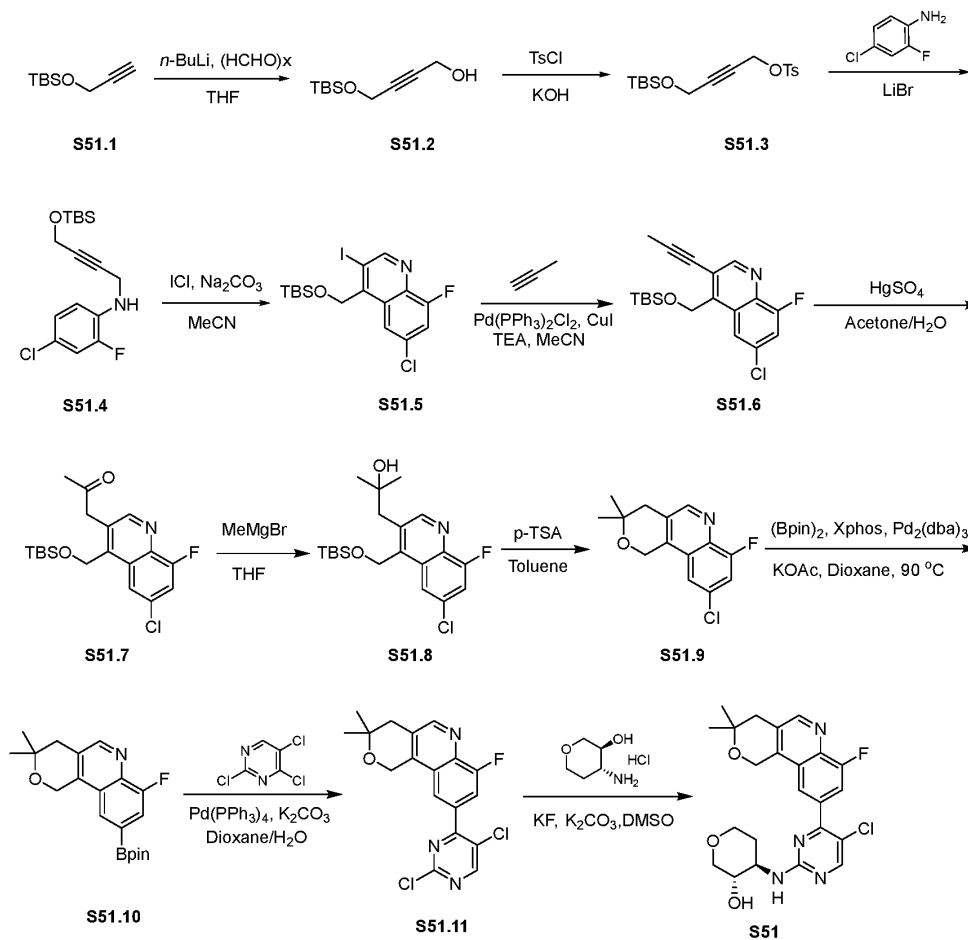
Example S49. (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-1,1-dimethyl-1,4-dihydro-2*H*-pyrano[3,4-*c*]quinolin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S49**)



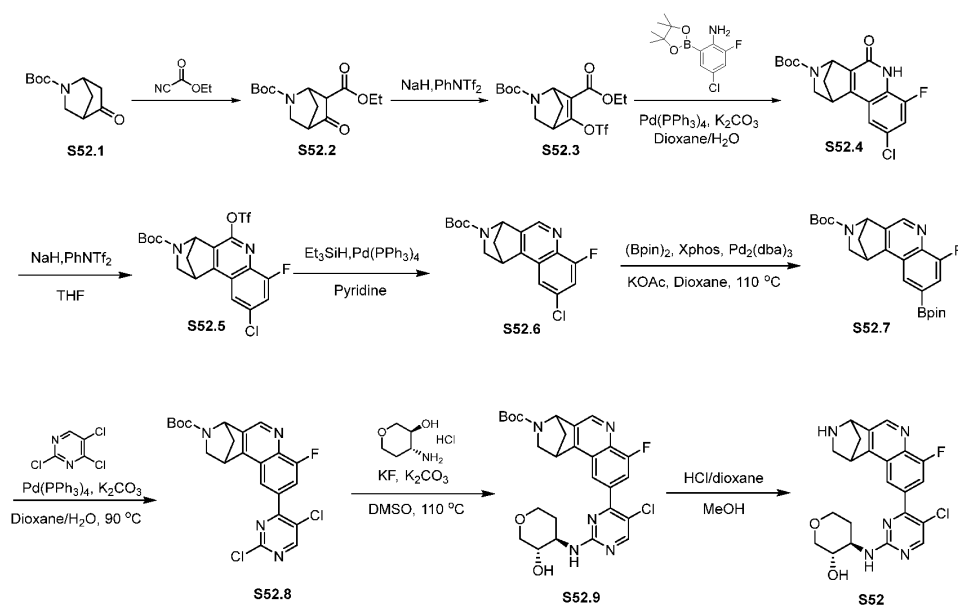
Example S50. 9-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-7-fluoro-1*H*-spiro[benzo[*c*][2,7]naphthyridine-2,1'-cyclopropan]-4(3*H*)-one (**S50**)



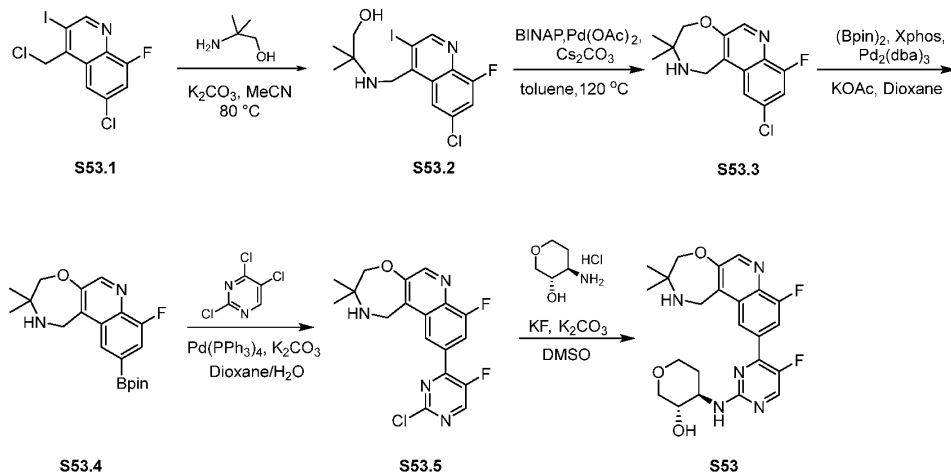
Example S51. (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[4,3-*c*]quinolin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S51**)



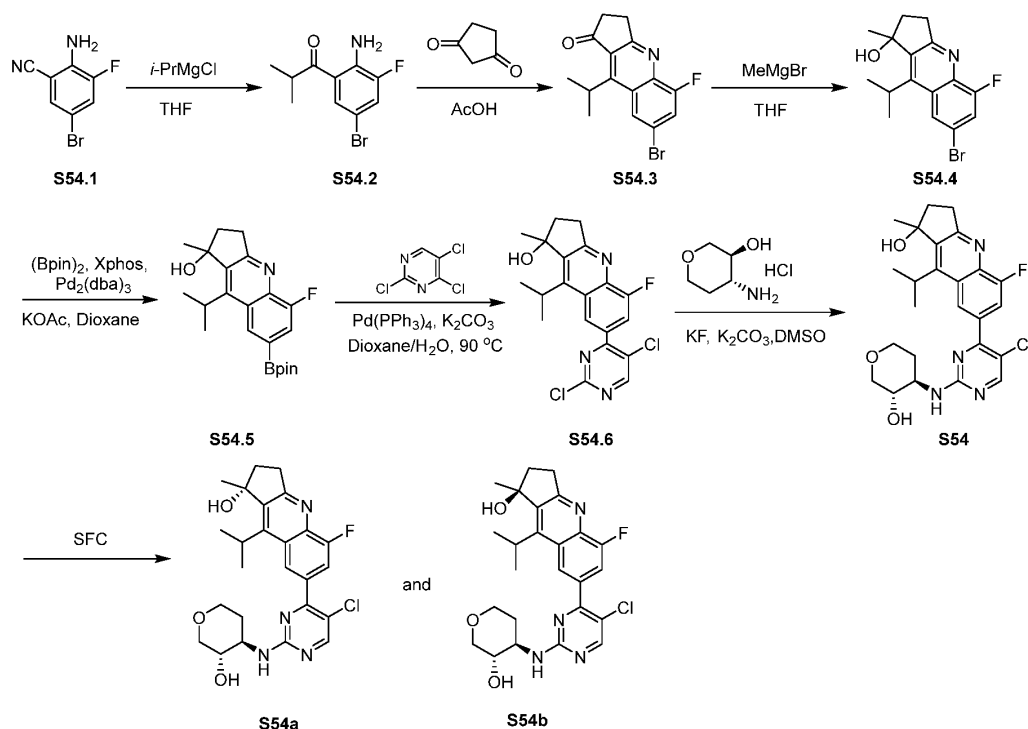
Example S52. (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-1,2,3,4-tetrahydro-1,4-methanobenzo[*c*][2,7]naphthyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S52**)



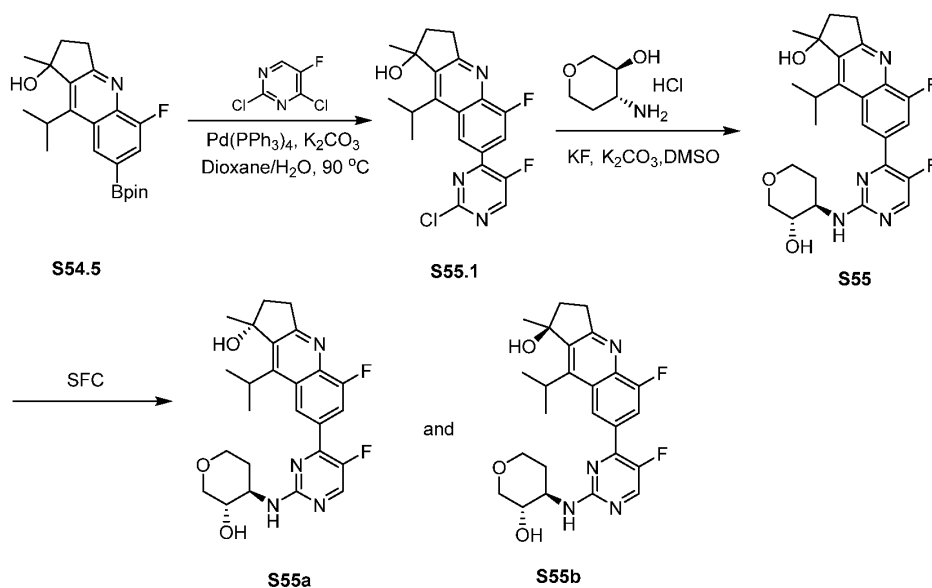
Example S53. (3*S*,4*R*)-4-((5-fluoro-4-(8-fluoro-3,3-dimethyl-1,2,3,4-tetrahydro-[1,4]oxazepino[7,6-*c*]quinolin-10-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (S53)



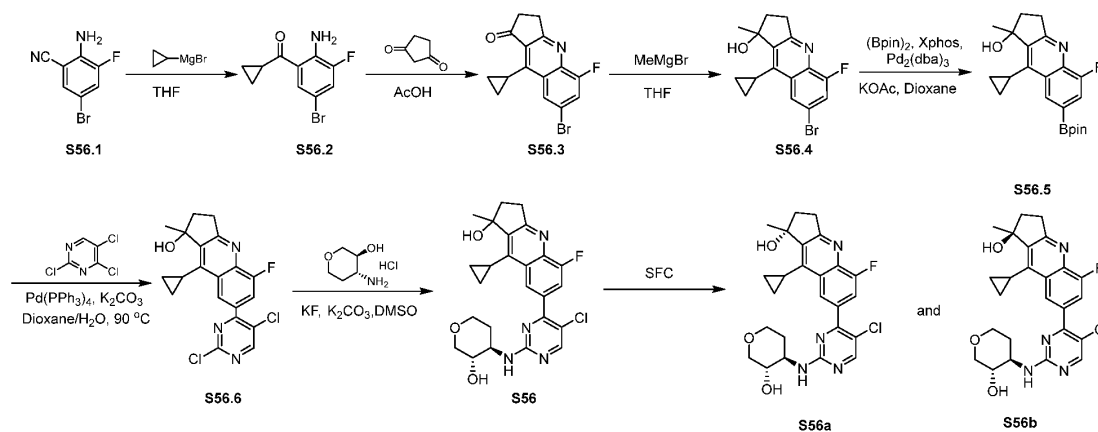
Example S54. (*R*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (S54a) and (*S*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (S54b)



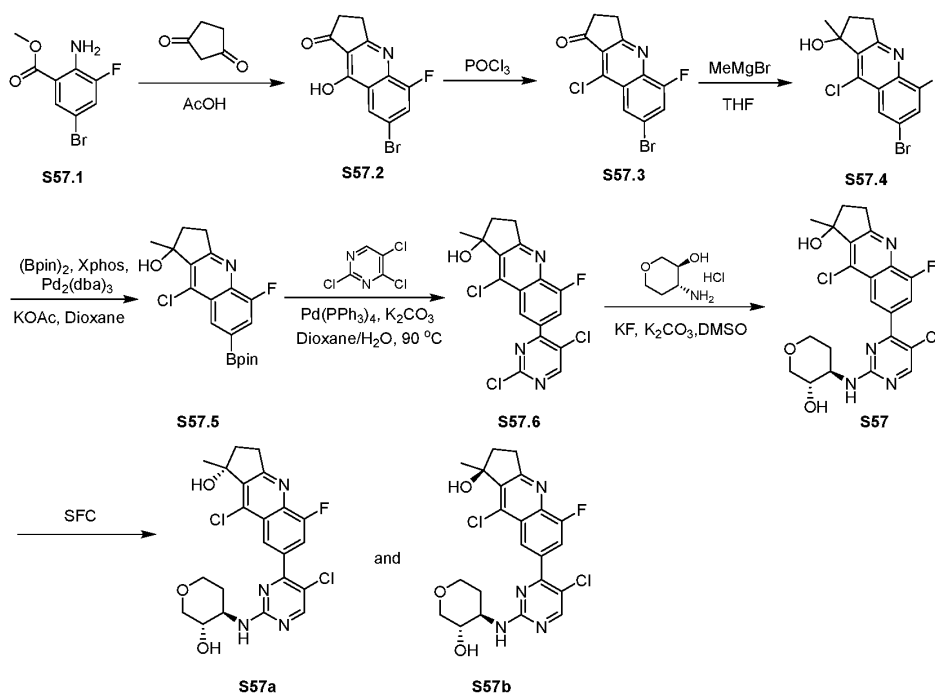
Example S55. (*R*)-5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (S55a) and (*S*)-5-fluoro-7-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-isopropyl-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (S55b)



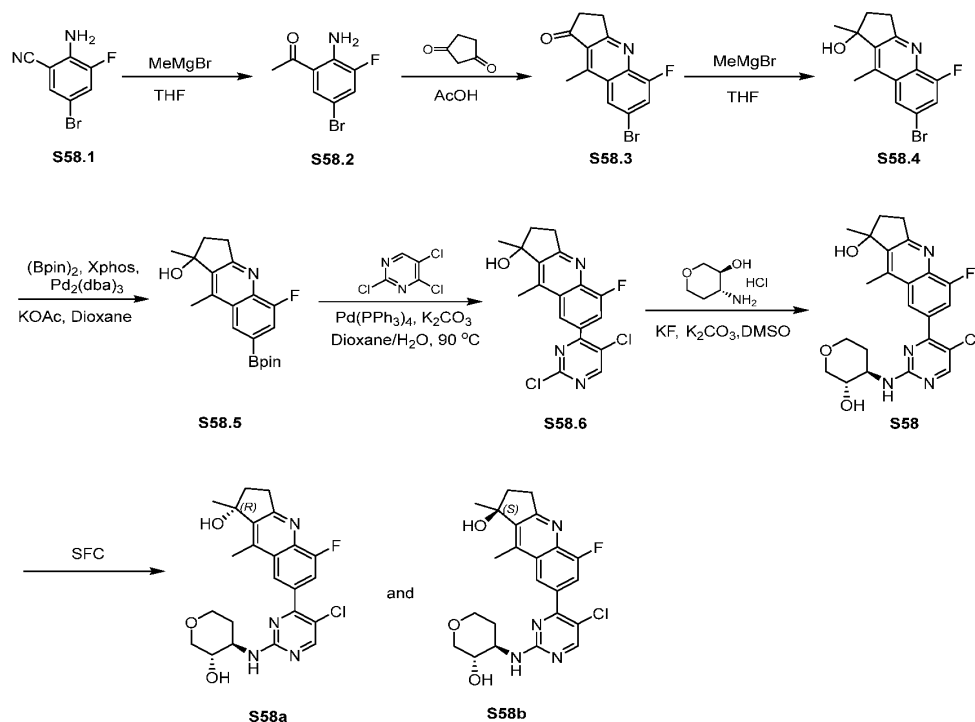
Example S56. (*R*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-cyclopropyl-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**S56a**) and (*S*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-9-cyclopropyl-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**S56b**)



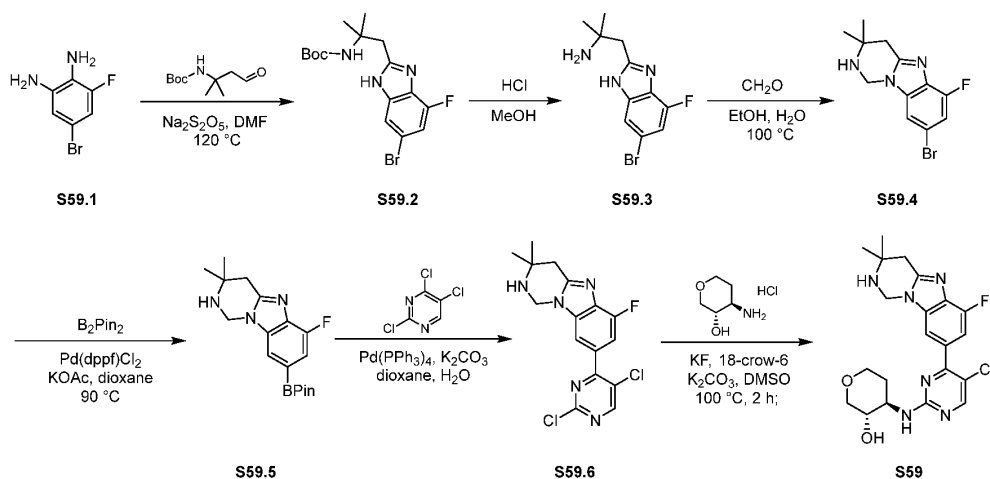
Example S57. (*R*)-9-chloro-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**S57a**) and (*S*)-9-chloro-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-1-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**S57b**)



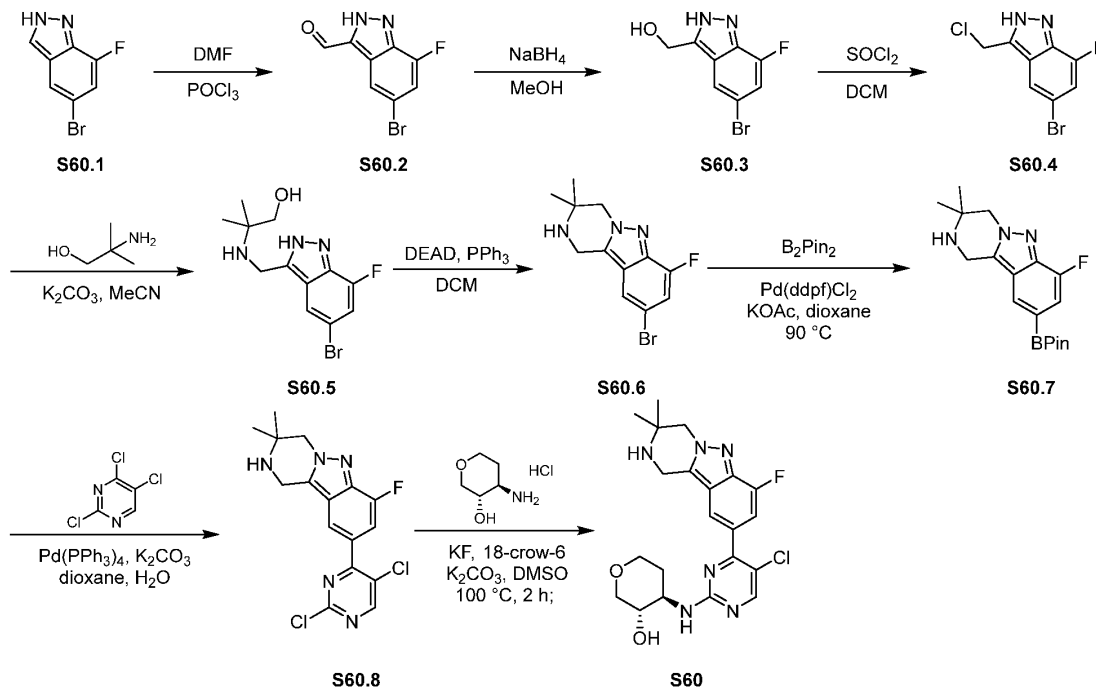
Example S58. (*R*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-1,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**S58a**) and (*S*)-7-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-5-fluoro-1,9-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-1-ol (**S58b**)



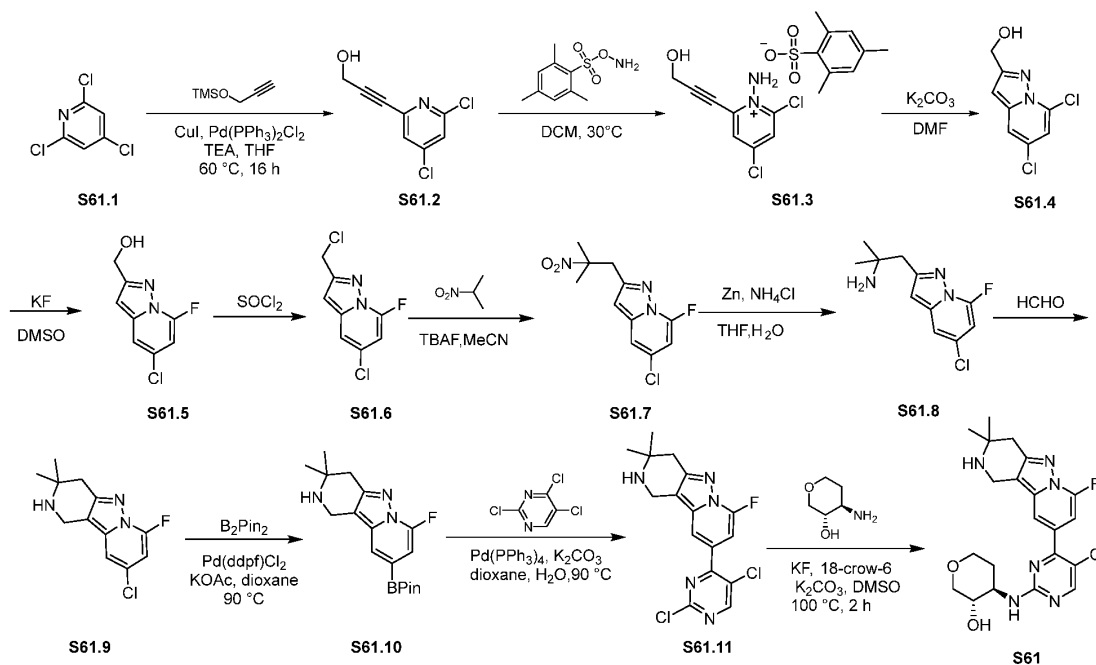
Example S59. (3*S*,4*R*)-4-((5-chloro-4-(6-fluoro-3,3-dimethyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-8-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S59**)



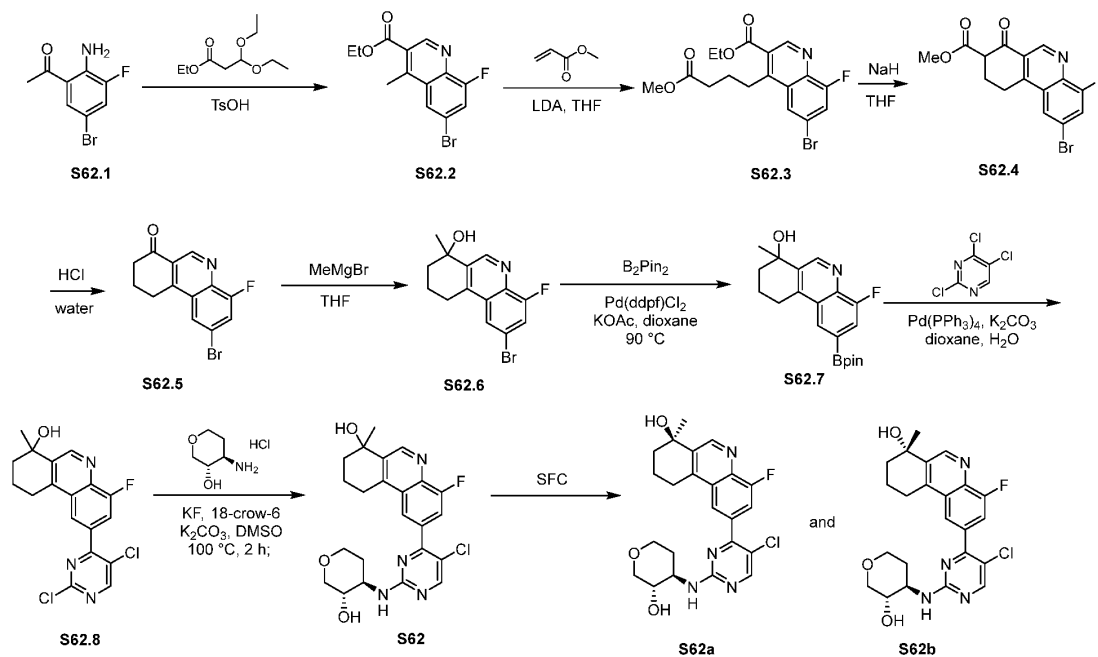
Example S60. (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-3,3-dimethyl-1,2,3,4-tetrahydropyrazino[1,2-*b*]indazol-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S60**)



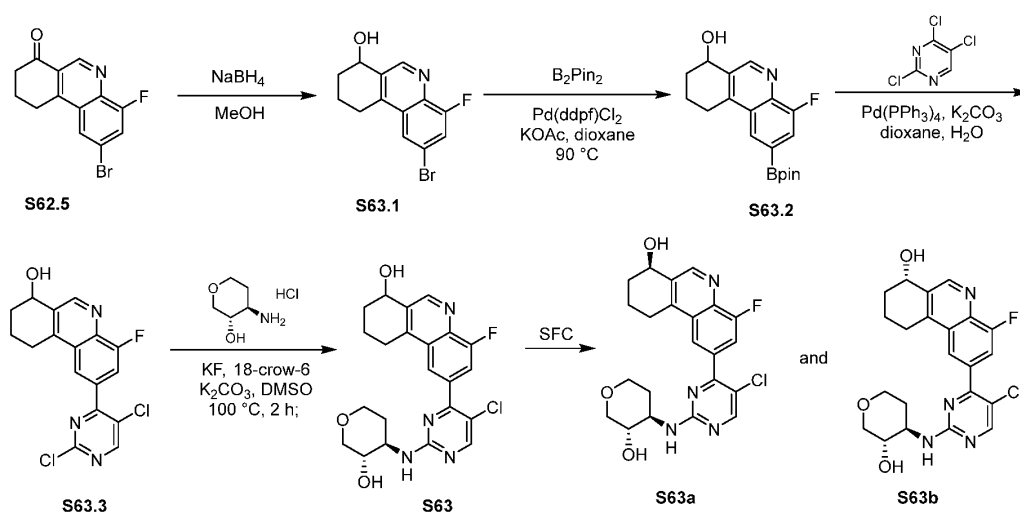
Example S61. (3*S*,4*R*)-4-((5-chloro-4-(7-fluoro-3,3-dimethyl-1,2,3,4-tetrahydropyrazolo[1,5- α :4,3-*c'*]dipyridin-9-yl)pyrimidin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (**S61**)



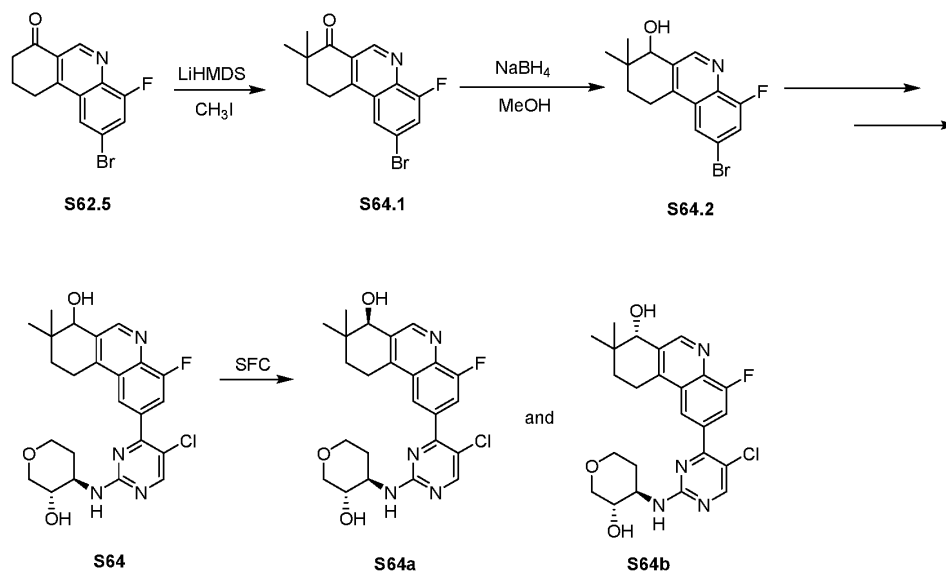
Example S62. (*R*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,8,9,10-tetrahydrophenanthridin-7-ol (**S62a**) and (*S*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,8,9,10-tetrahydrophenanthridin-7-ol (**S62b**)



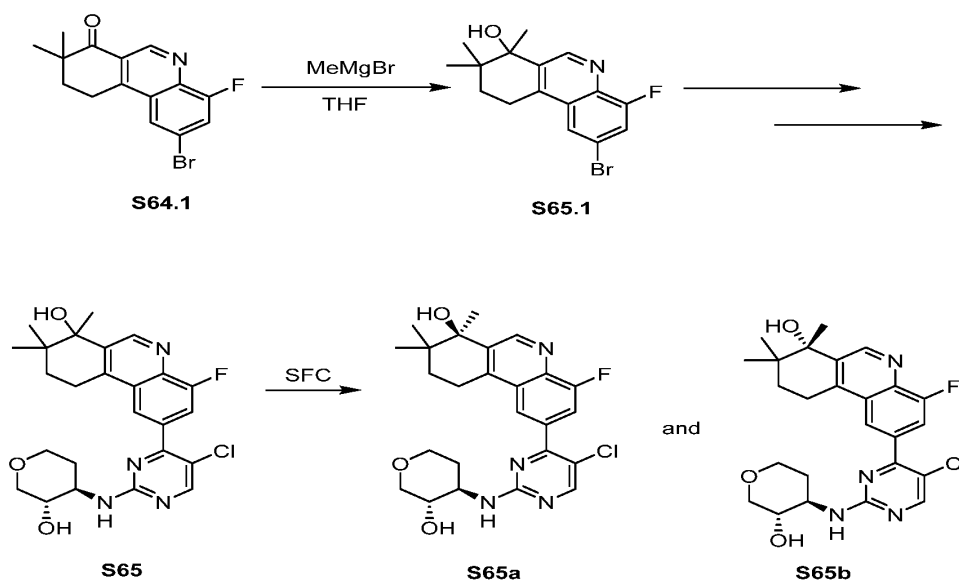
Example S63. (*R*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,8,9,10-tetrahydrophenanthridin-7-ol (**S63a**) and (*S*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,8,9,10-tetrahydrophenanthridin-7-ol (**S63b**)



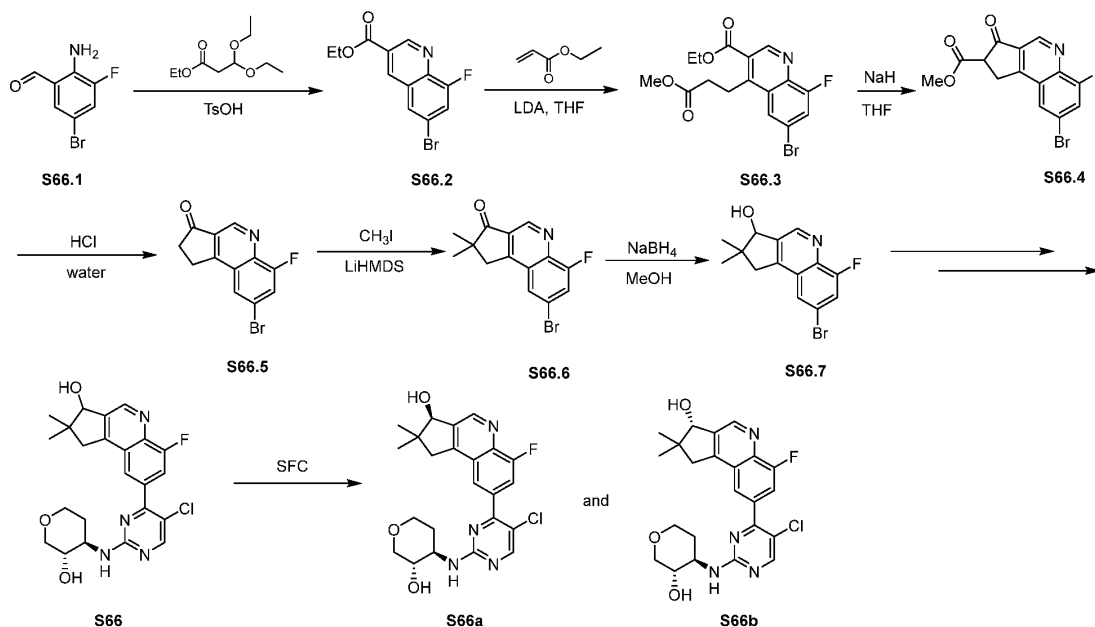
Example S64. (*R*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-8,8-dimethyl-7,8,9,10-tetrahydrophenanthridin-7-ol (**S64a**) and (*S*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-8,8-dimethyl-7,8,9,10-tetrahydrophenanthridin-7-ol (**S64b**)



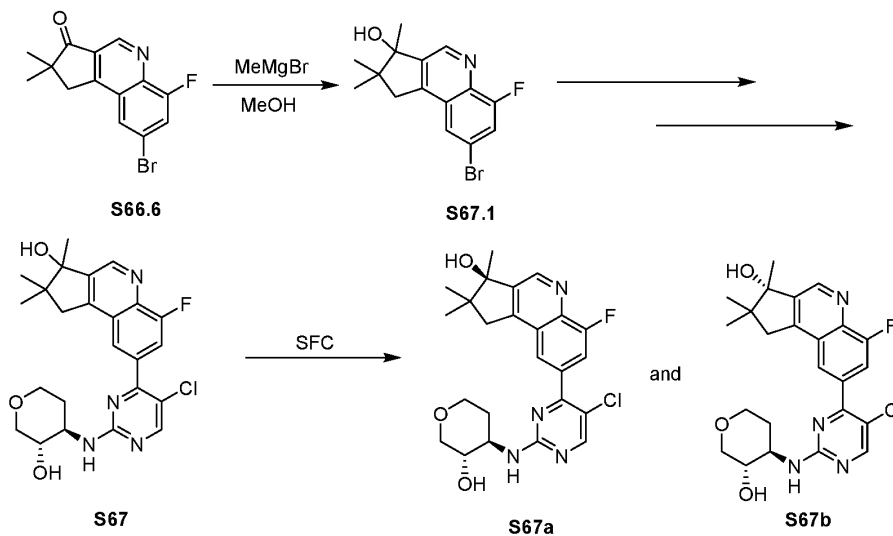
Example S65. (*R*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,8,8-trimethyl-7,8,9,10-tetrahydrophenanthridin-7-ol (**S65a**) and (*S*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,8,8-trimethyl-7,8,9,10-tetrahydrophenanthridin-7-ol (**S65b**)



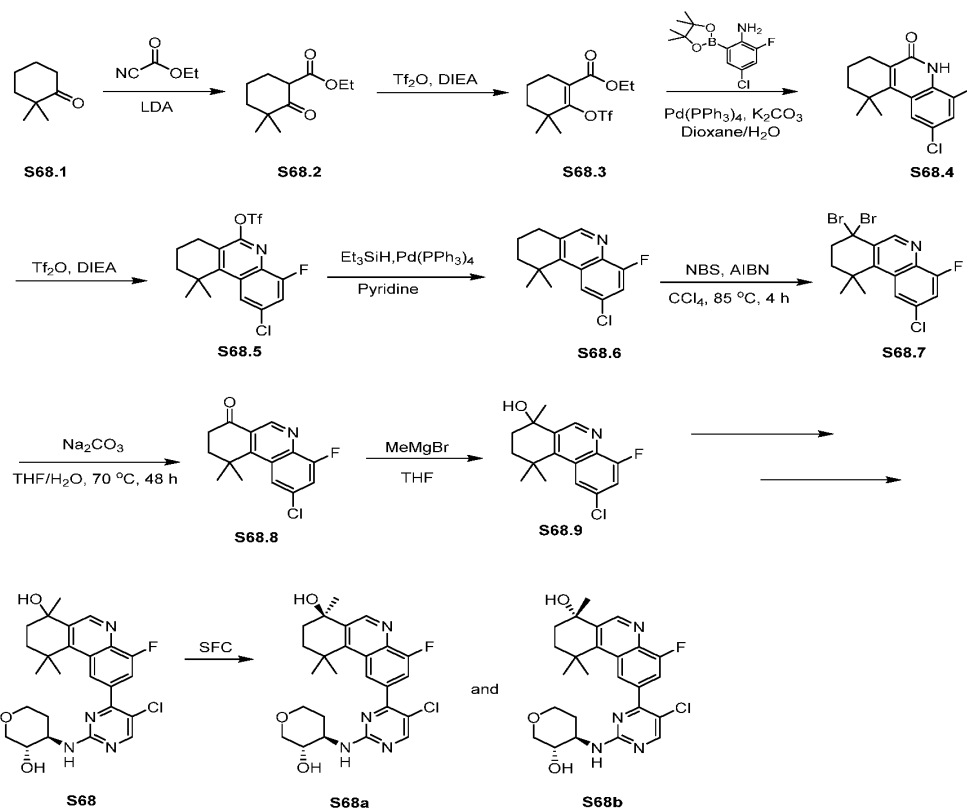
Example S66. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**S66a**) and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**S66b**)



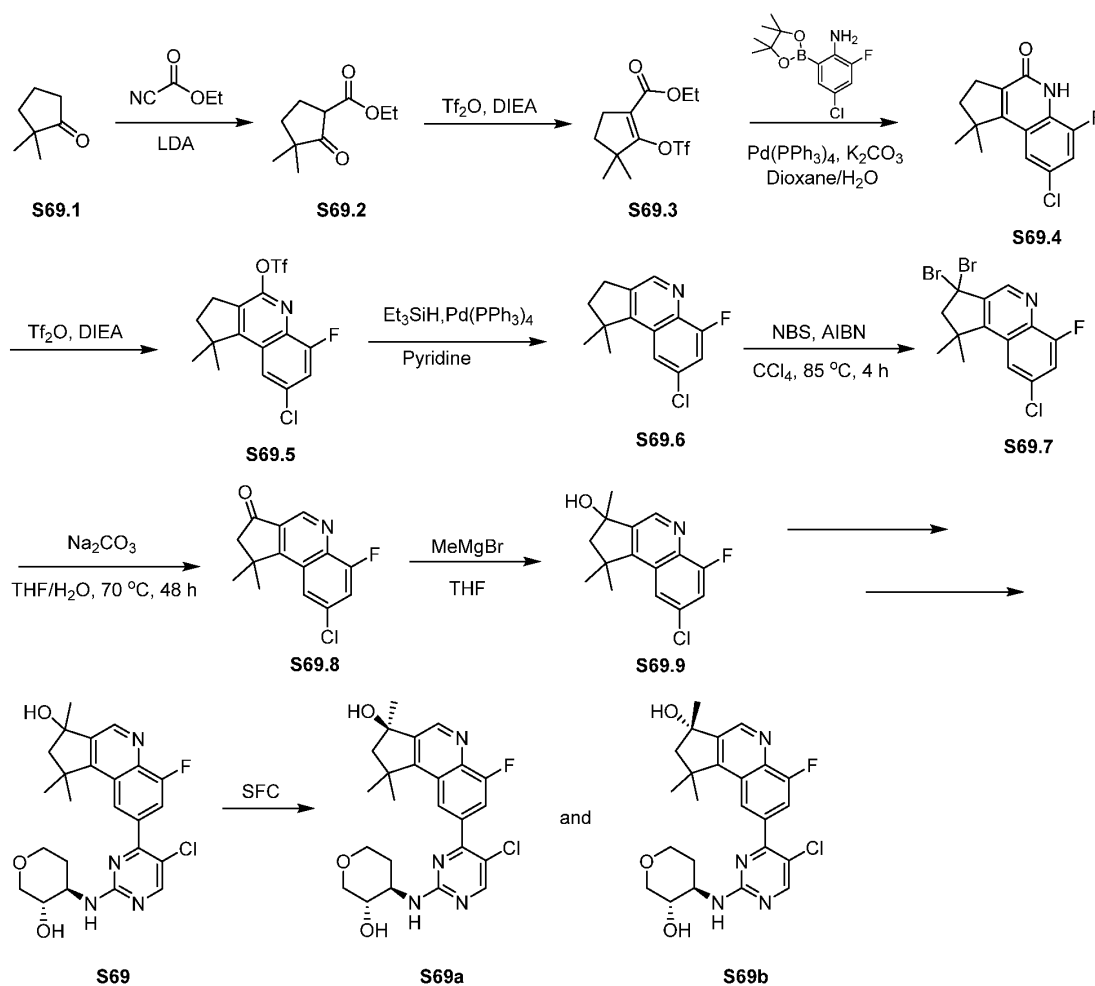
Example S67. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2,3-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**S67a**) and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-2,2,3-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**S67b**)



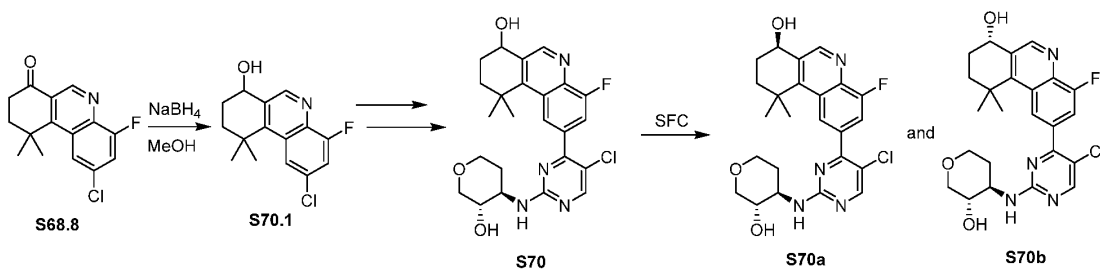
Example S68. (*R*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,10,10-trimethyl-7,8,9,10-tetrahydrophenanthridin-7-ol (**S68a**) and (*S*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-7,10,10-trimethyl-7,8,9,10-tetrahydrophenanthridin-7-ol (**S68b**)



Example S69. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-1,1,3-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**S69a**) and (*S*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-1,1,3-trimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (**S69b**)

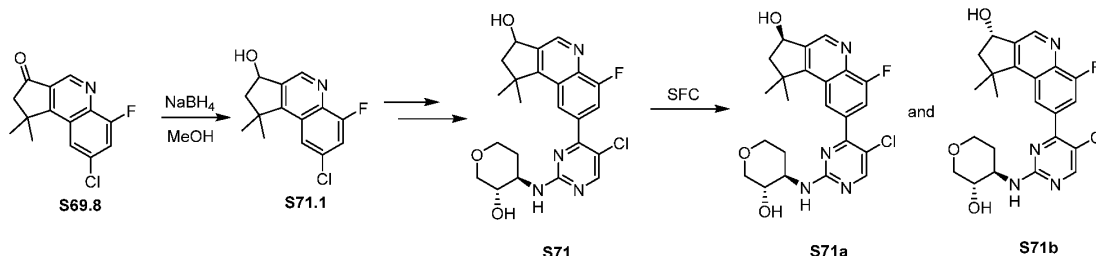


Example S70. (*R*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-10,10-dimethyl-7,8,9,10-tetrahydrophenanthridin-7-ol (**S70a**) and (*S*)-2-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-4-fluoro-10,10-dimethyl-7,8,9,10-tetrahydrophenanthridin-7-ol (**S70b**)



Example S71. (*R*)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-1,1-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol

(S71a) and (S)-8-(5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6-fluoro-1,1-dimethyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-3-ol (S71b)



Biological Example B1. Measurement of Kinase Inhibitory Activity

[0452] CDK2/CyclinE1 kinase inhibitory activity (IC₅₀): 5 µl of various dilutions of test compounds in 1x kinase buffer (50 mM HEPES pH 7.5, 10 mM MgCl₂, 2 mM DTT and 0.01% Brij-35) were mixed with 10 µL of CDK2/CyclinE1 (Carna, 04-165#, final concentration 3 nM in 1 × Kinase buffer) in 384 plates and incubated at room temperature for 10 min. To initiate each reaction, 10 µL of peptide solution containing fluorescently-labeled-peptide18(5-FAM-QSPKKG-CONH₂) (GL, 114202#, final concentration 3000 nM) and ATP (final concentration 77µM) in 1 × Kinase buffer was added to each of the wells containing test compound and CDK2/CyclinE1 mixture. The reaction was then allowed to proceed at 28°C for 30min and terminated by the addition of 25 µL stop buffer (100 mM HEPES pH 7.5, 50 mM EDTA, 0.2% Coating Reagent #3 (Perkin Elmer, 760050#) and 0.015% Brij-35).

[0453] Following the kinase reaction, Caliper EZ reader II (Downstream voltages:-500V, Upstream voltages:-2250V, Base pressure -0.5 PSI, Screen pressure -1.2 PSI) was used to separate the phosphorylated (product) and the unphosphorylated (substrate) fluorescently-labeled peptide 18 based on their different mobility. Both substrate and product were measured and the ratio of these values were used to generate % conversion by Caliper EZ reader II. These conversion values were then transformed into % inhibition of kinase activity using the formula: % Inhibition = [(MA – X)/(MA - MI)] × 100% where MA = conversion value of DMSO only controls, MI = conversion value of no enzyme controls and X = conversion value at any given compound dose. IC₅₀ values were then calculated by plotting dose-response curves and then using the XLfit application in Excel software.

[0454] CDK1/CyclinB kinase inhibitory activity (IC₅₀): 5 µl of various dilutions of test compound in 1x kinase buffer (50 mM HEPES pH 7.5, 10 mM MgCl₂, 2 mM DTT and

0.01% Brij-35) was mixed with 10 µL of CDK1/CyclinB (Millipore, 14-450M#, final concentration 3 nM in 1 × Kinase buffer) in 384 plates and incubated at room temperature for 10 min. To initiate each reaction, 10 µL of peptide solution containing fluorescently-labeled -peptide18(5-FAM-QSPKKG-CONH2) (GL, 114202#, final concentration 3000 nM) and ATP (final concentration 20µM) in 1 × Kinase buffer was added to each of the wells containing test compound and CDK1/CyclinB mixture. The reaction is then allowed to proceed at 28°C for 30min and terminated by the addition of 25 µL stop buffer (100 mM HEPES pH 7.5, 50 mM EDTA, 0.2% Coating Reagent #3 (Perkin Elmer, 760050#) and 0.015% Brij-35).

[0455] Following the kinase reaction, Caliper EZ reader II (Downstream voltages:-500V, Upstream voltages:-2250V, Base pressure -0.5 PSI, Screen pressure -1.2 PSI) was used to separate the phosphorylated (product) and the unphosphorylated (substrate) fluorescently-labeled peptide 18 based on their different mobility. Both substrate and product were measured and the ratio of these values were used to generate % conversion by Caliper EZ reader II. These conversion values were then transformed into % inhibition of kinase activity using the formula: % Inhibition = $[(MA - X)/(MA - MI)] \times 100\%$ where MA = conversion value of DMSO only controls, MI = conversion value of no enzyme controls and X = conversion value at any given compound dose. IC50 values were then calculated by plotting dose-response curves and then using the XLfit application in Excel software.

[0456] **CDK4/CyclinD1 kinase inhibitory activity (IC50):** 5 µL of various dilutions of test compound in 1x kinase buffer (20 mM HEPES, pH 7.5, 10 mM MgCl₂, 2 mM DTT and 0.01% Triton X-100) was mixed with 10 µL of either CDK4/Cyclin D1 (ProQinase, 0142-0143-1#, final concentration 20nM in 1 x Kinase buffer) or in 384 plates and incubated at room temperature for 10 min. To initiate each reaction, 10 µL of peptide solution containing fluorescently-labeled -peptide 8(5-FAM-IPTSPITTTYFFFKKK-COOH, GL, 112396#, final concentration 3000 nM) and ATP (final concentration 672uM for CDK4/CyclinD1) in 1 × Kinase buffer was added to each of the wells containing test compound and CDK4/CyclinD1 mixture. The reaction is then allowed to proceed at 28°C for 30min and terminated by the addition of 25 µL stop buffer (100 mM HEPES pH 7.5, 50 mM EDTA, 0.2% Coating Reagent #3 (Perkin Elmer, 760050#) and 0.015% Brij-35).

[0457] Following the kinase reaction, Caliper EZ reader II (Downstream voltages:-500V, Upstream voltages:-2250V, Base pressure -0.5 PSI, Screen pressure -1.2 PSI) was used to separate the phosphorylated (product) and the unphosphorylated (substrate) fluorescently-labeled

peptide 8 based on their different mobility. Both substrate and product were measured and the ratio of these values were used to generate % conversion by Caliper EZ reader II. These conversion values were then transformed into % inhibition of kinase activity using the formula: % Inhibition = $[(MA - X)/(MA - MI)] \times 100\%$ where MA = conversion value of DMSO only controls, MI = conversion value of no enzyme controls and X = conversion value at any given compound dose. IC50 values were then calculated by plotting dose-response curves and then using the XLfit application in Excel software.

[0458] CDK6/CyclinD3 kinase inhibitory activity (IC50): 5 μ L of various dilutions of test compound in 1x kinase buffer (50 mM HEPES pH 7.5, 10 mM MgCl₂, 2 mM DTT and 0.01% Brij-35) was mixed with 10 μ L of CDK6/CyclinD3 (Carna, 04-107#, final concentration 15 nM in 1 $\times$ Kinase buffer) in 384 plates and incubated at room temperature for 10 min. To initiate each reaction, 10 μ L of peptide solution containing fluorescently-labeled -peptide 8(5-FAM-IPTSPITTTYFFFKKK-COOH, GL, 112396#, final concentration 3000 nM) and ATP (final concentration 800 μ M for CDK6/CyclinD3 in 1 $\times$ Kinase buffer was added to each of the wells containing test compound and CDK6/CyclinD3. The reaction is then allowed to proceed at 28°C for 30min and terminated by the addition of 25 μ L stop buffer (100 mM HEPES pH 7.5, 50 mM EDTA, 0.2% Coating Reagent #3 (Perkin Elmer, 760050#) and 0.015% Brij-35).

[0459] Following the kinase reaction, Caliper EZ reader II (Downstream voltages:-500V, Upstream voltages:-2250V, Base pressure -0.5 PSI, Screen pressure -1.2 PSI) was used to separate the phosphorylated (product) and the unphosphorylated (substrate) fluorescently-labeled peptide 8 based on their different mobility. Both substrate and product were measured and the ratio of these values were used to generate % conversion by Caliper EZ reader II. These conversion values were then transformed into % inhibition of kinase activity using the formula: % Inhibition = $[(MA - X)/(MA - MI)] \times 100\%$ where MA = conversion value of DMSO only controls, MI = conversion value of no enzyme controls and X = conversion value at any given compound dose. IC50 values were then calculated by plotting dose-response curves and then using the XLfit application in Excel software.

[0460] CDK7/CyclinH/MAT1 kinase inhibitory activity (IC50): 5 μ L of various dilutions of test compound in 1x kinase buffer (20 mM HEPES, pH 7.5, 10 mM MgCl₂, 2 mM DTT and 0.01% Triton X-100) was mixed with 10 μ L of CDK7/CyclinH/MAT1 (Millipore, 14-476M#, final concentration 12.5nM in 1 $\times$ Kinase buffer) in 384 plates and incubated at room temperature for 10 min. To initiate each reaction, 10 μ L of peptide solution containing

fluorescently-labeled -peptide CTD3 (5-FAM-ACSYSPTSPSYSPTSPSYSPTSPSKK, GL, SY346885#, final concentration 3000 nM) and ATP (final concentration 70 μ M) in 1 $\times$ Kinase buffer was added to each of the wells containing test compound and CDK7/CyclinH/MAT1 mixture. The reaction is then allowed to proceed at 28°C for 30min and terminated by the addition of 25 μ L stop buffer (100 mM HEPES pH 7.5, 50 mM EDTA, 0.2% Coating Reagent #3 (Perkin Elmer, 760050#) and 0.015% Brij-35).

[0461] Following the kinase reaction, Caliper EZ reader II (Downstream voltages:-500V, Upstream voltages:-2250V, Base pressure -0.5 PSI, Screen pressure -1.2 PSI) was used to separate the phosphorylated (product) and the unphosphorylated (substrate) fluorescently-labeled peptide CTD3 based on their different mobility. Both substrate and product were measured and the ratio of these values were used to generate % conversion by Caliper EZ reader II. These conversion values were then transformed into % inhibition of kinase activity using the formula: % Inhibition = $[(MA - X)/(MA - MI)] \times 100\%$ where MA = conversion value of DMSO only controls, MI = conversion value of no enzyme controls and X = conversion value at any given compound dose. IC₅₀ values were then calculated by plotting dose-response curves and then using the XLfit application in Excel software.

[0462] **CDK9/CyclinT1 kinase inhibitory activity (IC₅₀):** 5 μ L of various dilutions of test compound in 1x kinase buffer (20 mM HEPES, pH 7.5, 10 mM MgCl₂, 2 mM DTT and 0.01% Triton X-100) was mixed with 10 μ L of CDK9/CyclinT1 (Millipore, 14-685M#, final concentration 12.5nM in 1 $\times$ Kinase buffer) in 384 plates and incubated at room temperature for 10 min. To initiate each reaction, 10 μ L of peptide solution containing fluorescently-labeled -peptide CTD3 (5-FAM-ACSYSPTSPSYSPTSPSYSPTSPSKK, GL, SY346885#, final concentration 3000nM) and ATP (final concentration 10 μ M) in 1 $\times$ Kinase buffer was added to each of the wells containing test compound and CDK9/CyclinT1 mixture. The reaction is then allowed to proceed at 28°C for 30min and terminated by the addition of 25 μ L stop buffer (100 mM HEPES pH 7.5, 50 mM EDTA, 0.2% Coating Reagent #3 (Perkin Elmer, 760050#) and 0.015% Brij-35).

[0463] Following the kinase reaction, Caliper EZ reader II (Downstream voltages:-500V, Upstream voltages:-2250V, Base pressure -0.5 PSI, Screen pressure -1.2 PSI) was used to separate the phosphorylated (product) and the unphosphorylated (substrate) fluorescently-labeled peptide CTD3 based on their different mobility. Both substrate and product were measured and the ratio of these values were used to generate % conversion by Caliper EZ reader II. These

conversion values were then transformed into % inhibition of kinase activity using the formula:
 $\% \text{ Inhibition} = [(MA - X)/(MA - MI)] \times 100\%$ where MA = conversion value of DMSO only controls, MI = conversion value of no enzyme controls and X = conversion value at any given compound dose. IC₅₀ values were then calculated by plotting dose-response curves and then using the XLfit application in Excel software.

[0464] Biological activity data for representative compounds provided herein are provided in Table 2 below. Exemplary results are presented as calculated IC₅₀ values. In Table 2, "A" represents a calculated IC₅₀ value of less than 10 nM; "B" represents a calculated IC₅₀ value of greater than or equal to 10 nM and less than 100 nM; "C" represents a calculated IC₅₀ value of greater than or equal to 100 nM and less than 1 μ M; and "D" represents a calculated IC₅₀ value of 1 μ M or greater.

Table 2. Selected in vitro data on different CDKs

Example number	CDK1/ Cyclin B1 IC ₅₀ (nM)	CDK2/ Cyclin E1 IC ₅₀ (nM)	CDK4/ Cyclin D1 IC ₅₀ (nM)	CDK6/ Cyclin D3 IC ₅₀ (nM)	CDK7/ Cyclin H /MAT1 IC ₅₀ (nM)	CDK9/ Cyclin T1 IC ₅₀ (nM)
1			C	D		
2			C	D		
3			B	C		
4			B	D		
5a			A	B		
5b			A	C		
6			A	B		
7			A	C		
8			A	B		
9			B	C		
10			B	C		
11			C	D		
12a			A	B		
12b			B	D		
13			B	D		
15			A	C		
16			A	C		
17a			A	C		
17b	C	C	A	B	C	C
18a			B	D		
18b	C	B	A	C	C	C
19a	C	C	A	B	D	D
19b	B	B	A	A	C	B

20a	C	B	A	B	C	C
20b	B	B	A	B	B	A
21a			B	C		
21b	B	B	A	B	C	B
22a			B	C		
22b	C	C	A	B	C	B
23a			B	C		
23b	C	C	A	B	D	C
24	D	C	A	C	D	C
25a			A	B		
25b	C	B	A	B	C	B
26a	D	C	A	C	C	C
26b			A	C		
27a	B	B	A	C	B	B
27b	D	D	A	C	D	D
28a	C	C	A	B	C	B
28b			A	B		
29a	C	B	A	B	D	B
29b			A	C		
30a			B	C		
30b			A	C		
31a	C	C	A	B	C	C
31b			A	B		
32a	C	B	A	B	C	B
32b			B	C		
33a	C	B	A	C	D	C
33b			B	C		
34a			A	C		
34b	B	B	A	B	C	B
35a	C	B	A	C	C	C
35b	B	A	A	B	B	A
36a	C	C	A	B	C	B
36b	D	D	A	B	D	D
37a	C	C	A	B	C	B
37b			A	B		
38a	C	B	A	A	C	A
38b			A	B		
39a			A	B		
39b			B	C		
40			A	B		
41a			A	C		
41b			B	C		
42			A	C		
43a	B	B	A	B	B	B
43b			B	C		

44	A	A	A	B	C	B
45a			B	C		
45b	C	B	A	C	C	B
46a	B	B	A	B	C	B
46b			A	C		
47			B	C		
48a			A	C		
48b	C	C	A	C	D	B
49a			A	B		
49b	B	B	A	B	C	A
50a			B	C		
50b	D	C	B	C	C	C
51a	C	C	A	B	C	C
51b	D	C	A	C	D	D
52a			A	C		
52b			A	C		
53a	B	B	A	B	B	B
53b			A	B		
54a			A	C		
54b			B	C		
55a			A	B		
55b			A	C		
56a			A	C		
56b			C	D		
57a			A	B		
57b	D	D	B	C	D	D
58			B	C		
59			B	C		
60			B	D		
61			A	C		
62			B	C		
66			A	C		
67a			B	C		
67b			C	C		
71a	C	B	A	B	D	C
71b			B	C		
72a	C	B	A	B	C	B
72b			B	C		
77			B	C		
79			B	C		
87a	C	B	A	B	D	B
87b	C	B	A	B	D	C
91a			A	C		
91b			A	B		
92	C	C	A	C	C	C

93a	D	D	A	B	D	D
93b	D	C	A	B	C	C
94			B	C		
95			B	D		
96			C	D		
97			B	C		
98			A	C		
99			A	C		
100			A	B		
101			A	C		
102			B	C		
103			A	C		
104	C	C	A	C	D	B
105			B	C		
106			B	C		
107			C	D		
108			C	D		
109			B	C		
110			C	C		
111a	C	C	A	B	D	C
111b			A	C		
112a			A	C		
112b			B	C		
113a			A	C		
113b			A	B		
114a	B	A	A	B	C	A
114b			B	C		
115a			B	C		
115b	D	D	A	C	D	C
116a			B	C		
116b			A	C		
117a			B	C		
117b			B	C		
119a			A	B		
119b			B	C		
120			A	C		
123			A	C		
124			A	C		
125a			A	C		
125b	C	C	A	B	B	B
126a			A	B		
126b	C	C	A	B	C	C
127a			A	C		
127b	C	C	A	C	C	C
128a			A	C		

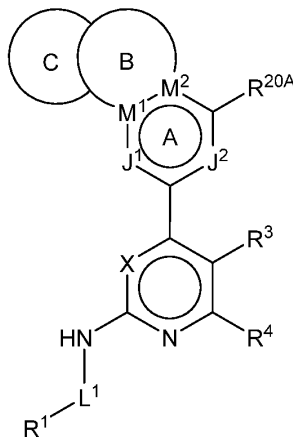
128b	B	B	A	B	C	B
129a	C	C	A	C	D	C
129b	B	B	A	B	B	A
130a			A	B		
130b	C	C	A	B	D	C
131a	D	D	A	C	D	D
131b	C	C	A	C	C	C
132a	D	C	A	C	D	D
132b	C	C	A	C	B	B
133			B	D		
134			C	D		
135a			A	B		
135b			B	D		
137			A	B		
138			A	C		
139			A	B		
140			B	C		
141			B	C		
144			A	C		
145			B	C		
147			A	C		
148			A	C		
149			A	C		
151			A	B		
152			A	C		
153			A	C		
154			A	C		
156			A	C		
157			A	B		
158			A	C		
159			A	C		
160			A	B		
161			A	C		
162			A	C		
163			A	B		
164			A	C		
165			A	B		
166			A	B		
167			A	D		
168			A	B		
169			A	B		
170	C	A	A	C	C	B
171			A	B		
172			A	C		
173			A	B		

174			B	C		
175			A	C		
176			A	C		
177			A	B		
178			A	B		
179			A	B		
181			A	C		
182			A	B		
183	B	B	A	B	B	B
184			B	C		
185			B	C		
186			A	B		
188			A	B		
189			A	B		
190			A	B		
191			A	B		
192			B	C		
193a	D	D	A	C	D	D
193b	C	C	A	C	C	C
195a			A	C		
195b	C	C	A	C	C	C
197a	D	C	A	C	D	D
197b	C	C	A	C	B	C
199a			A	C		
199b	B	B	A	B	C	B
201a	C	C	A	C	D	C
201b	B	B	A	B	B	B

[0465] The embodiments provided herein are not to be limited in scope by the specific embodiments provided in the examples which are intended as illustrations of a few aspects of the provided embodiments and any embodiments that are functionally equivalent are encompassed by the present disclosure. Indeed, various modifications of the embodiments provided herein are in addition to those shown and provided herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I),

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

L¹ is an optionally substituted phenylene, optionally substituted 5- or 6-membered heteroarylene, optionally substituted 4- to 8-membered heterocyclylene, or optionally substituted C₃₋₈ carbocyclylene;

R¹ is hydrogen, OH, NH₂, NHCH₃, or N(CH₃)₂;

X is N or CR¹⁰;

R³ is hydrogen, deuterium, halogen, CN, OR¹¹, NR¹²R¹³, C(O)NR¹²R¹³, COOR^A, COR^B, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₄ alkenyl, optionally substituted C₂₋₄ alkynyl, optionally substituted C₁₋₄ heteroalkyl, optionally substituted C₃₋₈ carbocyclyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted 5-10 membered heteroaryl;

R⁴ is hydrogen, deuterium, halogen, optionally substituted C₁₋₆ alkyl, or NR¹²R¹³;

R¹⁰ is hydrogen, halogen, CN, -OH, an optionally substituted C₁₋₄ alkyl, optionally substituted C₁₋₄ heteroalkyl, optionally substituted C₃₋₈ carbocyclyl, or optionally substituted 4-10 membered heterocyclyl;

R¹¹ is hydrogen, an optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₈ carbocyclyl, optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted 4-10 membered heterocyclyl;

each of R¹² and R¹³, at each occurrence, is independently hydrogen, an optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₈ carbocyclyl, optionally substituted phenyl,

optionally substituted 5- or 6-membered heteroaryl, optionally substituted 4-10 membered heterocyclyl; or R^{12} and R^{13} together with the nitrogen they are attached to form an optionally substituted 4-10 membered heterocyclyl or an optionally substituted 5- or 6-membered heteroaryl;

R^A is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted 4-10 membered heterocyclyl;

R^B is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted 5- or 6-membered heteroaryl;

J^1 and J^2 are independently N or CR^{30} , wherein R^{30} at each occurrence is independently hydrogen, halogen, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F;

R^{20A} is hydrogen, deuterium, halogen, CN, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, C_{1-4} heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or an optionally substituted 3-6 membered ring structure;

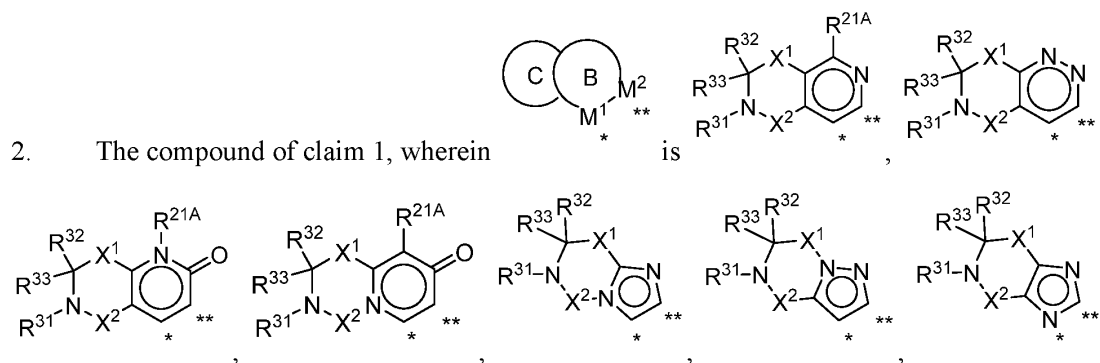
M^1 is C or N;

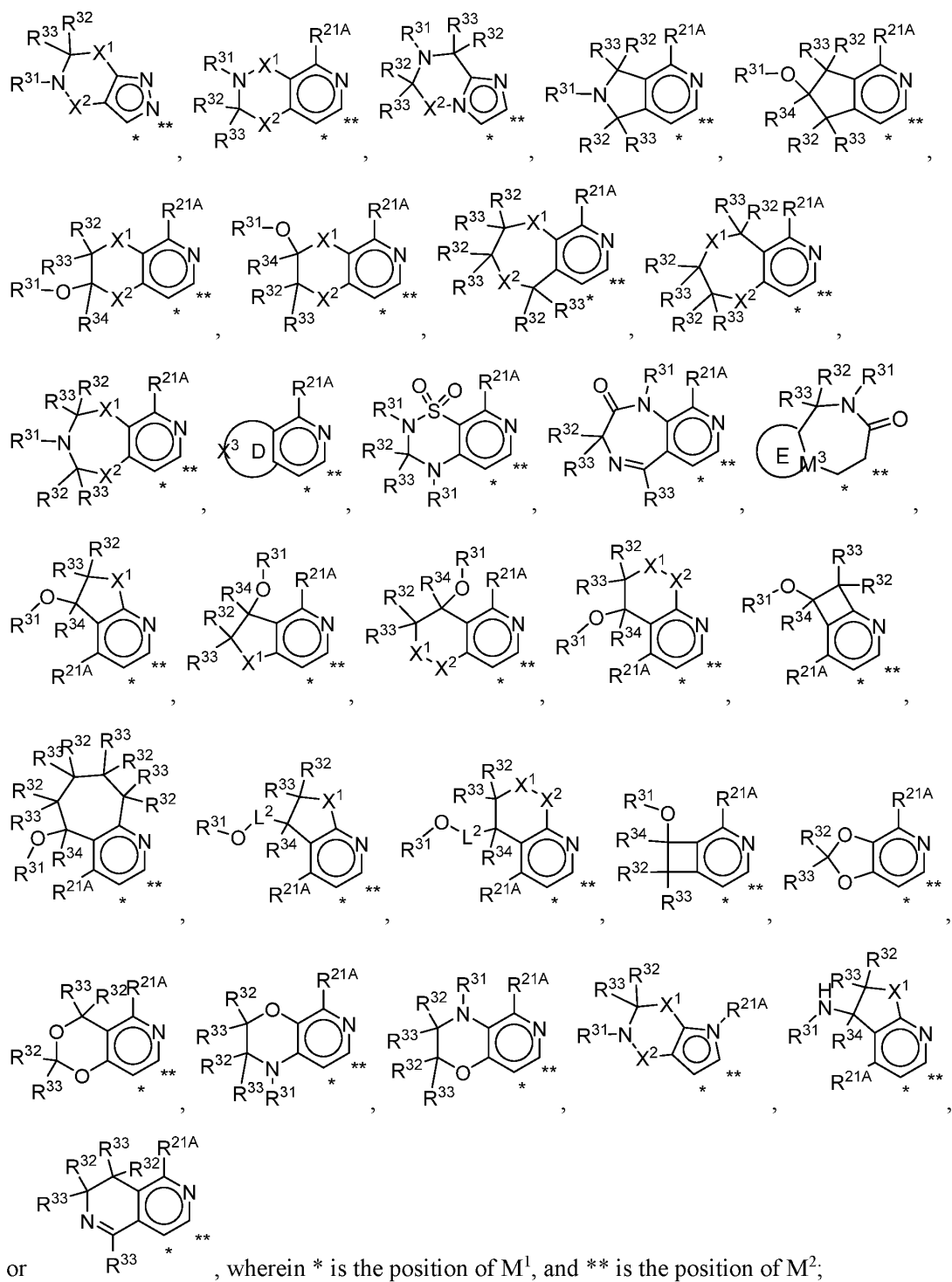
M^2 is C or N;

Ring B is an optionally substituted 5-7 membered ring that is fused to Ring A at the bond formed by M^1 and M^2 ;

Ring C is an optionally substituted 5-7 membered ring that is fused to Ring B; and

provided that the compound is not a compound of Table X, or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof.





R^{21A} is hydrogen, deuterium, halogen, CN, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, C_{1-4} heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or an optionally substituted 3-6 membered ring structure;

X^1 is O, NR^{31} , or $CR^{32}R^{33}$;

X^2 is O, NR^{31} , or $CR^{32}R^{33}$;

Ring D is an optionally substituted 5-7 membered ring, wherein all the ring atoms other than X^3 are carbon atoms, and X^3 is -O-, -S(O)-, -S(O)₂-, -S(O)₂- NR^{31} -, - NR^{31} -S(O)₂-, -S(O)(NH)-, -P(O)(R^{34})-, -P(O)(R^{34})- NR^{31} -, or - NR^{31} -P(O)(R^{34})-;

M^3 is C or N;

Ring E is an optionally substituted phenyl, or optionally substituted 5 or 6 membered heteroaryl;

R^{31} at each occurrence is independently hydrogen, C_{1-4} alkyl, O(C_{1-4} alkyl), C(O)H, C(O)(C_{1-4} alkyl), C(O)O(C_{1-4} alkyl), C(O)NH₂, C(O)NH(C_{1-4} alkyl), C(O)N(C_{1-4} alkyl)₂, C(O)(C_{3-6} carbocyclyl), C(O)(phenyl), C(O)(4-6 membered heterocyclyl), C(O)(5- or 6-membered heteroaryl), SO₂(C_{1-4} alkyl), SO₂NH₂, SO₂NH(C_{1-4} alkyl), SO₂N(C_{1-4} alkyl)₂, SO₂(C_{3-6} carbocyclyl), SO₂(phenyl), SO₂(4-6 membered heterocyclyl), SO₂(5- or 6-membered heteroaryl), C_{3-6} carbocyclyl, phenyl, 4-6 membered heterocyclyl, or 5- or 6-membered heteroaryl; wherein the alkyl moiety in R^{31} at each occurrence is independently optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each of which is independently deuterium, halo, OH, O(C_{1-4} alkyl), SO₂(C_{1-4} alkyl), NH₂, NH(C_{1-4} alkyl), N(C_{1-4} alkyl)(C_{1-4} alkyl), NH(C_{3-6} cycloalkyl), N(C_{1-4} alkyl)(C_{3-6} cycloalkyl), or N(C_{3-6} cycloalkyl)(C_{3-6} cycloalkyl); and wherein the carbocyclyl, phenyl, heterocyclyl, and heteroaryl moieties in R^{31} at each occurrence is independently optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each of which is independently oxo, halo, OH, NH₂, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F;

each of R^{32} and R^{33} at each occurrence is independently:

- (1) hydrogen or deuterium;
- (2) halogen or cyano;
- (3) OH, NH₂, NH(C_{1-4} alkyl), or N(C_{1-4} alkyl)(C_{1-4} alkyl);
- (4) C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each of which is independently deuterium, F, OH, NH₂,

NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)(C₁₋₄ alkyl), NH(C₃₋₆ cycloalkyl), N(C₁₋₄ alkyl)(C₃₋₆ cycloalkyl), N(C₃₋₆ cycloalkyl)(C₃₋₆ cycloalkyl), or SO₂(C₁₋₄ alkyl);

- (5) C₁₋₄ alkoxy optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C₁₋₄ heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F;
- (6) an optionally substituted C₃₋₆ carbocyclyl, optionally substituted phenyl, optionally substituted 4-6 membered heterocyclyl, or optionally substituted 5- or 6-membered heteroaryl;
- (7) R³² and R³³, together with the carbon atom they are attached to, form a carbonyl (CO);
- (8) R³² and R³³, together with the carbon atom they are attached to, form a C₃₋₆ carbocyclyl or 4-6 membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each of which is independently oxo, halo, OH, NH₂, C₁₋₄ alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C₁₋₄ heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F; or
- (9) two R³² are joined together with the intervening atom(s) to form an optionally substituted 3-7 membered ring; or

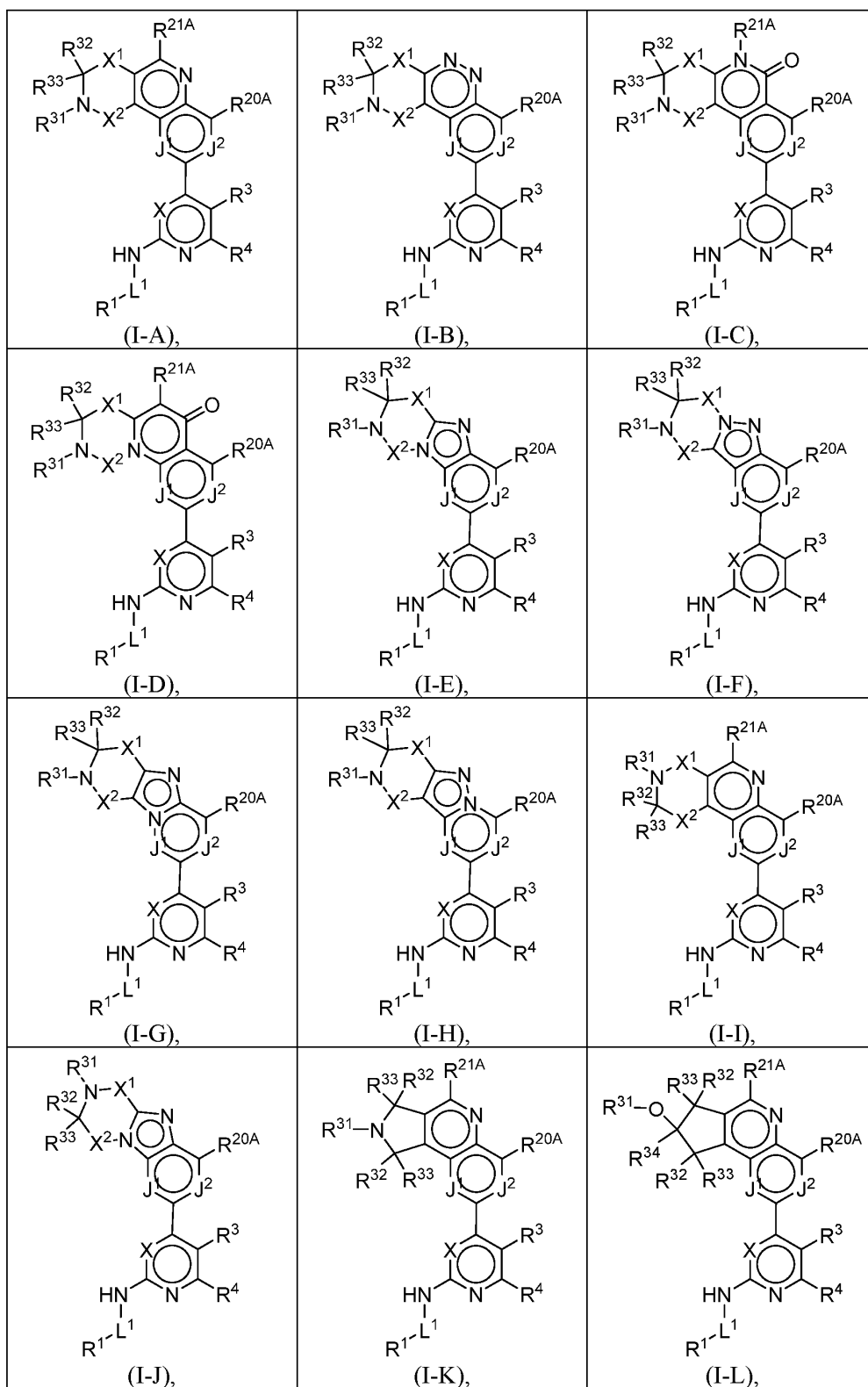
a R³¹ and an adjacent R³² are joined together with the intervening atom(s) to form an optionally substituted 3-7 membered ring;

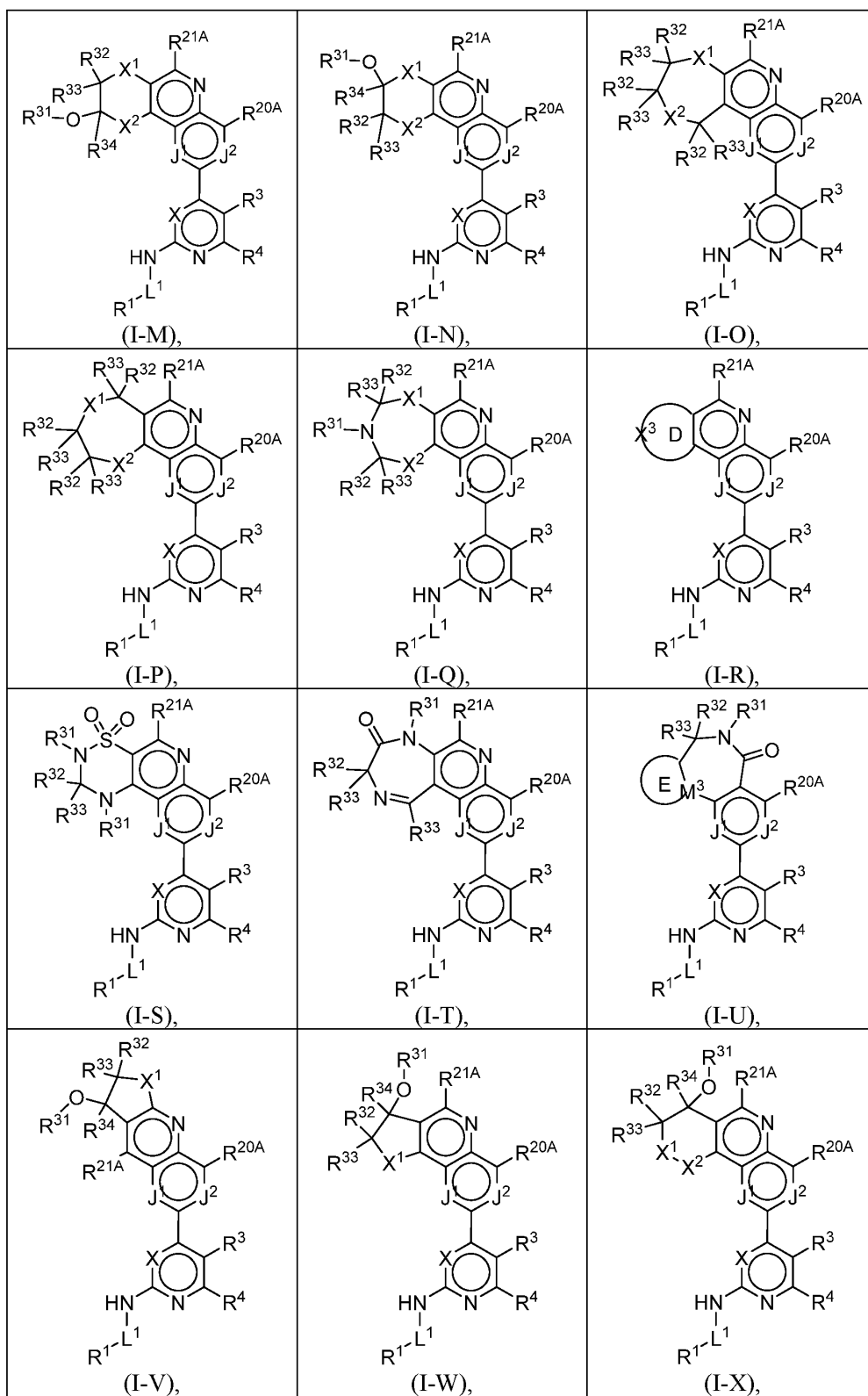
R³⁴ at each occurrence is independently hydrogen, C₁₋₄ alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, optionally substituted C₃₋₆ carbocyclyl, optionally substituted phenyl, optionally substituted 4-6 membered heterocyclyl, or optionally substituted 5- or 6-membered heteroaryl; or

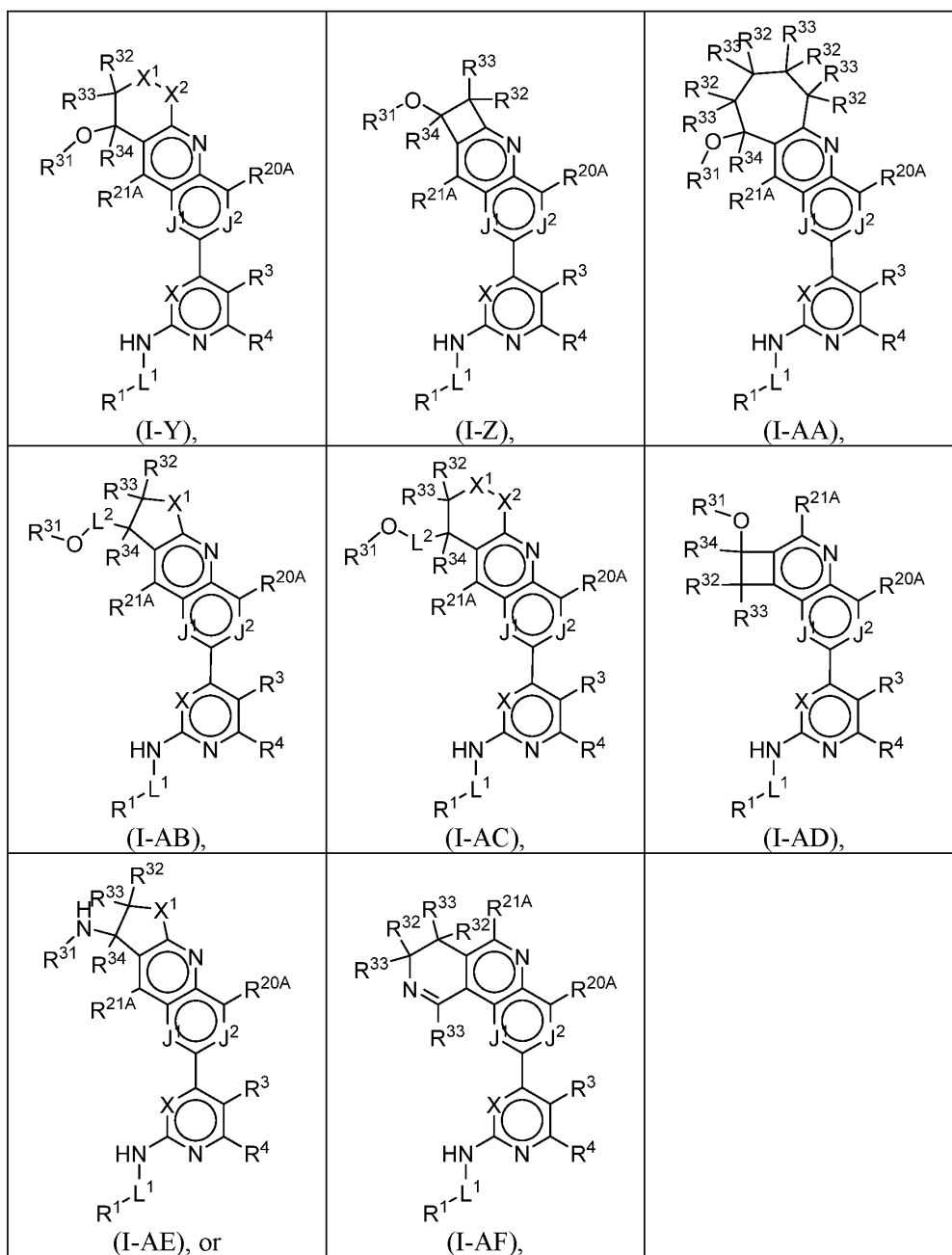
a R³⁴ and a R³² are joined together with the intervening atom(s) to form an optionally substituted 3-7 membered ring; and

L² is an optionally substituted C₁₋₃ alkylene.

3. The compound of claim 2, which is a compound of Formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (I-I), (I-J), (I-K), (I-L), (I-M), (I-N), (I-O), (I-P), (I-Q), (I-R), (I-S), (I-T), (I-U), (I-V), (I-W), (I-X), (I-Y), (I-Z), (I-AA), (I-AB), (I-AC), (I-AD), (I-AE), or (I-AF):

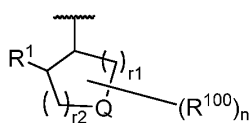






or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1 to 3, wherein $-L^1-R^1$ has a structure of Formula (A):



Formula (A),

wherein:

Q is

- (1) O;
- (2) NR^{14} , wherein R^{14} is hydrogen, G^{A} , $\text{SO}_2\text{G}^{\text{A}}$, $\text{SO}_2\text{NG}^{\text{B}}\text{G}^{\text{C}}$, $\text{S}(\text{O})(\text{NH})\text{G}^{\text{A}}$, COG^{A} , COOG^{A} , or $\text{C}(\text{O})\text{NG}^{\text{B}}\text{G}^{\text{C}}$;
- (3) $\text{CR}^{15}\text{R}^{16}$, wherein R^{15} and R^{16} are joined with the carbon atom they are attached to form an optionally substituted 4-6 membered heterocyclic ring having 1 or 2 ring heteroatoms independently selected from O and N; or
- (4) absent;

r_1 is 1, 2, or 3; and

r_2 is 0, 1, or 2;

n is 0, 1, 2, 3, or 4, as valency permits; and

- (i) R^{100} at each occurrence is independently selected from halogen (*e.g.*, F or Cl), CN, OH, COOH, G^{A} , OG^{A} , $\text{NG}^{\text{B}}\text{G}^{\text{C}}$, $\text{NG}^{\text{B}}\text{G}^{\text{C}}\text{SO}_2\text{G}^{\text{A}}$, $\text{NG}^{\text{B}}\text{G}^{\text{C}}\text{SO}_2\text{NG}^{\text{B}}\text{G}^{\text{C}}$, $\text{NG}^{\text{B}}\text{G}^{\text{C}}\text{S}(\text{O})(\text{NH})\text{G}^{\text{A}}$, $\text{NG}^{\text{B}}\text{G}^{\text{C}}\text{COG}^{\text{A}}$, $\text{NG}^{\text{B}}\text{G}^{\text{C}}\text{COOG}^{\text{A}}$, $\text{NG}^{\text{B}}\text{G}^{\text{C}}\text{C}(\text{O})\text{NG}^{\text{B}}\text{G}^{\text{C}}$, $\text{SO}_2\text{G}^{\text{A}}$, $\text{SO}_2\text{NG}^{\text{B}}\text{G}^{\text{C}}$, $\text{S}(\text{O})(\text{NH})\text{G}^{\text{A}}$, COG^{A} , COOG^{A} , or $\text{C}(\text{O})\text{NG}^{\text{B}}\text{G}^{\text{C}}$; or
- (ii) two instances of R^{100} are joined together with the intervening atom(s) to form an optionally substituted ring, such as an optionally substituted 3-6 membered ring, and any remaining R^{100} at each occurrence is as defined in (i);

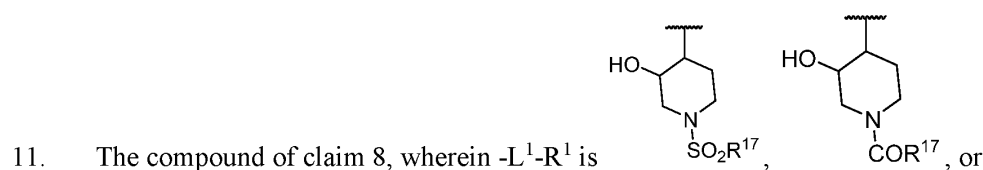
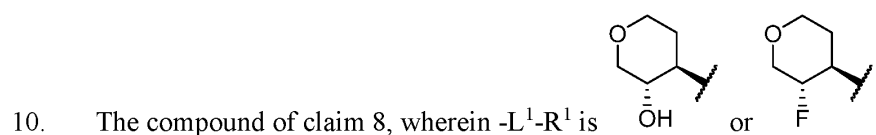
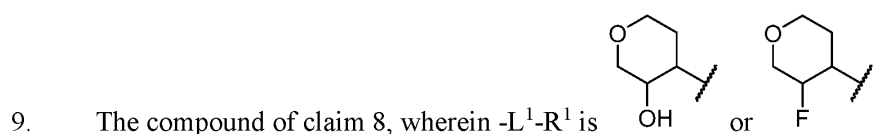
wherein:

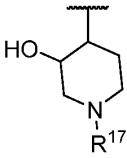
G^{A} at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl (*e.g.*, 5- or 6-membered heteroaryl), or optionally substituted 4-10 membered heterocyclyl; and

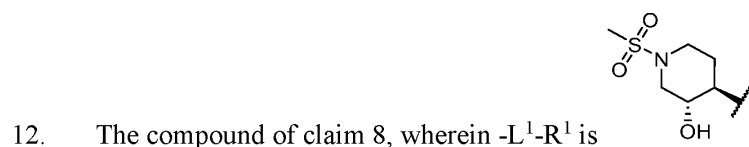
each of G^{B} and G^{C} , at each occurrence, is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl (*e.g.*, 5- or 6-membered heteroaryl), optionally substituted 4-10

membered heterocyclyl; or G^B and G^C can be joined to form an optionally substituted 4-10 membered heterocyclyl or 5- or 6-membered heteroaryl.

5. The compound of claim 4, wherein Q is O.
6. The compound of claim 4, wherein Q is NR^{14} .
7. The compound of claim 4, wherein Q is absent.
8. The compound of any one of claims 4 to 7, wherein n is 0.

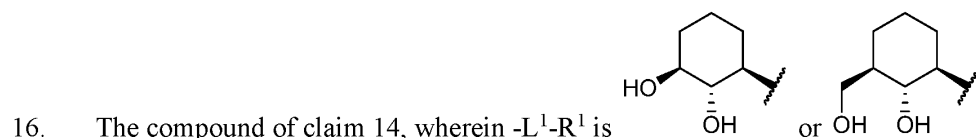
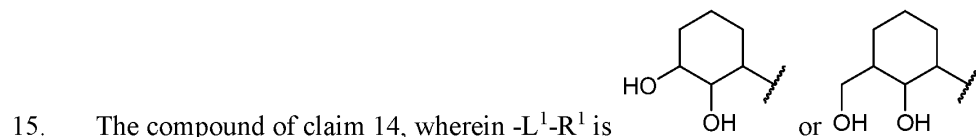


, and R^{17} is an optionally substituted C_{1-4} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted phenyl, optionally substituted 4-8 membered heterocyclic ring, or optionally substituted 5 or 6 membered heteroaryl.

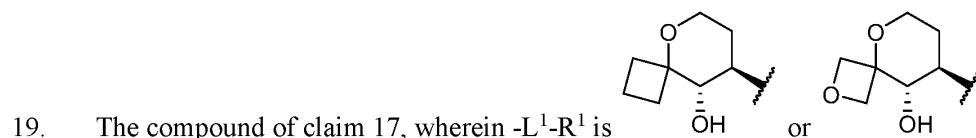
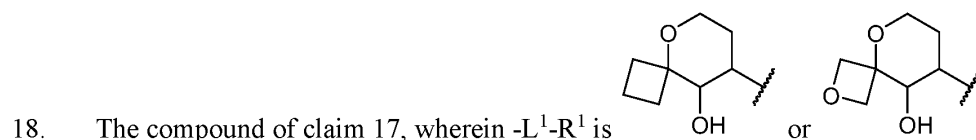


13. The compound of any one of claims 4 to 7, wherein n is 1 or 2, and R^{100} at each occurrence is independently selected from F, Cl, CN, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F or OH, C_{1-4} alkoxy optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, and C_{1-4} heteroalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F.

14. The compound of claim 11, wherein n is 1, and R^{100} is F, Cl, CN, OH, methyl, $-\text{CH}_2\text{OH}$, fluorine-substituted methyl such as CF_3 , methoxy, or fluorine-substituted methoxy.

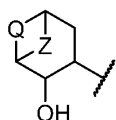


17. The compound of any one of claims 4 to 7, wherein n is 2, and two geminal R^{100} are joined together with the carbon atom they are attached to form an optionally substituted 3-6 membered ring.

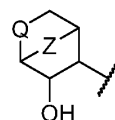


20. The compound of any one of claims 4 to 7, wherein n is 2, and two non-geminal R^{100} are joined together with the intervening atom(s) to form an optionally substituted 4-6 membered ring.

21. The compound of any one of claims 4 to 7, wherein $-\text{L}^1-\text{R}^1$ has a structure of Formula (A-1) or (A-2):



Formula (A-1), or



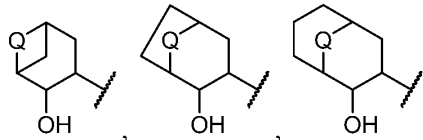
Formula (A-2),

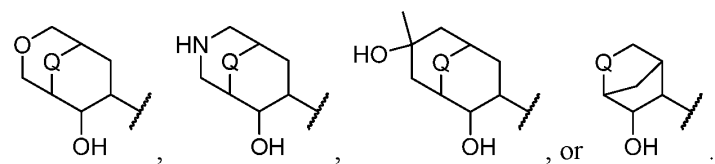
wherein Z is C_{1-3} alkylene, wherein the non-terminal CH_2 is optionally replaced by O or NH, and wherein Z is optionally substituted with one or more (*e.g.*, 1 or 2) substituents each of which is independently halogen, OH, or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F.

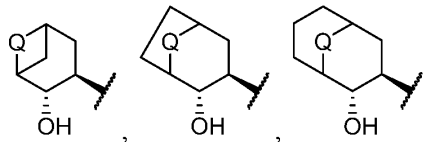
22. The compound of claim 21, wherein Q is O, NH, NHR^{17} , NHC(O)R^{17} , or $\text{NHS(O)}_2\text{R}^{17}$.

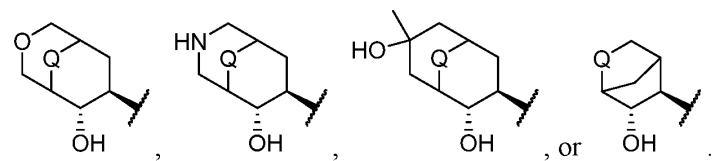
23. The compound of claim 21 or 22, wherein Z is -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂OCH₂-, or -CH₂NHCH₂-.

24. The compound of any one of claims 21 to 23, wherein Z is unsubstituted.

25. The compound of claim 21, wherein -L¹-R¹ is ,

, or

26. The compound of claim 21, wherein -L¹-R¹ is ,

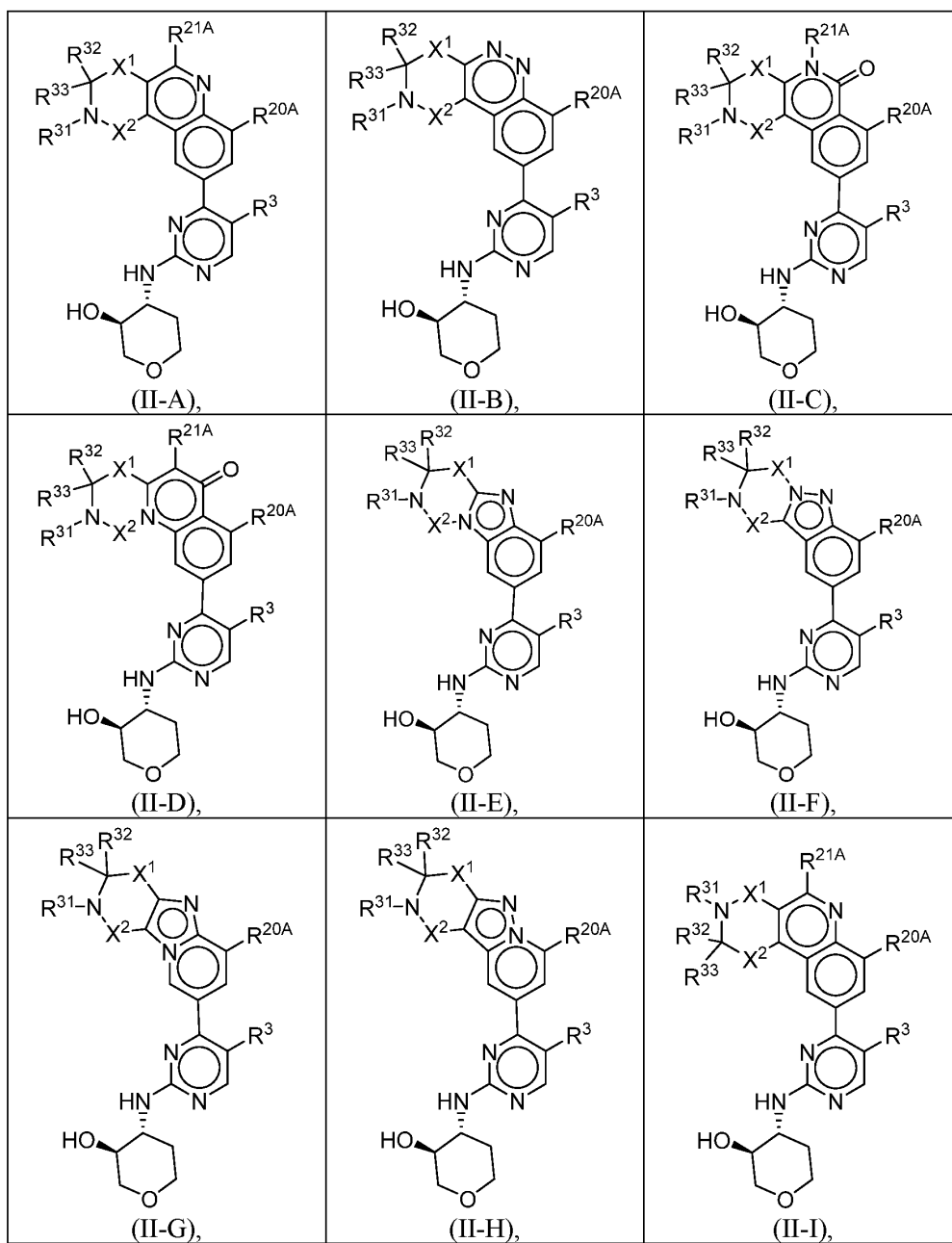
, or

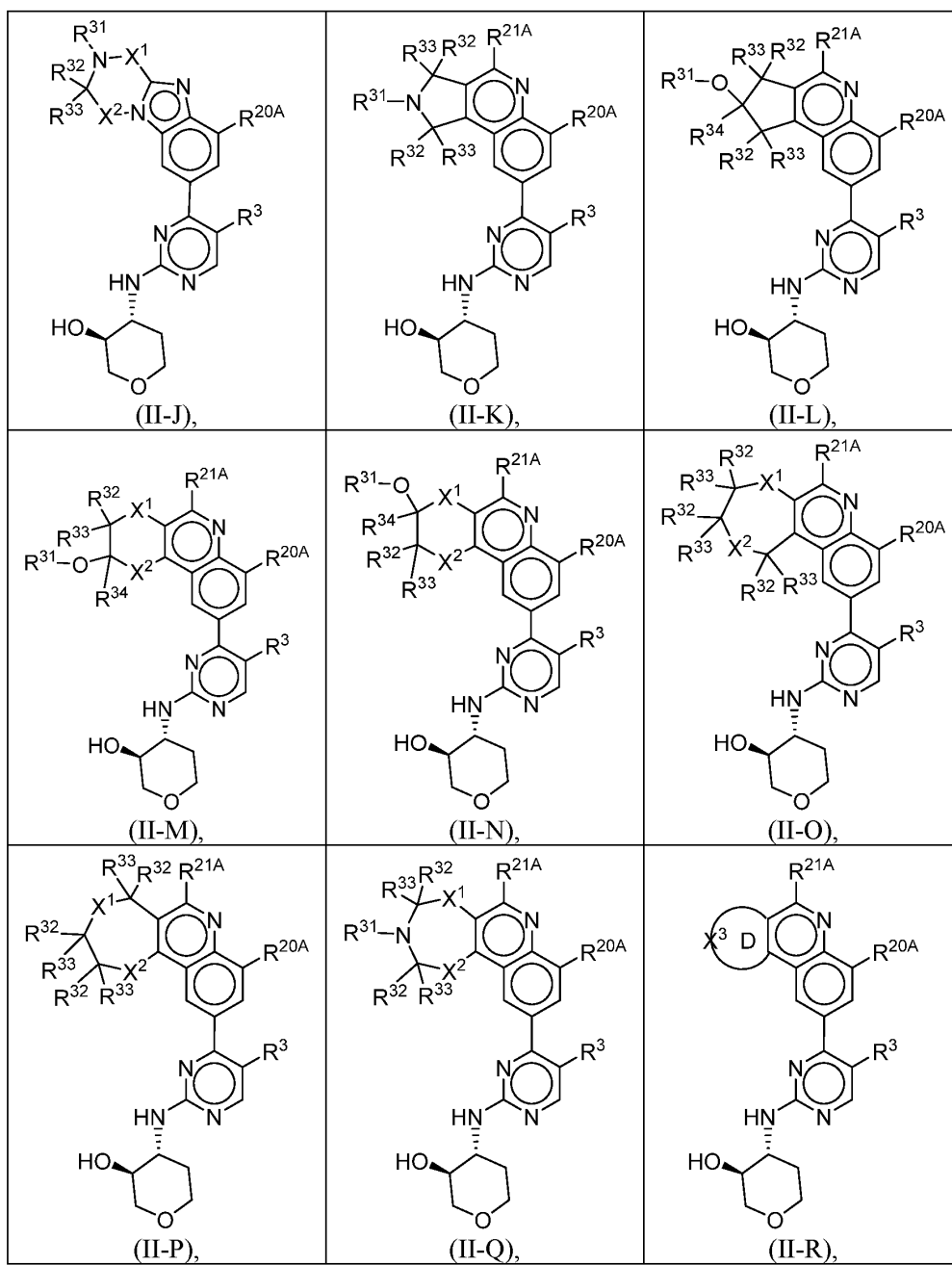
27. The compound of any one of claims 1 to 26, wherein X is N.

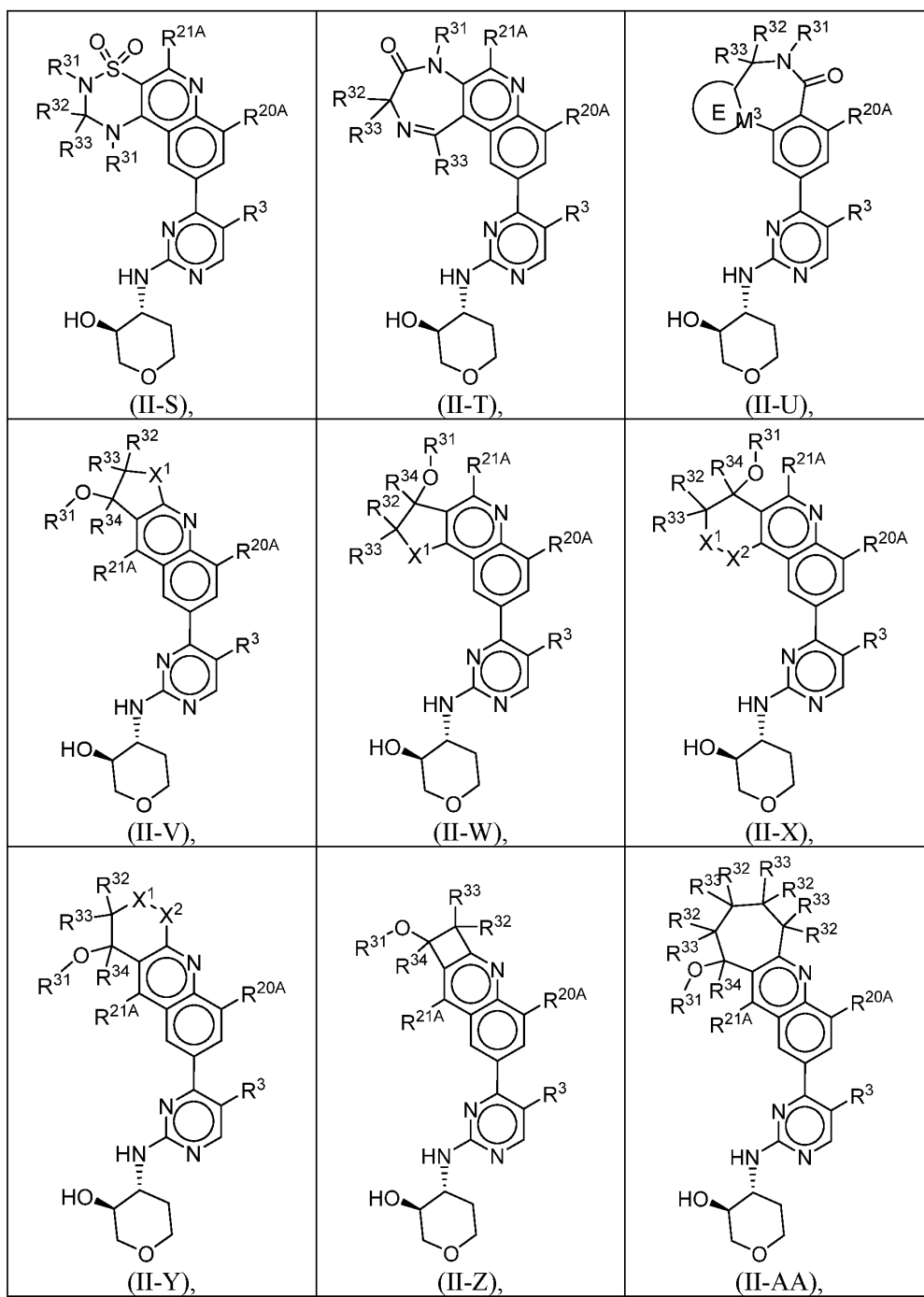
28. The compound of any one of claims 1 to 27, wherein J¹ is CR³⁰ and J² is CR³⁰.

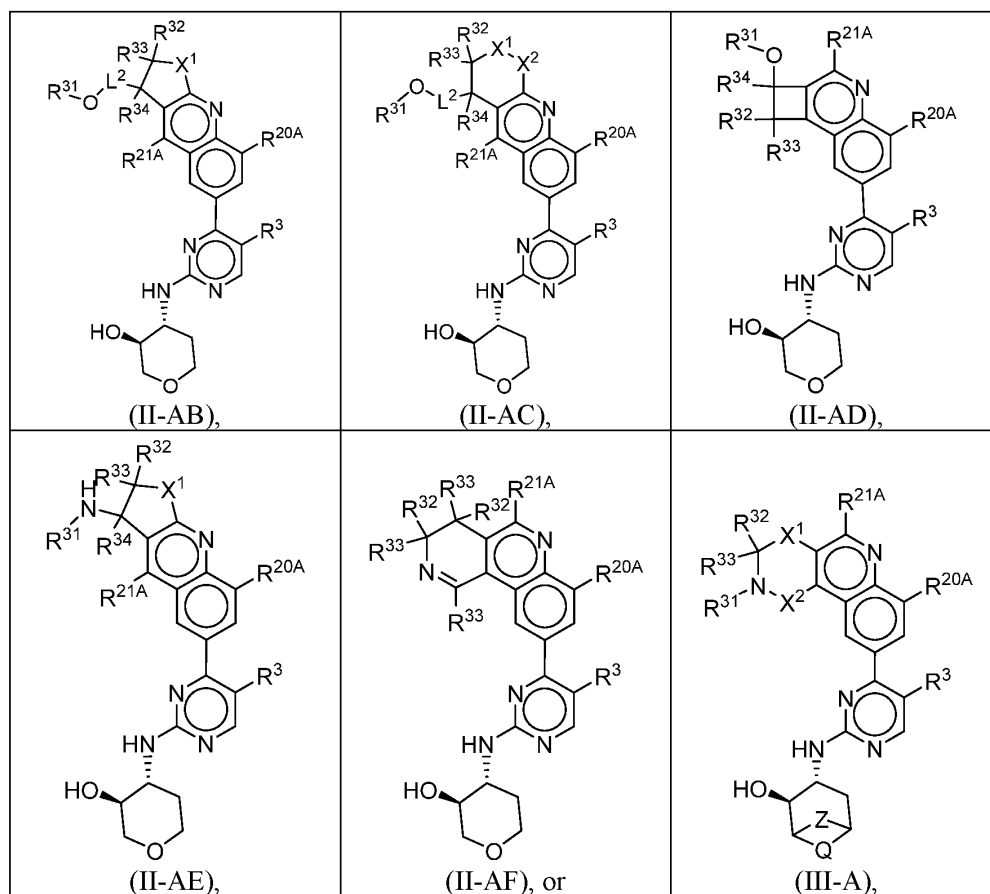
29. The compound of claim 28, wherein J¹ is CH and J² is CH.

30. The compound of any one of claims 1 to 3, which is a compound of Formula (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), (II-H), (II-I), (II-J), (II-K), (II-L), (II-M), (II-N), (II-O), (II-P), (II-Q), (II-R), (II-S), (II-T), (II-U), (II-V), (II-W), (II-X), (II-Y), (II-Z), (II-AA), (II-AB), (II-AC), (II-AD), (II-AE), (II-AF), or (III-A):





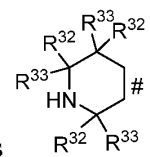




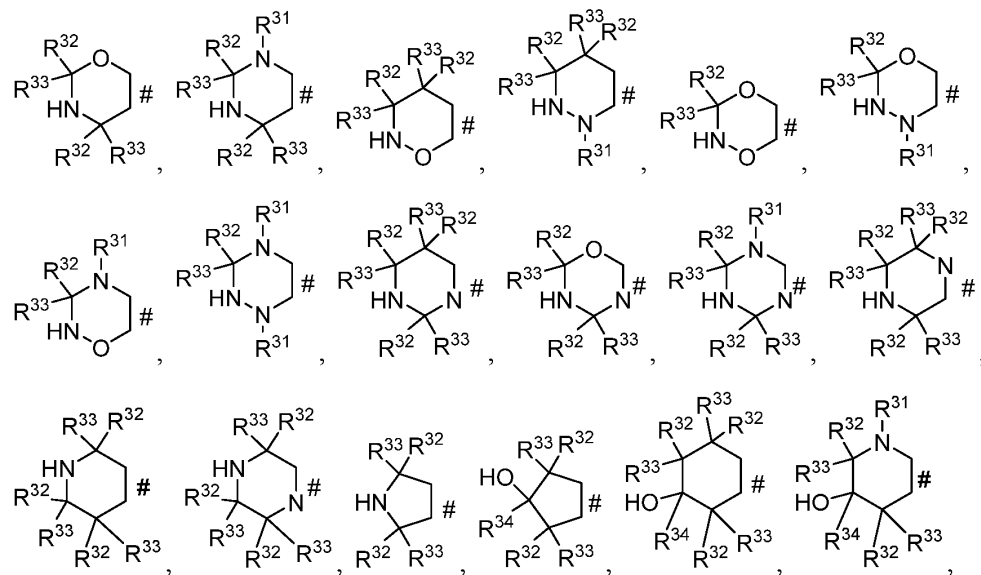
or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof.

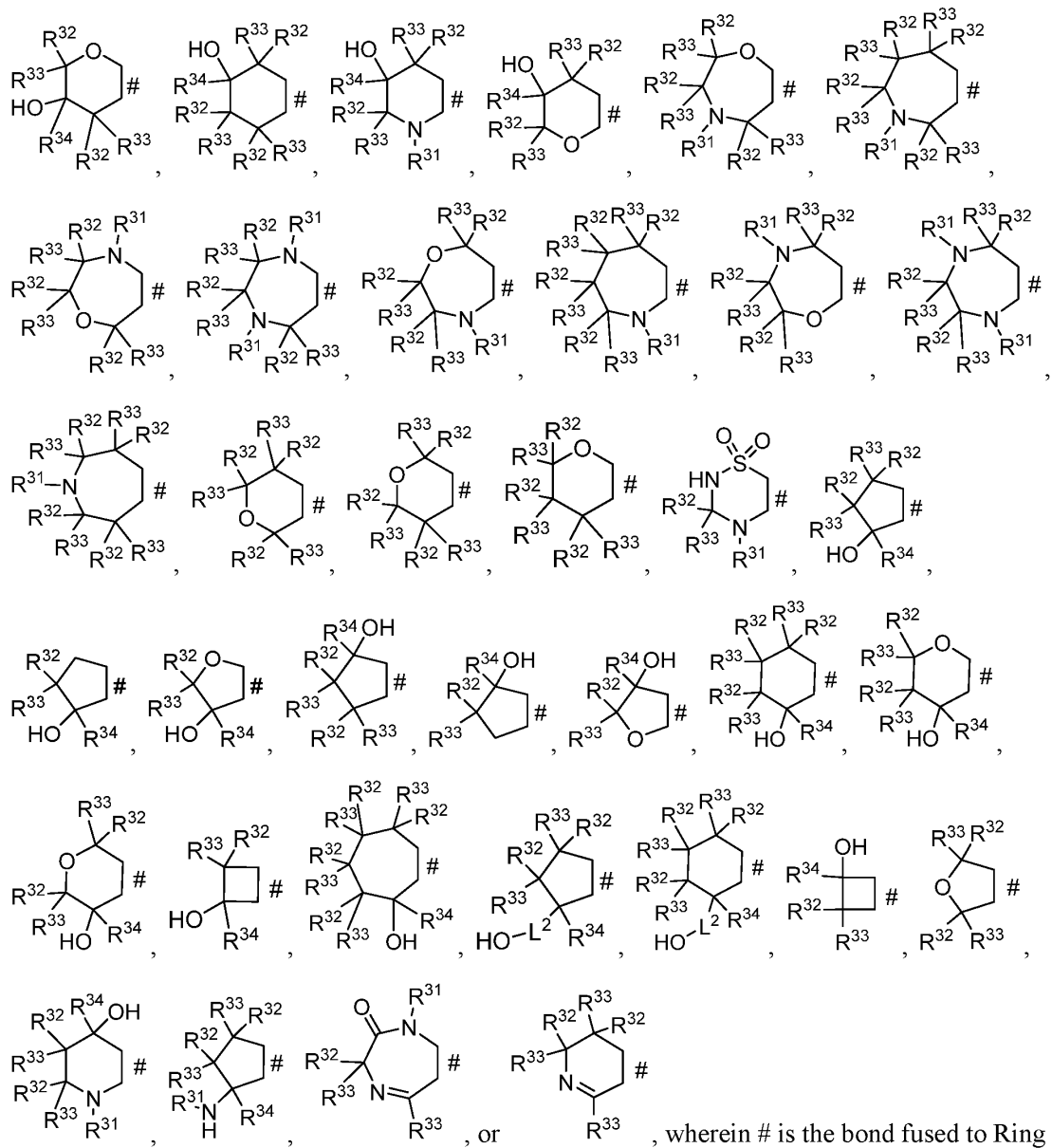
31. The compound of any one of claims 1 to 30, wherein R^{20A} is hydrogen, halogen, or C_{1-4} alkyl.
32. The compound of claim 31, wherein R^{20A} is F.
33. The compound of any one of claims 2 to 32, wherein R^{21A} is hydrogen, deuterium, halogen, C_{1-4} alkyl, or C_{1-4} heteroalkyl having 1 or 2 heteroatoms independently oxygen or nitrogen.
34. The compound of claim 33, wherein R^{21A} is hydrogen, deuterium, F, or methyl.
35. The compound of any one of claims 2 to 34, wherein X^1 is O.
36. The compound of any one of claims 2 to 34, wherein X^1 is NR^{31} .
37. The compound of any one of claims 2 to 34, wherein X^1 is $CR^{32}R^{33}$.

38. The compound of claim 37, wherein X¹ is C=O.
39. The compound of any one of claims 2 to 37, wherein X² is O.
40. The compound of any one of claims 2 to 37, wherein X² is NR³¹.
41. The compound of any one of claims 2 to 37, wherein X² is CR³²R³³.
42. The compound of claim 41, wherein X² is C=O.
43. The compound of any one of claims 2 to 42, wherein R³¹ at each occurrence is independently hydrogen or C₁₋₄ alkyl.
44. The compound of claim 43, wherein R³¹ at each occurrence is independently hydrogen or methyl.
45. The compound of claim 44, wherein the R³¹ on the nitrogen that is not X¹ or X² is hydrogen.

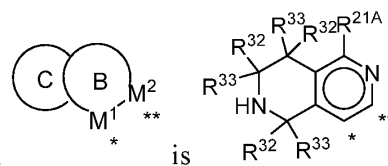


46. The compound of any one of claims 1 to 45, wherein Ring C is

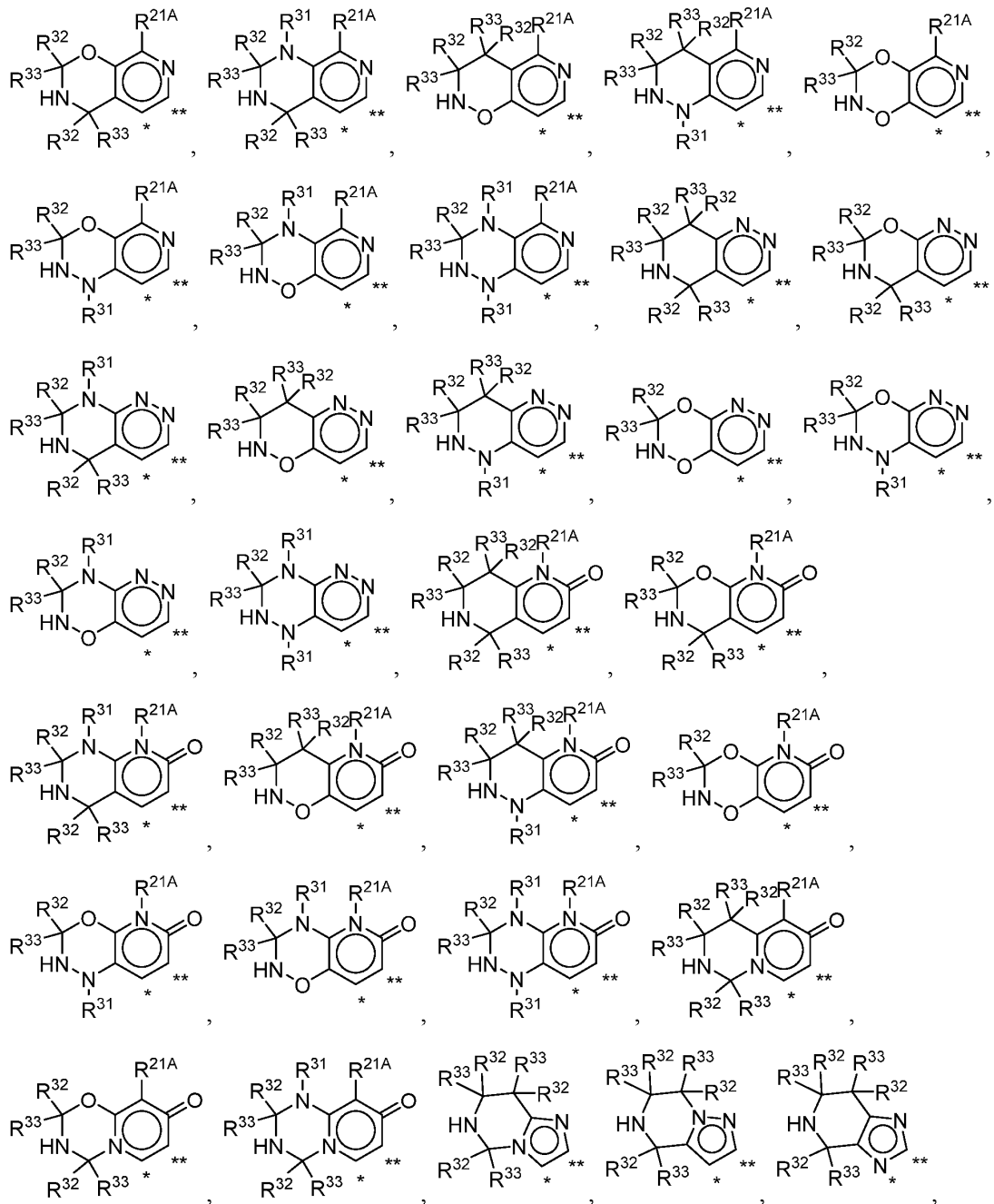


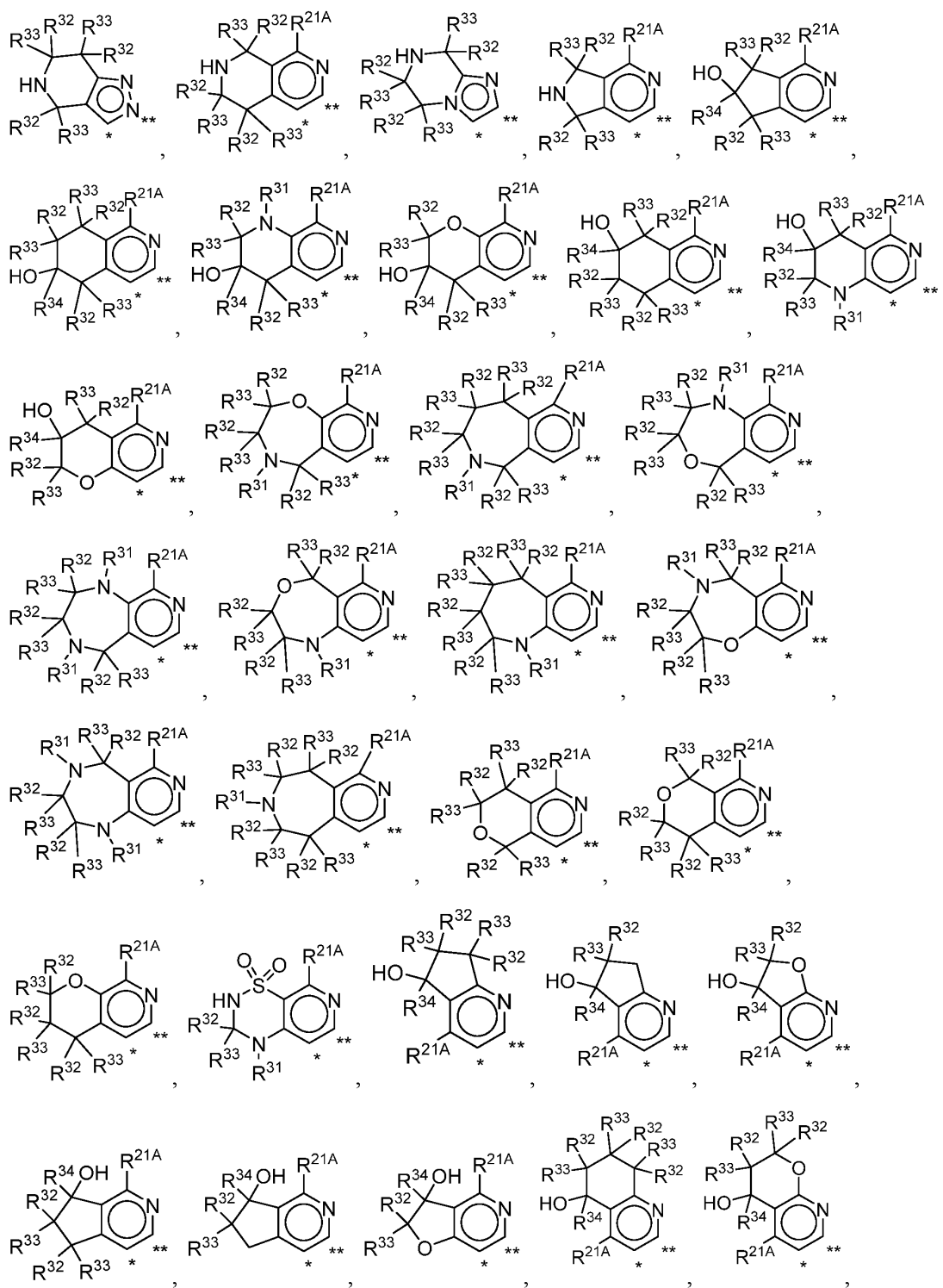


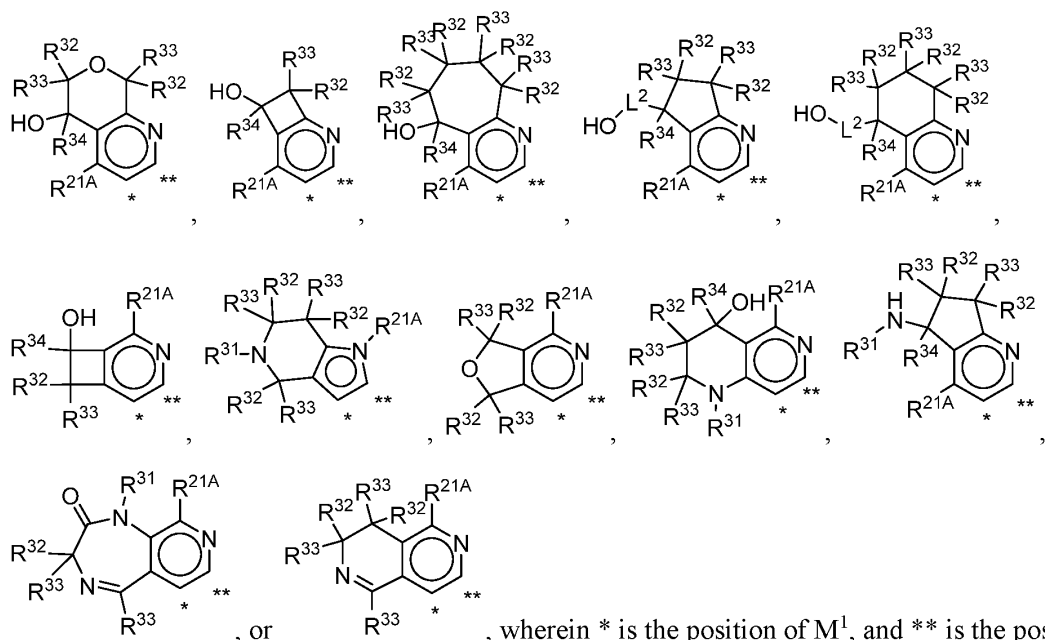
B.



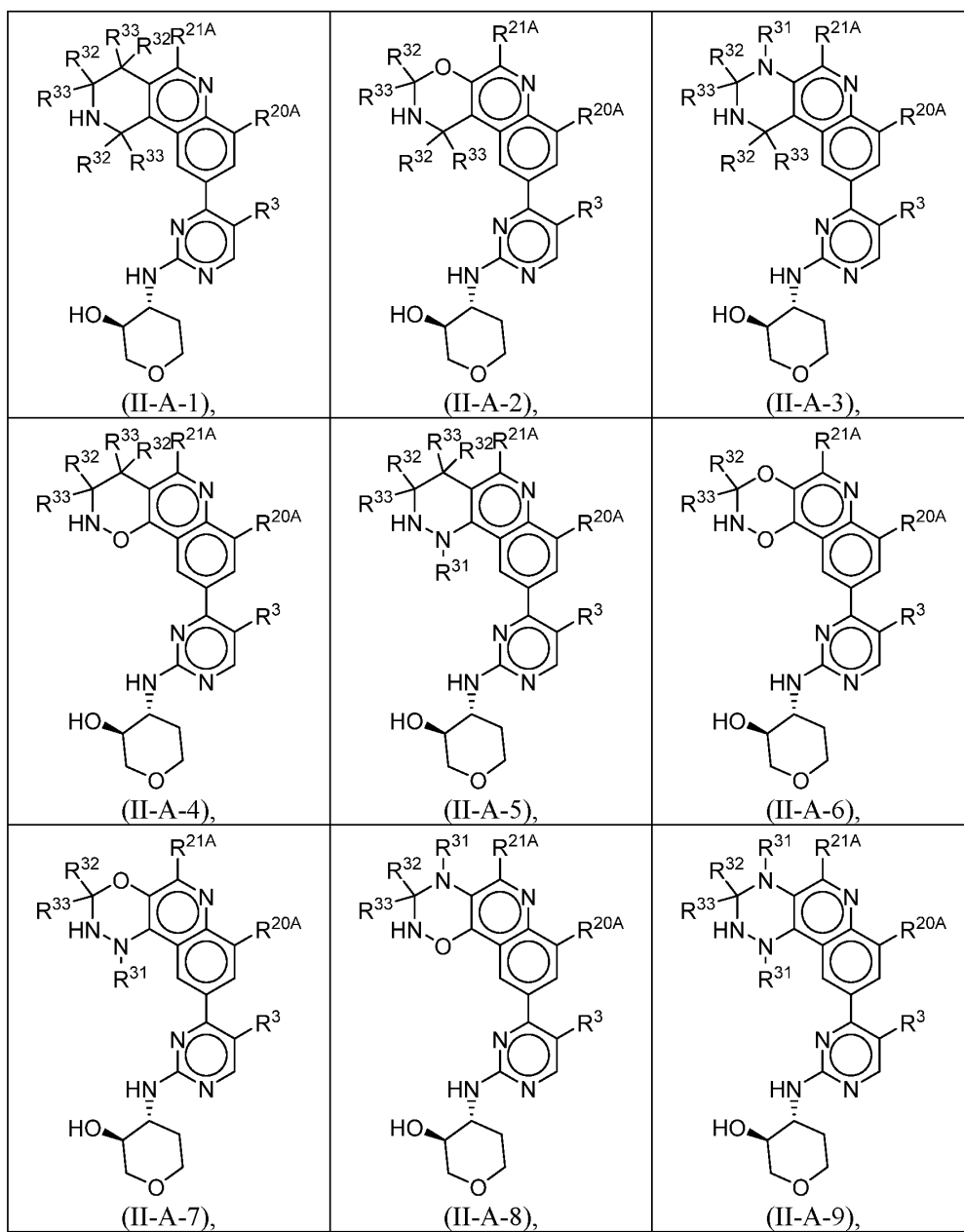
47. The compound of any one of claims 1 to 46, wherein

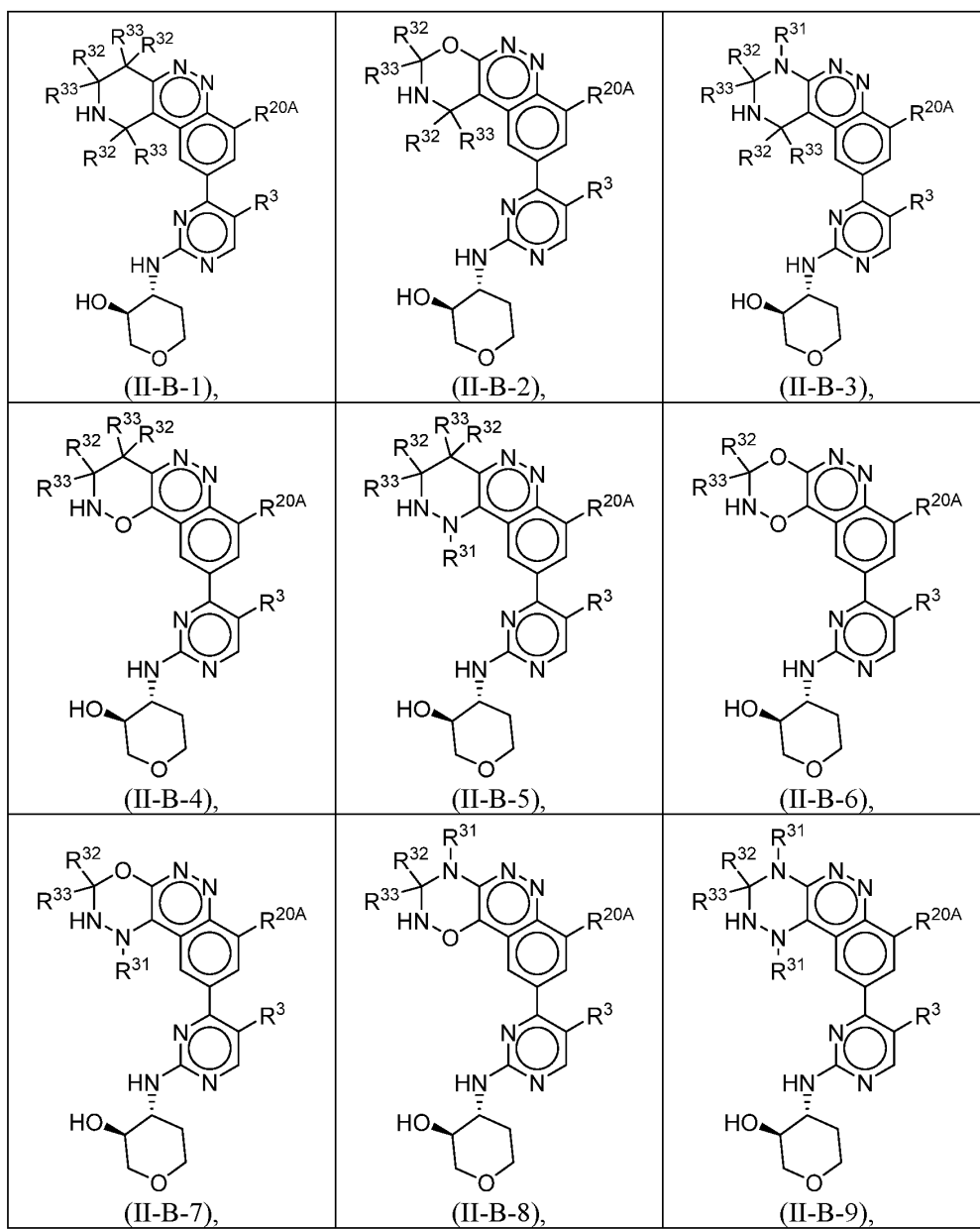


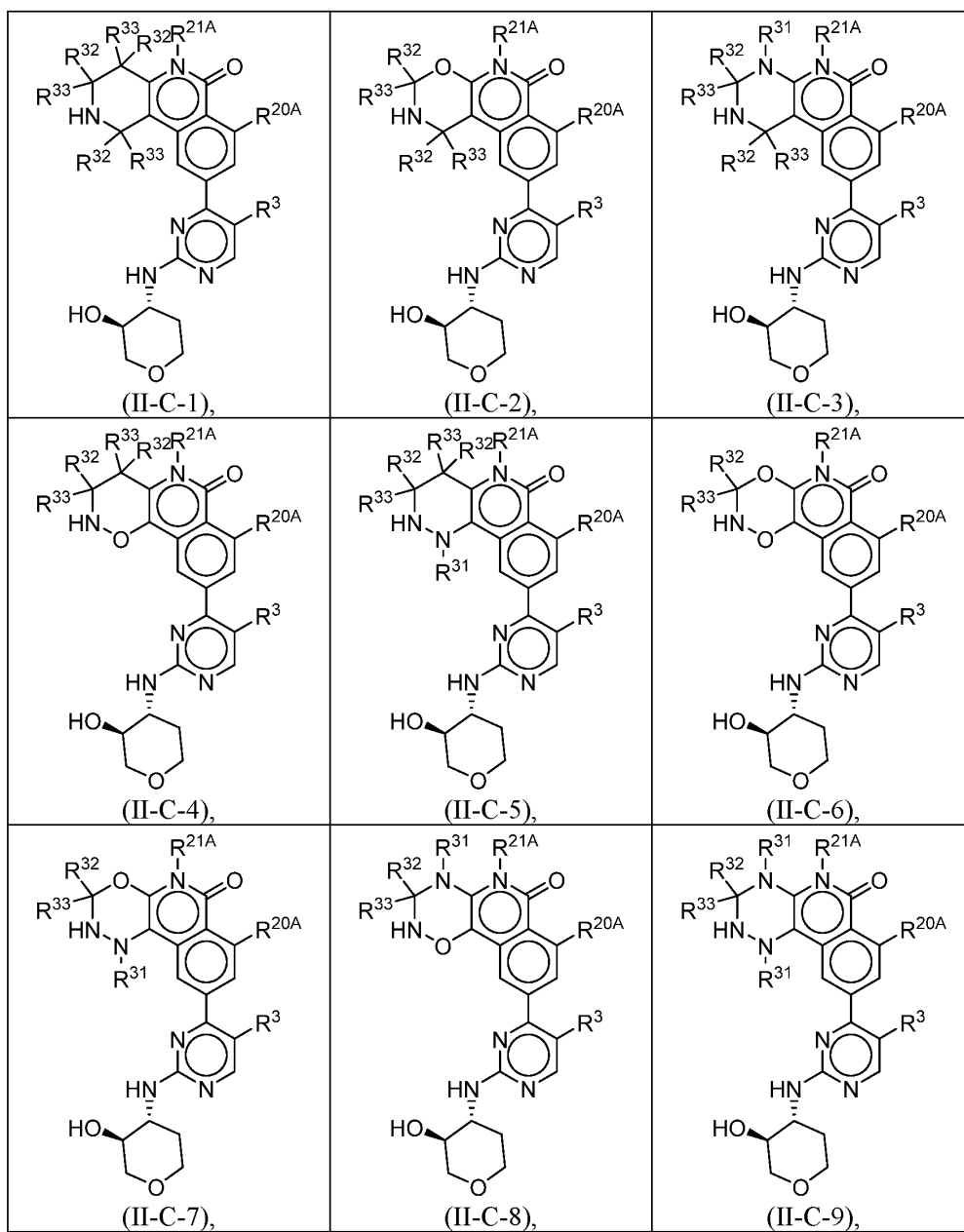


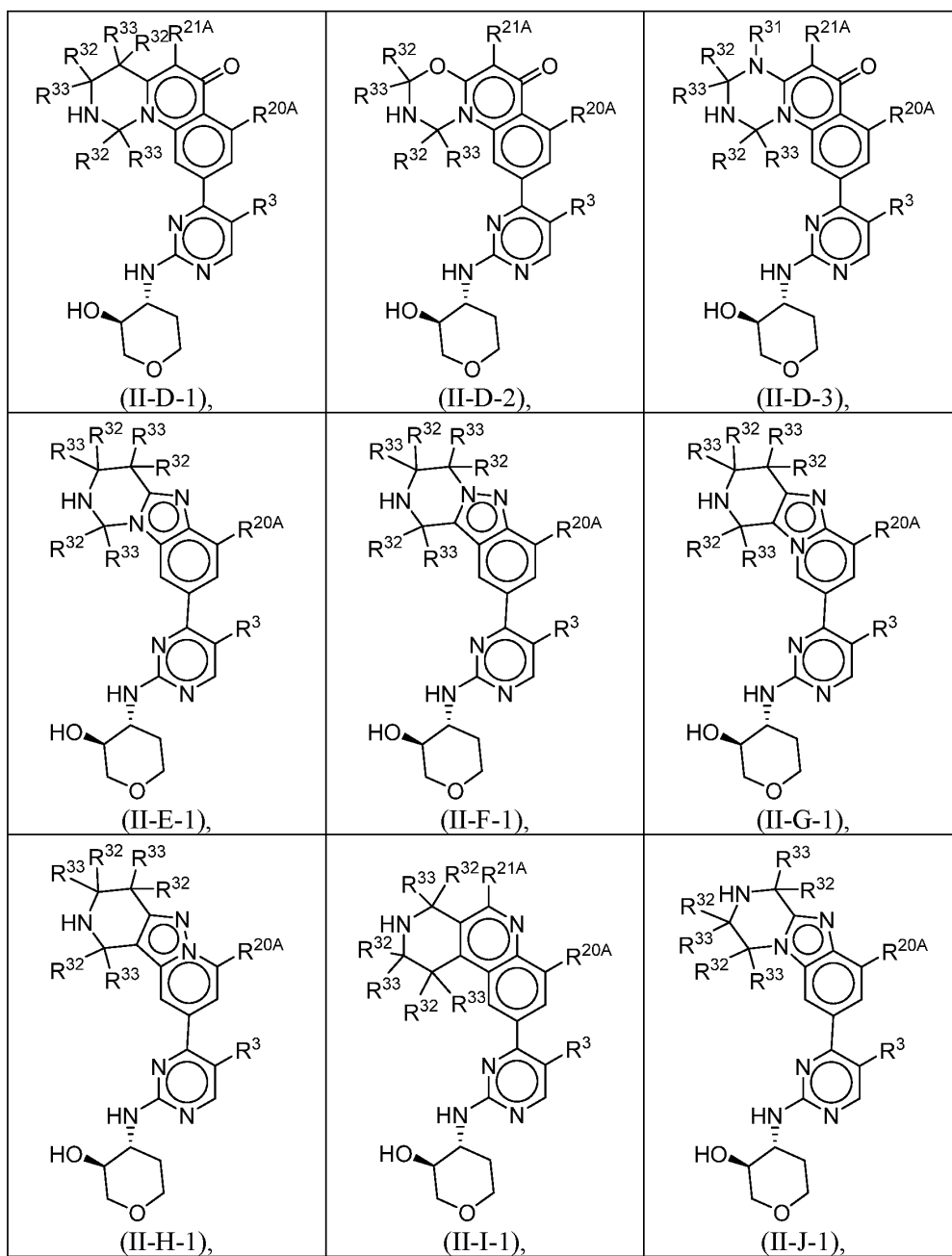


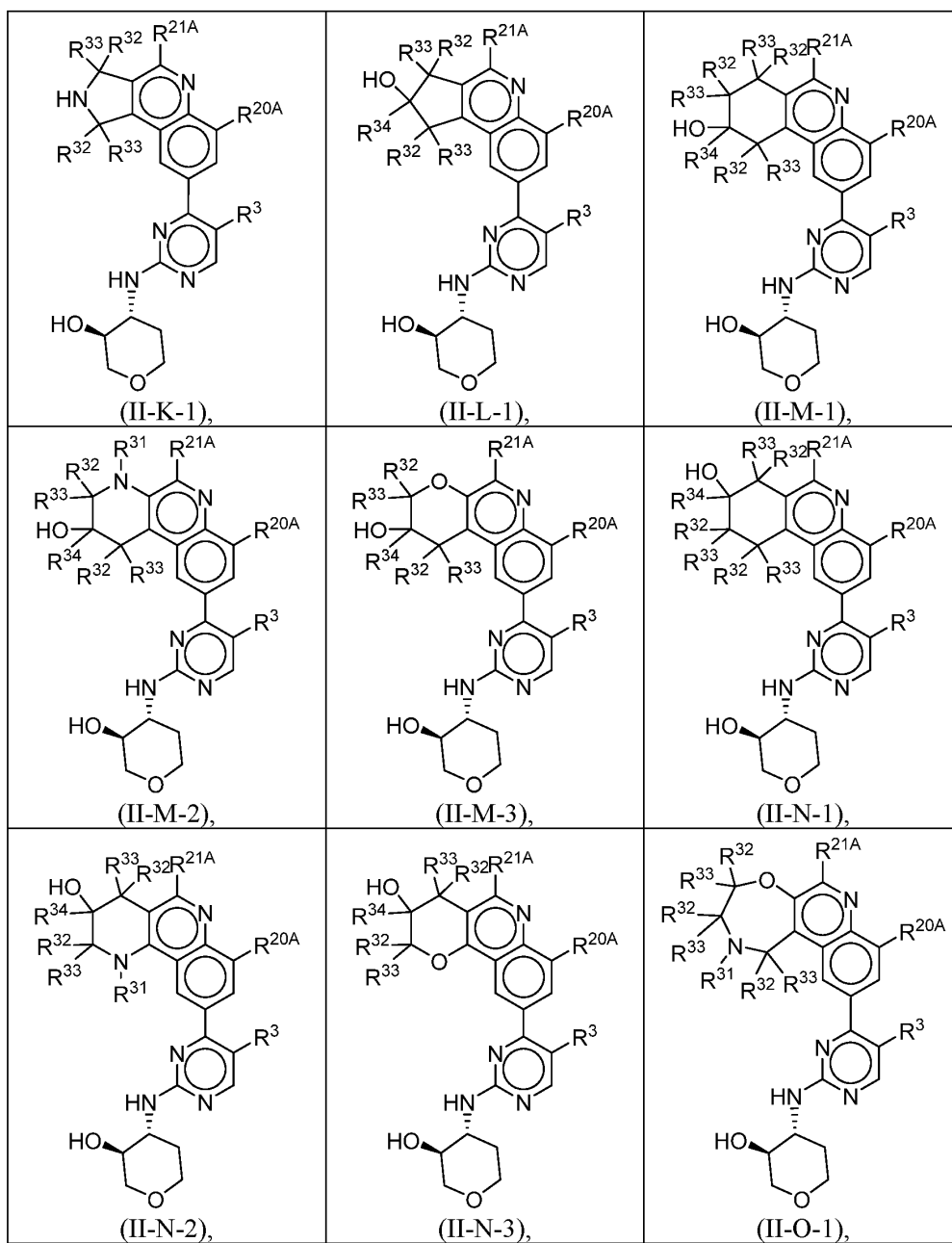
48. The compound of claim 30, which is a compound of Formula (II-A-1), (II-A-2), (II-A-3), (II-A-4), (II-A-5), (II-A-6), (II-A-7), (II-A-8), (II-A-9), (II-B-1), (II-B-2), (II-B-3), (II-B-4), (II-B-5), (II-B-6), (II-B-7), (II-B-8), (II-B-9), (II-C-1), (II-C-2), (II-C-3), (II-C-4), (II-C-5), (II-C-6), (II-C-7), (II-C-8), (II-C-9), (II-D-1), (II-D-2), (II-D-3), (II-E-1), (II-F-1), (II-G-1), (II-H-1), (II-I-1), (II-J-1), (II-K-1), (II-L-1), (II-M-1), (II-M-2), (II-M-3), (II-N-1), (II-N-2), (II-N-3), (II-O-1), (II-O-2), (II-O-3), (II-O-4), (II-P-1), (II-P-2), (II-P-3), (II-P-4), (II-Q-1), (II-R-1), (II-R-2), (II-R-3), (II-R-4), (II-R-5), (II-R-6), (II-R-7), (II-R-8), (II-R-9), (II-R-10), (II-S-1), (II-U-1), (II-U-2), (II-U-3), (II-U-4), (II-U-5), (II-U-6), (II-U-7), (II-V-1), (II-V-2), (II-V-3), (II-W-1), (II-W-2), (II-W-3), (II-X-1), (II-X-2), (II-X-3), (II-X-4), (II-Y-1), (II-Y-2), (II-Y-3), (II-Z-1), (II-AA-1), (II-AB-1), (II-AC-1), (II-AD-1), (II-AE-1), or (III-A-1):

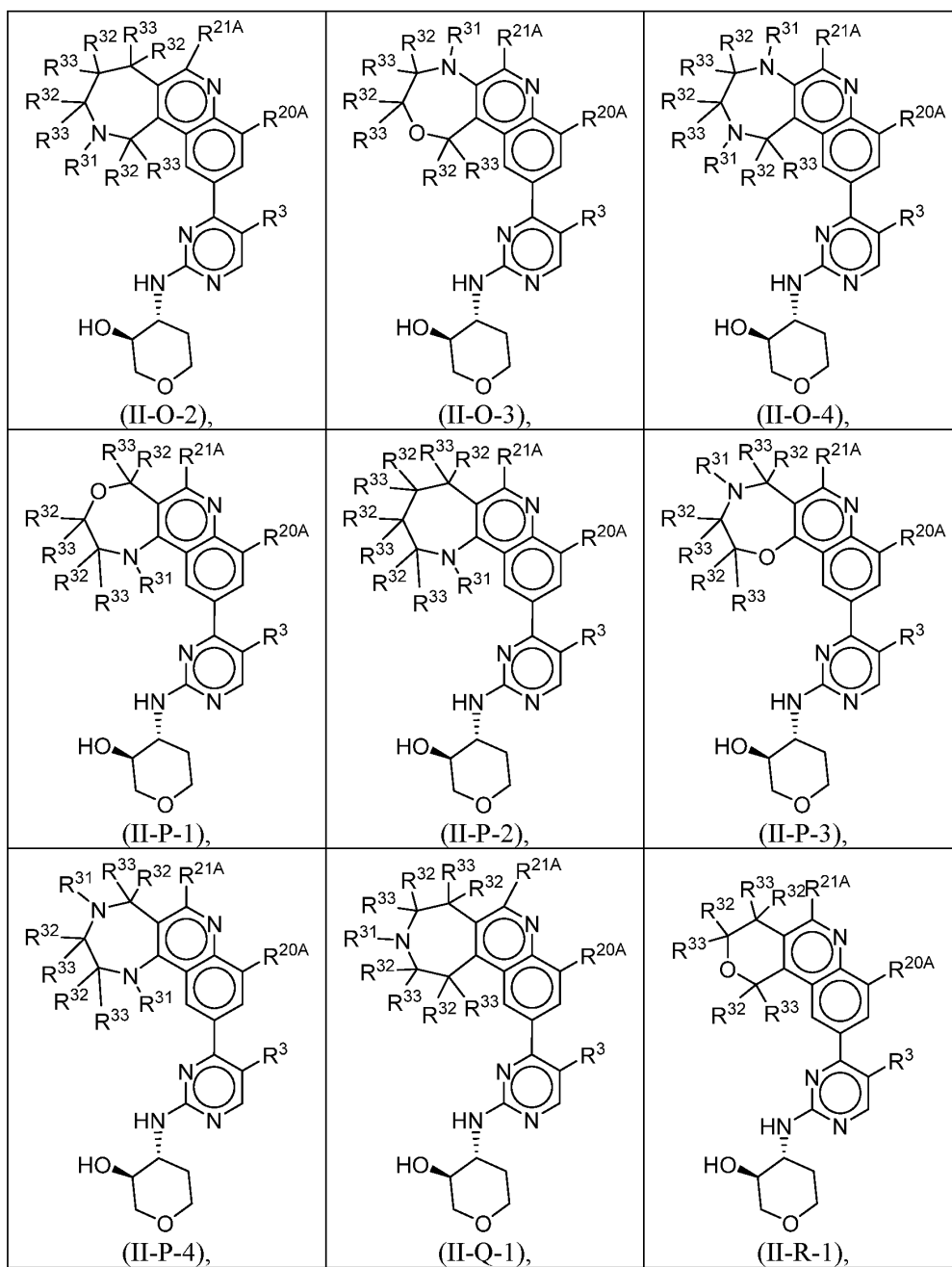


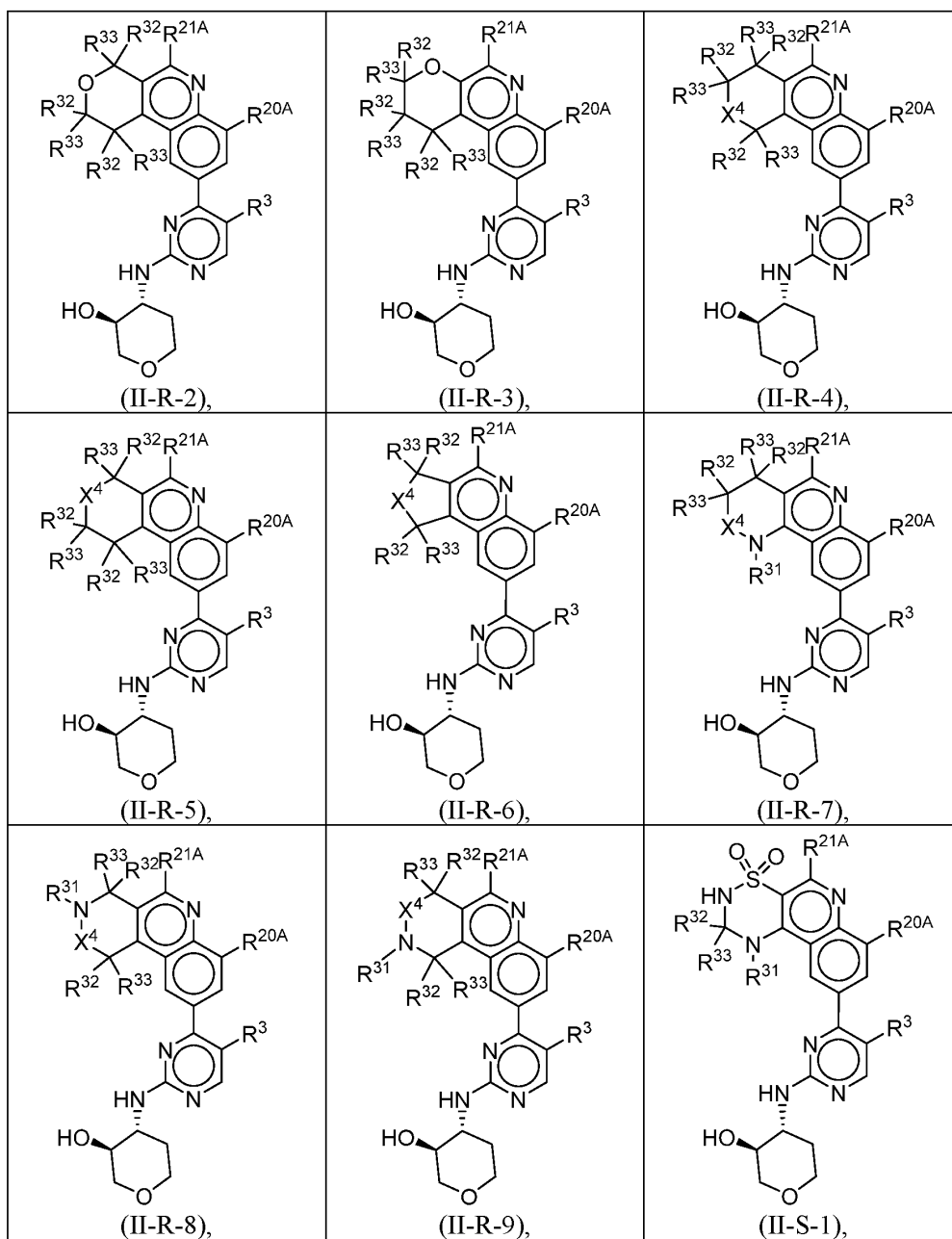


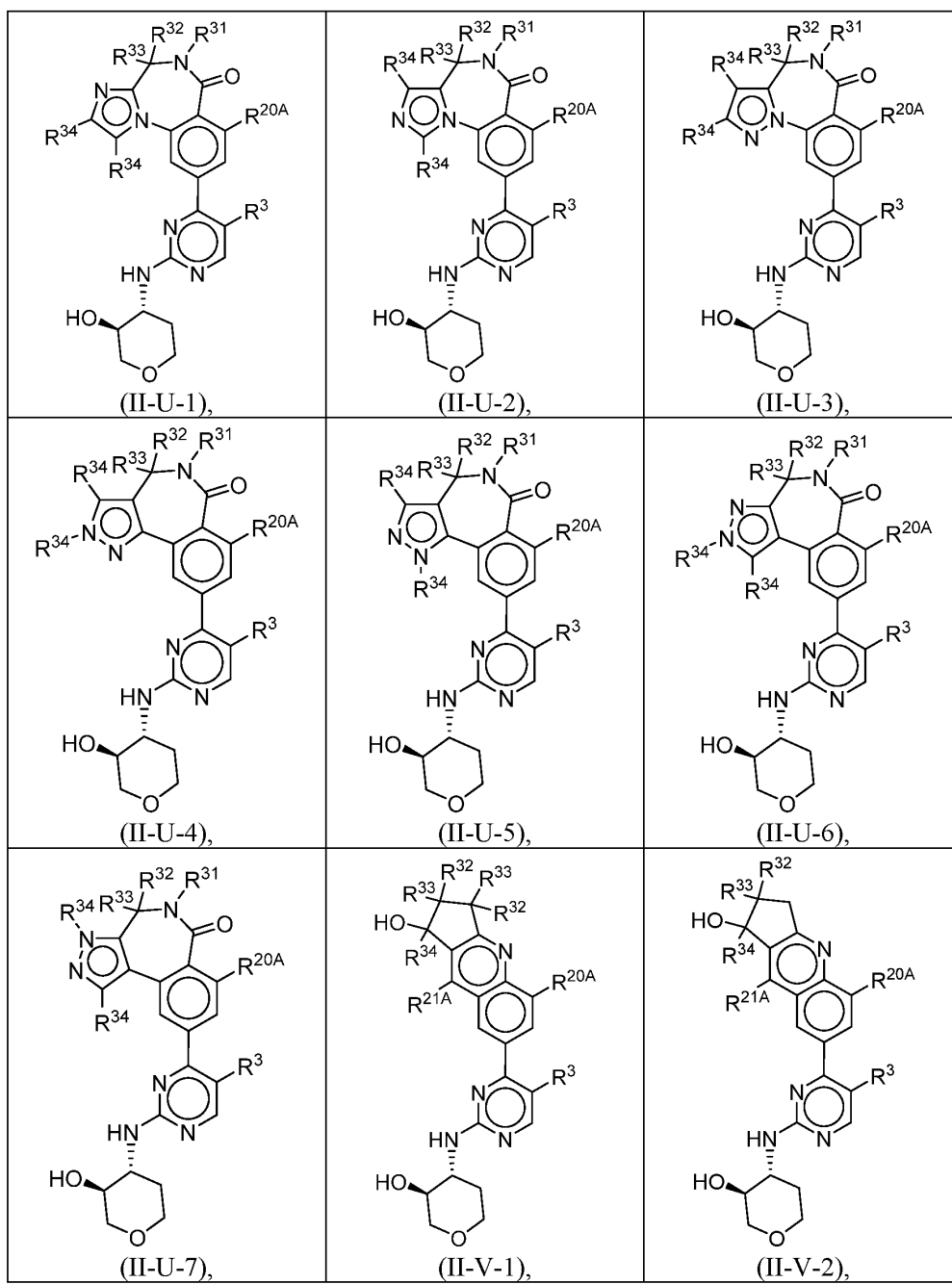


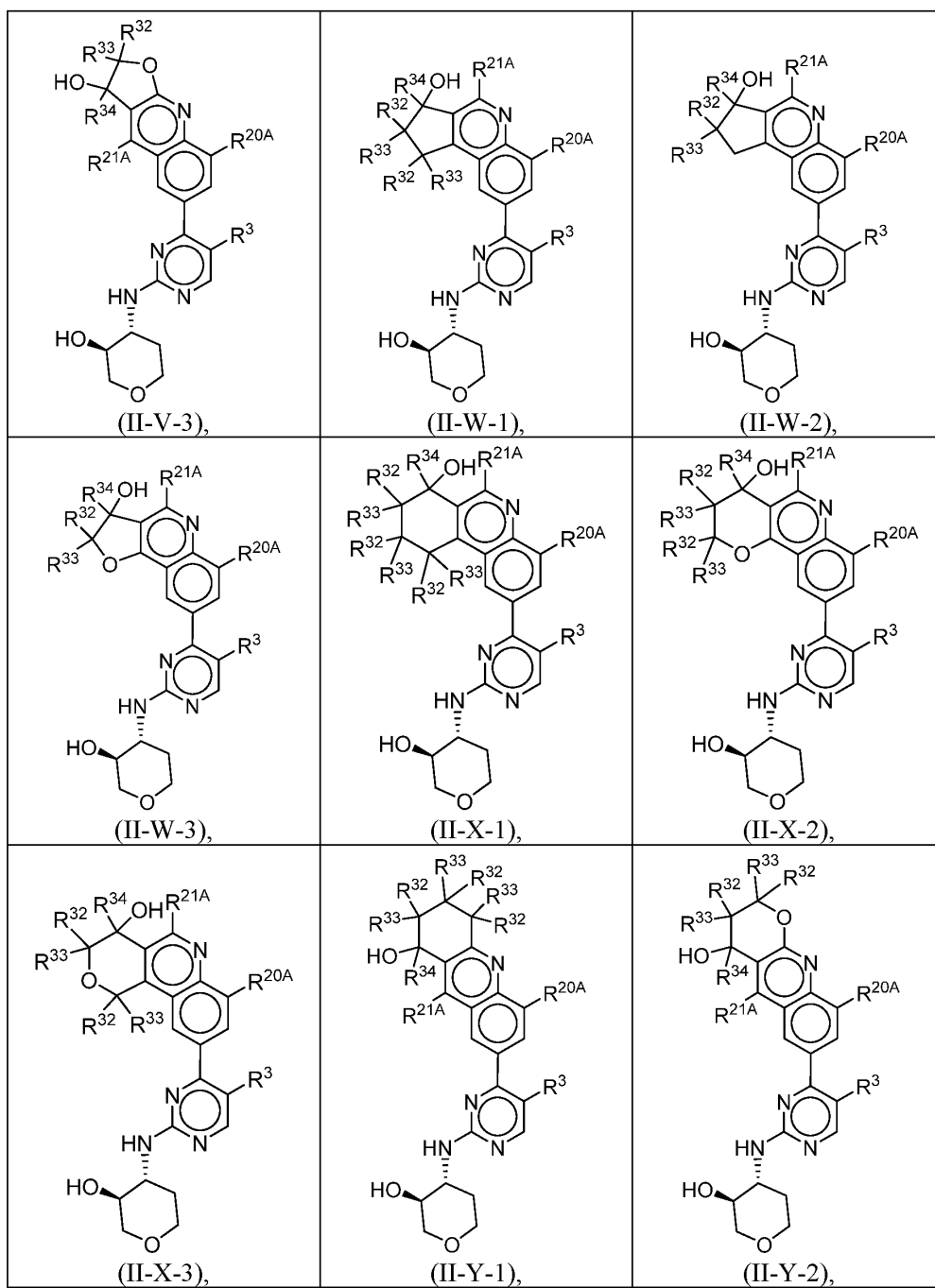


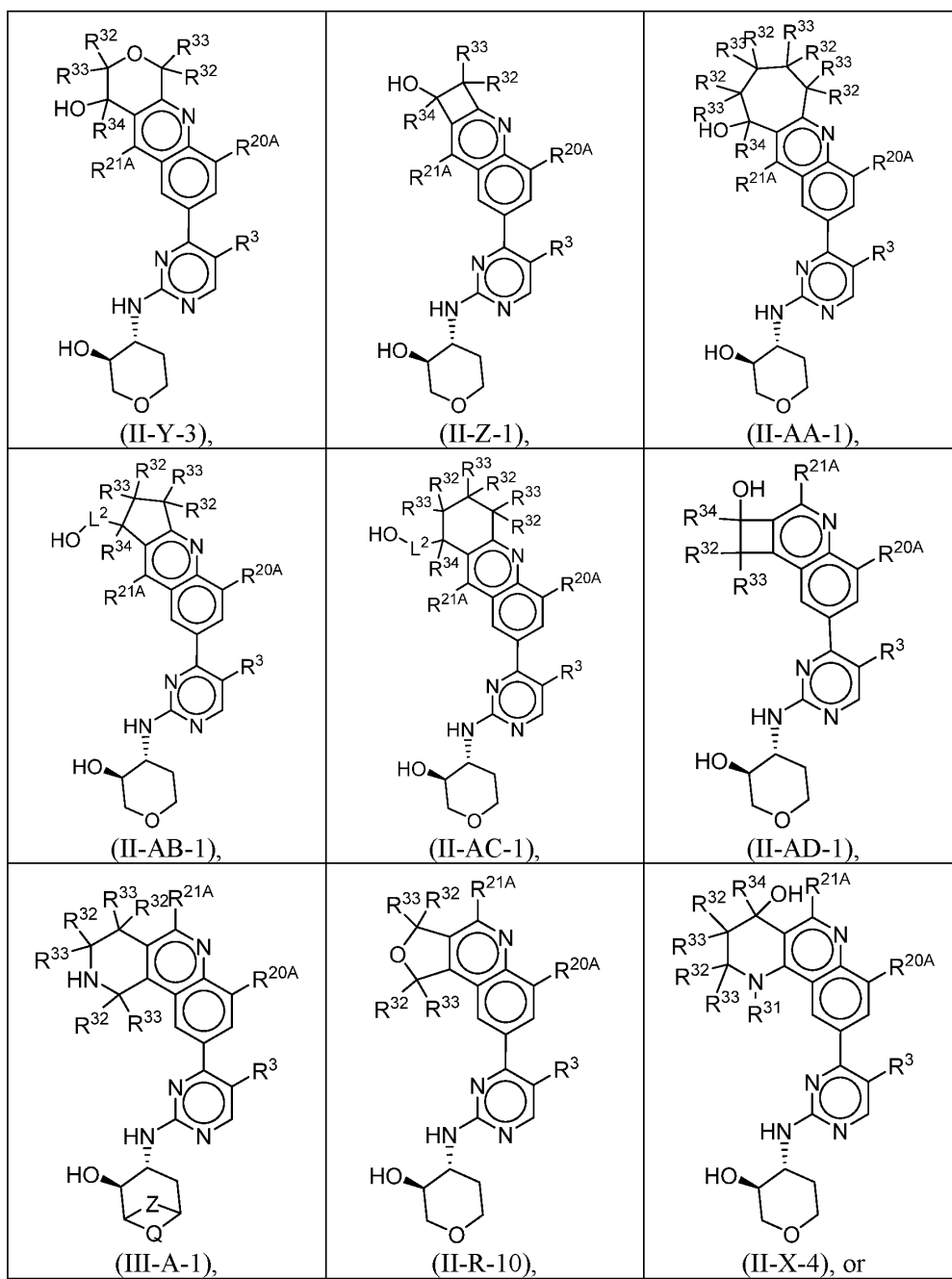


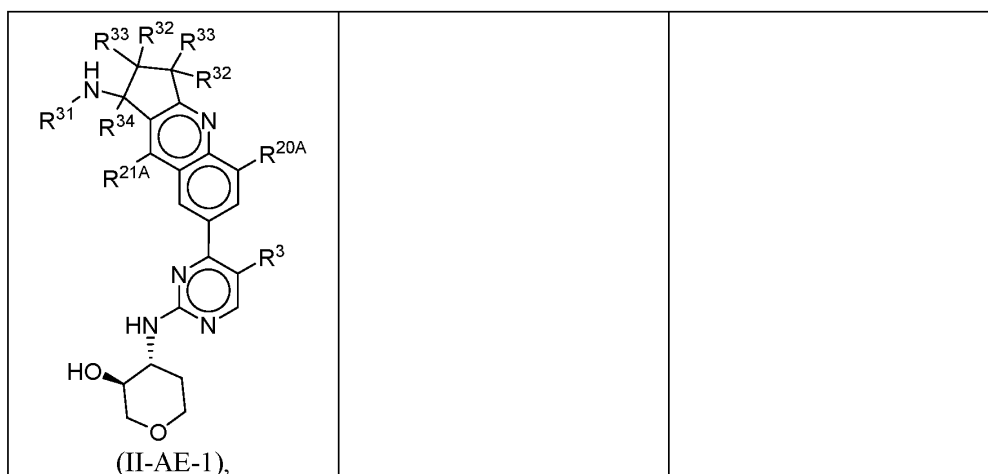












or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein:

X^4 is $-S(O)-$, $-S(O)_2-$, $-S(O)(NH)-$, or $-P(O)(R^{34})-$.

49. The compound of claim 48, wherein X^4 is $-S(O)_2-$.

50. The compound of any one of claims 2 to 49, wherein R^{32} at each occurrence is independently hydrogen, halogen, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} alkoxy optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, and R^{33} at each occurrence is independently hydrogen, halogen, or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F; or R^{32} and R^{33} together with the carbon atom they are attached to form a carbonyl (CO); or R^{32} and R^{33} together with the carbon atom they are attached to form a C_{3-6} carbocyclyl or 4-6 membered heterocyclyl.

51. The compound of claim 50, wherein R^{32} at each occurrence is independently hydrogen or methyl, and R^{33} at each occurrence is independently hydrogen or methyl; or R^{32} and R^{33} together with the carbon atom they are attached to form a cyclopropyl.

52. The compound of claim 50, wherein, for the $CR^{32}R^{33}$ that is not X^1 or X^2 , R^{32} and R^{33} are both C_{1-4} alkyl, or R^{32} and R^{33} together with the carbon atom they are attached to form a C_{3-6} carbocyclyl or 4-6 membered heterocyclyl.

53. The compound of claim 52, wherein, for the $CR^{32}R^{33}$ that is not X^1 or X^2 , R^{32} and R^{33} are both methyl.

54. The compound of claim 52, wherein, for the $CR^{32}R^{33}$ that is not X^1 or X^2 , R^{32} and R^{33} together with the carbon atom they are attached to form a cyclopropyl.

55. The compound of any one of claims 1 to 54, wherein R^3 is hydrogen, F, Cl, Br, CN, or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F.
56. The compound of claim 55, wherein R^3 is Cl.
57. The compound of any one of claims 1 to 56, wherein R^4 is hydrogen or deuterium.
58. A compound of Table 1 or Table 1A, or a pharmaceutically acceptable salt thereof.
59. A pharmaceutical composition comprising a compound of any one of claims 1 to 58, and one or more pharmaceutically acceptable excipients.
60. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 58, or a pharmaceutical composition of claim 59.
61. Use of a compound of any one of claims 1 to 58 or a pharmaceutical composition of claim 59 in the manufacture of a medicament for treating cancer.
62. Use of a compound of any one of claims 1 to 58 or a pharmaceutical composition of claim 59 for treating cancer.
63. A compound of any one of claims 1 to 58 or a pharmaceutical composition of claim 59 for use in the treatment of cancer.
64. A compound of any one of claims 1 to 58 or a pharmaceutical composition of claim 59 for use in a method of treating cancer, wherein the method comprises administering to a subject in need thereof an effective amount of a compound provided herein.
65. The method of claim 60, the use of claim 61 or 62, or the compound or composition for use of claim 63 or 64, wherein the cancer is breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer, esophageal cancer, head and neck cancer, colorectal cancer, kidney cancer, liver cancer, pancreatic cancer, stomach cancer, or thyroid cancer.
66. The method of claim 60, the use of claim 61 or 62, or the compound or composition for use of claim 63 or 64, wherein the cancer is breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer, esophageal cancer, liver cancer, pancreatic cancer, or stomach cancer.
67. The method of claim 60, the use of claim 61 or 62, or the compound or composition for use of claim 63 or 64, wherein the cancer is breast cancer.

68. The method, use, or compound or composition for use of claim 67, wherein the breast cancer is ER-positive/HR-positive, HER2-negative breast cancer; ER-positive/HR-positive, HER2-positive breast cancer; triple negative breast cancer (TNBC); or inflammatory breast cancer.

69. The method, use, or compound or composition for use of claim 67, wherein the breast cancer is endocrine resistant breast cancer, trastuzumab resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/CDK6 inhibition.

70. The method, use, or compound or composition for use of claim 67, wherein the breast cancer is advanced or metastatic breast cancer.

71. The method of claim 60, the use of claim 61 or 62, or the compound or composition for use of claim 63 or 64, wherein the cancer is ovarian cancer.